taking that into account. We're actually trying to demonstrate the worst case scenarios here. We're not taking into account the influence of calcium on the absorption and so forth.

So, in conclusion then, these are the levels we're getting. That's the highest one and they drop pretty precipitously from there. So in conclusion then, you know, I think we have -- we're getting a better idea of what the blood lead levels look like -- I'm sorry, what the lead impurities look like in pharmaceutical materials. It does not seem to be terribly high. In fact, they seem to be quite low. And to my way of thinking that indicates that the current manufacturing technology is capable of producing pharmaceutical products that have very low lead contamination. And that's it. So, thank you.

MR. MORRIS: So these are clarifying questions at this point and then

we'll do discussions at the end. Harriet.

MS. NEMBHARD: Thank you for explaining this study. I would like to ask a couple of questions, starting from about the slide 11, I believe, where you talk about sample replicates. Could you just explain for me please why the range in replicates from 1 to 14, and whether the replication was intended to measure the variance in the product or in the machine or measuring equipment.

MR. KAUFFMAN: Yes, I put the replicates in here because if you want to do a statistical analysis on our results you need to know the number of replicates. And what I don't say here but is said in the paper is that each of these replicates represents in the measurement five measurements. Okay, so each replicate is five measurements. And that's how we generate the statistics.

MS. NEMBHARD: So why to 14?

MR. KAUFFMAN: Right. In most of the cases we're trying to analyze a large number of samples. It's a fairly time-consuming analysis. So in many cases we only did one measurement. In some cases we did multiple measurements, as you said, to try to get an idea of the accuracy -- or I should say the precision of the instrumental method. In many of these cases, particularly when we saw high levels, when we saw high levels we always did replicate measurements.

So, for example, this one where we see relatively high measurements, we did that four different times. And we would do it at different dilutions, for example, because a highly concentrated solution can sometimes give somewhat low results because the instrument can be saturated.

So, when we saw high levels, or in other cases where we saw maybe problems in the digestion, we always did replicate measurements. And we rarely saw any problems

on the basis of the replicates.

Does that answer your question? You can see that here, too. So here are a couple of other ones that were high, and we did multiple replicates in that case.

MS. NEMBHARD: Okay, so still why then 14 for the Children's Motrin, product 17, for example?

MR. KAUFFMAN: I think we chose that one -- it's now four years since we did this, but I believe we chose that one as -- the 14 was so that we could determine how much variation there was in the measurement itself.

MR. KOCH: Mel Koch. Did you have another question?

MS. NEMBHARD: No, that's all right.

MR. KOCH: Just a point of clarification. On slide 8 you talk about the ICP and the level of detection as in a part per trillion. But when you go to slide 10,

you're also talking about ICP mass spec. But it seems to be confused with neutron activation.

MR. KAUFFMAN: In terms of the limited detection?

MR. KOCH: Well, limited detection, you know, all of a sudden now you're part per billion, but when you talk about the research reactor.

MR. KAUFFMAN: No, the research reactor has an elemental analysis facility that is capable of doing ICP optical emission, ICP mass spec, neutron activation, X-ray fluorescence. They have everything.

MR. KOCH: Okay, so you're just taking a beam line off of the neutron activation?

MR. KAUFFMAN: No, this is a standard ICP mass spectrometer.

MR. MORRIS: They're just sharing the same space.

MR. KOCH: Okay.

MR. KAUFFMAN: We're using their instrumentation and their expertise.

MR. KOCH: So the research reactor is a little bit misleading.

MR. KAUFFMAN: Oh.

MR. KOCH: Okay.

MR. MORRIS: If there are no other questions, clarifying questions, we'll break and come back at 3:30 and continue with the presentations.

(Recess)

MR. MORRIS: Can we reconvene please? And while we're finding our seats if I could just remind everyone to turn off their cell phones and pagers. You should consider that a favor. You have an excuse to turn them off. Don't just turn off the antennas, kill them. A few moments of peace in your life.

All right, so our next speaker is Dr. Darrell Abernethy, who is the USP CSO. We're happy to have him here. If you would

like to proceed. Thank you.

DR. ABERNETHY: Thank you. And thanks for the invitation. What I'd like to do is discuss briefly what's in the what we call book. The USP at the moment. And then try to convey to you some of our thinking as we're moving forward. This turned out to be very timely as you'll see with respect to not only our thinking but the people at the European pharmacopoeia as well.

What is in the USP right now? Well, Chapter 231 is the one that is generally focused on.

And I've been at USP for one year now. I have to say when I started hearing about some of our tests I was interested or astounded. But in any case, this is a method that I haven't really found the original reference for. I suspect it comes out of the Dark Ages somewhere. And I mean literally the 1400, 1500s. The metals are detected by sulfide ion precipitation. And a number of

metals are said to be detected by this method. And then a color is developed with this precipitation technique, and then that's compared to a standard of lead or something like that. So that's for the most part what's in the pharmacopoeia at the moment.

And the controls are colorimetric controls. With regard to other possibilities for testing for lead specifically, while we heard discussed briefly in an earlier talk what some of the options are, and obviously technology has moved forward and continues to move forward. We have been talking about -- and this predates my arrival to USP -- but talking about really for some years what to do about this. And so a number of thoughts have been floated in our pharmacopoeia forum. A stimuli article has been published some time ago. And we've essentially floated the idea of replacing the methodology that is currently in place with what we think might be more contemporary methodology.

As you might guess, that's created some discussion, particularly among members of industry.

And so the activity has kind of been there for quite a while. Now, at the present time it is fair to say that pharmaceutical companies can use alternative methods provided that they are -- the terms we would use at the moment are equivalent or better, and that's not very hard to achieve. And our belief is that that probably fairly routinely happens. We believe at least most major pharmaceutical companies do have updated methodologies, and presumably they are in fairly routine use. But then to go ahead and meet the USP standard they have to keep the other methodology up and running so that they can be used.

So the fair question here is is there a need for a newer test? A part of this are what are the implications if you do make a change. That always comes up,

especially when it's a general chapter like this that then would cover many different drug substances. Well, there are about 4,300 monographs; 1,300 of which are for drug substances, and many of which have a heavy metals limit. And most of these are specified by Chapter 231. And then there are the exicipients in NF. And here are two that create some more numbers. And then drug product monographs as well. So that we are talking about a change that does have some consequences with regard to then going through and updating and revising the other chapters for specific substances that would be involved.

Now, the limits that exist are predominantly for drug product components, not the drug products themselves or the APIs. And here you can see simply a breakdown. And I think you have these slides of where these substances fit. These slides are reasonably updated. They're probably current to the

last three or four months. We went through when I was asked if I'd participate here and updated it to the extent that we could without spending a huge amount of time. So I suspect these numbers are not exactly right, but they're close to right.

This is then a listing, and actually, Bob, you provided this from, I guess, an earlier talk that had been made two, or three, or four years ago here at FDA in which someone did go through and tried to understand for the monographs that did have heavy metals limits where they ranged in terms of parts per million. And this is simply a recapitulation of that. So you can see for drug substances some range, but really here in the 20 ppm or so range catches a good number of them. And then the excipients and drug products being in the same.

So this would be what's written at the moment and what people are being asked to

meet.

And then this is for the monographs that have limits. And again, we can see we're still talking about the same general range.

Now, this moves us to here we are actually right now in this summer. As I say, we've been working toward trying to make changes so that we believe the pharmacopeial compendium comes into something consistent with current contemporary methodology. We've had ongoing discussions. At USP an advisory group was formed some years ago to look into this issue, and I'll show you some data that they've developed over time. And as I say, this has continued to create a fair amount of discussion with members of industry. And by that I suspect you know what I mean by discussion. So that it's been slow going.

The Europeans and the European pharmacopoeia have been having some of the same experiences, and they put forth a draft

guidances -- actually I think a couple of years ago -- that had to do with setting new limits and approaches for metal catalysts. And so we've had some discussions with our European colleagues and made a commitment to try to work in concert. So we might come to at least a very similar solution to this problem, if not an identical solution. Frankly, our hope is to have an identical solution.

To that end we were trying to think of what approaches might work in this particular setting. So we approached the Institute of Medicine and said why don't we set up an independent group to really bring in expertise to the table, have this be an international activity not just a national activity. And then spend some time in a typical Institute of Medicine advisory group meeting to see if we can come to some insight understanding, and then perhaps approaches to think about moving forward. That's set for

the last week in August. So that will occur.

And currently we have the European Pharmacopoeia actively participating and participants speaking and attending from Europe, Canada, the United States. We have worked to get participation from Japan, and to this point have not been successful with that. But we're hopeful that the Japanese would be somewhat in concert with this activity, as well. We'll see.

The hope was to expose what could be known about clinical toxicology and link that with what might be appropriate analytical methodology so that we could come to what I've been trying to characterize as a sensible set of standards that make sense for the public health and make sense for the pharmaceutical industry. So that's the hope.

This is now a little background from where we are and why we have moved in this direction. Heavy metals have been monitored, as I've said. Some of these

metals shouldn't be there for sure. Some of them we'd like not to be there. It might not be a huge health issue, but it might be an issue in terms of quality of manufacturer.

Where might they come from? Well, those sources might be viewed as obvious. From catalysts, from starting materials, from process activities themselves. I think we've already discussed this.

Now, this is really some of the first shots across the bow to try to understand how the UPS methodology was working. And so this was a stimuli article. It was in the Pharmacopeial Forum in 1995. And so this again as an advisory group going back more than a decade. And you can see from the quote, which I won't read, that it would be fair to say this is worrisome. But some would argue, including me, that it's probably better to not do any testing at all than to do testing which doesn't work.

Now, this is a more recent paper

that came from another group and is essentially saying the same thing -- that the real problem is with this approach. And more of the same, but simply if you read that last paragraph -- I think raising the possibility that the last speaker did -- that there are methodologies that are available. That there is instrumentation that perhaps somewhat expensive, but it's rather routinely available in analytical and drug development laboratories at this point.

Now, here is a slide that I find worrisome. And this is simply looking then in a screening across the metals you see listed on the X-axis. In looking at the USP result in terms of percent recovery as compared to the same methodology as described in the last talk. And that's ICP-MS. And, you know, I guess partly you can see that those lines don't look the same. But perhaps even more worrisome, they don't look the same for some things you'd really like for them to

look the same. And if we look kind of across here, it just doesn't get better. And here we go, mercury.

And so we believe that's kind of where we are right now. That this is what our pharmacopeial standard is able to say. As I said, we have formed an expert committee -- excuse me, the expert committee on general chapters has developed a heavy metal subcommittee, and they were the ones actually -- Nancy Loo and that subcommittee -- developed the data I showed you on the last slide.

So, these are some of the questions that that group had raised. And this was as long as a couple of years ago. And they seemed like reasonable questions. The first one is kind of what I would say is a compendial ease. And that is what term should you use? Should you broaden the term to inorganic impurities? And I think there is some interest in doing that. If we're

saying metals, then perhaps we better be cautious about saying heavy metals because there are a variety of other metals. And one might get into a definitional sort of thing. What ones need to be monitored, and I think as was nicely addressed in the last presentation, what kinds of limits should we be thinking about setting. And then this gets into much more the methodologic issues of, well, what approaches might make sense going forward.

An important piece is down here, I think. And this has to do perhaps a little less with this immediate committee, but not less to do with FDA. And that is, as you know, about a year and a half ago the USP took responsibility for the food chemicals codex. And so a parallel question that we're trying to raise would be where do we need to be thinking about this kind of a standard with respect to the food ingredient standards. And then as a subset of that, the

dietary supplements standards that we also do have compendial methodologies for.

And, of course, for some food ingredients daily dosage may be quite different than would be for pharmaceutical. And so we're trying to think through and work through those kinds of questions. Further considerations, and this is what we're hoping -- there's a fair amount written about this already -- but we're hoping to learn more and to really gain benefit from a workshop like the IOM activity. To think about the toxicity of metals that we should be measuring and certainly this relates to not only the metal itself but in many cases the valence of the metal. For example, arsenic plus 3 and arsenic plus 5 are really quite different breeds of cat. They show up in different places and certainly have totally different consequences with exposure.

What target organ should we be thinking about, and then certainly and

interestingly our Japanese colleagues have been less immediately involved with this. But certainly there will be cultural and political issues that surround at least some of the metals. And how to handle those, as I said earlier, we hope in a sensible way, that really meets the needs of safety and society. And at the same time makes sense for the pharmaceutical industry.

What concentration limits should we be thinking about? Well, certainly if the ibuprofen case that we saw earlier holds, then you could argue that let's hope that really all drugs products we see are held to that quality. We frankly don't know the question to that, and we don't get a huge amount of information from industry with regard to what kinds of data they may have in house with respect to lot-to-lot variation, sourcing APIs from various sources around the world, and what have you. That information may or may not be available. It would be

helpful to know.

But in any case, these are fairly obvious sorts of considerations that certainly there will be more vulnerable patient populations and less vulnerable. I guess our thinking at the moment would be we think of the most vulnerable and then try to set standards surrounding that in terms of exposure limits. And then, of course, duration of therapy with whatever the exposure is will be important. And so we'll have to think that through as well.

So, as we've said earlier, the current chapter, we believe anyway -- I would go so far as to say fatal limitations. I guess if we're unsuccessful in really moving this revision forward I shouldn't use that word and I should say real limitations -- that the test limit as it currently stands really is this precipitation and colorimetric method. We believe we have solid data saying what's currently used is not reliable. It's

difficult to perform with any sort of precision, much less accuracy.

As I mentioned, the Europeans -- actually, I believe that's no longer a graph guide -- so anybody that knows about that rumor, but I think that now is final. They went ahead and developed some thinking around metal catalysts. And we're thinking that it would be better or more useful to try to do this in one swoop and think beyond catalysts to other sorts of metals that have known clinical toxicity.

We believe that using more modern instrumentation would make a lot of sense. And the question of what instrumentation -- well, that's where we hope to gain advice as we move forward. And then to set realistic and sensible toxicological limits.

We have put up a few suggestions of what we think limits might make sense. Really as much as anything for something to shoot at so that we can start the discussion

about with good detection methodology where should we be thinking. And so this is just a brief listing. And this is based partly on our own literature review and partly on what the Europeans put together. And these may be in the right ballpark anyway, but they certainly may require considerable refinement. And I think you have these slides.

We're still thinking through, and we hope to benefit from as much input as possible in what these limits should be. It's been very arbitrary to say that oral dosage form should have a tenfold higher limit than parenteral. To try to put this in some sort of perspective, this limit for lead from FDA bottled water of a limit of 5 micrograms per liter assuming 2L/day -- so that would give you a sense of where a number for lead came from. And that's just a back of an envelope calculation. But we need to move forward in refining these so that we

come up with reasonable sorts of limits.

The Europeans, with the guidance that they put out, has classified the impurities by risk level. And simply separated the metals into classes as a first cut to allow them to think about limit setting in a little more global fashion rather than slogging through one metal at a time. And they, too, tried to make distinctions between oral, parental, and inhalation dose forms. And importantly, what duration, age of exposure, and then what sort of toxicological safety factors should be written in.

So, the thinking that we're going through right now will be to move towards updating the general chapter that relates to inorganic or metal impurities -- that there will be a number of considerations that we need to have as we evolve this revision. And that we're hoping that we can encompass APIs -- that we can encompass dietary supplements

and perhaps food ingredients as we think this process through so that we can have a common standard across these various compendia that we look after.

With regard to detection techniques, this was discussed briefly before but obviously there are a variety of possibilities. And so the questions would be, well, what ones will work? What ones make sense from a methodologic point of view in a quality control kind of setting -- (off mike) research kind of setting, and then what kinds of methodologies are out there and fairly routinely available. And these are some of them. And the data we saw earlier was with ICP-MS.

You probably can't see this, and you may or may not be able to see it on your slide, but this was thinking through, okay, how would this work? And so we tried to say, well, let's see is this something that would be soluble in an aqueous solution? Would

this require an organic solvent? What would preparation need to be? Does it need to undergo a digest? And then a preparation to then use a methodology, perhaps ICP-MS or other methodology. And then to see recoveries. And then to see if, indeed, this kind of a flow sheet would work and perhaps would be useful to people. That's simply a proposal, and will benefit greatly from having lots of people work with it, lots of people put their eyes on it who know a lot about it, and then try to come up with a reasonable sort of compendial approach.

Some more of our questions we face at the moment are how many elements do we want to be monitoring on a routine basis, setting the limits, of course. And then these are some considerations that at least our advisory committee put forward. And that would be there might be some instances in which atomic absorption would be useful or there might be some instances in which

ICP-OES might be useful. Some instances which we would think in particularly difficult situations ICP-MS might be necessary.

Actually, this is in August. This is the meeting I was talking about. We're working actively with other pharmacopeias to try to come to a consensus. And I hesitate to use the word harmonize, but we'd like to come to something like that in terms of where we end up so for the pharmaceutical industry, which is for the most part global in nature, not having to meet slightly different standards in different places.

And so that's where we are at USP with, we think, somewhat dated compendial methodologies that are the current standard and an enthusiasm to move forward. I was delighted when I was asked to come over here and talk about this because we'd like very much to work closely and collegially with FDA and others to move this forward in a way that

is really best for the public and best for the pharmaceutical industry in looking after the public safety.

So I'd be happy to try to take any questions.

MR. MORRIS: So, we'll have Liz and then Marv. I'm sorry, did I miss you, Carolyn? Did you beat Marv? Because we'll put you ahead of him in a minute. I'll tell you.

MS. TOPP: This is Liz Topp asking this question. I have a question -- sort of a silly one for clarification. About halfway through your talk, on my page 11, you say that the USP is proposing limits and they're listed for various different metals on an exposure level on the level of micrograms per day. But in other parts of conversation I've heard here today I've heard people talk about parts per million or parts per billion in the product. Is USP going the direction of exposure based on this micrograms per day, or

are you going based on sort of concentration of the heavy metal in the product, or both?

DR. ABERNETHY: Well, I think that requires discussion. In terms of for the public health, I guess you'd think of exposure per day or something like that. In terms of what the pharmaceutical industry might be able to implement across maybe a fairly wide range of doses, you might be talking about, okay, what would be the maximum amount that could be in a product in order to keep the exposure below what we think a reasonable daily exposure is.

MS. TOPP: So really both are open?

DR. ABERNETHY: Yes.

MS. TOPP: Considering perhaps implementing both?

DR. ABERNETHY: Well, we need to implement a thing because put yourself in the shoes of someone in the pharmaceutical industry who has a standard they need to meet. Well, they basically need a number.

And they need a method. And then they need to just do it. And so they won't, I think, be interested in saying, well, if the dose is going to be 500 mg/day it needs to be this, but if it's going to be 10 mg/day it needs to be that. I think what they'll probably need is a number and a method.

It sounds simplistic but when I put myself in those shoes I have to say I get it. That's kind of how you need to proceed if they're in a development place.

MR. MORRIS: Okay, Marv.

MR. SCHMUFF: I might just mention that in the PF article you do have -- the first column is oral daily exposure in micrograms per day as well as the oral limit in micrograms per gram and the parenteral limits. So I mean you sort of some estimate of daily exposure in addition to the micrograms per day figure.

So, actually, one question I had as it wasn't clear to me which one you were then

going for, but it sounds like the oral limit in terms of micrograms per gram.

DR. ABERNETHY: What we're going for, quite frankly, is to get this discussion moving. We're kind of way before where you are at the moment. We need to get this moving forward. We need to get buy-in from the public, buy-in from members of the pharmaceutical industry, and move it forward so that -- you know, quite honestly we're down the road, not in a -- somewhere between an embarrassing and sad situation -- and there having been a major metal exposure that past the USP test.

And it passed it because the USP test doesn't work. I mean, we don't want that.

So that's kind of where we are. Those kinds of units and all that are up in the air. We're hopeful that through the summer and fall we'll begin to hone down on that.

MR. SCHMUFF: Okay. I have another question but I'll defer to the people who were ahead of me who I usurped.

MR. MEYER: Darrell, congratulations on only a year and you got USP to move. That's an outstanding accomplishment.

DR. ABERNETHY: No, no.

MR. MEYER: Oh, talk about moving.

DR. ABERNETHY: We're trying to get people to start thinking about moving.

MR. MEYER: Okay. On page 15 you had your flow sheet. And just for clarification, one of the lower boxes said did the monitor and USP reference solution recover to within plus or minus 20 percent.

That sounds like an awfully large number. Is that not an awfully large number?

DR. ABERNETHY: No, that's just a number. See, I think the thought here is that we presumably will be setting limits well below what we think should be associated

with a toxicological effect. So to say that then that needs to be at 100 plus or minus 2, or something like that, that's a precision that just doesn't seem like it would be needed. And so I think what we're really trying to say is that what we need is a reasonably good method that clearly gets down to the levels we need to. And then to have boundaries around that that are not too broad. Now, 20 percent may not be sensible. Maybe it should be 5 percent. We don't think it should be 0.1 percent or something like that.

MR. MEYER: Okay.

MR. MORRIS: Carol.

MS. GLOFF: Thanks. I have a question that maybe I'm just not getting it. That is very possible. But if I look at slide 23 I think it is -- draft USP oral limit, micrograms per day, you know, initial discussion lead -- since our focus is lead -- is 1. So that's 1 microgram per day. Two

slides later it says oral PDE for dosage forms are 10 times higher. So does that mean that the acceptable -- I don't get the difference there. If the proposed oral limit per day is one, and then also on two slides later, slide 25, the last bullet, PDE limit for lead from bottled water is 5 microgram per liter times two liters -- that's 10. I'm just disconnecting something there. Can you explain that to me?

DR. ABERNETHY: Okay, here if we said, okay, the lead -- the oral limit for lead should be 1 microgram a day, then the parenteral limit should be 0.1 microgram a day. Now, that comment about bottled water, I believe that the current lead level for bottled water -- if we assume a 2-liter a day intake -- would say that that would be an exposure -- that the water couldn't have more than 5 micrograms of lead per liter in it. That's simply saying that the limits that are out there right now do specify a certain

exposure level, and then let's float out there what kind of an exposure level would make sense. Water, obviously, would be more in the food ingredient or actually food product sort of world in which there are high ingestion amounts so that to achieve the same daily exposure would require a much lower concentration per unit. Whereas, in the pharmaceutical arena where the ingestion amounts would be much smaller even in the case of a high milligram dosage drug, that to achieve a certain daily exposure there could be more of the lead or whatever metal there. So I think you're being far too quantitative here.

MR. SCHMUFF: Well, if I might just suggest this. I think maybe there's a typo in that slide because in the PF article, which I have here, it has those numbers as micrograms per gram. I think it was slide 11. Not micrograms per day. So that would explain it. See, in the draft it's not

micrograms per day. It's micrograms per gram.

DR. ABERNETHY: Then I apologize for that typo.

MR. SCHMUFF: And then it does come out to micrograms per day for lead exposure.

DR. ABERNETHY: Okay, my apologies.

MS. GLOFF: Thank you.

DR. ABERNETHY: Sorry for the confusion.

MS. GLOFF: I was really worried those Tums that I take for calcium would end up being pulled off the market or something.

MR. MORRIS: I think Norm you're in, and then Mel, and then --

MR. SCHMUFF: Yeah, the other question I had just was about at one point you mentioned there are something like 4,300 monographs. And then on your penultimate slide you say that 231 would apply to 1,000. I guess my thinking was, I mean, it looked to me the way it was written it would apply to

all of them unless there was a more stringent guidance. So I'm not sure about what that 1,000 is on that next to last slide.

DR. ABERNETHY: Where there would be a specified limit is what that's trying --

MR. SCHMUFF: Yeah, what I understood is that, you know, you would have that table in the general chapter. And consequently, it would apply everywhere except where there was an exception. And but on this slide just previous to this you just mentioned 1,000 monographs. And I just don't know where that 1,000 came from or if you did mean it would essentially apply to all monographs.

DR. ABERNETHY: It would apply to all based on the revision. Based on what's currently in the book, there need to be 1,000 to have things switched.

MS. NEMBHARD: Oh, like maybe 1,000 additional?

MR. MORRIS: Darrell, can you talk

in your mike a little better?

DR. ABERNETHY: Oh, I'm sorry.

MR. KOCH: Yeah, Mel Koch. Maybe a suggestion. Where you talk about coming up with something that refers to these as inorganic impurities, if there was something that would be more like inorganic content or compounds, because I don't know across the board whether everything would really be seen as an impurity if it was a salt or something like that.

And then when you mention this meeting coming up you've invited Japan and hope that they would attend. But is China on the list at all for participation?

DR. ABERNETHY: That's an interesting question. Certainly they're aware of the activity we have ongoing. And at the moment we haven't asked the Chinese pharmacopoeia to become involved. We do work closely with them, and we hope they'll be interested. And they're in the process, we

hope, of translating the U.S. pharmacopoeia into Chinese, or doing a legal translation I should say. And so we hope that there will be interest and, you know, uptake. We'll see. The reason for those three is that's a derivative of the so-called pharmacopeial discussion group, and we like when we can for those three pharmacopoeia to reflect each other.

MR. GOOZNER: This is Merrill Goozner. You confused me a little bit, so I just want to make sure I'm clear on this point. Because if the suggested limit for lead was going to be 10 micrograms per day on that chart -- and I thought we heard -- do I have that right?

MR. SCHMUFF: Yeah, that's what the PF article -- I have the PF article. That's what the PF article suggests. Ten micrograms per day, oral permitted daily dose.

MR. GOOZNER: Which -- okay. Is that what you are recommending then?

DR. ABERNETHY: I don't know how many times I can say this. We're floating a proposal to stimulate discussion so that we can get the right people around the table.

MR. GOOZNER: Well done.

DR. ABERNETHY: To come to a good recommendation. So we put, perhaps foolishly, numbers up to give people something to shoot at. That's all. And I don't mean to sound, you know, frustrated. But I can tell you in a similar discussion we had with members of what we call a stakeholder forum, but members of industry, they really just zeroed right in on those numbers, too, and just went nuts.

MR. GOOZNER: Thinking, I take it, that they were too high.

DR. ABERNETHY: I don't know. Thinking it was something --

MR. GOOZNER: Too low, I meant, excuse me.

DR. ABERNETHY: Something new and

different, and they didn't like it.

MR. GOOZNER: Well, you stimulated discussion, so you've done your job.

DR. ABERNETHY: So I've achieved my job. So hopefully everyone goes home and thinks about what the sensible number would be.

MS. MORRIS: Marilyn Morris. I'm not going to ask you anything about those numbers. But on one of your slides, on the EU approach, you mentioned that there's a classification of metals by risk. And certain ones are classified as significant safety concerns. And in your talk you also talked about the concern with when you have combinations of heavy metals. With the EU approach, are they looking at different limits if there's combinations present? Have they looked at that at all?

DR. ABERNETHY: I don't think so. I'd have to go back and reread that document. But what they've done is to select out

catalysts and metals that they know are used as catalysts in preparation or synthesis of pharmaceutical products. And then focused on them and moved forward with that. But not in terms of then, okay, what if you had a mixture of things. And is that important? I'll be honest and say I don't really know. It sounds like an interesting thing to think through.

MS. MORRIS: Thanks.

MR. MORRIS: Pat, do you have --

MS. TWAY: I think I can answer that question. Because in Europe -- and we do have products there -- they were focused on catalyst residues. And so, basically the limits were set based on safety. And so based on a risk analysis and if you have multiple metals -- because in those cases, at least in our experience, we're using the more sophisticated methods -- so you can quantify metal by metal. You have specifications appropriate for each metal. So it's really

quality by design or what the level of science and controls you need on that specific metal in order to assure safety to the patient.

MS. MORRIS: So there's no differences if you have multiple, you know, heavy metals present in any product?

MS. TWAY: The ones we had -- I mean, we're talking about two. There are two metals, and one was -- I'm going from memory. I think one we controlled based on safety at 5 ppm and one was at 20 based on the risk. And they don't synergistically look at them, no. But all the limits are very low and quite a bit below the safety limits.

MR. MORRIS: And I think that -- are you trying to get at is there a known synergistic toxicity effect, Marilyn?

MS. MORRIS: Yeah, well, certainly additive.

MR. MORRIS: Or additive.

MS. MORRIS: Or synergistic

toxicity.

MR. MORRIS: So maybe is that a point of clarification perhaps?

MS. TWAY: I don't know. I mean I don't know how they came up with the numbers they came up with, but these are the numbers that they said, you know, if you have ruthenium you need this; if you have lead you need this. So I'm not a toxicologist.

MR. MORRIS: Okay, so Norman, do you want to lead the discussion in this? Well, maybe we should have the presentation first then.

MR. SCHMUFF: Good thought, Ken.

MR. MORRIS: Can we vote on that? Sorry, go ahead.

MS. NEMBHARD: We really are also fortunate in that we have someone who participated actually at a center briefing that we did when Steve Galson was the center director. And Dr. Kashtock at that time agreed to participate because we did think it

was important to look at how CFSAN had been regulating lead levels and to understand what the thinking was, and particularly, since they had just gone through an exercise related to lead levels in candy. So Dr. Kashtock then will talk to us about and give us that perspective on regulation of lead in foods.

DR. KASHTOCK: Thank you. Good afternoon. I should have subtitled this 100 years of activity boiled down to 20 minutes because that's how long the food part of FDA has been dealing with lead.

We have a seizure of about 85 bags of green coffee beans that were nefariously colored with lead chromate to artificially enhance their appearance because these were green coffee beans seized by FDA, or at that time Harvey Wiley's Bureau of Chemistry back in 1908. That may be the first action on record dealing with lead in food. But the major issue that we dealt with on the food

side was really not a nefarious practice at all. It was intentional and condoned. Through World War II, almost all commercial apple production in the U.S. -- in that apple production the orchards were sprayed with lead arsenate to control the coddling moth. And because of this spraying, the apples had to be washed to remove lead and arsenic residues. And FDA monitored apple products extensively, and enforced tolerances for lead and arsenic through the 1940s. And it was after World War II that better insecticides like DDT came along. And the arsenates were no longer used. The first extensive testing for foods took place in the 1930s. That was when the methodology was developed to reliably and rapidly determine lead to low parts per million levels. FDA looked at about 2,000 foods at the time and actually found very few foods where there appeared to be problems, but many, many foods had small amounts of lead. And this appeared in a FDA

1935 report. Absolute freedom from lead is impossible of attainment in civilized and perhaps even primitive society because of the widespread occurrence in natural products of minute, though appreciable amounts of this metal in the order of a few thousandths of a grain per pound.

I love the old terminology there. But as Susan showed, the Industrial Revolution had already left its footprint by this time in that it was recognized that foods grown in the natural environment were going to be a product of that natural environment. And it to some extent was contaminated with lead. And we do not believe that zero lead in our food is the appropriate goal.

But what we do try to do is this -- and this has been the foundation of our policy going back to the 1930s -- prevent the avoidable introduction of lead into food. Control the unavoidable introduction of lead

into food.

Now, what's avoidable and what's unavoidable concepts of those two have changed over time. But an example, going back to that time, again, the lead arsenate spraying, there were alternatives available for vegetables and agriculture. So lead arsenate residue was not tolerated on vegetables at all. If it was found the product would be seized. On the other hand, there were no alternatives to control the coddling moth in apple orchards. So spraying of that fruit with lead arsenate was permitted subject to the food having to be washed and subject to our enforcing a tolerance.

The tolerance, by the way, was about 20 thousandths of a grain per pound, which equates to about 2.85 ppm. If you ate apples in the 1930s and 1940s you could expect to get about a couple of parts per million lead residues in those apples.

And that was the way things kind of stayed. Again, the arsenate spraying was done by the end of World War II until around 1970 when concerns began to increase about the particular vulnerability of children to lead's effects and the thresholds for adverse effects began going down. The early 1970s was really a watermark time. That was when the most effective efforts to begin getting lead out of food began. The EPA phased down leaded gasoline, though not specifically for the purpose of reducing lead levels in food. It had an enormous effect on reducing lead levels in food over time.

Also at the time, FDA initiated efforts to reduce lead levels in canned foods. At the time, soldered cans were really the only type of food can that was available. It wasn't until about 20 years later that non-soldered can food technology eliminated lead soldered cans. So the efforts in the 1970s were that solder was

going to be used in cans, let's find ways to lessen the potential for the lead to become a component of the food.

And then there was the Lead-based Paint Poisoning Prevention Act passed in 1971. So these really major efforts got under way in the early and mid-'70s. And most of the progress that's been made really was made as a result of what was going on in the '70s and '80s. A lot more lead reduction efforts took place in the '90s, but this is really where the progress was made.

We have had since the early 60s what we call a total diet study. It's a market basket study that estimates dietary levels of certain analytes. It was initiated in the '60s to track levels of radionuclides in foods during the era of nuclear testing and it has been expanded to include heavy metals, pesticides, certain dietary nutrients and other contaminants. This is a program that is still in effect. We do about four

market basket collections per year, and estimate dietary lead intakes for age, gender groups throughout the population.

The 14- through 16-year-old male is the age gender group with the longest continuous reporting. And in that 1972 through '82 decade, there was a different calculation methodology being used at the time, and they reported daily lead intake from diet for the 14- through 16-year-old male was in the 60 to 90 microgram per day range. In the decade spanning from the early '80s to the early '90s we see a reduction -- and again this was a different method of calculation from 38 micrograms a day down to about 3 micrograms per day.

And then as I said before, in the '90s, although efforts were continuing, the dietary reduction kind of leveled off. We really don't see additional reductions taking place in the 1990s. But this reduction success that was achieved in the '70s and

'80s occurred in all TDS population groups.

And then by the time we got to the 1990s, we had the Needleman findings of the 1980s beginning to shape our policy efforts that lead had effects on cognitive development in children and fetuses. Ten micrograms per deciliter was established as the blood lead level of concern by CDC, but it was recognized that there might not be a threshold.

And this took us from the actions in the '70s which focused on the lead soldered cans into things that we did in the 1990s. And I'll go over those in just a second. Also in the 1990s was when we established our provisional tolerable daily intake for lead to support our policy development and to use in enforcement actions should we take legal actions against lead in any adulterated products. And PTDI, sometimes referred to as PTTIL -- it's really a reference dose type concept. It

corresponds to the daily intake that would induce a 1 microgram per deciliter rise in blood lead levels for children and women of childbearing age. And that's predicated on cognitive development effects at 10 microgram per deciliter of blood lead level. So it's a safety margin of 10 or a margin of protection of tenfold over the 10 microgram per deciliter blood lead level of concern for children and pregnant women.

And then for the remainder of the adult population it's predicated upon a 3 microgram per deciliter rise. The effect of concern was hypertension and the threshold used for that was 30 micrograms per deciliter. So again you have the 10- fold margin of protection.

So that's what our reference dose PTDI actually means. For children under 7 it's 6 micrograms per day. For women of childbearing age it's 25. And then we later began using a level for slightly older

children of 15. And for all other adults, again, 75 micrograms per day.

So, based on our most recent published total diet study information, where does dietary intake of lead stand with respect to the TDI? There are actually two ways that we come up with this estimate. First of all, most foods that we collect in our TDI when we test them for lead we get nondetects. If you equate the nondetect zero, you come up with this range. If you equate the nondetect to the limit of quantitation in the method, you come up with this range. What we're saying is based on what we find in our TDI for all age gender population groups, dietary lead intake when compared to the 6 microgram per day, or 25 microgram per day, or whatever PTDI, is no more than 5 percent of that PTDI when one set of assumptions is used. No more than about a quarter of that PTDI when another set of dietary assumptions is used.

Now, keep in mind that our total diet study is basically focused on conventional foods. We don't necessarily look at things like supplements. We don't look at pharmaceuticals. So we're talking about dietary exposure for the general population. It's low with respect to the PTDI, and it likely -- because we're not aware of ongoing significant sources of lead in food anymore like canned foods once was -- it likely reflects background presence of lead in food.

This is what we did in the 1990s. We continued trying to calm back potential sources of lead in food. Not necessarily -- the driving factor was not that we necessarily expected to see the kinds of reductions that we saw in the '70s and '80s, but going back again to if there are avoidable sources of lead in food we want to eliminate them. If there are unavoidable sources of lead in food, we want to control

them.

The ban of lead soldered food cans was really an after-the-fact thing. Industry had converted two non-soldered cans well before this ban was accomplished. I believe this was 1995. But now as a matter of law, lead soldered cans cannot be used for food in the U.S., so they'll never come back. The lead foil seals on the wine bottles were banned.

The lead level from bottled water was lowered. It had been 50. It was lowered actually to five. Five was the limit of detection of the method that was available at the time the lower limit was put into place. So we're not saying that we believe that 5 ppb of lead in bottled water is what we expect to see in the food supply. When the best available methodology is used, you should not be detecting lead in bottled water. And that was -- so it's really a feasibility-type approach.

We did the same thing for lowering leech lead limits for glaze ceramicware. They were already fairly strict. We made them more strict. It's a feasibility-type thing. We want to do whatever we can to control any potential for there to be an avoidable introduction of lead in the food.

We established the lead limit for wine when we found out that wineries using brass fixtures -- their products could become contaminated with lead.

We issued guidance to the states regarding shellfish. That regulation has done more at the state level because it's not interstate commerce. And then we initially established in 1995 and then tightened in 2006, a lead limit for candy. I'll say more about that in just a minute.

Now, with all the success that's been achieved, we still have incidence of elevated lead levels in food that occur, and lead poisonings still occur. These are

largely going to deal with imported products; poorly fired traditional Mexican pottery is an ongoing concern. We will periodically receive reports of lead poisonings in a family that used a traditional Mexican bean pot. This was -- not MMWR. This was Environmental Health Perspectives reporting on a mother and infant becoming lead poisoning from an urn that was purchased in Iran that was used to prepare infant formula and tea. Massachusetts 2002, this was a family of nine reported in MMWR. All lead poisoned due to an Iraqi spice that was brought into the country. Michigan 1998. And the Mexican candy problems we had with chili and salt containing candies.

These are new types of challenges. Number one, we're in an era of global food trade. We learned this with the problems with the Mexican candy. But not all these products are traded in commercial channels. Some of these products may not be formally

imported at all. Some of them may be personally brought into the country. The samovar, the urn is a good example of that.

The Mexican pottery -- we have a bordering country where a lot of pottery is made by primitive methods that are culturally rooted and not necessarily going to disappear anytime soon. It's a different kind of problem than the problem we dealt with when we had a cooperative industry that was ready to evolve out of the lead soldered cans and into the non-soldered can technology. We don't necessarily have producers abroad ready to partner with us like we did in the 1970s.

And what we learned with the candy is a lack of understanding of foreign production practices. We didn't know a whole lot about Mexican candies -- the fact that they had a lot of minimally refined ingredients in them like chili powder. We initially thought that printing in the candy wrappers was the source of the lead

contamination. Ultimately we found out that ingredients like chili powder were produced in Mexico using processes where the peppers were not washed, where soil particles that would get on the peppers in the field would remain on the chili powder. And that was the principal source of the contamination of these candy products. And if we don't have a lot of knowledge of foreign agricultural practices or food production practices, it puts us a couple of steps behind in trying to come to an understanding of where some of these problems might be arising from if and when they come to our attention.

So, we have to meet these new types of challenges with some different types of tools than we used in the past. Obviously there's going to be a role for the traditional regulations and guidances. But for something like the pottery, targeted health risk communication outreach -- in 2007, several federal agencies partnered with

the California outreach office of the Office of Bi-national Border Health, and undertook a risk communication project for individuals of Hispanic descent in the U.S. producing products such as pamphlets, brochures, radio announcements, public service announcements that were language calibrated to communicate on the level of the audience alerting them to the concerns that could accompany the use of traditional Mexican pottery in the home. Just one bad pot could lead poison a whole family.

We have a certification program for ceramicware produced in the People's Republic of China where certification is done by a third party to certify that the ceramicware meets FDA standards for leachability. FDA is about to open an office abroad in China. Again, getting back to the issue of -- we need to learn better how products are produced abroad -- the agricultural practices, the actual food processing and

production practices. So it's not all going to be done the way that it was in the 1970s when you had mainline industries that evolved in their technologies overnight and eliminated uses of lead. We have different types of concerns, and different types of challenges, and different types of response that will have to be focused on this global food economy and the threats that it poses to us in the future.

The guidance level for candy I'll just quickly say was 0.1 ppm necessitated by repeated findings of elevated lead levels in chili and salt containing Mexican candy supported by a safety assessment, and supported by vigorous federal and state enforcement. There are significant enforcement efforts that -- we believe this is a very conservative estimate of potential lead exposures. Firms realize that they don't want to be close to this level and risk enforcement action because the enforcement

commitment is there. So we think that as the ability within Mexico develops to improve the agricultural and processing practices, that levels of lead in candy well below 0.1 will ultimately be the norm.

In conclusion, the challenges for lead in food in the 20th century were successfully met, but there are new and different challenges in the 21st century that are going to require new methods of response. But the goal still remains the same. We want to prevent the avoidable introduction of lead in the food and control the unavoidable introduction of lead into food.

That is it. I'll turn it back over to Norm.

MR. SCHMUFF: Okay, any points of clarification? Marv.

MR. MEYER: No.

MR. SCHMUFF: Okay, if there are no points of clarification we can move onto the question.

MR. MORRIS: I'll have to read the question.

MR. SCHMUFF: Oh, you have to read the question.

MR. MORRIS: Right. They're not questioning your ability to read it.

MR. SCHMUFF: Okay, Ken.

MR. MORRIS: So the question on the table for discussion is what additional information would be necessary for us to gather to appropriately determine the next steps? So let's open with Mel. No, Marv. Sorry. Fred. Marv.

MR. MEYER: This is Marv Meyer for the confusion.

It seems to me I really like what Darrell Abernethy had to say. It sounded like FDA has a handle on what needs to be done and is going about it in a global and rational way. The only caveat would be let's hope they can move more rapidly than typical even FDA, but certainly USP activity.

I think to me the two primary questions are what are acceptable limits and how can we assay for them? And if you solve those two issues -- the limits being the more difficult one, certainly -- then you have what you need to know. And I would suggest that FDA, to the extent possible, partner with USP and at least contribute to their ongoing effort.

MR. SCHMUFF: Yeah, I believe that John is the one that's on that subcommittee, right? The USP subcommittee for heavy metal? Yeah. Yeah, John is on that group. So we do -- and we do really generally have pretty good FDA participation and USP groups.

MR. MORRIS: Yeah, Art is next. I was going to say Norm should feel free to jump in.

MR. SCHMUFF: To defend FDA at any possible time.

MR. MORRIS: Or wherever you feel it's appropriate.

MR. KIBBE: Art Kibbe. What additional information -- after listening to our colleague from the USP, the first thought that came to mind is how many of the regulated industries -- companies that we regulate -- actually use the USP method? Because I sure would like them not to use it. Since he demonstrated they're unreliable, I'm hopeful that my faith in the industry that it usually the best methods available and the ones that fit with their QC is actually true. And that they are actually using a more sophisticated methodology.

I think we need to know that because if we don't then the data that they're submitting is suspect according to the USP's only test. And that's the first fact that we need to know. Then I agree with Mark. Once we know that we're getting reliable data, we need to have some toxicologist group tell us what those levels should be for a safe population.

Last comment, what about end stage renal disease? Every time we talk about using heavy metals we have to consider that there is a subset of our patients whose kidneys don't function. We use aluminum pots to cook in. You put those aluminum pots in the kitchen with an end stage renal disease and they begin to get aluminum toxicity. And that's because they can't eliminate it. And we're talking about exposure to lead on a regular basis. What does that mean for these individuals? Does dialysis take it out? I'm not a nephrologist. I don't know.

It would be nice if we had someone who could help us with that.

But that piece of information -- if it's not going to affect the rules for the general manufacturer of drugs -- out to at least be something that the renal community knows about. And it goes into DOK standards so that they know what they're dealing with. That they use Tums to reduce their phosphate

load because that's a morbidity issue -- phosphate. And regardless of how small amount the normal person gets who can handle it, we have a different population. That population worries me. The rest of this is not nearly as worrisome. Because I think from all these presentations over the last 50 years we've done a really good job of bringing everybody's exposure load down. So if we could look at that it would be great.

MS. ROBINSON: Anne Robinson. I just wanted to add to that. I mean, it seems clear from the data that's been presented that there's combination effects. For example, with calcium, and lead. And that's something that perhaps should also be incorporated.

MS. NEMBHARD: Harriet Nembhard. As far as additional information to gather, I might suggest some procedures for the statistical efficacy of the methods. For example, on the USP presentation there were a

number of detection techniques that were suggested there. Everything from ICP-MS to LIBS, et cetera. And my question there would be what would be the reliability and repeatability of those measurement methods? So I think that's necessary to understand first.

And then, secondly, to establish a reasonable sampling plan. I suspect that the plan presented in the Kauffman paper could be improved upon, and perhaps the cost reduced for collecting the type of data that is needed with a good sampling plan.

MR. MORRIS: I know Mel is first but since I've been badmouthing Mel (off mike).

MR. KOCH: Mel Koch. Just to build on some of the things we've heard with combined, say, calcium with the lead or some others, and the ability of today's analytical tools to really give a spectrum of what's present, I'd suggest that some multivariate

panel recognition chemometric-type technologies be applied to data so that maybe there's a combination of metals that can enhance absorption, can enhance other problems. But take not only the new instrumental technology methods but also find other ways to work with data where you can get arrays of measurements.

MR. SCHMUFF: Well, let me just mention one thing that John didn't talk about that he did is he did some Monte Carlo simulations to look at total lead levels based on exposure to various pharmaceuticals. And the St. Louis slab does have some expertise in chemometrics. So that's certainly something within our scope.

MS. TOPP: Just real quickly I want to echo what Art said. I think that's a really terrific idea -- just to find out what kinds of tests are actually being used by the industry to determine lead levels. It's a little disturbing to me to think that they

may be using higher resolution methods to determine the actual lead levels and then need to keep old fashioned methods that are lower resolution and that they're running these just to make the FDA happy. I mean, that seems kind of silly. And I hope that's not actually the case. But that may be less sensitive and may give less information. So, I want to just second what Art said.

MR. SCHMUFF: Well, let me comment on this without trying to be too FDA defensive.

We did recently put out, and it has been our general practice, that in order to comply with the USP monograph, you don't necessarily have to do the USP test. And we now put that out. And it's now -- I mean, previously it was widely acknowledged. So if you come in and you show us that you have a better test and that you're quite likely to comply with the compendial test, then you don't have to do the compendial test.

MS. TOPP: Can I just rebut a minute? So suppose I have a relatively insensitive compendial test, you know, the bar graph that was shown shows recovery from the ICP-MS test is up here and the USP test is really down here. So if I don't like the answer that I get with the ICP-MS then I just do the compendial test and everybody is happy?

MR. SCHMUFF: We're restricted by legislation by the FD&C Act to recognize USP. So by law we're required to do that currently.

MS. MORRIS: There has been a real emphasis on use in young children in these talks. But I'm still somewhat concerned about the limits in very young children -- infants, you know, one to two years old. Because I would think that this would have the greatest effects, maybe on cognitive abilities, IQ. And I'm just wondering, you know, exactly what is known about ingestions

of, say, 1 microgram per day in these very young children. What sort of plasma, or blood, or bone concentrations result from this? And what are the known significant effects? I know Dr. Cummins has spoken about this. And maybe a consideration of maybe different recommendations. Look at maybe different recommendations for foods that would be taken by this group of young children.

MR. MORRIS: And I think we're restricting ourselves just to pharmaceuticals, but the point is well taken. The data in the young children. Merrill.

MR. GOOZNER: Sort of along the same --

MS. MORRIS: Or pharmaceuticals or anything of that nature. And I also had another comment. Sorry, I had forgotten. I was also, you know, another source of impurities is porous biologics or herbal preparations, dietary supplements. And I

know we're not specifically addressing those, but I think that is, you know, really a concern with regards to impurities.

MR. MORRIS: Yeah, to our point is that's clearly an issue. We're going to advise or recommend basically for the pharmaceuticals, but well taken. Merrill.

MR. GOOZNER: Sort of along the same -- Merrill Goozner. Sort of along the same lines because I think the amount of lead that any small child or kids would get, it's cumulative from a lot of different sources. So if we're just giving recommendations or we're just thinking about how it impacts pharmaceuticals, I guess the thing for the FDA to be thinking about, at least from my vantage point, is to say you have to think about all the other things. Because this is just one component of what a child might be exposed to. So I know, for instance, even this week I just happen to have seen yesterday a letter at the EPA where they're

setting the Clear Air Scientific Advisory over there -- is setting what should be the lead levels for, you know, ambient air. And, you know, what the EPA is recommending is significant higher -- if I read the letter from the advisory committee -- what the advisory committee is recommending -- whatever they ultimately arrive at, they're probably not thinking about pharmaceuticals. Nor are they thinking about the other things like supplements or food.

And so this is one of those issues, it seems to me, that we know what Dr. Cummins presented to us -- we've known increasingly over the last 20 years -- is that the impact of lead has on the cognitive abilities. And based on the data that was presented today, we know that it goes -- it goes all the way down to zero as far as we can tell. So when we're saying what's the limit, what we're really doing is we're drawing a line in the sand that's practical. We're not drawing a

line in the sand about what's safe. And given that, it seems to me that the FDA really needs to take into account all the possible exposures.

MS. AU: Yes, Jessie Au. I have two questions. First of all, I remember the first speaker talked about a 10 microgram per deciliter for cognitive defects. How was that measured? Was it using the USP method or --

DR. CUMMINS: The CDC guideline of 10 micrograms per deciliter is a public health action guideline. It's not a limit. There was --at the time when that number was -- it's a very complicated issue. But most lead poisoning in most children is from paint. The next most common likely source is from paint -- deteriorated lead-based paint in their homes, in their soils, in the dust where they crawl and they pick stuff up, get it in their mouths, and they are exposed.

A lot of work has been done to

reduce leaded housing stock in the U.S. in the last 25 years. But it's still the most common source. Probably the next most common source, other than the soils or part of the paint problem, is occupational take-home exposures by parents who work with lead and bring it home. The next most common sources is a whole panoply of other potential sources like pottery, Mexican pottery, ethnic remedies, et cetera.

MS. AU: I'm sorry. I didn't phrase my question properly, I guess. My question really is how was that number come about, and what kind of assay --

DR. CUMMINS: I'm getting to that. When you take public health action to reduce -- most counties and states in the United States do case management. They have programs in place to identify lead poisoned children and to provide individualized case management to them. All the range of interventions depends on the level of the

child's lead in the blood. At about a blood lead level between 10 and 20, the kinds of interventions you can do at an individual level have limited to no impact on the child's blood lead level. The only thing you can really do is try to find sources in the home and get rid of them. And sometimes that's very difficult.

So, you reach a point where it's a conundrum between taking care of individual children and setting standard for case -- for a goal -- a public health goal -- that's a population level goal. The level of 10 micrograms per deciliter was set as a public health goal. If you look at Healthy People 2010, it's a goal to lower all children's blood lead levels below 10 micrograms per deciliter.

Actually, CDC recently -- and the Advisory Committee on Childhood Lead Poison Prevention recently issued a document that had some recommendations about lowering

children's blood lead levels below 10. And the ideal is to keep their lead levels as low as possible.

Does that help explain and clarify?

MS. AU: Actually, that's not my question. My question goes back to the assays sensitivity and the USP method.

DR. CUMMINS: Oh, that's very different. I'm sorry. I apologize.

MS. AU: Right. Because we are basing it on that number. Everything we do is based on the 10 micrograms per deciliter. That number -- how did we get it to begin with?

MR. SCHMUFF: Well, I can't say, but I can tell you this. Nobody would measure blood levels by the USP method because it wouldn't work. And it's not -- I mean, it's clearly not intended to measure -- none of the USP methods are intended to measure levels -- low levels in biological fluids. So you can be pretty sure that those

levels were not measured by the USP method.

MS. AU: I'll come to my second question because they are linked. We have -- I mean 10 is the number we've been looking at. Everything you do -- Monte Carlo simulation -- everything is done with those numbers and you base it on that. So how you measure, I think -- how you come to the 10 is very critical as we move forward.

And secondly, we heard comments about how is a young child going to handle absorption, you know, elimination. And we heard about having calcium is going to change absorption. So what do we really know? What are the factors? All the factors? They can change absorption and accumulation in a young child? Those are the most susceptible to lead poisoning. That's the question I was coming to. How do we handle that?

I like the Monte Carlo simulation. I thought it was very clever use. But I don't know how you're going to handle this

number as you said.

Recognition may not be a threshold for the neurodefects that we look at.

MR. SCHMUFF: Well, I should just say -- and John can correct me -- the Monte Carlo simulation was based on the levels that were actually observed. So he took the levels that were actually observed and then figured out, okay, if a person took, you know, polytypical -- typical poly pharmacy, you know, what would people be exposed to.

MS. AU: But you base it on the 10.

MR. SCHMUFF: No, we didn't consider the at all.

MR. MORRIS: Can I interject something? This is Ken Morris. I think the point though, in part, Jessie, is that the method that St. Louis used was actually the ICP-MS, so it was more -- so the Monte Carlo simulation as done on the data that they had. So I think for that particular issue the assay wouldn't be a question, but correct me

if I'm wrong, please. It's a fair point though, in general to how the assay affects the data in general. In this study I think it was taken out. The statistics is a different question.

MS. NEMBHARD: Harriet Nembhard, again. I noticed in the concentration of lead for the orally disintegrating tablets of Claritin that it was about three times the lead level in the regular tablet form. I wonder if such a result might hold for other drugs. And if so, would the FDA consider advising people away from the orally disintegrating tablets in favor of the regular tablets, especially if the lead concentrations are cumulative in children?

MR. MORRIS: Do you want to comment, Norman?

MR. SCHMUFF: I guess John is -- I mean, I don't know that data like John, so he should probably comment.

MR. MORRIS: We still have a minute

before quitting time, so you're on the clock.

MR. KAUFFMAN: Yeah, it would helpful if I could find the numbers. My slide is so small I can hardly see them.

MS. NEMBHARD: I can point you to the paper at any rate. It's product number 34 -- has the average lead concentration of 19 plus or minus 1. And the regular Claritin, product 35, has a concentration of 5 plus or minus 1.

MR. KAUFFMAN: I would say that, you know, this is -- remember also that we're only looking at one lot of each of these. So we are not really doing a very thorough job of sampling as you mentioned. So I would be cautious about drawing conclusions on the basis of comparisons of individual products here.

MR. MORRIS: This is Ken Morris. I think to Harriet's point though, John, it's just sort of the more general question, I think. Right?

MS. NEMBHARD: Right.

MR. MORRIS: Were that result to be observed as a statistically significant difference -- whether it was orally, you know, dissolving or whether it was two other products, would that be an appropriate action for the agency to take?

MR. WEBBER: I think it's worth looking into. I think one thing we would have to take into account -- Keith Webber -- is the difference in mass. Because these are in parts per billion numbers and orally disintegrating tablets may weigh considerably less than a tablet -- a normal tablet would. So we would have to really look into that, whether the actual dosage of lead is greater.

MS. NEMBHARD: Right. I did see that there was some distinction between concentration and the ingested mass in terms of a value to assess. In this case the ingested mass, I believe, was about similar but the concentration was three times as

high. So it maybe ties back into the USP discussion of which will you advise on. It seems that perhaps there's some indication that you should look at both. But in any event, my broader question would be should this be considered for other products? I know we'll take up the orally disintegrating tablets issue more tomorrow, but particularly for children.

If, indeed, the concentration levels are cumulative for them, should we advise people to be more careful in those cases?

MS. WINKLE: And maybe what we need to be considering is putting the amounts of lead in the label on the products. And I mean, there are other products besides this that may have a higher level of lead than you really feel like you want to take based on cumulative doses. So maybe that's something that we can consider to look into.

MR. MORRIS: Yeah. I'm sorry, Pat,

did you --

MS. TWAY: No, that's okay. I was going to say you'd have to understand. It probably is strictly a mass issue. Or if it's not, it's probably different excipients that are used because you clearly use different excipients on an OBT than a regular. So you need to understand it. And in reality, if the ingested amount of lead is the same, that's what the patient see. The parts per million are not really relevant to the patient. It's what the patient ingests as far as how much lead do they get. The ppm is easier for a company to measure how much is in their product, but in reality -- at least what I believe is important to the patient -- is how much they ingest.

MR. MORRIS: Yes, the glycemic index, glycemic load question. Art.

MR. KIBBE: Just a quick point. If you look across on that same table from those numbers that were dramatically different to

the maximum daily ingested mass of lead for both products, it's the same. So that's really --

MR. SCHMUFF: Yeah, which is less than 5 nanograms.

MR. KIBBE: .05, yes.

MR. MORRIS: Right. Any other comments or discussion? I sort of tried to summarize a little bit of what we said. It seemed to me that we came down essentially with two major areas of information that needs to be gathered -- not that it's a huge surprise, but one is the methodology and the other is on the toxicology. And with the methodology, I think based on what we heard from USP, it's clearly not that. But the idea that we not be limited in the consideration of limits by the limits of the sensitivity of the method. And I think that was more or less stated several times, most prominently by Liz, I think. The issue being that you don't want to give a backdoor for

somebody who might want to avail themselves of the less demanding specification.

And then with the toxicology, the idea that we really have to have toxicologists set limits that make sense based on the data that will have to be based on not only the exposure for healthy patients but broken up by demographics, if you will, with special attention given to end stage renal patients, for example. Although there are other -- other disease states would be similar in very young children where there's sort of a posity of data for obvious reasons. And also that some of this could be combined as Helen was discussing with respect to labeling. One way of informing patients is to include on the label the information so that if there's a mass -- as Pat says a mass denotation of the amount of lead there, then perhaps even in additional labeling or in consultation with physicians, the strategy for exposure can be formulated.

I'm not sure that I had anything else major in our sort of assumptions -- I mean, our synopses. Is there anything that anybody can think I missed that we should include? Jessie?

MS. AU: I thought we'd talk a bit about ETNY studies. There is more academic interest because we know so little about what interferes with the absorption of lead's elimination (off mike) worry about. But you do have a healthy margin in the recommendation and the toxic level. So at this point I only can think it was academic issues.

MR. MORRIS: No, actually, I think that's actually a good point. I forgot it. I do have it down here and I forgot it. And that is the synergistic effects. I mean, not that that would necessarily be part of a label, but it might be at some point as Professor Weaver talked about. I mean, if you're taking calcium and we know that has an

effect or other things are blocked -- so that's a good point. I had left that out. The synergies between -- positive or negative synergies between components along with lead.

Yes, Marv.

MR. MEYER: Marv Meyer. Ken, I really didn't like that idea. I understand the concern. Coming from Memphis, Elvis Presley did not have a single toxic level of prescription drug inside of him at autopsy, but it was an autopsy. So something worked together.

But I think in terms of getting something moving -- if we start adding in a lot of variables -- what about lead and beryllium -- well, then they'll debate that for a week. Let's just focus in on what we can handle fairly expeditiously and do it. And then as we learn more and more about beryllium and lead, add that, too.

MR. MORRIS: That's a fair point. Are there any other comments or discussions?

All right, well, with that we'll close the session and we'll reconvene tomorrow at 8:30 in the same room. There's a van to take everyone back to the hotel. And anybody who wants to walk can come with me. Thank you.

(Whereupon, at 5:10 p.m., the PROCEEDINGS were adjourned.)

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