SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

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Reported by: Frances M. Freeman

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DR. ROBERTS: (In progress) -- Scientific Advisory panel. As our first agenda item, I would like to ask Ms. Olga Odiott, our designated federal official for this meeting, for her instructions and announcements.

MS. ODIOTT: Thank you, Dr. Roberts. Once again, I would like to welcome everybody to this important meeting of the FIFRA Scientific Advisory Panel concerning CCA-treated wood.

For the benefit of those who are joining us today for the first time, this meeting is being conducted under the provisions of the Federal Advisory Committee Act, also known as FACA.

All applicable ethic requirements of the federal conflict of interest laws have been met by the members of this panel.

At the conclusion of the meeting, the panel will prepare a report as a response to the questions posed by the agency. The report will serve as meeting minutes and we anticipate to have that report ready within 30 days.

All background materials and other documents related to this meeting are available from the OPP docket and also from the EPA web site. The contact information for both the docket and

the web site is listed at the top of your agenda.

During the past two days, we have had very informative presentations. The discussions have been very productive and key to the issues that this SAP panel has been asked to address.

I want to thank the panel for the enthusiasm and the dedication demonstrated during the past two very long days.

We have a full agenda today, and that's probably an underestimation. But the agency is looking forward to the panel's feedback on those issues presented by the 14 questions that we have before us today.

DR. ROBERTS: Thank you, Olga. We also need to introduce the panel. Let me begin, and we'll go around the table.

I am Steve Roberts. I'm from the University of Florida.

Dr. Freeman?

DR. FREEMAN: . Natalie Freeman from Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute.

DR. KOSNETT: Michael Kosnett, University of Colorado Health Sciences Center.

DR. KISSEL: John Kissel, University of Washington.

DR. BRUCKNER: Jim Bruckner, University of Georgia.

DR. GORDON: Terri Gordon, NYU.

DR. LEES: Peter Lees, Johns Hopkins University. Liedy.

DR. LEIDY: Ross Leidy, North Carolina State University.

DR. SOLO-GABRIELE: Helena Solo-Gabriele, University of Miami.

DR. BATES: Michael Bates, University of California at Berkeley.

DR. STYBLO: Miroslav Styblo, UNC-Chapel Hill.

DR. STEINBERG: J.J. Steinberg, Albert Einstein College of Medicine.

DR. CHOU: Karen Chou, Michigan State University.

DR. MUSHAK: Paul Mushak, PB Associates.

DR. FRANCOIS: Rony Francois, University of South Florida, College of Public Health.

DR. SMITH: Andrew Smith, State of Maine, Bureau of Health, Department of Human Services.

DR. SHI: Xianglin Shi, NIOSH.

DR. MORRY: Dave Morry, California Environmental Protection Agency.

MR. CLEWELL: Harvey Clewell, Environ.

DR. ADGATE: John Adgate, University of Minnesota, School of Public Health.

DR. WARGO: John Wargo, Yale University.

DR. HEERINGA: Steve Heeringa, University of Michigan.

DR. ROBERTS: Thank you, panel.

We have quite a bit of work ahead of us today. We have 14 questions left on the agenda and, if you do a little bit of math, that means it averages about 30 minutes of discussion per question, if we're going to get through by a reasonable hour and leave some time for discussion of other questions.

As we go through the questions today, I'm going to have to insist that the comments be directed specifically to the questions.

As I told the panel before, there will be the opportunity to comment on other scientific issues not covered in the questions at the end. But the only way we're going to have time to do that and do that well is if our comments are focused and concise and

efficient as we go through the discussion.

So we really need everybody to think about your points. By all means, I want every panel member who has an opinion, give them the opportunity to express it. But please express it as concisely as possible.

If you get off on a tangent, you are really just wasting your time and the rest of the panel's time because there is not going to be any way to get that information into the panel' response to the question. It's just lost information.

Also, I would like the panel members to confine their comments to scientific issues. There are avenues for input to the agency on policy issues, and I would encourage you, if you feel strongly about a policy issue, to explore and use those avenues, but we're here today to provide the agency with scientific input on some technical matters and questions they have brought before us.

Now, we finished our discussion of question 1 kind of late, after a long day yesterday.

I would like to provide the opportunity, if there are any panel members who, upon further reflection last night, have a different opinion that they would like to express or renew or modify their opinion, to give them the opportunity to do so. I

don't expect, nor frankly do I want to rehash all of the issues that we talked about in issue 1 last night, but I do think that it's important to give panel members the opportunity to, after a night's sleep, to make any comments they might want to add to the record on question number 1.

So let's begin with that. And let me ask if there is anyone.

Dr. Kosnett?

DR. KOSNETT: Thank you, Mr. Chairman, for the opportunity to finish that issue briefly, I hope.

Basically, I just want to make clear for the record I think an important opinion regarding the discussion about the safety margin yesterday.

There was -- I was in agreement with the LOAEL of .05, but I have serious concerns about this 30-fold safety factor both with respect to how it was derived and the interpretation as to what it might mean.

ATSDR and EPA guidance, in the document developed by Dr. Benson, recommended a 10-fold safety factor in establishing what ATSDR calls a minimum risk level or MFL of .005 milligrams per kilograms per day. Approximately a 10-fold

safety factor or a 10-fold safety factor from the .05.

And I think the 30-fold safety margin is just not supported by the data. Essentially, I think we have to subject it to a bit of a reality test. A 30-fold safety margin would essentially establish a value of about .002 milligrams per kilogram per day.

And in the case of a 15-kilogram three-year-old, that's essentially saying that 30 micrograms a day should be flagged as a level of concern for an exposure as brief as six months.

In my experience as a physician and toxicologist who has been interested in the clinical toxicology of arsenic for almost 20 years, there is no basis in my experience or any published material that would suggest that anyone needs to be concerned about having acute non-cancer effects within six months for exposure of a three-year-old to 30 micrograms per kilogram per day.

And in fact, if one considers the fact that a three-year-old consumes approximately one liter of drinking water a day and that the United States maximum contaminant level for arsenic in drinking water has been 50 micrograms per liter for approximately 60 years, and there are numerous communities in the country that have had water that is in the range of up to 50 up

to that time, we have no experience or basis on that record to be concerned about acute health effects.

That essentially, for example, would, since the background level of arsenic in the diet is 5 micrograms a day for a three-year-old, inorganic, that's essentially saying that we would be concerned of a level of 25 micrograms per liter in the water, adding 25 micrograms per liter in the water, one liter a day, to the 5 background to get 30 micrograms per day, which would be 2 micrograms per kilogram, which is the acute hazardous level which has been suggested to flag for concern.

That just does not meet our experience. It does not meet the studies that have been actually done on communities. Granted, they are not necessarily large or exhaustive studies, but there have been studies done on communities with levels up to the range of about 200 micrograms per liter in this country which have looked for non-cancer effects, studies by Chrise (ph) in Alaska, Southwick in Utah, Harrington in Alaska. And they have not found in those communities any basis for being concerned at a level of 2 micrograms per kilogram per day for up to six months.

So I just want to go on the record as saying that I could not support that and I don't think it's advisable. I would concur

with ATSDR and EPA's guidance with a 10-fold margin, which -- I could concur with it being justified on the basis of the serious nature of the LOAEL and the possibility of inter-individual variability.

And just to complete my comments, I just want to tell you how I think that level ultimately should be interpreted. As it states in Dr. Benson's document, that should be used as a screening level to identify contaminants for further evaluation in public health assessments and to identify potential health effects that may be of concern at hazardous waste sites.

It's important to note that MRLs are not intended to define cleanup or action levels. They are guidance values, below which non-cancer adverse effects are unlikely, and below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects.

Exposure to a level above the MRL or above this level, .005, does not mean that adverse health effects will occur. MRLs are intended only to serve as a screening tool to help public health professionals decide when a more detailed toxicological evaluation is necessary.

They may also be viewed as a mechanism to identify

those hazardous waste sites that are not expected to cause adverse health effects in an exposed population.

DR. ROBERTS: Thank you, Dr. Kosnett. So basically you concur with a LOAEL of .05, but would recommend a margin of exposure of 10 rather than 30 as we discussed.

Any other comments?

Dr. Clewell, then Dr. Mushak.

DR. CLEWELL: Thanks. Actually, that's very informative.

I think what you are basically indicating is that it's a very steep dose response for arsenic in that you can have effects at .05, but are you fairly comfortable there wouldn't be at .02, and I follow your logic.

I think it's important to know that what EPA was -- EPA did not come up with the same number as ATSDR. The MRL is .005, but EPA was suggesting using 10 for variability in addition to the 10 for LOAEL. So they would be at a really low number, .0005. So -- part of that, I'm sure, being due to a kind of a difference in philosophy concerning an MRL versus the number that EPA was trying to come up with.

And I have to say I don't feel I have the precision to

say whether 30 versus 10 is better, and I actually bow to your experience in terms of the likelihood of effects in children. But I hope this doesn't mean we have to try to refine the consensus.

DR. ROBERTS: No. I think, basically, unless people modify their conclusions from yesterday, they would stand.

Dr. Mushak?

DR. MUSHAK: Mike, I have a problem with your logic because yesterday you made it clear for the record that you were concerned about the proximity of those effects that Mizuta reported to very serious effects, especially to cardiovascular. And I think you were comfortable with a 10-fold for a LOAEL to a NOAEL.

So how do you stratify out an overall 10? If you are comfortable with a 10 for LOAEL to NOAEL, presumably you don't allow any uncertainty for children versus -- in intra-human variabilities. I mean, how are you stratifying this 10?

DR. KOSNETT: I would think the 10 would encompass both factors.

DR. MUSHAK: But you are already strongly feeling about this -- are you revising your sense of a LOAEL to a NOAEL?

DR. KOSNETT: I think that --

DR. MUSHAK: I mean, you can't have it both ways. If you say you are comfortable with a 10 for a LOAEL to a NOAEL, then you are saying you have no basis or no sense that there is any intra-individual variation that comes into the equation.

DR. KOSNETT: The 10-fold factor that I would endorse, which concurs with what ATSDR came up with in coming up with the MRL, encompasses both the seriousness of the effects and, in my opinion, the capacity for intra-individual variability.

DR. ROBERTS: Dr. Smith?

DR. SMITH: I would just like to ask a question of Dr. Kosnett as well, because I understand what you are arguing is that basically you are posing a reality test in your experience as a clinician. This doesn't seem to pass a reality test.

As a clinician, which I am not, I would like to ask you the question of, do you have any concerns that there could be subtle effects that would not be obvious to a clinician that would justify the 30-fold?

Do you have any worries about there could be more subtle effects that might not be apparent or is that not of concern to you, that you feel that, with the existing database and your experience as a clinician, that you know if there was something

there, it really should have manifested itself, given what I agree with you is unquestionably substantial exposure for some individuals at these levels?

DR. KOSNETT: I just think, based on our experience and knowledge, that the 10-fold factor for up to a six-month period would be a sufficient margin of safety.

DR. ROBERTS: Dr. Bruckner.

DR. BRUCKNER: So I understand what you are saying, you are advocating the 10-fold, then, from a LOAEL to a NOAEL. What are you advocating beyond that for intra or for childhood --

DR. KOSNETT: I want to just say I agree with 10, combining all the concerns, both the seriousness and the variability.

DR. ROBERTS: I suppose you could be two factors of three, I guess. We're all a little -- which is, frankly, a way to get there. I think we're all probably a little guilty about describing exactly how we got to the margin of exposure we're most comfortable with.

DR. KOSNETT: And people can look at Bob Benson's document and note that that's what ATSDR recommends.

DR. ROBERTS: So you are basically comfortable with their rationale?

DR. KOSNETT: Yes.

DR. ROBERTS: Dr. Steinberg?

DR. STEINBERG: Just responding also, as a clinician, as a senior attending in a very large New York hospital, clearly I think we don't know, and I think there is a large gap of information. I think there is no -- there is certainly no attending clinician that can tell me that many of the subtle effects that one could see neurologically, in neurologic examinations, attention deficit or learning disabilities, whether any of this could be related to lead or metals or arsenic or other things.

I think it's this neurotoxicology -- I think it's this neurodevelopmental gap that urges us to be very, very, very careful.

The second reason to be very careful is we clearly don't know why many cancers are going up, some cancers are going down. We don't understand this. We now have an insight and a window and a mechanism of action related to arsenic that also forces us to be very cautious.

Good Science is urging us here.

DR. KOSNETT: But we're not addressing cancer risks.

DR. SMITH: The first question clearly answered neurotoxicology, and I don't want to dismiss cancer risks, either.

DR. ROBERTS: Would anyone else like to weigh in or modify their opinion in response to the discussion that we've had today?

Dr. Ginsberg?

DR. GINSBERG: I think really appreciate Dr. Kosnett's viewpoint from the clinical standpoint and taking a look at the studies, which -- he has looked at the epidemiology database much closer than I have.

I guess my concern is that endemic nature of arsenic exposure in children in any given population may be, as Dr. Smith was suggesting, difficult to tease out, in effect, a true, quote, unexposed cohort. So I am concerned that we don't really have the right control population to completely evaluate low dose effects.

And given that we were searching for a NOAEL study and we felt uncomfortable yesterday, or at least some of us did -- I think Dr. Roberts said he was uncomfortable with the definition of that one study as being a NOAEL for all effects -- and that we are basing things on a LOAEL, when you are dealing with a LOAEL,

you don't quite know what the NOAEL is because you don't know how low you have to go to really define the clear NOAEL. And given the uncertainties in epidemiology studies about a true unexposed group, I would just stick with my 30-fold factor.

DR. ROBERTS: Has anyone changed their opinion from yesterday?

Dr. Smith?

DR. SMITH: I guess, for the record, I never voiced my opinion yesterday.

DR. ROBERTS: Then you have the opportunity to weigh in now.

DR. SMITH: I am comfortable with getting to the 30X uncertainty factor using the 10 and 3, as we've described. But I am unsettled by Dr. Kosnett's observations. But, nevertheless, I still feel comfortable with a 30-fold uncertainty factor as long as we recognized it's being interpreted and used in the typical we use RFDs for short-term exposure, that being a negligible risk of any deleterious effect from that sort of exposure window, and that we don't anticipate any sort of necessary effect immediately above that level.

DR. ROBERTS: Dr. Mushak?

DR. MUSHAK: I'm comfortable with a 30 factor. I think, Mike, that a lot of the absence studies that show subacute, subchronic effects have been kind of dealt with simply on the basis of sample size to show these effects. I mean, Andelman (ph) and his co workers at Pittsburgh addressed both cancer issues and, I think, non-cancer issues. Small populations make it difficult to see these effects.

So, you know, absence of evidence is not evidence of absence.

DR. ROBERTS: Anyone else want to weigh in on this?

Hearing no other comments -- Dr. Bates?

DR. BATES: This is more of a question. Perhaps it should be directed to the EPA. But I just wanted what are the practical implications of setting this level?

I understand and I sympathize with what Michael Kosnett is saying, although, in toxicological principles, I kind of go along with the 30-fold margin. But there seems to be a bit of a conundrum here, almost a conflict between the level which we are proposing and possible practical implications. But maybe that's not the case. And I'm just wondering whether EPA could tell us a bit more about what the implications are.

DR. EDWARDS: Because we haven't actually generated risk numbers yet, it's difficult to say exactly what the implications would be. And it partly will depend upon what the panel recommends with respect to deterministic versus probabilistic type assessments for these short-term and immediate-term exposures. But, obviously, I think you understand that the lower the value is, the more children will appear to be at risk in our estimates when we do that.

And if it's a deterministic estimate, it could be used more like a -- you know, almost like a yes/no trigger that's unlikely to happen because we do discuss uncertainties. But you see what I mean.

DR. ROBERTS: Dr. Hopenhayn-Rich?

DR. HOPENHAYN-RICH: I want to just voice my opinion supporting what Dr. Bates says or maybe just expanding it a little bit or clarifying it, that I am not sure either of the practical implications of setting a safety limit for CCA exposure for six months or less because I can't imagine children being exposed to playgrounds for only that limited amount of time.

DR. ROBERTS: It is kind of a different question. And maybe not to answer for the agency, but as Dr. Kosnett pointed out

in his reading from the ATSDR, when you exceed this, it doesn't necessarily mean that there are health effects, but what it does is it triggers a closer examination of the situation.

Alternatively, if the exposures are less than that, it's concluded that there is no significant probability of any harm.

Dr. Benson, did I state that reasonably correctly.

DR. BENSON: Yes. But let me answer the question that Dr. Bates posed about the practical implications. In region 8, if you take the value that you derived yesterday in a residential scenario for a 15-kilogram child, every residential site in metropolitan Denver and probably most cities in region 8 are acutely poisonous to that child.

And all the way from Denver to Kansas north to Canada.

DR. ROBERTS: Dr. Vu.

DR. VU: I just wanted to clarify -- to add also what Dr. Benson and Dr. Edwards explained. The margin of exposure concept would help the agency to determine which kind of exposure scenario would provide more risk than others, and then make a judgment with regard to the use and whatever. So it's not necessarily a finite thing, as Dr. Edwards explained .

So if we're going to compare different exposure scenarios, playground setting, what kind of risk might be associated long-term, short-term, whatever -- and those are things that the agency will consider when we are going to assemble all the information and develop a risk assessment.

DR. ROBERTS: Dr. Smith?

DR. SMITH: I'm not going to go there.

DR. ROBERTS: Thank you.

Dr. Clewell?

DR. CLEWELL: I am. I feel like I just slid down a slippery slope while somebody was holding my hand saying, it's okay, when you get to the bottom you will feel just fine.

So what you are telling me now is that we're falling into the same trap that the NAS -- or was it the SAB? The ones who said that there were so many hundreds of thousands of children that were probably already affected by methyl mercury. You know, I don't want to say that all of the children in Denver are, you know, acutely intoxicated.

This is a fairly common problem, actually -- or a not uncommon problem in risk assessment, that what seemed like very reasonable uncertainty factors put you in a place where you're

either below the minimum essential daily requirement or in a region where you consider it to be fairly ludicrous that you would suggest that there be health effects, and I'm beginning to see the point that Dr. Kosnett was trying to make.

Unfortunately, these numbers can be used as bible gospel, touted in the media, and the next thing you know is Denver papers are saying that all of our children are -- so I think one of the things we may have not fully considered is the fact we're not just asking how much can a child be exposed to by a playground, because people will be folding in the dietary and drinking water exposures. And dietary being 5 or so and drinking water, in some places, being 20 or so, that doesn't leave much room.

So I'm just uncomfortable. I don't know what the solution is, but I have a great deal of discomfort with someone taking a number that I agreed with and then coming to conclusions that I would very seriously disagree with. We scare people enough with things that aren't really going to harm them.

DR. ROBERTS: Dr. Benson, let me just ask you to -- I just was doing a quick math in my head. I think this number would correspond to about 100 parts per million in soil. Is most of Denver over 100?

DR. BENSON: Typical backgrounds in region 8 vary between maybe 5 to 20 milligrams per kilogram soil. Sometimes less, sometimes more.

DR. ROBERTS: Well, I was going to say that -- just kind of running the numbers quickly in my head, the number that we had sort of settled on with -- some folks thought the 30 margin of exposure would correspond, I believe, to about 100 parts per million in soil.

DR. CLEWELL: Are you subtracting drinking water and food exposure?

DR. ROBERTS: No. I'm just basing it on a straight proportion. I know what the number is for the chronic reference dose, and I'm just using a multiplier for this reference.

So I think we ought to think about those kinds of calculations and implications, but unfortunately, I'm not sure we have time to do that this morning.

DR. GINSBERG: This is a good seque into our next question. Were you thinking in terms of a relative bioavailability of arsenic in soil? Because I don't know if Dr. Benson uses one of 50 percent, 25 percent or whatever when you did your thought process about Denver in K.C.'s soil -- and I don't know if you

factored that in, but I know that it's fairly new in the risk assessment thinking about arsenic in soil.

DR. ROBERTS: I did not, but I don't know that we're -- rather than seque into number 2, I want to get closure on number 1 very soon.

Dr. Solo-Gabriele?

DR. SOLO-GABRIELE: I just wanted to follow up with what Dr. Ginsberg had said. That's what I had in mind was, even though you have arsenic in soil, is it at all available for consumption?

DR. BENSON: The calculation that I did last night included a relative bioavailability of 50 percent, which is the measured value in the site in metropolitan Denver from several hundred yards. Well, it was a composite sample.

DR. ROBERTS: Dr. Smith?

DR. SMITH: I don't think we really need to even get into that debate because there are plenty of people with exposures above that from drinking water, you know, for Dr. Kosnett to make his point. So I really think the fundamental issue is just how do you want to deal with this reality check he is posing to us?

And the real question is whether or not that reality

check is sufficient to cause anyone to want to move from the 30X that we have already discussed.

DR. ROBERTS: Dr. Chou?

DR. CHOU: I think we're facing an unusual decision here because in the normal practice of risk assessment, we look at the scientific data, then we do the regular safety factor practice, and that's what we did last night, and we decided to use 30. And then the reality check is a very different issue than many of us never faced before.

The question I ask myself is, just because there is more arsenic out there in the food or in the drinking water, are we going to make a different scientific decision? And that's why I what I have been struggling with.

I think this thing becomes sort of like a policy or a paradigm, risk assessment paradigm issue. You know, are we going to switch to a regular practice paradigm for arsenic?

That's the question I ask myself.

DR. ROBERTS: Let me ask this. Let me post to it the panel this way.

We have had some discussion on this issue this morning. The question is, is a LOAEL of .05 reasonable and a

reasonable point upon which to base margin of exposure analysis, and what would your margin of exposure be.

Has anyone heard anything that would cause them to either now make a decision that they hadn't made before or to change their decision?

MR. CLEWELL: Well, I would like to jump over onto the 10 side.

DR. ROBERTS: Okay. That's fine.

Dr. Mushak?

DR. MUSHAK: I think that, before we look at this issue of whether minds are changed or not, I think reality checks are really a separate issue, and we're at the case that we then factor in reality checks. We're back to where the NAS was with reality checks for how much internal and systemic cancers we should have with drinking water.

The fact remains that you can always do site-specific or area-specific reality checks that tend to contradict a risk assessment model.

And this is no different than what the academy has been wrestling with with the U.S. picture for arsenic-associated cancers.

So I think that's a separate issue. There are separate conferences that could probably be held on that, and I think that that ought not to color people's judgment. This hopping of some people all over the place with safety margins I think is a bit unsettling because I'm not quite clear what the basis of that is.

DR. ROBERTS: I really just want comments from folks -- not on the philosophical issues, but have we sufficiently -- have we had enough discussion that we can put together some input on the specific question, number 1?

DR. SMITH: For the record, I would like to say I remain in the 30X camp. However, I would like to strongly encourage the agency to attempt in any way they can to follow up on Dr. Kosnett's concerns and find out if there is any empirical data to help guide us.

DR. ROBERTS: Okay. With that, let's move on to question number 2.

Dr. McMahon, would you read the question for the panel, please.

DR. McMAHON: Yes. Thank you, Dr. Roberts. Our second to the question to the panel, as was alluded to, deals with the relative bioavailability of inorganic arsenic from soil.

Our question reads: Please comment on the choice of this data set; that is, the data of Dr. Roberts, using a value of 25 percent bioavailability for representation of the relative bioavailability of inorganic arsenic from ingestion of arsenic-contaminated soil.

Please discuss the strengths and weaknesses of the selected data, and also provide an explanation as to whether this 25 percent value is appropriate for estimation of bioavailability in children.

DR. ROBERTS: Dr. Bates, can you lead off our discussion on that topic.

DR. BATES: I think Dr. Kosnett is going to --

DR. ROBERTS: Dr. Kosnett, would you lead off our discussion on this question?

And before you do, Dr. Bruckner has to leave the panel shortly, and it's important that I guess we get his comments into the record before he takes off.

Would you object if he made his comments very quickly?

DR. KOSNETT: No. Please go ahead.

DR. BRUCKNER: The first question I would like to

address is a little bit different. I'm a little bit concerned about your assumption of 100 percent availability from, let's just say, the soluble salts of sodium arsenate. I'm just looking back at some of the data.

Some of the human studies by Buchet and some of the others -- it looks like the numbers in humans vary from about 55 to 80 percent. And then with the two monkey studies we have by Roberts and by Freeman, we're looking at 68 percent and 74 percent.

And then, from Dr. Aposhian, we heard 10 to 20 percent, although I do have some concerns about -- one we talked about before, biliary excretion may have affected that one. He was saying 10 to 20 percent absorption.

I guess my point, summing it up here, is that the data don't support a 100 percent assumption.

And availability from soil, I think the thing that strikes all of us, probably, is the variability that we have in those estimates. There's not really the consistency.

There is consistency, I guess, in the two primate studies. One, I think, shows 14 to 19 percent; and the other, 11 to 25 percent. Of course, the whole point is in what form is the

arsenic in? What source -- we have only looked at a very limited number of uncharacterized soils, so there is an incredible variability, incredible inconsistency.

The only consistency I see is really in the two primate states where the values don't vary that differently. So I just -- I guess, we have the Rodriguez study in the swine, 3 to 43 percent which just shows, again, variability.

I guess I'm most comfortable with the two primate studies. But, again, I'm very concerned because those are so limited in numbers of soils, numbers of animals, numbers of samples.

Just one other question. My area is more or less -- I think the reason I'm here is pharmacokinetics in infants, children, juveniles and adults. It appears we don't have any information on relative pharmacokinetics, the child versus the adult. We don't know whether there is a difference in methylation. I guess we're not really sure if methylation increases or decreases toxicity.

And I just wanted to put in a strong urge that there be a high research priority just to look and see if the kinetics and metabolism and tissue deposition and toxicity, in turn -- I don't see any toxicity studies even in an animal model between, you

know, juveniles and adults. So I just would like to say that's really a black box, which really needs some research.

DR. ROBERTS: Thank you, Dr. Bruckner.

Dr. Kosnett would you quickly give us your comments?

DR. KOSNETT: I think an area in which there is general scientific consensus is that there is a large number of physical, chemical and biological factors that impact the extent of gastrointestinal absorption of a substance, such as metal, in soil relative to the absorption of the same substance if it was in solution.

And chemical factors are manifold, including the molecular form, the arsenic species, the nature of the chemical and physical interaction with the constituents of the soil matrix, whether it's chemically bound, absorbed, complexed, encapsulated, the size peroxidi, compaction and surface area of the arsenic-containing soil particulates.

And there are a number of biological factors as well: Species-specific metabolism; physical condition of the animal at the time of ingestion -- animal including a human; the effect of drugs; physical stress; toxins; nutritional pertubations; disease states; the presence of other ingested food, whether it's given on

an empty stomach or not; whether there are other drugs or other substances in the intestinal tract and, in some cases, as you mentioned, the age of the -- or the developmental stage of the animal.

And another key factor is the dose regimen in which it's administered. For example, the absolute bioavailability in terms of percent of the administered dose could vary depending on whether it's administered as a single large bolus or whether it's the same amount, overall amount is given in smaller divided doses.

And because of this variability, both from the aspects of the soil and the matrix in which the arsenic is present and host-specific factors and because of some limitations and uncertainties in the existing studies, I think it would be -- I don't think that the studies cited by EPA in the material they provided affords us a sufficient basis for establishing a relative bioavailability of 25 percent for arsenic in soil as a consequence of CCA-related release.

And in terms of the specific aspects of the study, one of the key major concerns I had with the study by Roberts, et al., and Freeman, et al., is the fact that it did not simulate to a reasonable degree the relatively low dose repeated hand-to-mouth

behavior of children with respect to their ingestion of soil.

The arsenic concentrations used in those studies ranged from a low of 101 to high of 743 parts per million which, based on discussions we had yesterday, appear relatively high compared to those that had been measured in the vicinity of CCA-treated structures in children's playgrounds.

And also, in the studies in question by Roberts, et al., and Freeman, the soil was introduced into the test monkeys in a single high dose bolus. For example, in the single soil sample that is in the Roberts site, which is cited as coming from a wood treatment site, it can be calculated that the soil-associated arsenic dose of .3 milligrams per kilogram of body weight was achieved by administering to a three-kilogram monkey a single oral dose of 9,000 milligrams of soil.

In like manner, in the Freeman study, monkeys which weighed between two to three kilograms were given single oral doses of 3,000 to 4,500 milligrams of soil, containing 410 parts per million arsenic.

And I think, under those circumstances, when you have a high-mass single bolus, it could cause the relative bioavailability to appear lower than it actually might be.

In fact, I think there is reasonable confidence that had the same amount been given in smaller divided doses or the same concentration been given in smaller doses, the bioavailability would be higher.

I think there is also significant uncertainty used in the available database. Specifically, the studies by Roberts, et al., and Freeman, et al., reflect the character of the arsenic in the soil matrices encountered in the vicinity of CCA contamination at a playground.

Although we have that single soil sample from the investigation by Roberts, et al., as identified as coming from a wood treatment site, the sample was not characterized further. And we don't know whether the arsenic in that soil might have resulted from direct spillage of raw CCA product onto the soil rather than the leaching of arsenic from a weathered piece of CCA wood.

And even had it been reflecting leaching from weathered wood, the characteristics of the soil in that particular area could -- we have very low confidence, I think, that that would be representative of the soil matrix elsewhere around the country.

There are some additional factors as well, and these

pertain to the animal model. The animal is a primate model, and although that may have certain strengths with respect to the fact that humans are primates as well, obviously, it's of note that certain non-human primates actually have a metabolism of arsenic that might be substantially different than that of humans.

For example, the marmoset monkey, which is a New World monkey, like the monkeys used in these studies, is noteworthy for not methylating arsenic at all and for having a phase of retention of arsenic which is substantially longer than that of humans.

And the four-day urine collections that were used in this study to obtain the amount of arsenic excreted in the urine could conceivably not be sufficient in this single dose model that was used.

In addition, I think, although I can't say certainly, that the magnitude of any effect that it might have -- I think there has to be some concern that, in this particular model, particularly in the model by Dr. Roberts and colleagues, the animal was administered the dose under general anesthesia and during intubation. And it's conceivable that anesthesia has effects on gastric motility and cardiac output and other factors that might

influence the mobilization, metabolism and excretion in the short-term. And the short-term may have substantial factor in studies of this nature.

So with that in mind, I feel that there is not sufficient confidence in relying on those two studies as a basis for setting an across-the-board relative bioavailability of 25 percent.

I would echo what our colleague, Dr. Benson has said the other day, that in region 8 -- I live in region 8, and I agree with him that it's valuable to do site-specific evaluations.

I also think that future study designs should consider not just doing a single dose administration, particularly a single dose high-dose administration, that it would be better to use multiple-dose studies at a range of doses. And on the handout that just went around, this three-page handout -- for example, if you turn to the second page where there is a series of graphs, if you look in the lower right-hand corner, for example, this is from a swine study that was recently done on a number of soils in north Denver.

And these soils contain various amounts of arsenic, inorganic arsenic. And you can see that what they did is they took multiple-dose ranges administered over several days and

established a regression relationship, a slope. And it was a slope of multiple dosing as opposed to a single high-dose bolus that was used as a basis for looking at the relationship between the amount of arsenic excreted in the urine and the amount of arsenic administered. And I think studies of this nature have certain advantages in terms of offering more robust estimations.

It may be necessary in the context of looking at low-dose studies to consider more elaborate methods such as radio tracer methods, which would have the capacity of accurately measuring low-dose absorption.

So with that, I would just conclude by saying that I think that the current database should be expanded upon with additional research and site-specific studies.

DR. ROBERTS: You won't be surprised that I may have several responses, I think, to some of your comments. But I would like to hold those for a little bit. But let me ask you if you would -- since going out and collecting more data would -- you know, that's a very time-consuming proposition. So do you have an interim recommendation for the department in terms of an assumption of bioavailability from soil?

Should they default to the 100 percent relative

bioavailability or should they -- I guess I'm asking you, and you may not have an opinion on this. What should they do in the interim?

DR. KOSNETT: I actually omitted one additional point for the record, which I also want to make my colleagues aware of, and that is there is a broad range of -- their has been a broad range of bioavailability in other studies, looking at inorganic arsenic in soil that's exceeded 25 percent. These have recently been -- recently tabulated in an article in Environmental Science and Technology that recently appeared.

And, in fact, there was one particular study, although it used low-dose, relatively low-dose soils, in Aspen, Colorado -- and Bob, you are probably aware of this -- in which the bioavailability was actually well in excess of 50 percent.

So the existing database doesn't identify a clear number. The nature of bioavailability of arsenic in soil is that it's very variable. And I think decisions on remediation and action at a site should be based on studies done at that site on site-specific data.

I think that no generic basis can be invoked. I think sometimes in the process -- and perhaps Dr. Benson could answer

as well -- in situations where there just isn't any information, it's often left to the PRP to take action to do that. Or else sometimes a default level of 100 percent, which we generally feel would not be the case, would be accepted. But that's a motivation to do studies.

DR. ROBERTS: I just want to be clear on this. Is your recommendation to use a default of 100 percent until site-specific data could be available? What are you proposing that they do?

DR. KOSNETT: I'm proposing that they ask for site-specific study and promptly fund more research.

And in the absence of that, they use their judgment on a case-by-case basis, taking into consideration all the factors in reaching a decision.

DR. ROBERTS: Yes, but I think one of the things they are trying to do initially is get sort of a broad cut on these and, rather than looking at playground by playground, come up with sort of an initial assessment.

So I don't mean to press you, Dr. Kosnett if you don't have an opinion on this. But I'm trying to get from you what I think the agency is looking from the panel in terms of recommendation, which is, if the study or 25 percent is not satisfactory, what does the panel recommend?

And I think that, you know, going out and collecting -- I think at this point we're not looking at individual sites. I think we're looking at sites with playscapes, so we kind of need a number.

DR. KOSNETT: Okay. One could do the following, and sometimes in a case when one does a range of exposures, a range of possibilities and does a sensitivity analysis, that would range everything down from the full spectrum of what's been observed in bioavailability down to from, say, 5 percent up to 98 percent, and enter that into the possible equation.

If, based on every other, factor it's considered that within that range there still might be action taken, then a site-specific decision based on limited data and based on the range of possibilities and how that factors in can be made.

And that's a decision that, I think, the agency is not going to be uncomfortable with. They face that now with many other things as well, where they don't have good data to drive it and they have to use a site-specific basis or else just set a broad range and see, even at the extremes of range, there might be a need for action.

But I think -- and I firmly believe this -- on the issue

of the bioavailability of arsenic from soil, it will almost always have to be driven by site-specific answer and not necessarily by a generic number.

DR. ROBERTS: Dr. Vu, I think you perhaps had a point to make.

DR. VU: I appreciate Dr. Kosnett's perspectives and recommendations. As you know, in the Superfund program, you could afford doing site-specific kind of sampling. One of the decisions that the Office of Pesticide Programs is to make is, as a whole for nationwide, what would be the appropriate scientific data that should be used.

And I think you have also recommended the other approach. If you don't have site-specific or kind of playground-specific kind of scenario, then use the range. And that's one recommendation we certainly consider.

The Office of Pesticide Programs has proposed to pick 25 percent only because of looking at -- the Office of Pesticide look at the range of data and select the monkey as most appropriate data, et cetera.

But given your perspective, what I'm hearing, is that pick a range as part of the analysis if we have to.

DR. ROBERTS: Let me ask the other lead discussants on this question if they have anything to add.

Dr. Bates, I think you were originally first on the list. Did you have anything to add to this?

DR. BATES: I just would like to say -- well, I'm not an expert on this, but I would like to make a few comments.

First of all, I appreciate what Dr. Kosnett says about the limitations of the study and small numbers of animals and so forth.

But from a practical point of view, I accept that the EPA needs to have some sort of perhaps default value which it can use in these circumstances.

And I have had the privilege of being able to read a more detailed manuscript for the study, even though it's not yet published, and I appreciate that the great difficulties that are entailed in doing a study of this nature. It's very expensive. And I don't believe, myself, that it would be practical to do any sort of site-specific estimates.

I think some sort of general -- perhaps occasionally it would be possible. But in general I can see the need for some sort of value that can be applied broadly. So I accept that.

I also think that, despite the limitations of the studies, these are the best data that we have. And I support the need for more research to be done, particularly to confirm these results.

But I think, in the absence of any other data, I can certainly go along with a relative bioavailability of either 25 percent or perhaps, say, the upper confidence limit of the mean, which would be about 18, I think. So something in that region I would be entirely comfortable with, personally.

DR. ROBERTS: Let's see. Who else is on the hook for this one? Dr. Bruckner has given us his comments. Dr. Styblo?

DR. STYBLO: Well, I'm last in the row and there is not much I can add.

Unlike Dr. Bates, I agree completely with what Mike Kosnett said, which covers basically what we discussed prior to this session.

I think the only correct approach for estimates for bioavailability is to go to real-life sites, to use real-life samples.

The advantage of this approach is that samples taken from these sites, soil or dislodged material, would reflect correctly arsenic speciation in both organic and inorganic background that is associated with particle size to get even better

estimates. It is essential that several sites from different regions with different soil types are chosen.

We can guess numbers here based on studies that are available, but I'm not sure we are here to guess numbers.

I don't think it would take too much to do this study. I think that it is essential that this study is done.

I don't know how else we can derive numbers. As Dr. Bates said, we can pick any of the numbers presented in previous studies and we could be wrong, you know, by two, three times margin. We may be correct.

One more issue that was briefly mentioned by Dr. Bruckner is the biliary circulation of arsenic which may bring another uncertainty to delivery of the availability coefficient as it is calculated now using urinary excretion versus total, meaning fecal plus urinary, disregarding the excretion of arsenic in hair, which could be, or it may not be, significant.

The optimal arrangement for an experiment would be to use possibly primate or several primate species with known metabolic profile for arsenic as close as possible to human metabolic profile and with known biliary circulation of arsenic, with known pattern of biliary excretion of arsenic. That would be

the optimal arrangement. The question is how close we can get to it.

I'm reluctant to come up with any number at this time unless these requirements are at least partly, partially met.

That's about it.

DR. ROBERTS: Let me go ahead and take -- we do have another designated discussant that was added, and it's Dr. Mushak. And let me get Dr. Mushak's comments.

DR. MUSHAK: I'm in the amen corner with a lot of what Dr. Kosnett says. I would add to that the factor of developmental age.

We assume that children absorb at a higher rate across metals and metalloids. This is established in the case of lead. It's established for other metals in the case of animal models. And absent evidence that it doesn't show this -- that kids, you know, are not different in terms of their uptake, we have to assume that they are.

I think that the age of the monkeys here are a problem. Dr. Roberts, could you tell me the age of the monkeys you used. Harry Freeman's monkeys were three years old.

DR. ROBERTS: They'e adults. They're probably about

in the same age range.

DR. MUSHAK: So there may be question of uptake, as well as the other factors.

I think maybe the best thing to help the agency with would be, in the interim, to offer maybe a range of, say, the monkeys on the low end and the UCL for the pigs on the upper range, maybe 25 to 45 percent as an interim measure.

I don't think that it's useful to consider that you have to do site-specific stuff for every playground in the country. I mean, without engaging in understatement, this has potential for considerable logistical mischief.

I think that what we might want to do is look at selective soils by region or selective soils by type, impact type, kids who use playgrounds that have buffering soil underneath. In other words, classify by group as interim measure. You are not going to be able to look at every playground site. I think that's infeasible for anyone.

And it's not useful to compare this to Superfund. Superfund, basically, has PRPs who are corporate defendants who will, if they don't like, say, a generic uptake rate in an IEUBK model, they can go out and do their own animal studies. In fact, a

lot of the literature that's out there on bioavailability are commissioned by PRPs to essentially rebut EPA default factors in their modeling.

So I would say that probably a range that accommodates younger animals such as we see embedded in the young pig model might be useful as a number. I don't want to discard the monkey models. I think, though, they have a number of problems with them. I agree, I think the bolus problem is a real concern.

And as Dr. Benson indicated yesterday, if you are going to look at the best animal model, you have to standardize everything. And that hasn't been done.

And also the metabolic factor that Dr. Styblo has been talking about, depending on how you characterize or quantify bioavailability, the metabolic profiles may or may not be a major factor.

DR. ROBERTS: Any other comments?

Dr. Gordon?

DR. GORDON: I'm also uncomfortable with the use of data using soils, as I said a couple of days ago, that aren't the real stuff.

So -- but I'm comfortable with saying that maybe it should be over 25 percent, given what Dr. Mushak pointed out, the other animals --

DR. ROBERTS: I'm sorry. Just for clarification, by "not the real stuff," can you --

DR. GORDON: The dislodgeable or the runoff of the leached material from the playground soil and the soil underneath is what should be used in these studies, not from a CCA-treated plant or sawdust.

And because of that, I think the value should probably be above 25 percent for the uncertainty factor that we don't have the data from studies with animals using the correct soil.

DR. ROBERTS: And would you care to venture a number?

DR. GORDON: No.

DR. ROBERTS: Fair enough.

Dr. Ginsberg?

DR. GINSBERG: I think that there is -- a lot of uncertainty has been said at this table. I agree with a lot of what Dr. Kosnett started us off with. I do think that we have to think about what the materials are that are going to be underneath a

playscape. A lot of it will be sand, which may be independent of part of the country; it may not.

I don't know if you get Atlantic Coast beach sand out in Denver for a playscape or whatever. But sand in general with large particle size and with good leaching properties, I would think would have higher RBA than backyard dirt, you know, if there is a residential playscape where somebody didn't use a buffering material.

So I think it does depend upon how you construct the exposure scenario.

I think, for the purpose -- well, my personal bias, without having a lot of data in front of me, would just be that, sure, you know, arsenic bioavailability from a solid matrix, absorbed onto a solid matrix is going to be less than sodium arsenate in water.

How much less? You know, if I had to do a risk assessment right now and throw a fudge factor at it or look at all the data sets that I've seen and come up with a fudge factor, I would probably use 50 percent, given -- so there is my number -- given that it's probably, in this case, a lot of sand that we're talking about, so it's going to be higher than some other soil

matrices that make it lower, might retard it more.

The concern about children. Closure of the small intestine villi in terms of pinocytotic action where a lot of metal absorption occurs, in animals is at weaning; in humans, we don't know what that age is.

There are some theories that a lot of milk in the stomach enhances lead absorption. There is also other nutritional interactions with some metals that may be different in young children than at older ages.

By the time that kids are out in playscapes, at parks, ingesting a lot of dirt and soil, I think a lot of that really high phase of bioavailability in the GI tract is probably over. It's still a factor, but I don't think it's nearly as big as in, you know, the first six months of life.

So I'm not sure I would put a lot of stock into the young child concern about bioavailability, but I think it would weigh in somewhat. But these are all gut-feel, qualitative thought process. You know, I'm not basing on a good, solid study which I'm concerned about and which might tend to make me default a little bit higher than I would otherwise if there was a good -- if that 25 percent number was on a study that I really liked in terms

of the way the dosing occurred and, you know, just the relevance to an exposure scenario.

So I guess I would just sort of -- because I feel that, compared to water -- sodium arsenate in water, it does make sense that there would be some decrement due to retarding on a solid matrix.

You know, I could believe it would be somewheres around 50 percent as a general average, applicable to playground sand and other playground materials.

DR. ROBERTS: Dr. Chou is next. Then Dr. Mushak and then Dr. Clewell.

DR. CHOU: I agree with all my colleagues said. I feel very uncomfortable making a decision based on not enough scientific evidence. However, I also understand this is a decision we're asking to make across the nation. Therefore, the site-specific is not possible in this case.

We talk about how to make this decision. One concern is the children-adults difference. Usually, we say children probably would take in a higher substance -- there is many evidence. However, in this case, especially in soil case, we are also looking at digestion, not only the absorption.

There is no evidence to say that children would have a higher ability to digest; therefore, would have more available.

So without any data to tell me left or right I should go, then I have to assume there is no difference in this case, at least at this moment.

Then we look at what numbers can we choose. Often, when we are not sure what number to choose, we say 100 percent. That's one of the practices.

The other one is we say, okay, based on the existing data, what is the maximum, the most conservative number. I would go with 50 or 60 percent. That's the highest number we know possible based on the existing data.

Then we can go with another decision, what is the best judgment, what is most likely. Based on the existing data, again, I would say 25 is probably -- you know, we can say, well, most likely.

So without the -- the three numbers I've been thinking about, I think this case I'm willing to look at a possibility between 25 and 50.

DR. ROBERTS: Thank you.

Dr. Mushak?

DR. MUSHAK: I would like to respond to Gary Ginsberg's comments about when the differential for uptake might terminate vis-a-vis when kids are mobile.

I think to the extent we can hang any comparison on the lead picture, there are data that basically take this out to three to four years at least.

You can look at Ellen O'Flagerty's (ph) studies in the aggregate when she does her PB/PK model development. I have worked with that model and Ellen and I have interacted fairly closely in terms of where she thinks and can calculate where the differential uptake, at least for lead, occurs. If you look at Alexander's studies, it's clear that while there is a broad range there, that there is a fairly uniformed differential uptake, probably out to four or five.

If you look at stratified age data in the longitudinal studies out of Port Pirie (ph), Australia, and look at -- if you plot the blood lead behavior on a group basis, you find that around three to five you start seeing a marked decay of what appears to be uptake difference contributing to overall blood lead.

So I would take exception to the comment that playground kids are not -- uptake differences are not an issue for

playground kids. I think they are. Unless you keep day care, certainly, I think, where kids are apt to be young are apt to have much more exposure. Probably those kids could be three or four years old. And there, I think, there is an argument for this.

Scientific reasonableness would dictate it can't be ignored.

DR. ROBERTS: Dr. Clewell?

DR. CLEWELL: I have a little trouble with the analogy to lead since lead is a cation and a metal and arsenic comes in as an anion and a metalloid.

But I don't really have any specific information on arsenic uptake, although it was mentioned the other day that it's a phosphate transport for the arsenate and passes diffusion for arsenite.

So I think we can get too tangled up in this question of whether there is enhanced uptake. There have been several good points made about reasons why one might want to be conservative about the selection of the relative bioavailability. One is that there is less than 100 percent uptake of the water-borne arsenic.

In the relative bioavailability studies, are those numbers -- 25 percent, is that a comparison of the uptake for

arsenic in water versus arsenic in soil?

DR. ROBERTS: Yes.

MR. CLEWELL: So then that is figured in for those. And I believe, in my mind, as a pharmacokineticist, that takes care of the question about biliary excretion because they are both subject to that. So what you are looking at is the relative systemic availability of these as shown by the elimination in the urine where they are both subject to the same biliary excretion.

And I believe Dr. Kosnett's concerns are well spoken, but experiments are like that.

And so I have a lot of confidence in the 25 percent number. The pig numbers, which are higher, also have a lot to be said for them. I kind of like the suggestion that, since there is some uncertainty here, perhaps rather than having to focus on a single study, the general weight of evidence should be used and a number in between the kind of the ranges of 25 and 50 should be chosen, something around 35 or 40.

DR. ROBERTS: Dr. Styblo, before you comment, because I think I know what you're comment on, let me just make a brief statement about the biliary excretion and some information.

People have looked at this, at biliary excretion of

arsenic -- and I can tell you from our studies on intravenous administration of arsenic, you get less than 1 percent of total arsenic excreted in the feces. And that's probably the best way to assess biliary excretion.

DR. STYBLO: No, it's not.

DR. ROBERTS: Well, there can be some reabsorption, but I think it's certainly -- even that I'm not sure is a problem with the model.

Let me finish. And the same thing. Studies in humans looking at radio-labeled tracers find less than 1 percent excreted in the feces which, again, suggests that if there is biliary excretion, it's probably very small.

Just kind of wanted to throw that in. Obviously, if you were to do the experiment -- if you wanted to eliminate it entirely, I agree you would do a cannulated animal, you would interrupt the bile flow and then you could know for certain.

But I would have to say that, in all the animal models or animal studies that I'm familiar where arsenic has been administered intravenously, there is also a very, very low excretion in the feces which suggests minimal biliary excretion.

Dr. Styblo.

DR. STYBLO: I cannot disagree more.

The problem with all the studies that you just mentioned is that people inject one particle form of arsenic, which is usually arsenate or arsenite in aqueous solution, usually. Agree? All right.

There is a number of work done, mostly in group of Dr. Gerasich (ph) and Gregrich (ph) in Hungary. This group actually came up with very nice data on biliary excretion in animals.

The last piece of the work published -- actually, not published; it's submitted for publication -- I was lucky to actually see the manuscript -- showed clearly that the amount of arsenic excreted in bile or present in bile circulation -- and the rate by which this arsenic appears in bile depends strongly on arsenic species that are administered to the animal. Okay. And we are bad in the species issue and metal interactions issue.

So I suggest that biliary excretion, the rate, both quantitative and qualitative issues, would differ when you use arsenate, especially in aqueous solution, and when you have complex mixture of arsenic species or combined with other organic and inorganic matter.

I would be inclined to agree with you that biliary excretion may not be a big issue, but it gives us certain level of uncertainty.

Just to make this point stronger, we have little information of arsenic speciation. As I mentioned yesterday, it is generally accepted that arsenate is the main species.

We heard some -- and I appreciate data provided yesterday by Dr. Townsend from the University of Florida. These were done in two samples, as far as I understood. In talking to him afterwards, I found out that there is significant fraction of arsenic that could not be analyzed from these samples because it's not soluble or it's not analyzable by HPLC, which is an unknown kind of species.

So another argument to consider arsenic species is presence of microbial organisms on both CCA-treated foods and in soil. I ask the EPA staff to distribute copies of paper that deals with biochemistry and environmental biochemistry of arsenic. And I think we would need environmental chemists on this problem. It would help a lot.

To point out that presence of this microbial species, especially those that are able to methylate arsenic -- and there are

many of them on the wood, including CCA-treated wood suggests that there could be other types of arsenic present in both dislodgeable material and in the soil.

Because of that, we don't know what would be the contribution of biliary circulation to arsenic excretion.

DR. ROBERTS: Let me say, because I'm the author on the study that the EPA has relied upon, I don't know it's appropriate for me to comment whether or not they should use it. I think that's sort of a conflict of interest or something. But at any rate, I'll recuse myself from that recommendation.

But I would like to comment a little bit about the model because it's germane for the discussion about future research, which I would endorse. And I would also say that I generally agree with most of the comments that have been made about the uncertainties associated with taking soil samples from mine tailings or even a CCA site and trying to extrapolate that to other kinds of situations. I agree that the evidence indicates that there are several factors that can influence -- associated with the chemical and the soil -- that can influence bioavailability.

But in regard to the animal model, one is, I think that in terms of -- Dr. Kosnett mentioned that the animals were

administered the dose under general anesthesia, and I'd like to correct that because the animals are sedated lightly while we administer the dose, and that's to minimize stress to the animal which can have an effect also on gastrointestinal absorption.

We spent about a year and a half finding ways to dose animals that minimize effects on the GI tract and absorption.

And there's also going to be some uncertainties with the way that you do this. But judging by our comparisons with absorption excretion in humans, I think we got it pretty close.

There is an issue about bolus doses. I agree with that. And that's an issue with -- not only with the monkey but I think with the swine, too. They give more doses, but they are still much larger doses than what children would be getting in terms of soil. And they are also for, obviously, much shorter periods of time.

This is not an issue that we haven't thought of. I think the reason that these studies are done the way they are done is just the practical hurdles and limitations of trying to measure bioavailability in animal models.

I guess what I'm saying is that I don't know. Ideally, we would measure -- give repeated doses of 100 or 200 milligrams of soil and measure bioavailability, but I don't think right now,

with the technology we have, that that can be done.

Now, it was suggested that perhaps you could use radio-labeled material, and that would give you the sensitivity in measurement that you need. But the problem is if you spike it into the soil, you don't allow the aging process to take place, which could affect bioavailability and that's, of course, a criticism of one of the dermal studies that we're going to talk about. If you age the soil, then you don't have any radioactivity left.

So there are some real issues and problems, and I certainly acknowledge the uncertainties, but we talk about going ahead with research. I want the panel to be aware that people that are trying to assess bioavailability have thought about these things and are trying to do the best they can, but there are some real technical problems associated with doing that.

I think that for -- let me also talk about the role of metabolism because that was raised by a public commenter and has come up a couple of times today.

I think that bioavailability, as we're looking at it now, which is simply movement of arsenic into the animal and movement of arsenic out of the animal -- I don't think metabolism really matters. Now, I say that knowing that, certainly, depending

upon how you define bioavailability and what you are interested in -- metabolism in the liver, of course, can be very important, classically-defined bioavailability is the fraction of the material that enters the system circulation and in a particular form.

But -- and maybe at some point we will have enough information about various metabolites and species and maybe some suggestion that, depending upon the form in which you come into contact with it can influence its metabolism, it will be very important to have a model where the metabolism mimics humans. But right now, for the kinds of bioavailability studies that are on the table right now and we're talking about, I don't think metabolism is really an issue. What's at issue is, is the absorption of arsenic the same into the body and is the excretion essentially the same as humans such that whatever the animal is serves as a good model?

So I would say, at least at this state in our understanding of absorption bioavailability studies, I don't know that metabolism is as important as getting a species for which arsenic -- the digestive handling and absorption is the same, or as close as we can get to humans.

There is another point that I -- another uncertainty that

I might as well throw out into the table, and that is that all of these studies are done on animals that are fasted or at least have an empty stomach. And does the presence of food affect bioavailability?

Perhaps. And maybe -- and I guess if you had to guess, you might guess that the presence of food might interfere with absorption. So in that sense you might say the bioavailability measurements are, in a sense, kind of conservative because they are being -- from that one aspect, because they are all done on empty stomachs or on fasted animals.

But, again, it's another uncertainty in terms of how what we're able to measure on animals reflects what's going on in children in playgrounds, for example.

Anyway, I just wanted to throw those points out. I think I got them all.

Any other comments on this issue?

Dr. Ginsberg?

DR. GINSBERG: I don't want to lose site of EPA also presenting to us data on in vitro simulations of gastrointestinal, I guess, digestion or breakdown of -- I guess dissolution, leaching of arsenic off of particles.

I don't have an opinion one way or the other of how relevant those. Before we leave this topic, I just wanted to hear people who know more than I do about it how much EPA should rely upon those kind of data which, by the way, do show 15 to 20 percent -- you know, suggest that amount of leaching off of soil. So that would tend to make you think that it would be on the low side. But I don't know how important those data are.

DR. ROBERTS: Dr. Mushak?

DR. MUSHAK: The problem with any kind of in vitro study which has as its focus bioaccessibility, just simply solubilization is that it's a simplistic surrogate for what is integrated in the body of the child, or the adult for that matter.

We have seen this problem with other elements, that you have everything from a thermodynamic difference because you have an open reservoir in a GI track of a child versus a closed thermodynamic reservoir system with a vessel, this sort of thing.

You have all kind of mobilization mechanisms that may go on that you don't have in an in vitro model. You pointed out pinocytosis. There's micellar formation and all of these other things.

So I think that one is probably going to set a lower

boundary to probably -- you know, an in vitro approach would be lower boundary to what an in vivo model would be.

DR. ROBERTS: Dr. Kosnett?

DR. KOSNETT: I appreciate your comments, Dr. Roberts, with respect to the issue of metabolism.

The argument is made when you are looking at relative bioavailability model, that the fact that how -- you are looking at the arsenic in a soil compared to arsenate and to the extent that the metabolism in the animal with respect to urinary excretion is going to be handled the same with the reference substance as opposed to the test substance. Then that -- you are not as concerned with there being a confounding effect or complicating effect, I should say.

But supposing -- I think we still have to bear in mind the fact that it's not necessarily a given that the nature of arsenic in the test substance, in the soil, is going to be metabolized or handled in the same manner as the test substance -- as a reference substance such as sodium arsenate.

And even if there, for instance, was, as Dr. Styblo has mentioned, the impact of the presence of other metals -- we're dealing with CCA; you have copper and chromate,

copper-chromated arsenate -- if that could influence biliary excretion relative to the parent compound, that, I think, would make a difference, even though you don't see significant biliary excretion in the model that you used with just the arsenate.

And if there was a time delay or if there was a difference in the relative length of time that the one compound was excreted -- the test compound was excreted with respect to the reference compound, there could be a considerable factor.

And with that in mind, I just think it's worth pointing out -- and correct me if I'm getting this wrong, but in the monkey model that you looked at with sodium arsenate, in the four days of observation, the combined excretion that was recovered in both urine and feces as a percentage of the administered dose was 50.7 percent, plus or minus 3.1 percent, so there was a lot of room there. I mean, half of the arsenic was not accounted for.

And there may be -- even if there was just a time delay issue with respect to how much were to come out within that period of observation, that could have influenced your results. Would you agree?

DR. ROBERTS: Let me try and put that in perspective. Yes. And basically when you give an intravenous dose in humans

over five to seven days, you only get 60, 70 percent back. And it has to do with the kinetics of the elimination of arsenic.

There are some radio tracer studies done after intravenous administration of arsenic in humans that indicates there's an initial very rapid elimination. There is a second slower phase of elimination that goes on out to about one week. And then there is a late, very slow phase of elimination.

And what that means is, because there is a deep compartment or a long phase of elimination, you get most of the dose back very early. But there is a significant fraction that really takes a long time to get back, actually several days.

The fact that the total recovery is low is consistent among models, frankly, and has to do with the kinetics of arsenic.

In all of our studies -- and I believe it's the experience of Stan Casteel (ph) with the swine model -- is that there doesn't seem to be any evidence of sort of a late peak or a late elimination.

Basically, you really get most of the dose out, frankly, in the first 24 hours or so. And after that, it falls off quite a bit.

I don't know that there is some bunch that's going to come out as a bolus later on so much as it's just a function of the kinetics of arsenic.

DR. KOSNETT: The time kinetics, even the relative amount -- the absolute amounts coming out could differ, but the time course of arsenic excretion with respect to like when the peak occurs and the tails does vary between different arsenic moieties.

For instance, Revotter's (ph) work has shown that there are sometimes differences with respect to whether or not you give trivalent versus pentavalent arsenicals.

So there could be -- even if there was a shift in the kinetics of excretion of the test substance relative to the reference substance, in a four-day period of observation, there might be room for changes in the overall amount recovered.

DR. ROBERTS: I don't disagree that there is going to be a shift, but just in my opinion, I don't know that we are going to miss it in the four-day period based on the data that's out there and the various samples that have been run so far.

Dr. Vu?

DR. VU: Thank you, Dr. Roberts.

I really think the issues of Dr. Styblo and Dr. Kosnett and Dr. Roberts are very important, but I want to bring back the context of why we asked this question.

The health effects data of arsenic is in aqueous

solution, is in drinking water or the soy sauce study, et cetera. And we have to extrapolate. So that's the known health effects.

And even though I know that Dr. Styblo was talking about, maybe you have methylated arsenic in soil as opposed to drinking water, but all we have right now is the health effects data with regard to in drinking water or in aqueous medium.

We now have to extrapolate if children exposed to soil contaminated with arsenic -- what would be the differential uptake from aqueous versus soil. And that's the issue on the table.

And that's why I think Dr. Roberts said the metabolism doesn't enter into the equation because, if you only look at relative uptake in aqueous medium versus soil, that's what the issue is about, even though I think all the other issues are important with regard to the overall uncertainties of a health effects database with regard to this issue.

DR. ROBERTS: Thank you for clarifying that, Dr. Vu. And, of course, I would be happy to talk about bioavailability all day, but there's a couple of other issues that I think we probably need to get to.

So can we come to -- we have had a number of individuals express their uncertainty about -- or at least indicate

some specific sources of uncertainty in the data set. We have also had some recommendations, differing recommendations about how the agency ought to proceed on an interim basis.

Is there anything that anyone would like to add to our feedback to agency at this point?

Dr. Styblo and then Dr. Kissel.

DR. STYBLO: Is isn't that common approach when we have a higher level of uncertainty, we go with the worst scenario?

DR. ROBERTS: Dr. Vu?

DR. VU: I'm sorry. I was distracted and conferring with my colleague here. Could you repeat that question?

DR. STYBLO: What I said is, isn't it the case, when we have a higher level of uncertainty, that we go with the worst level scenario?

DR. VU: It's typical the agency is using precautionary principle that we always use more -- public health conservative numbers. And I think that really goes down to what I'm hearing from different viewpoint from members of the panel.

We have from -- Dr. Kosnett recommend a range. I forgot who wanted 50 percent. Then Dr. Chou suggested 25 to 50 percent. Dr. Clewell, 25 percent.

And I think Dr. Edwards explained to us that, if we use a range, in a way you really have to do a probabilistic risk assessment, which I'm sure later on the exposure issues -- all that is going to come up.

The Office of Pesticide Programs has, as we explained earlier, we want to do more realistic kind of scenario. But we couldn't do all of these kind of scenarios.

So we certainly will look into your recommendation as a whole, how we do the -- the approach of the Office of Pesticide Programs is more deterministic at this time. And so you can do more, you know, default assumptions, so it's more public health concern to see whether there is risk or not, or you do more realistic and probabilistic.

So these are the options we are looking at. So I really think that the panel needs to recommend, with regard to this issue, given the best available information, given the fact that we will need to support more additional research, what will be the best approach given the available information.

DR. ROBERTS: Dr. Kissel?

DR. KISSEL: I just wanted to, I think, endorse Gary's comment that maybe we should go with 50 percent here.

I view this -- there is an incredible disconnect here between this discussion and the way you are doing the risk assessment which is to multiply five numbers together that are point estimates, which is extraordinarily primitive.

And under those circumstances, really getting all the nuances is -- it just doesn't match up.

And given that much of the argument here is about relative bioavailability in soil, when we don't even know that what's under these things is soil because there is the bark and the pea gravel and other sorts of things, that it makes the uncertainty very large. And so I would be inclined to just take a stab at 50 -- if you are going to do one of these back-of-the-envelope things, guess 50 percent and run with it.

Otherwise, I think what this points out is that you want to go to a probabilistic assessment. And one of the ways that you can deal with that is that you take variability from individual studies and you take uncertainty by incorporating all the studies by picking randomly among the available studies. And what you wind up with is very large error bars which then you have to decide what to do with. Where are you going to regulate out there in those upper percentiles?

But that's really where you need to go because there's limited returns to try to refine a parameter if you are just going to multiply five numbers together and say that's a risk assessment.

That's probably question 8, but --

DR. ROBERTS: Dr. Clewell?

DR. CLEWELL: For the record, I came in at 25 to 50, splitting the difference being around 35 to 40, Vanessa. And I agree with what John said, 100 percent.

But the only way to get around this -- you are going to have the same problem with the residue levels on the wood. You know, what's the number? Well, there isn't a number; there's lots of numbers.

So it's going to be difficult to escape the rush to the probabilistic risk assessment, which we'll get to later. But for now, if you have to have a number, I'm happy with 50 percent, 40 percent, whatever you want, as long as we can get some sense of consensus. I believe we really do need to give them a number.

DR. ROBERTS: Dr. Styblo.

DR. STYBLO: I think I'm coming to agreement with two previous speakers. Saying so, I would like to ask a question. Is there any mechanism we can trigger that would bind the agency

to launch studies, experimental studies with appropriate design that would come with some corrections, because I'm really scared here? I'm in exact science and we are far from that now.

So is there anything we can not just recommend, but really get certain level of certainty that, in two years, you know, in latest term, we get better numbers from better experiments?

DR. ROBERTS: I think the answer is probably no.

DR. STYBLO: That will make it difficult for me then.

DR. ROBERTS: I think the panel can certainly strongly recommend, urgently recommend. Beyond that, I don't know that we have any ability to compel the agency. We're an advisory body.

Dr. Heeringa and then Dr. Mushak.

DR. HEERINGA: Just a quick comment on this. I appreciate the scientific discussion here, but as was pointed out by John on the path here, that we're talking about a factor that, at maximum, can have sort of a four-fold variability within the ranges that we have observed. And if we set it within the context of the ranges we were discussing, it may be two-fold variability.

And as I look down the path to the composite risk assessment, if I could get something down to two to one

variability, I would be very, very happy.

So I think it's very important to carry that out. But in terms of the overall exposure and looking at the components of this composite risk assessment, that ultimately, this is probably not going to be the parameter that's going to drive the outcome.

DR. ROBERTS: Good point.

Dr. Mushak?

DR. MUSHAK: If we look at the fact that two soils tested by two animal models suggest a range from, say, 25 -- whatever the set of conditions -- and 42 as an UCL in the pig model, and if we take Gary's caveat about there are media out there that are probably going to release arsenic much more avidly than soils, then I think 50 percent is quite scientifically reasonable as a first stab. I think also this would accommodate the children issue.

And I think -- let me just briefly point out that one problem with trying to say that there may not be any difference, children versus adults with arsenic, is that -- you know, one of the reasons that kids do differ from adults with metals -- and, again, Dr. Clewell, I appreciate the basic chemical difference between a metalloid and a metal -- is the fact that, you know, one of the reasons why children, in fact, show higher uptake rates are these

nutritional deficiencies. And one basic nutritional deficiency in a lot of children is phosphate.

So to the extent that an arsenate/arsenite partakes of phosphate pathways in any fashion, this is a nutritional connection that defines a developmental parameter. So I would say 50 percent is scientifically reasonable.

DR. ROBERTS: Again, recusing myself from this, but we seem to be approaching a consensus of 50 percent.

Is that -- without taking a vote, but looking at heads sort of nodding or shaking their head, would that be a reasonable consensus recommendation from the panel on this, and that we would move on to the next question?

Dr. Vu, do you have any questions that fall upon our feedback on this particular --

DR. VU: I don't think the agency has any questions. Thank you.

DR. ROBERTS: Great. Let's go ahead and tackle the next question while we're on the subject of absorption.

Can you pose the next question to the panel.

DR. McMAHON: Yes. Thank you.

Our next question deals with ther dermal absorption

value for inorganic arsenic. And as you have seen, we have selected or proposed a value of 6.4 percent based on the data of Wester in 1993.

Our question to the panel is to please comment on the selection of the value of 6.4 percent for dermal absorption of inorganic arsenic and whether or not this value will be appropriate for use in all scenarios involving dermal exposure to arsenic from CCA-treated wood, including children's dermal contact with wood surface residues and contaminated soils.

DR. ROBERTS: Dr. Bates, what do you think about 6.4?

DR. BATES: Well, if we think that -- oral bioavailability is a difficult thing to assess. I think dermal bioavailability is perhaps an order of magnitude worse. However, I'll do my best, again, being a non-expert on this area.

As Dr. Kosnett pointed out for oral bioavailability, there are many factors that influence it, and that's definitely the case for dermal bioavailability.

Factors such as the concentration on the skin or in the mass of material on the skin, pH, the moisture content, temperature, chemical form of the substance, degree of fat or

water solubility, the matrices, including the particle size and so on, they all influence the degree of dermal bioavailability.

Now, for the purposes of this assessment, of necessity, I have relied on the study which has been selected by the EPA by Wester, et al., published in 1993. I haven't had the opportunity to do an independent literature research and see if there are any other studies. I assume the EPA has done that and zeroed in on this particular study.

It was useful to read the study, and perhaps I'll just summarize some of the key aspects.

The study involved female rhesus monkeys. There were groups of three and four. I'm not quite clear whether those were separate monkeys, but I'm assuming there were seven different monkeys.

They were administered H3 AS04. Now, I'm not sure what the actual name of that chemical is, but it's clearly pentavalent. And this was administered in two ways: As a water solution and after adding it to soil.

And for both the water solution and the soil solution, they administered in a low dose and a high dose, so there were two dose groups.

Now, the low-dose group was -- the low-dose amount was described in the paper as the minimum arsenic that could be used given the specific activity of the compound, so they used radio-labeled arsenic for this investigation. And they said this represents general background arsenic.

And the high dose is representative of what would be encountered in more contaminated areas. And, as I said, the higher dose is also equal in mass to other compounds experimentally dosed on skin, and this can be used for comparative purposes.

The low trace dose gave an arsenic skin concentration of 0.00004 micrograms per centimeter and the high dose was 0.6 micrograms per square centimeter, so there was the quite a difference between the two.

The results show an apparently anomalous result that the -- well, perhaps it's not anomalous. But the low-dose absorption was higher both for water and for soil than the high-dose absorption. And the EPA had selected the value of 6.4 bioavailability for the low dose in water.

The perhaps difficult to explain situation was that the water -- for the soil, the corresponding low-dose value was 4.5

percent. However, for the high-dose water, there was 2 percent, and for the high-dose soil, it was 3.2 percent, which raised the anomalous situation that, with soil, there was a greater degree of absorption than from water itself, which was perhaps what lead the EPA to choose the value of 6.4 percent for the low-dose water exposure.

Now, from basic toxicological principles, I would have said that it would be more appropriate to rely on the high-dose exposures because these are more consistent with what one would expect in a real life situation. However, we're left with the result that soil appears to be more bioavailable than water itself.

So there are two ways -- two possible explanations for that. It could be that there is some factor in the soil which actually promotes bioavailability.

The alternative explanation is that this is a small numbers problem and that what we're experiencing here is the result of just random biological variation. And I suspect that that's really what has happened. And that has lead to the soil high-dose value being more bioavailable than the high-dose water value.

And I think that that also explains where the Superfund

program got their value of 3 percent. It was pointed out yesterday by Dr. Benson that there was a discrepancy that the Superfund program was using 3 percent, which is very close to that high-dose soil value here of 3.2 percent. So I think that possibly explains the discrepancy between the two values.

So what I would say, on the basis of toxicological principles, is it would be better to go for the high-dose value, which is more representative of a real exposure situation, and also means making a decision between the soil and the water values. And I think probably the soil value of 3.2 percent is the most appropriate there, and it does correspond very much with the Superfund value of 3 percent.

So if I had to pick a number, I would lean towards the 3.2 rather than the 6.4 percent.

I also would like to point out that a couple of the public commenters, I think Exponent and Gradient, have suggested multiplying the value from Wester, et al., by another factor which represents the oral bioavailability to take into account the fact that, in this study, they didn't use the arsenic from CCA; they used a more water-soluble value, which may, in fact, lead to a more -- to a higher bioavailability than you would expect in reality.

However, my problem with that is that appears to be, to some extent, double counting factors in the soil, which would tend to retard bioavailability, so you've got them on the skin, you've got them in the gut, and I don't think it's necessarily appropriate to multiply those two together.

So taking all this into account, I think probably the most appropriate value to use is the 3.2 percent bioavailability for the high-dose soil.

However, having said that, I think it's clear that there are limited data here and they are using a type of arsenic which is not the same as in the CCA. On the other hand, it is probably -- my suspicion is probably more water-soluble and bioavailable in this instance, so it's probably overestimating the true value.

So weighing all these things up, I would lean towards a value of 3.2 percent as being more appropriate than 6.4.

DR. ROBERTS: Thank you, Dr. Bates.

Dr. Hopenhayn-Rich, what is your number?

DR. HOPENHAYN-RICH: I'm not going to propose or endorse any specific number.

I think that Dr. Bates has covered most of the issues that I was going comment on. I will just sort of reiterate the fact

that I do think that there is definitely a small number issue here that could explain the differences between the high and low dose and between the soil and the water, so that effectively probably none of these numbers are significantly different from each other.

If you play around with the confidence intervals, you could come out with the low-dose water being lower than the high-dose water and et cetera.

But I am concerned about, besides the small number issue of the design of the study, the fact that just one arsenic compound was used instead of CCA, which seems to be the compound, obviously, of interest here and that we are supposed to be making decisions on. And I'm not sure, again, how much we can recommend further studies being done to address this problem.

And also the issue of the type of soil that was used and, as was mentioned below, the fact that this was not aged soil but freshly impregnated soil with the arsenic compound.

So I'm not ready to endorse the 6.4 of the 3.2.

If I had to pick a number, though, I think I would go with the more conservative assumption, based on all the uncertainties, again, on the worst case scenario of 6.4. So maybe I have chosen a number.

DR. ROBERTS: I wrote it down.

Dr. Kosnett?

DR. KOSNETT: I agree with Michael that if we think that the data set is limited with respect to oral bioavailability, we have even a tougher problem with the lack of a lot of data with the skin issue.

One issue I don't know if you mentioned, Michael, but I think we have to bear in mind that in this particular study by Wester, the had prolonged contact. Did you mention that?

DR. BATES: No, I didn't, but that is a good point.

DR. KOSNETT: The way the study was designed, the soil and water were held in continuous contact with the skin for 24 hours, which could conceivably -- there could be conceivably a situation where the soil would be held in contact directly with a child's skin for that period of time, but it probably -- on most of the situations, it might not stay in contact for that long and that could have influenced the results here in the direction of increasing absorption.

And with that said, you know, I don't think that -- I don't feel strongly about taking one number over the other. There's actually four values that are given in this paper, anywhere

from 2 percent to 6.4 percent. And maybe it would be safe to split the difference and note the range or something like that.

But I guess I would make the -- I would probably say that, you know, what EPA should do is consider a range approach. Considering the limitations of the data, that's always the safest things to do. It may be small factor overall in the decisions that are ultimately made, but with the lack of uncertainty, that's sometime -- I mean, the lack of certainty, that's sometimes the way to go.

And I would also make a call, as I think most people could endorse, for prompt and urgent research in this area.

DR. ROBERTS: So a range?

DR. KOSNETT: Yeah.

DR. ROBERTS: I won't pin you down any more.

Other comments?

Dr. Thrall?

DR. THRALL: I would just recommend that when you are guessing, that you not go beyond a decimal point. It implies that you are not guessing.

DR. ROBERTS: Well stated, Dr. Thrall.

I might as well jump in on this one, too.

Basically, I think it is a small number kind of thing. I think all of these things are essentially equivalent. And probably because of the way the study was done with soil and it was added without a chance for much interaction with the soil matrix, you are really probably measuring the dermal bioavailability of soluble arsenic applied to the skin.

So there is the question of had the arsenic had an opportunity to interact with soil, how much reduction would there be?

And I don't think there is any data to address that. I know that one of the public commenters tried to make a shot at it, but I agree with one of the previous comments that I just don't know that there is a sound scientific basis for using that number.

So I don't think we have any data. I think we can look at these numbers, though, as being probably conservative because that interaction hasn't been taken hasn't taken place.

And that would tend to make me want to pick a number more in the middle like 3 or 3.2 than maybe one at the upper end. Those are just my thoughts.

Dr. Styblo?

DR. STYBLO: Let me give you an additional piece of

information to consider.

This comes from experiments, in vitro experiments done in Dr. Hughes' lab in research triangle park some time ago, and it's about arsenic species, again, because that's my specialty here.

He did in vitro experiments using skin removed from mice and tested the dermal absorption of arsenate pentavalent methyl and pentavalent dimethyl arsenic. They are unique data considering that nobody else did the other species.

If you look at the absorption rates and compare them between these three species, you come with a rough conclusion that arsenate permeation are three to four times higher than those for methyl arsenic 5 and about two times higher than for dimethyl arsenic 5.

An interesting issue for methyl arsenic is that there is a significant portion that stays absorbed in the skin. It doesn't get through the skin to a vehicle, to the medium that is below the skin, which could be an interesting point for dermal toxicity.

So using just this data in very rough estimation, if there are any other species, methylated species present in our samples and if they are in pentavalent form, the bioavailability

would be rather lower than greater, although I would like to point out, we don't know much about dermal absorption of trivalent arsenic. And something I just asked Michael and I will ask other people: Is anybody familiar with data on dermal absorption of trivalent arsenic, obviously inorganic? Nobody did anything else? Are there any data out there?

DR. ROBERTS: Dr. Kosnett, are you aware of some data?

DR. KOSNETT: One thing that -- it's unfortunately not, in a sense, as quantitative as we would like. But one thing that we should bear in mind is that there is some experience with people bathing frequently in high arsenic waters and then having their urinary arsenic examined.

There is one particular study of which I only have the abstract, but it was performed in the Japanese Journal of Hygiene in 1978, and it involved a health examination on two subjects -- excuse me -- seven subjects, two males and five females who used arsenic-containing hot water from the geothermal power station in Kyosho (ph), Japan. They used the hot water to take only a bath for four years. The arsenic concentration in the water was 3,530 micrograms per liter. So it's pretty high.

And they did an evaluation in which they measured arsenic concentration in the urine three times per day for each subject. And they said it was in the normal range for Japanese, which was 58 to 178 micrograms per liter total arsenic, bearing in mind, too, that the Japanese with the fish diet, that it is considerably higher than it is in the United States.

So, I mean, their essential finding there was that even though these people were bathing in this very high arsenic water, they did not have a massively -- you know, they didn't have a detectably elevated arsenic excretion in the urine with the urine being measured three times during the day.

I don't have the full study, and perhaps it would behoove the agency to obtain the full translation and any further follow-up studies that had been done.

I think Dr. Smith mentioned the other day that there is -- he and I have discussed -- Dr. Smith is doing and should comment on, if you would, on the study that you are going to examine about bathing because that might --

DR. ROBERTS: Let me get to -- let me let Dr. Styblo complete his comments and then we'll go around and then maybe Dr. Smith can fill us in.

DR. STYBLO: Well, I just want to make one conclusion. If pentavalent arsenicals are present in the environment, the bioavailability of the overall amount of arsenic would be rather lower than that for simply arsenate from aqueous solution.

Again, the uncertainty is, are there any trivalent arsenicals present.

DR. ROBERTS: And did you want -- since you are speaking, did you want to venture anything on this particular question?

DR. STYBLO: No.

DR. ROBERTS: Fair enough.

Dr. Freeman, then Dr. Kissel.

DR. FREEMAN: I would like to go back to this idea from the study that you are sticking this moist material onto the skin for 24 hours. This is not what would be happening to children under this scenario of playing in a -- one of these jungle gyms.

They may have contact on the skin, presumably with something which we might characterize as a dislodgeable residue in which there is arsenic.

Because it is dislodgeable from the play place or the

soil, it may also dislodge from the skin after some period of time. And so to assume that you have reasonably high uptake dermally for this metal when no other metals seem to behave like this, other than for maybe mercury, doesn't make an awful lot of sense to me. So I would choose a low number rather than a high number. What low number?

DR. ROBERTS: If you are willing to venture a recommendation.

DR. FREEMAN: 2 or 3.

DR. ROBERTS: 2 or 3. Okay.

Dr. Kissel?

DR. KISSEL: Yes. I'm actually somebody who has done some dermal absorption work, although not in vivo, and so I have probably more to say about this protocol. But first I wanted to say this notion of a fixed percent absorption is nonsensical.

We're taking the gastrointestinal model and applying it to dermal which -- in the gastrointestinal tract, there is some normal kind of retention time in the population, so it flushes through and you report that because people are doing experiments in one species where there is some kind of normal retention period.

In soil, there is no normal retention period. We don't

know what that is. If you leave soil on the skin forever and there is a positive thermodynamic gradient from soil to skin, the chemical agent will be absorbed forever.

Obviously, that doesn't happen in the real world. What we're talking about here are probably several-hour kind of exposures, maybe from a few minutes, if somebody washes promptly, to several hours if they don't.

But taking 24-hour numbers and then applying them to short-term or what we think are probably shorter term experiments or actual exposure is out of whack with trying to do good risk assessment.

And dermal doesn't often show up as very important, and so people don't care too much, and so they are happy to do things kind of sloppily, but this notion that you just take this 24-hour number and apply it, regardless of whether the child touched the swing set playing tag and then ran into the house and washed his hands is the same as if the kid went out and played on the thing all day and then went to bed without taking a shower or bathing and slept in the accumulated dirt for 24 hours -- that you would get exactly the same uptake is just not very plausible.

So I would strongly urge EPA to start thinking of a

better way to model dermal absorption, and I really think you ought to be doing this as a rate with consideration of variable time periods of exposure. So that's kind of point number 1.

Then I have a problem with how these experiments are done. We're trying to model some kind of an exposure where somebody gets dirt on their skin and it stays on there for a while. There is argument about whether we should deal with static versus dynamic exposures where you might rub the soil into the skin using kind of pressure which probably applies to hands and maybe knees, but wouldn't apply to foreheads and other parts of the body that you don't normally rub against things strenuously. But it's mostly a static kind of experiment.

Now, in order to do this in vivo -- and there is a prejudice among toxicologists that in vivo is better than in vitro because of clearance limitation and other sorts of things, and mystery things that go on in organisms that don't happen in vitro, and so you want to do in vivo work. But there is a trade-off here that in order to get an organism in vivo, we have to do something very strange with the dirt here, which is to put it on the outside of the skin and then somehow figure out how to keep it there while the animal is then alive for the exposure period.

And what Wester and his group do is anesthetize the animal, lay it down flat, apply the stuff, I suspect, while it's still moist. This is another gripe is that they never describe actually how they put the stuff on the skin or adequately describe how they put it on the skin or the time period and the contact between the agent and the soil when they put it on the skin -- it's probably still damp.

And one of the reasons you might expect that you get the same uptake from water and soil is that, in fact, what you have is a water application in one case and a water mixed with dirt application in the second case, in which case it's really just absorption from water in both cases, and that might be going on.

So they put the stuff on the animal while it's anesthetized and then they cover it with two aluminum eye patches which makes a little dome over the top with a Gortex sandwich in between, and then they tape that down.

Well, then the monkey sits back up.

Another criticism of the Wester work is that they have used a large particle size which allows them to avoid dust in their laboratory. I think that one way to avoid dust in the laboratory is do the work in a hood. If you are worried about exposing your

people to dust, then you use what is an abnormally large soil size. They are using 180 to 300-micron soil particles, which is much larger than the soil that would actually stick to skin if you had a real exposure.

So now you have taken this monkey and you sit it up and you have huge soil particles. My hunch is that it falls down into the bottom of the space under this concave kind of device. Now, I don't know what that is.

What exposure are we modeling there? I mean, in order to get an in vivo application, we have created this thing where a child has a cup of soil taped to its side and is sitting, in this case, in a restrained chair -- somebody else has done these experiments where they allow the monkey free range, which means that the think is shaking around in there and you're shaking dirt on the outside of the monkey instead of having a layer of dirt on the skin. And it gets to be kind of a strained scenario to say that that's indicative of what happens to a real person in a real exposure. So I don't have too much confidence in what's going on here.

On top of that, if you read the paper, you won't see much cognizance of environmental chemistry. The water in which the stuff is dissolved is not even described.

When you are dealing with inorganic compounds, partitioning among phases has a lot to do with what else is in the water with the ion that you're interested in. If you don't describe anything about the water quality, it makes it kind of difficult to understand what's going on because you don't know the speciation of the agent that you are interested in. And they compare, as if they were directly comparable, the arsenic acid which is applied to the monkey and some separate partitioning experiments which they've done, which were done with arsenic chloride as if arsenic is arsenic and it doesn't matter what complimentary ions might be in the solution with it. That doesn't inspire confidence.

There is also a history of other work done by this same group where they have reported the same absorption for organic compounds, statistically indistinguishable absorption from organic solvent, which is then evaporated on the skin, so pure compound and stuff loaded on soil.

Now, you can either believe that the thermodynamic activity of organic compounds like PCBs and pentachlorophenol on soil are the same as the thermodynamic activity of the pure compound or you can believe that the experiment was done in a way which doesn't allow you to distinguish between things that are

obviously different.

Given that context, I'm very nervous about accepting any specific recommendations with respect to this work.

Also not described in here is anything about cage wash, whether anything could escape from this. You know, does the tape peel up? Does anything get out? Is that being counted? Is that why you get big numbers? I don't know. It's not described.

Normally, you like to know what's going on if you are going to evaluate stuff, and work from that group is remarkably sparse in terms of description of environmental details.

With respect to the monkeys, my understanding is that there were not seven monkeys. I think the total colony that they were dealing with -- and I could be wrong on this -- but from conversations, I think they have never had more than five or four or five monkeys. So this is repetitive use of monkeys and there is a question of sequencing. Was the low-dose soil before the low-dose water, before the high-dose soil, before the high-dose water, or was it some other sequence and could we just be seeing slow leaking from monkeys that's confounding results from different -- I don't know. And maybe they thought about that and did it right, but they certainly didn't tell us that they thought about

it and did it right.

I notice that if you take the flux to concentration ratio, for soil it's uniformly about 10 times higher than the flux to concentration ratio for water, which actually argues against my argument that it's the same experiment in both cases and just adds to my general puzzlement about what the hell is going on here.

And I would also like to point out that there are not four numbers here, there are six numbers, because there were some in vitro experiments done also, and they tend to be -- the water number is the same as the high-dose water and the soil number tends to be a little lower.

For an inorganic compound, I think the clearance limitation thing probably wouldn't apply, or it might not, anyway. You have to check the solubility kind of considerations.

In this case, the in vitro numbers might be just as good as the in vivo numbers. At least with the in vitro numbers, you know that the stuff was sitting flat on a horizontal surface on the skin for the 24-hour period, and you can then draw some interpretations about that, whereas in the in vivo case, you had stuff lumped at the bottom of this protective device.

So, overall, the results are counterintuitive that

availability from soil would be greater than availability from water.

I would be inclined to take the lower soil number, either 1 percent from the in vitro work or 3 percent from the soil work, and divide it by 24 hours and say that maybe .1 percent per hour is a number that you could use, and then modify that further with some estimate of how long somebody is actually going to be in contact with soil.

Certainly, I want to endorse the comment that two significant figures here is not justifiable.

DR. ROBERTS: Dr. Kissel, I just have a follow-up question for you.

When you say to divide by 24, so you would assume that the flux is linear? I mean, it's a zero order process?

DR. KISSEL: Well, it's probably not. You actually expect it to be more rapid, initially. But since I think these numbers are probably too high, anyway, it doesn't bother me too much that linearizing would kind of undercut what the actual shape of the curve was.

In another case, I might want to use -- linearize something over a shorter time period, not take the 24-hour number

and linearize it, but take a four-number and linearize that.

DR. ROBERTS: Let me ask a follow-up question since you recommended a different approach and seemed to encourage a flux model rather than just a straight percentage, I think for some good and logical reasons. Are there any flex data for arsenic or arsenic from soils, if they decided to go that approach instead of picking a percentage that they could use?

DR. KISSEL: The current EPA document has got a KP calculator for inorganics in general, which is probably too high by a couple of orders of magnitude.

For inorganics, we're really in bad shape. Actually, for organics, we're really in bad -- for anything from soil, we're in really bad shape in the dermal world. The existing database is grossly inadequate to what it's being used for.

DR. ROBERTS: I just wanted to be clear that basically -- and I would agree; I think this is direction they need to go, but perhaps the data aren't there in the immediate term for them to use this approach.

DR. KISSEL: Which is why you could take these numbers -- and I think they are going to be conservative and I think the dermal pathway is going to be more impacted by an

adjustment I'm going to recommend to the soil loading number that they are using, so it's going to get knocked down a lot anyway.

DR. ROBERTS: Other comments?

Dr. Smith, then Dr. Francois.

DR. SMITH: I think this may be directed to Dr. Kissel, but I'm looking for some clarification here because we have two, as I understand it, dermal exposure scenarios. One is going to be the one associated with soil loading onto the skin from children playing around the structure; the other is going to be the dislodgeable arsenic.

Many of the concerns I just heard you voice I felt were directed more to issues around the soil issue. Can you tell me or talk to us a little bit about your thoughts of to what extent your concerns apply to the dislodgeable arsenic that's going to be on hand surfaces. I mean, would you still recommend the same approach? Do you still have all the same concerns?

DR. KISSEL: You are right, I was talking about soil. And that does create the problem of what do we do with the dislodgeable residue. And I don't actually know what the bioavailability -- it would be hard to even put an order of magnitude kind of guess, although I'm sure it's a lot less than 100

percent. But pure inorganic compound on the skin, I'm not sure what to do with that.

DR. ROBERTS: Dr. Smith.

DR. SMITH: I just wanted to follow up on -- Dr. Kosnett made a comment and I just wanted to respond to it.

First, I'm not going to talk about the work that we're doing, only because I don't think it's going to be available for a year or two. It's also something that has much more to do with children's behavior than really a dermal study, per se. But if anyone wants to talk about it, I'll be delighted to talk about it.

What I do want to comment on is my awareness is that there is a study with rats, I believe, where the tail is left in the beaker for a period of time to measure sort of dermal uptake. And that if you measured the blood arsenic concentrations over the seven days following, it remained high, is my recollection, over the entire seven-day period.

So I'm just saying that I would have concerns about the sort of study design with the Japanese you mentioned where they just happened to look at urine levels for that day for dermal exposure and conclude, therefore, that there can't be much dermal uptake. And you and I have talked about the Alaska data, how

that's open to interpretation.

DR. ROBERTS: Thank you.

Dr. Francois?

DR. FRANCOIS: I don't mean to confuse the issue any further, but I just wanted to remind the panel that skin permeability in humans varies depending on the site of the body that you are looking at.

DR. ROBERTS: Thank you, Dr. Francois.

Dr. Morry?

DR. MORRY: Just a quick comment with regard to the exposure of the skin to the dislodgeable stuff from contact -- direct contact with the wood. It seems to me that we can't say whether we're talking about an inorganic compound on the skin or what medium the compound is going to be in because the wood is going to be covered with dew or rain or not, it's going to be dry. And the skin is either going to be sweaty or not sweaty or covered with part of lunch or something like that.

So, you know, who knows what the medium is going to be for that exposure.

DR. ROBERTS: Dr. Kissel?

DR. KISSEL: If I could add something to that. One of

the things that -- normally, when you think about exposure to water for dermal absorption, a lot of the experiments are done in diffusion cells where you have liquid water sitting on top of stuff and there is liquid water sitting there the whole time. And you calculate a -- you leave it long enough to get steady date and you do a permeability coefficient, and that's kind of a standard approach. This is actually five microliters of water applied to the skin and that's how much water there is. I don't know of what happened subsequently in the experiment.

Could that much water be absorbed into the skin so that, effectively, the inorganic salts are left as deposit on the skin? I don't know.

Would it run off when you sat the monkey up like I would expect the dirt to run off? I don't know.

So there is at least a possibility that the water numbers here are not too far off for having placed arsenical salts directly on the skin and left them.

But this is all shot in the dark kind of stuff. Because the experiments just aren't done in a way that's helpful to the question.

DR. ROBERTS: The limitations in the studies, I think,

have been well discussed here. And, also, I think it's fair to say that the situation is not going to get any better any time soon because of the problems that Dr. Kissel pointed out, and I would echo those. And there are a lot of difficulties in conducting in vivo studies.

In vitro studies are easier to conduct, but then there is always this issue of interpretation and that sort of thing.

Let's get back to the question.

Is 6.4 percent an appropriate value to use for the scenarios under discussion? And, if not, what value would this panel recommend? Is there a consensus value that this panel would recommend? Or what are we going to tell the agency to do?

Dr. Clewell?

DR. CLEWELL: I think that there have been a number of points made about why these are probably conservative values that have been provided in the study.

And John's point in particular is important about these being 24-hour occluded values and we're talking about much less than 24-hour retention on the skin for almost all children who have a mother.

So I think that we certainly would want to use one of

the more conservative -- one of the lower values from this study. And since the high dose values are 3 percent and 2 percent for water -- for soil and water respectively, as Dr. Thrall pointed out, 2 to 3 percent sounds good to me.

DR. ROBERTS: Dr. Kosnett. I want this to be a pretty numerical discussion.

DR. KOSNETT: I just had one question to ask, and I don't know if Dr. Beck is in the audience, but I read her comments that were submitted. And it's interesting, she references a study by Peeples -- and this is in the gradient comment book.

There is a study that's referenced, but the numbers aren't given. It's called the Dermal Absorption of Arsenic in Dogs from Sawdust From Wood Treated with ACA and CCA-C, University of California School of Veterinary Medicine, Department of Physiologic Science, Davis, California.

Do we have --

DR. ROBERTS: I believe those data were presented in the public comments, but I don't know if we have -- Dr. Beck is --

DR. BECK: I have to go back and look at the study. I do recall they didn't see any toxicological effects with the dermal studies, but I don't recall what was seen on the absorption,

specifically, and I'm wondering if John Butala is in the audience.

John, do you recall results from the Peeples study with --

DR. ROBERTS: Very quickly, Dr. Butala.

MR. BUTALA: I described those studies to you yesterday. We do have copies of the actual study report for you today. I think they are being photocopied as we speak. Specifically, your question was what?

DR. KOSNETT: I didn't see -- there was no quantitation given in the gradient submission. I just wondered what was the percent uptake that was observed.

MR. BUTALA: From that particular study, there was -- as you recall, there was a measurement made prior to the -- these were urinary concentrations of arsenic.

There was a measurement made prior to the dermal administration because the dogs were known to have about 135 milligrams per day dietary arsenic. And that was -- and I don't recall what the urinary concentration was, but I remember what I said yesterday.

Whatever the predermal dosing urinary concentration was of arsenic based on the 135 milligrams dietary exposure, the

administration of CCA-treated wood sawdust to the skin for two days and then for four days after --

DR. ROBERTS: I'm sorry. I don't mean to -- are the data adequate to develop an estimate of bioavailability?

MR. BUTALA: Well, there was zero increase in the urinary arsenic following dermal administration of sawdust.

DR. STEINBERG: It was a non-referenced article. There was no reference to this, so I don't know how this could be admissible. And I hate to see us get distracted on these tangents.

DR. ROBERTS: Let's let that sit for a second.

Let me ask, again, the panel: Does anyone have an opinion about -- that hasn't weighed in yet -- about 6.4 percent? Is that an appropriate value or should the panel -- what's your recommendation to the agency?

Dr. Heeringa?

DR. HEERINGA: Here again, I have no expertise on the specific value, but I think ultimately we're going to come forward, at least some of us, with a recommendation for simulation over reasonable ranges of these. And if difference is between 3.2 and 6.8, I think that's a reasonable range with which to simulate uncertainty in these parameters, and even zero to 6.8 percent is

probably reasonable range.

DR. ROBERTS: Any other comments?

Dr. Vu, I'm not sure we have given you a real clear feedback on this particular issue.

DR. VU: Well, thank you, Dr. Roberts.

I'm hearing a different viewpoint among the panel members. Some recommendation to look at a range. That means we need to conduct probabilistic risk assessment. And others would say go to the Superfund number, which is 3 percent. So the agency would prefer to have a consensus, but if not, the agency will take whatever the recommendation you come up with and we'll live with whatever you come up with.

DR. ROBERTS: Thank you, Dr. Gordon.

Are you going to make a last ditch attempt at a consensus?

DR. GORDON: A few percent seems reasonable, but it should be corrected for behavior and time of exposure, just like oral or any other route of exposure, not just -- don't take a 24-hour value.

DR. ROBERTS: Any other comments?

Dr. Kissel?

DR. KISSEL: Sorry, but I probably should say one more thing. I was just handed the Raman (ph) and Hughes sodium arsenate study which is not referenced in the EPA list. They've got the Duckawitz (ph) paper in there, which was a rat tail absorption thing.

This one shows much higher absorption from water than the Wester results.

The soil numbers are lower and the water number is much higher. And it may have to do with speciation. This is sodium arsenate instead of arsenic acid, and arsenic acid may just stay in the water and arsenate and sodium arsenate may partition. I don't know.

But I think we're in trouble on guessing a number for the dislodgeable residue. I don't have any -- I think the numbers here are high for soil, and so we're safe on that one, but I don't know what the number should be for dislodgeable residue.

DR. ROBERTS: I think there is probably -- I think there is agreement that the panel is a little uncomfortable about making a recommendation on dislodgeable material because there is very little to go on.

Any further comments on this question?

It's 11:00 in the morning and we have finished question number 3.

Let's take a 15-minute break and regroup and begin question number 4.

(A recess was taken.)

DR. ROBERTS: To the panelists, the ones we have present, please let me repeat my mantra, which is, keep your responses as short and to the point as possible so we can move our discussion forward.

We are beginning question 4. That means we have, if my math is correct, 12 questions to address.

Let me also point out that this is the last day of this meeting, and we'll go as long as we have to go to get through our business. I suppose, technically, we have to quit at midnight, but hopefully it won't come down to that.

Dr. McMahon, would you please pose question 4 to the panel.

DR. McMAHON: Yes. Thank you, again, Dr. Roberts.

Our question number 4 relates to inorganic chromium in CCA-treated wood and the selection of the hazard database.

Our question reads: As the available monitoring does

not differentiate among chromium species found in CCA dislodgeable residues on wood surfaces and in soils -- although, to qualify that, I think we saw some data yesterday from Dr. Townsend that updated us -- and as Chromium 6 is the more toxic species of chromium, please comment on whether the use of the hazard data for Chromium 6 is the best choice for characterizing hazard and risk from exposure to chromium as a component of CCA-treated wood. Please provide a scientific explanation and justification for your recommendation on the choice of either the Chromium 3 or Chromium 6 hazard database.

DR. ROBERTS: Dr. Chou, would you lead off our discussion -- Dr. Mushak has agreed to --

DR. MUSHAK: We caucused yesterday in the interest of time and agreed that -- and it was unanimous; it wasn't two to one -- we agreed that I would present for all three of us.

DR. ROBERTS: Okay.

DR. MUSHAK: We are in general agreement that, number one, available data from published material do not permit us to conclude that hexavalent chromium is or is not present in dislodgeable residues. And, two, available data do exist to show that when trivalent chromium species enter soils, Chromium 6 can

be formed and also can persist to some extent.

With regard to part 1, we should keep in mind that no one has shown conclusively that chromium valency in dislodgeable residues is identical to intact fixation structures; that is, evidence for or speculations about trivalency as an obligatory result of the very process of fixation may very well not carry over when treated wood surfaces begin to deteriorate and leach chromium, arsenic and copper.

One should be mindful of Stan LeBeaux's (ph) caveat in his 1996 review on page 18 where he noted that if Chromium 6 actually existed in these weathered surface residues, their high solubility and subsequent mobility would remove them rapidly in rain events while trivalent chromium would be more apt to stay put.

We would view this potential for selective removal through mobility differences being a case of, again, absence of evidence is not evidence of absence.

With regard to behavior of chromium as to valency in receiving soils, evidence for conversion of trivalent chromium to Chromium 6, once present in soil, is of two types, and I have some information that EPA will be circulating from peer-reviewed

published studies in EHP.

Peer-reviewed published studies of oxidation of trivalent chromium to Chromium 6 by natural moistured soils of non-acid pH by Richards and Bartlett in several papers published in J. Environmental Quality -- Bartlett and James, JEQ, 1984, and another one in 1979 -- show that Chromium 6 is generated from Chromium 3 via the redox coupling with manganese oxide. This applies for certain native soils.

Bartlett also discussed the ability of Chromium 6 over time, once formed, if the absorption of Chromium 6 to certain lignins occurs.

Before these studies, it was assumed, based on soils brought into the laboratory with various alterations to their natural state, that trivalent chromium was formed.

A second line of evidence is data from -- our data from studies disposal of chromite residues through sites in Hudson County, New Jersey. One of the reports of these residues is that of Burke and coworkers published in EHP from a chromium conference who showed that hexavalent chromium in soils with these residues, when mixed with soils, was present over a wide hexavalent chromium range of 1 to 50 percent.

Given that we can't rule out Chromium 6 on surfaces of treated wood and that Chromium 6 can be formed and be stable in certain soils, it is scientifically reasonable to employ the hexavalent database.

DR. ROBERTS: Thank you. And, Dr. Mushak, let me be clear. That represents the joint input from the three discussants?

DR. MUSHAK: Right. Although they didn't sign any contracts.

DR. ROBERTS: I understand, but let me congratulate the three of you for very efficient presentation.

Dr. Morry?

DR. MORRY: Yes. That statement does represent a consensus of the three of us, but I would like to add just a couple of comments to that.

Obviously, this question could be answered by getting more data, by taking samples of dislodgeable chromium from the swing sets and speciating whether it's chrome 3 or chrome 6. And the same with soils. You could take samples and speciate.

That hasn't been done yet. And in the absence of that, I guess we have to use the precautionary principle that Dr. Mushak

just described.

Also, in the absence of data, there is always a lot of arguments based on chemistry where people say, well, based on my knowledge of chemistry, it should be all chrome 3 or it should be all chrome 6. And we've had a lot of experience with that in California when we were trying to set regulations for -- or do risk assessment for chromium in drinking water. We got a lot of advice from the published literature and from chemists who appeared in person and told us that chromium in the environment would never be chrome 6; it would always be chrome 3 based on chemistry arguments.

So I became very suspicious of that because, after we did a risk assessment and made an assumption about what percentage would be chrome 6, people actually went out and started taking samples and analyzing them and speciating them, and we found a lot more hex-chrome than we expected to finds. We had drinking water samples where 80 percent or so of the chromium in the drinking water is hex-chrome, which chemists told us could not be possible.

And we've also found hex-chrome in air samples and soil samples that we speciated.

So based on that experience, I think that reinforces the precautionary principle of, in the absence of actual speciation, assume that all or most of it is hex-chrome where there is chromium present.

DR. ROBERTS: Great.

Dr. Chou; then Dr. Shi.

DR. CHOU: I want to say one more time we do have consensus in overall decision. A couple of things I want to add to indicate how difficult it is to theoretically decide how much is Chromium 6 or Chromium 3.

Another condition is the two different chromium valencies also preferentially accumulates in different kinds of soil. For example, Chromium 6 tends to accumulate in clay more than sandy soil. And we also know how much acidity we have what and kind of soil we're dealing with.

Another reason we decided to do this -- make a very conservative decision is even when we do have soil samples analyzed, even from the same source, if you assume exactly the same soil, the result coming from different laboratories can vary quite's bit.

So, basically, there are some data out there. Even that,

we don't know how reliable they are.

DR. ROBERTS: Thank you, Dr. Chou.

Dr. Lees actually had his hand up a little while ago. Let me take Dr. Lees' comment, then Dr. Shi, then Dr. Freeman.

DR. LEES: I think given the acknowledged huge difference in the toxicity data between chrome 3 and chrome 6, this is really a very, very important question to be answered.

My personal suspicion and at least some of the data indicate that the vast majority of chromium is present in the plus 3, the trivalent form. There certainly is indication of some hexavalent, and I certainly can't preclude -- and I certainly can't quantify the amount of chrome 6 in these different potential exposure sources.

And I think, given this uncertainty and the huge implications for the risk analysis, what we assume this chromium to be, some real exposure information is important. And to that end, the EPA CPSC playground study that we heard described -- it seems like 200 years ago, but I guess it was Tuesday -- I think it should provide, you know, crucial information to this decision.

Having said that, I need to point out that what is proposed in the EPA CPSC study is just a measure of total

chromium and that's just not going to give you the important information that you need to make this decision.

And, again, given the huge difference in the toxicities, the assumption has huge implications on the bottom line.

DR. ROBERTS: So your recommendation would be to collect empirical data on chromium speciation as part of that effort to -- strong recommendation that --

DR. LEES: Very hugely strong.

DR. ROBERTS: I think they had proposed to do a pilot, but I'm sensing you would suggest they do more than do a pilot; they should make that part of the study.

DR. LEES: Exactly.

DR. ROBERTS: Dr. Shi and then Dr. Freeman.

DR. SHI:

From NIOSH. I just wanted to make a comment concerning the difference between Chromium 6 and Chromium 3.

The bigger difference is Chromium 6 can enter into the cell, but the Chromium 3 does not.

But when the chromium enters into the cell, you can reduce to Chromium 3. But whether the Chromium 3 is inside the cell or the Chromium 3 is outside of the cell makes a big

difference.

For example, in some report -- EPA report, they said because Chromium 6 always reduces to Chromium 3 very rapidly, by ascorbic or some other reductant, it is therefore -- after a while, Chromium 3 and Chromium 6 may be different. It's not, because even though they can be reduced to Chromium 3, that Chromium 3 produced is inside the cell, not like the regular Chromium 3 that cannot enter the cell. This is the first difference.

Secondly, when the chromium is reduced to Chromium 3, you can reduce first to Chromium 5 and the second to Chromium 4. And the Chromium 5 and the Chromium 4 can produce a huge amount of hydroxyl radicals.

During the production of hydroxyl radicals, Chromium 5 and Chromium 4 go back to Chromium 6 again, so they can have some circle of the reaction.

So a small amount of Chromium 6 can produce a big amount of hydroxyl radicals.

And it's very hard to judge how much is Chromium 6 and how much is Chromium 3 because the Chromium 3 can react with hydrogen peroxide and with other species -- also produce Chromium 4 and eventually Chromium 6. And that's a different

condition.

For example, if the water have algae or some plant other reductants, it can be quite different.

So even though you know this is Chromium 6 or the ratio of Chromium 6 and Chromium 3, but it would only be in certain particular situation because it's just a change according to the condition.

In the laboratory, Chromium 6 can cause DNA damage and it can cause protein mortification, apeidosis, cause gene suppression. These are all results coming from my laboratory.

We have about 40 or 60 papers concerning the difference between Chromium 6 and Chromium 3. And OSHA tried to regulate the occupational standard of Chromium 6 and Chromium 3. They fund my research in an amount of about $100,000 a year since 1997 just to study the difference between Chromium 3 and Chromium 6.

And the Chromium 6 effect most likely is a free radical effect because all the reactions we saw can be inhibited by antioxidants. So Chromium 6 is much more toxic, is much more carcinogenic. This is the first.

Second --

DR. ROBERTS: Dr. Shi, I don't mean to cut you off. But is this leading to your answer on this particular question?

DR. SHI: I'll be finished just in one minute.

DR. ROBERTS: Okay.

DR. SHI: And the second is you don't know how much of Chromium 6 enters Chromium 3.

So I think to use Chromium 6 as a kind of judgment is much better than Chromium 3.

DR. ROBERTS: Thank you very much.

Dr. Freeman?

DR. FREEMAN: I would like to approach this from several different points of view. One, I think I agree with Dr. Lees that what we really need is to have some speciation done for the soils and the residues on these specific types of sites.

Some of the data that was presented yesterday by Dr. Townsend suggested that chrome 6 really is not an issue at these sites. And I say this because one of the things about Hudson County where we have done a number of studies is -- and, of course, you have to qualify this by the type of water and the type of soil that we have in Hudson County. But the stuff migrates across the surface.

Chrome 6 in Hudson County -- the New Jersey Department of Environmental Protection has data at surface and different depth levels which characterizes the amount of chrome 6. There are places where it was in the percent levels, usually about 10 percent. Where it was much higher than that, this was usually on the surface where the chrome 6 was in solution and when soil would dry, the stuff would crystallize and form chrome blooms. And then you get your 50 percents.

I have heard nothing that suggests that we're seeing little yellow crystals when the soils dry out around these things, nor have I seen any of the data that suggests that the chrome you are seeing isn't right at the drip line and that it does not seem to have migrated in the soils. However, the soils in Florida are different. You may not have -- the pH of the water may be different. So there are lots of different things to look at.

The thing about the Hudson County situation, which is basically 170 chromium slag sites -- very different conditions -- is that we also did biomonitoring of people and environmental exposures.

And the only thing that we could find among children, even though we observed these kids playing on the waste sites,

were slight elevations in urine chromium, which we could not attribute to chrome 6, but perhaps to total chromium in their environment.

So we weren't seeing any health outcomes that were indicative of the types of things that you would expect if there was a severe exposure.

We interviewed people about skin rashes, and while we found some people who said they had itchy skin, when the physicians examined them, we never saw any sort of dermatitis or skin irritations or anything else that could be attributed to a chrome 6 type exposure.

There was only one case with a child where there was any indication of an exposure. And this was a child who played on a chrome waste site and played marbles by pushing the marbles with his nose, and he irritation of the nasal septum. When he was removed from that -- and I think that was an inhalation exposure. Atypical. We sampled hundreds of kids; hundreds of families, in fact, and essentially under these conditions where we knew that there was high levels of chrome 6. We just didn't find things.

So I would say that this may not be an issue, but I would urge that more speciation be done.

DR. ROBERTS: Thank you, Dr. Freeman.

DR. MUSHAK: If I might respond. I think you are scrambling tox issues and environmental distribution of valencies, et cetera. I think if we retreat back to the valency in the environmental media relevant to CCA, I think Bartlett's data, Richards and Bartlett's data -- one of the papers for which I'm having distributed -- indicates that, in fact, soil types are critical for 6 versus 3.

And having gone through the graduate school system at the University of Florida, I could tell you that the media down there in terms of acidity versus alkalinity would favor trivalency. I'm surprised that there is as much hexavalency as there is.

And Bartlett did address the issue of whether you have such an artifactual situation in Hudson County that what you have are these high process flags that are so alkaline that they essentially have micro-environments for preserving Chromium 6.

But he argued in that -- and you can read the paper and form your own conclusion -- that, in fact, there is enough mixing with soil, presumably, for the issue of valency that soil is able to intrude and preserve the hexavalency.

The tox issue as whether we should use a database

because the tox says something -- you know, that wasn't our charge. I think that's a policy call or a question call from EPA and the chairman.

DR. ROBERTS: Let me dare to suggest at this point that the panel might endorse Dr. Lees' recommendation that speciation data be collected from these sites because I think that can resolve a lot of uncertainty about what the actual conditions are.

DR. MUSHAK: I would agree. In fact, I would argue that probably you ought to speciate all of it because one of the things about prematurity of this conference that struck me was that the chromium valency issue is best determined for the nation as a whole by these proposed studies. So we're kind of looking at an interim selection of what we think are mixtures of hexavalent and trivalent.

When we know the protocols, if they are expanded to include speciation across the board, that would probably answer exactly that.

DR. ROBERTS: Dr. Morry, Dr. Gordon and Dr. Solo-Gabriele.

DR. MORRY: Just three quick comments.

Dr. Shi referred to a statement that said that chrome 6 is reduced to chrome 3 in the body and that it becomes non-toxic. I have seen that statement hundreds and hundreds of times and it always refers to outside the cell. For example, when you ingest hex-chrome in drinking water or food, in your stomach it's reduced to chrome 3.

So I think that's what that statement is referring to, not intra-cellular reduction.

In California, we have lots of environmental problems with hex-chrome. And weekly or monthly we're finding new things. I mean, chrome can enter into the environment as trivalent or hexavalent and, in environmental situations, it can be oxidized or reduced to the other form.

I believe in -- I would like to see chemistry used to understand what happened after you found out -- after you find out what happened. But not -- I don't have much confidence in it anymore in predicting what will happen beforehand. So I think you have to take samples on every kind of soil or medium that you are concerned about.

In taking soil samples, speciation is -- speciating those for chrome 3 or chrome 6 is important. It's also important exactly

where you take the soil sample. You cab -- if you are two inches off, you can miss it. But it will be there.

So you have to be very careful about where you take those samples. Try to get them where the chromium is dripping onto the ground.

DR. ROBERTS: Thank you.

Dr. Shi, did you want to respond? I don't want to get sort of into --

DR. SHI: Just very short. I said Chromium 6 reduced to Chromium 3. I want to emphasize that this is not a detoxification process because, first, Chromium 3 cannot enter a cell. When the Chromium 6 is reduced to 3, this happens inside of the cell. And Chromium 3 inside the cell can bind to DNA. Chromium 3 out of the cell cannot.

So even though it can be reduced to Chromium 3, it's not a detoxification pathway. This is a first.

Second, in the reduction process, free radicals are produced. Also the free radicals can cause DNA damage and also cause a problem.

So Chromium 6 reduced to Chromium 3, not toxic. This is not a detoxification pathway.

DR. ROBERTS: Dr. Gordon?

And let me -- before you comment, let me say that I'm not hearing a lot of disagreement on the response to this question.

I've been hearing a lot of points, but I'm not hearing a lot of disagreement. So there is -- I was getting ready to ask you if you could see if you could capture what's going on as part of your comments and put us all on the same track.

DR. GORDON: No, I was going to disagree.

DR. ROBERTS: Oh, you are going to disagree. Okay. Well, feel free to do so.

DR. GORDON: While I agree that the hexavalent is the risk from CCA wood, soil or dislodged whatever, I don't think we can -- if we are being asked to assume that it's 100 percent, that all the chromium that's measured, all the data we have so far, it's 100 percent 6, then I disagree with that because I think even the minuscule data for Florida soils maybe that Stilwell and Townsend gave yesterday -- I mean, I think they said it was either undetectable and maybe a high value of 5 percent.

And given the fact that the CCA wood, if properly fixed -- hopefully if it's fixed, completely fixed -- that it's going to be up in the high 90s that, yes, that's reasonable. And I don't

think we should assume it's 100 percent 6 if, in actuality, it's probably in the high 90s of Chromium 3 and we have a paucity of measurements that say, yes, that's a reasonable --

DR. MUSHAK: If I might respond to the --

DR. ROBERTS: Dr. Mushak, I have a couple more people, and I'll put you down on the list. But I think Dr. Gordon has sort of put out on the table for discussion -- he doesn't object to Chromium 6, but he thinks that perhaps some sort of a default assumption or a generalizing assumption in lieu of the data that we're going to strongly recommend be obtained -- in lieu of that, that perhaps some adjustment on the total chrome concentrations would be in order?

DR. GORDON: I agree. That's my point.

DR. ROBERTS: Okay. Dr. Chou and then Dr. Solo-Gabriele, then Dr. Mushak.

DR. CHOU: It is true in the natural environment we will never find 100 percent Chromium 6. I agree with that. And we interpret the question as either Chromium 3 or Chromium 6 would be the choice of the decision.

But if we're going entertain the thought of doing a fraction -- we tried that thought -- it's getting difficult. It

probably will go very high, I would think at least about 50 percent to cover the known possibility already. Maybe even higher.

So I guess we could talk about.

DR. ROBERTS: That's good. Dr. Chou has put a number out there.

Dr. Solo-Gabriele?

DR. SOLO-GABRIELE: I see the chromium issue in two places. One is with the fixation process.

Chromium converts from 6 to 3. And probably by the time a playground is built, there has been enough time elapsed that a lot of that chromium would have been converted over to 3. So the fraction in the wood would likely be very low.

Once in the wood, there is a potential for it to leach out and interact with various environmental parameters for it to potentially convert.

However, the little data that we do have -- and it's very preliminary data and it's limited -- does show -- it was my interpretation of Tim Townsend's work that it's a relatively small fraction that was observed in Florida. Exactly what the fraction is I don't think we have a large-enough data set at this time to really quantify it, but I think to be very conservative, the 100 percent

chromium is one way to go. But once I believe data starts accumulating and you start getting more data, I believe it's going to fall. And there is going to be evidence to decrease it.

DR. ROBERTS: Dr. Mushak and then Dr. Lees.

DR. MUSHAK: Terry, keep in mind that our charge was not to dichotomize this stuff into 100 percent one or the other. It was left to us to sort of assume that if there were mixtures, then basically the default database for the more toxic component of the mixture would apply.

To the extent that we have, at least in some cases, non-trivial levels of hexavalent chromium, then I think it's the agency's problem to take that and adjust for how it wants to use the hexavalent database to adjust for fractions.

Our charge was not to adjust for fractions, even small fractions. It was basically, is it scientifically reasonable to use a hexavalent database? And we answered in the affirmative.

DR. ROBERTS: I believe we did. And I think -- well, what happened to the question? May I ask that we sort of keep the questions projected to sort of keep us all on the question.

Dr. Lees, I believe was next. And then Dr. Shi.

DR. LEES: Actually, this is partially in response to

what Dr. Mushak has to say, and Dr. Gordon.

Again, going back to the huge difference in the toxicities, one is a great carcinogen; the other is an essential nutrient.

I think the solution proposed by -- you know, in the absence of knowing what is actually there, and the interim working solution to assume that, based on the data, a certain percent is the more toxic hexavalent form is appropriate.

I think that the caveat here is that, in the risk analysis, if you use -- whatever you use, whatever your measure is in the risk analysis, you have to use the appropriate tox data.

As proposed right now, they are measuring total chromium, which, in this case, is probably predominantly 3, but applying the hextoxicity. And I think that's a mismatch that's inappropriate.

DR. ROBERTS: Dr. Vu, please help us with our discussion here.

DR. VU: Thank you, Dr. Roberts. Let me try to put this in context on behalf of my colleagues here in EPA.

We all recognize that the health effects of Chromium 6 is more toxic than Chromium 3, as Dr. Shi says, partly because

Chromium 6 can enter into the body.

And that's where we -- and what we need to know is the chromium in the environmental setting deal with CCA-treated, is it Chromium 6 or Chromium 3? Because Chromium 6 can enter the body and Chromium 3 would not elicit a reaction if it doesn't get in.

Right now, the agency is assuming that we have to use a total chrome until we have better data, and I think that's why Dr. Lees strongly supports the speciation to know -- and how exactly, what is the total amount environmentally? Is it 6 or 3? Because that's the critical crux of whether we overestimate the risk if we use this assumption.

The agency is using a precautionary preassumption until we have a better handle on it, and I think that's where we are at this moment.

DR. ROBERTS: Dr. Lees can respond.

DR. LEES: And along that line -- I guess my bottom line is you are assuming 100 percent chrome 6.

In terms of conservative, it's exceedingly conservative. We've heard other numbers thrown out -- you know, maybe 57 percent might be more appropriate. I think over here 5 to 10

percent of the total chromium could be assumed, could reasonably be assumed to be hexavalent.

And I think, you know, for this first cut purpose, some assumption having to do with the total chromium, that not all of it is hexavalent and a certain percent is hexavalent might be a good interim step to take before you get the actual data.

I personally think, from having analyzed such samples myself, that if you were to -- something in the order of, if you were to assume that 10 percent of the chromium was hexavalent, that is probably a very, very, very conservative measure. I suspect it's actually well less than that.

DR. ROBERTS: So it appears from several of the points that have been raised that the panel seems to be recommending that the agency not assume that all of the total chromium is hexavalent; that they perhaps should make some adjustment.

I don't know if we want to give a number, but maybe we should -- we can, if we think we can come up with one. If we can't, we can just tell the agency that we think that they ought to review the best available data they can find and factor that into their assumption on chromium.

Would that be adequate for the panel, or is there a sense that you want to recommend a specific value?

Dr. Mushak?

DR. MUSHAK: I have no problem with a range, but I do have a problem with hitting a number that, given the consequences for public health -- Dr. Lees, you talk about really impacting the bottom line. Is this an economic bottom line or is this a public health bottom line?

If it's a public health bottom line, then I think a lot of due deference in the uncertainty should be given to worst case scenarios.

I'm troubled by a 50 percent -- realizing, of course, that if we use the Hudson County data as sort of a worst case for all hexavalency in soils, then nothing will ever be above 50 percent -- well, that's one issue. I mean, I think we can quickly discuss that.

But taking a range that may be 50 -- you know, 20 to 50, 50 to some unknown higher number less than 100 percent may be --

DR. ROBERTS: And let me propose that -- again, this is a good reason not for us to spend a lot of time coming up with a

number because I think we could spend a lot of time and still not come up with an agreement. But we can certainly communicate to the agency that, in selecting that percentage, they consider a wide range of possible scenarios and that, in the interest of coming up with a protective value, that they pick a percentage that would be at the upper end of what might be encountered in these kinds of situations using the best available information. That kind of a recommendation.

Is that a recommendation that the panel could endorse?

Does anyone want to dissent or offer a different recommendation?

DR. CHOU: I would agree, this is a ver good approach.

DR. ROBERTS: Dr. Shi.

DR. SHI: I just want to add a little bit of comments.

For the issue of Chromium 3 and Chromium 6 in a soil, you cannot process really because the Chromium 3 go to Chromium 6 depends on pH, depends on the sunlight. UV also plays a very important role.

Now, the moisture, the water, it's just realistic to measure exactly what's at issue for the question of the matter -- and if we decide whether the issue should be Chromium 6 or

Chromium 3 used as the standard, I think Chromium 3 is the better choice. I do not think to get 50 percent or 40 percent or 10 percent is what we want right now. I think that Dr. Mushak uses that as an indicator. I think that's a good one.

DR. ROBERTS: Dr. Lees.

DR. LEES: I would support absolutely from the public health protection the use of a worst case, but I would interject one word. A reasonable worst case.

DR. ROBERTS: That's fine.

Dr. Vu, have we come to some clarity in our feedback to you?

DR. VU: I think the agency is very pleased to hear that recommendation. Thank you.

DR. ROBERTS: Let's go ahead then, and, with that, unless I hear objection from the panel, let's proceed to question 5.

DR. McMAHON: Question 5 relates to the short and intermediate-term endpoint selection for inorganic chromium.

The question to the panel is to please comment on the agency's selection of the 0.5 milligrams per kilogram per day NOAEL value for use in assessing risks to the general population as well as children from short-term and intermediate-term

incidental oral exposures to inorganic chromium as contained in CCA-treated wood.

Please provide an explanation and scientific justification for your conclusions as to whether the presented data are adequate or whether other data should be considered for selection of these endpoints.

DR. ROBERTS: Dr. Lees, I have you down as first off on this one. Would you start the discussion.

DR. LEES: I'd be happy to. I'll try to be as concise as possible, and I had two major points that I wanted to make.

Essentially, we covered the first point in the preceding discussion. So I would like to proceed directly to the question of this .5 milligram per kilogram per day NOAEL and the evidence that -- you know, the study that was used to support that.

First of all, this should be an interesting presentation because essentially this is a non toxicologist reviewing a tox study, so bear with me.

The study that has been used by the agency for the purpose of the NOAEL for the short and the intermediate term oral exposure is actually the same study that they used for the assessment of the reproductive developmental risks; that is, the

study by Tyl, I think it's 1991.

And just very, very briefly, this is a study of rabbits in which they were exposed to chromic acid via a bolus of -- by gavage, a bolus of essentially chromic acid.

And these were pregnant rabbits, as I said. That was the primary purpose, was to look at the developmental things.

In any event, there was a series of -- a dose range, the highest dose of five milligrams per kilogram per day. This involved -- as I said, these were chromic acid in distilled water, so it wasn't buffered at all.

And the resulting material that was gavaged had a pH of 1.5 in the highest dose. This continued -- I think it was a 12 day dosing regime.

The effects that were noted in the two high dose were, first of all, mortality. And, in the highest dose, reduced weight gain. The highest dose, diarrhea and labored breathing I think was the other thing that was mentioned.

There was no pathology. You know, the animals were autopsied at the end of the thing and there was no pathology noted in any of these animals.

Again, as a non-toxicologist here, I have great

difficulty differentiating or attributing, if you will, the effects noted here to chromium as opposed to just the plain old acid effect. And I would defer to my toxicology colleagues on the panel. But -- you know, I guess I wouldn't be surprised if this were -- well, we'll have a discussion on whether this is chromium effect or an acid effect.

Having said that, there is a supporting study that is cited by the agency, one of -- from China by Chiang (ph) and Lee -- which there is a population that was exposed to drinking water that had a chromium concentration, and it's not really clear whether it was hexavalent or trivalent or some mixture, of 20 milligrams per liter. The suggestion is that it's hexavalent.

And in this case, the exposure or the dose would be on the order of about .6 milligrams per kilogram per day.

And that were -- the effects that were noted there were sores in the mouth, digestive -- you know, vomiting, diarrhea, and those kinds of things for the most part.

So I guess the bottom line is that the Tyl study, the main one that's cited to substantiate this .5 level, I have serious questions about whether it demonstrates what they actually say it demonstrates.

DR. ROBERTS: Okay. So --

DR. LEES: I guess maybe we should first have a discussion whether it does demonstrate what it --

DR. ROBERTS: Fair enough. And then maybe we can decide.

DR. LEES: And if it does not, as I suspect, then there has to be -- and I'm not familiar with the animal literature, but it seems to me there has to be some more appropriate -- you know, instead of this bolus gavage, some dietary study or something like that that might be more appropriately used to establish this value.

(Thereupon, Volume I of II was concluded.)

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