And in one study looking at congenital malformations as a function of mercury exposure, there was no association between occupational exposure to mercury and congenital malformations.

Occupational exposures in dental professionals. I think we've heard that dental professionals are sort of a select group of persons working with mercury amalgam on a regular basis, probably high levels in some cases.

There was a study in which chelation data suggested that the mercury body burden in dental professionals is much greater than that indicated by pre-chelation urinary mercury levels, in that after these dental professionals were chelated, their urine mercury levels were literally ten times what they were prior to chelation, suggesting that the body burden in those persons, dental professionals, is probably substantially higher than other populations.

These studies reported that there were neurobehavioral deficits including finger tapping, hand steadiness, visual discrimination, other aspects of neurobehavioral function, and most of these measures correlated with measures of recent or current exposures which were interpreted by these authors as current mercury, not chelated mercury levels.

Chelated mercury levels were thought to represent exposures over a long period of time or represent residual exposures.

However, the neurobehavioral deficits reported are not shown in other occupationally exposed where urine mercury levels were higher.

Let me say that again. In the dental professionals where these findings were reported, in other studies using the exact battery of neurobehavioral tests, with persons with mercury levels, urine mercury levels much higher, these tests showed no effects.

In these studies, there was also no cohort of non-dental controls, so selection bias I think was an issue in these particular studies.

And in many cases there was a lack of association between many outcomes and indices of long-term mercury exposure, those being chelated urine mercury values.

These observations suggest that these effects may reflect confounding of mercury exposure with other occupational exposure, something that the study designs in these reports simply cannot rule out.

There is also some effort in these same studies to look at human genetic polymorphisms and

interactions with urinary mercury levels, with the thinking that certain persons with certain polymorphisms might be more susceptible to the effects of mercury than others.

In these studies, again, there was a lack of correlation between indices of long-term mercury exposure and neurobehavioral outcomes.

Generally, there was only an effect of current mercury exposure, indicated by urine mercury levels at the time of testing.

These studies actually did evaluate the effects of specific polymorphisms, including brain-derived neurotrophic factor and CPOX4 which is a polymorphism of the porphyrin oxidase system--I can't pronounce the entire CPOX word or I would--which appears to be associated with alterations in important behavioral responses, nervous system function, in other words, in humans.

The degree to which these polymorphisms might or might not affect a given individual's response to mercury remains unknown, however, largely because of the shortcomings mentioned about these study populations, and primarily related to the lack of proper control groups.

Moving on now to studies of humans, in

which only exposure to mercury amalgam was the metric. There have been two new very important studies that have been published recently, you've heard them mentioned before, the Bellinger-DeRouen studies, in which groups of children, usually five to seven years of age, had amalgam or alternative fillings placed, and then they were followed for five to seven years after treatment.

These were doubleblind clinical trials, and both or these studies, in which there were over 500 subjects in which study, found no adverse effects when these children were followed for five or seven years after amalgam placement.

The outcomes included extensive and repeated assessments of a multitude of neural behavioral function, including IQs, and these assessments were carried out repeatedly over this five to seven year period.

In adult retrospective studies with large sample sizes, the data don't support adverse effects for mercury amalgam. In one study, there was an association between mercury amalgam and the increase in hazard ratio for multiple sclerosis. However, the number of observations was very small, seven out of 20,000, and the multiple sclerosis incidence in the

study population was well below that of the general population, which is about 29 in twenty thousand.

In fact, the trend for other responses was not in the direction showing adverse effects. Kidney disorders, inflammatory responses and toxic neuropathy actually had lower relative risk.

In a cross-sectional study in adults, there was no correlation between urine mercury levels and end points assessing several levels of in neuraxis. Dr. Factor-Litvak talked about that study earlier, and in that study, there was an extensive neurobehavioral test battery also conducted.

Additional studies showed significant correlations between the number of amalgam surfaces and decreased vibrotactile response, but the effect was only demonstrable in select groups, and there were unfortunately no urine mercury data, making the interpretation and dose response analysis difficult.

Studies that focused on low birth weight infants and persons with Alzheimer's disease found no evidence that mercury contributed to either condition.

We also looked at a handful of animal studies that came up and we evaluated I think five. They demonstrated no developmental toxicity associated with mercury vapor exposures when conducted in utero,

that do not also cause maternal toxicity. So they had to administer levels that actually caused frank toxicity to the mother, before they found any developmental toxicity.

Exposure to high concentrations of mercury vapor during critical periods of gestation did not cause any significant adverse effects on the electrophysiological outcomes in the rats when they were tested as adults. Though these data are informative, these animal studies offered limited insights into the effects of mercury vapor at the levels experienced by persons with amalgam, because the minimal exposures used in the animal studies were 1000 microgram per cubic meter.

So based on the critical analysis of 34 peer-reviewed scientific articles published since 2003, an evaluation of the literature reviews conducted by the ATSDR and the EPA, and the health effects-based exposure reference values derived by those agencies, we conclude that the peer-reviewed scientific information published since 1997 does not substantially change our comprehension of the health risk of mercury in dental amalgam compared to previous analyses performed by the Public Health Service.

We reached this conclusion in

consideration of the information on mercury exposure from amalgams relative to demonstrated adverse health effect exposure levels and to health-based reference values, and in consideration of the potential for health effects in sensitive populations.

And with that, I will thank you very much.

DR. BURTON: Thank you for your presentation. Do the committee members have any questions for this? Yes? If you have questions, as we were doing yesterday, just turn your light on and we'll pick you up in order.

DR. LUSTER: I had a couple questions. You had indicated that a couple of the--indicated some of the key reasons, the EPA studies that were conducted with children or adults with amalgams, and they were using urinary mercury levels as a measurement, and you had said earlier that at the low levels, you felt that urinary mercury levels looked like it wasn't a very good indicator for exposure.

Can you comment on that a little further.

DR. PAULE: The urinary levels are not good levels of exposure when ambient air concentrations are below ten micrograms per liter cubed.

In addition, these studies not only looked

at urine mercury concentrations but also amalgam surfaces. So even in the absence of urinary mercury data, we have information on the number of amalgam surfaces in those studies.

DR. LUSTER: Okay. Another quick question then.

This is a little bit pre your--but I guess you had an opportunity to review that data. This is the benchmark that was used both by ATSDR and by EPA, was that Favrille study from 1983, and did you see any limit--well, did those agencies discuss during the development of their document and development of their reference concentrations, any problems, limitations with that particular study, and did you see something more recently, that might be a better study to establish reference sources?

DR. PAULE: Well, I think that part of the discussion involved the fact that those were observations in the Favrille study after chronic exposure, so there was no real, I think, knowledge of exactly what previous peak levels could have been.

And those are failings of most of the studies that are conducted after groups have been exposed for long periods of time and then assessed. There's really no way of knowing what peak exposures

were prior to that time of assessment.

But we've not really identified other studies that have produced better data, if that was your question.

DR. LUSTER: Yes, that was the question, and EPA had indicated that there might be other studies that they would look at but decided not to.

Can you give us a little more detail, what happened in that process, what was the study? What was the reason not to go back and look at it using other data?

DR. PAULE: I can't recall that off the top of my head; sorry.

DR. LUSTER: Okay.

DR. BURTON: That's fine. We'll move on Dr. Amar. Just for the panel members: We cannot have more than four of these little red lights. So if you hit your button and it doesn't come on, it just means that we're waiting. So you'll just have to wait, and we'll just try to start, actually, just work our way around here from the right around to the left and we'll get to everyone to answer their questions.

Can we move to Dr. Amar. Please.

DR. AMAR: Can you comment on the search engine that you used or that the study used for the

review of the literature in light of recent information that we have. That, for example, if Medline is used, that search may not be comprehensive and we may miss 30 to 40 percent of the literature doing only one search?

DR. PAULE: Since I did not actually personally conduct that review, I can't comment on that. I know it was a PubMed search and the search specifics are in an appendix in the report.

DR. AMAR: I saw them but everything was run on one search engine; am I correct? There was no cross-referencing--

DR. PAULE: Correct; correct.

DR. AMAR: --using a different search engine?

DR. PAULE: Yes. Yes.

DR. AMAR: Thank you.

DR. BURTON: Okay. Next.

DR O'BRIEN: Your posted presentation was a condensation of what we received as a draft and I wonder if we have a copy of that, of your printout from your--I mean, not your posted presentation, your PowerPoint presentation.

DR. PAULE: You should have a copy of the white paper report; yes.

DR. O'BRIEN: The white paper report. Is that identical to the PowerPoint?

DR. PAULE: Yes. I believe that there is a copy of that--

DR. O'BRIEN: I have so many papers here; it's hard to find that.

DR. PAULE: Yes. There is a copy in there.

DR. O'BRIEN: Thank you.

DR. DOURSON: Mike Dourson. I have three questions but I'll maybe just limit it to one and we'll let everybody get a chance here.

My question is similar to what I asked yesterday. On page ten of your nice report, and again, thank you, Dr. Paule, for your presentation. I was interested in--

DR. PAULE: Is this the white paper or the handout for the--

DR. DOURSON: The white paper.

DR. PAULE: Okay.

DR. DOURSON: Yes. And I can refer to it. I don't think you need to pick it up. You use a value of 5 micrograms per day or less, which is the range of exposures to mercury from folks with amalgams, and my question is, is this estimate--what

is the average dose? This looks like sort of an upper limit.

And after establishing the average dose, what is the upper bounds, statistically, if you can give that? And then what percent of the amalgam population really exceeds the 5 micrograms per value?

Actually, these are all related questions. It's just characterizing the distribution of, as best possible, to the mercury exposure from amalgams.

DR. PAULE: Yes, and although I don't have the exact numbers in front of me, most of the data in terms of mean levels are below 5 micrograms per liter. Those are the range of averages usually.

And it's my recollection that 95 percent of persons with dental amalgams fall below that 5 percent.

DR. DOURSON: Okay. That 5 micrograms per gram.

DR. PAULE: Five micrograms per gram.

DR. DOURSON: So we have 5 percent above that. Okay. And then just one other clarifying question and then I'll pass the torch on to Dr. Goldman.

On page six of your nicely done white paper, there are a couple quotes and I'm just going

to--again, these are quotes from FDA and the first one is, "Oh, they're saying there doesn't seem to be any evidence except for an exceedingly small number of allergic reactions--okay, fair enough--and a similar quote later on--"Except for a rare allergic or hypersensitivity reaction."

And my question is somewhat nebulous. Can you, or have you attempted, as FDA or individual investigators, to try to describe the number of people that fall into this "exceedingly small"?

Now as a risk scientist myself, I've been asked this question, haven't been able to do it. So, you know, full disclosure.

But have you, has FDA tried to quantify what that means, "exceedingly small"?

DR. PAULE: No, we have not done that, as far as I know. I mean, I think what we're dealing here with, like any other situation, are bell-shaped curves, and you have persons at one end that are incredibly insensitive and you have persons at the other end that are incredibly sensitive, and to put a number of a figure on that I don't think has been done.

DR. DOURSON: Okay; thank you.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: I wanted to ask you a couple of related questions that get into the issue of maternal fetal transfer and neurotoxicity to the fetus. And what I'm seeing, and I tried to find, you know, the relevant articles, and I couldn't find a lot, but on maternal field, transferred the Boder paper in 2000, nice longitudinal study, I thought it was really--after the time of these other reviews, which I think is pretty persuasive in terms of, you know, the fetal blood levels being about the same as the mother's levels, at birth.

And also then, you know, for neurotoxicity just a couple of rat studies on Danielson and Fredrickson, same group, and a nice little monkey study that Nulan did, which if I were at EPA trying to do a reference dose, I'd say I can't use them because they don't provide NOAELS or LOAELs. So you couldn't use them to establish a reference dose, or an MRL, or something.

But I think that they certainly shed a lot of light on phenomena that are going on in terms of the fetus, and there are some dosage levels that are very nicely presented in those studies, and so I was just wondering what you make of all of that.

I mean, is this an area that at this point

in time, that you guys consider to be kind of, you know, a settled area, that you understand what the dose response relationship is and what's going on? Or is there an area that you would consider to be more an area where we don't really know what the effect levels might be?

DR. PAULE: I think that there needs to be a lot more, or that we could benefit from a lot more research in that area, but the studies that--I mean, and again, ours was a limited review--the studies that we looked at suggested that there was no "repro tox," at very high levels, at least in the rodent model.

So--

DR. GOLDMAN: But the rat studies are positive. Danielson and Fredrickson's studies are quite positive, and, you know, other than the completely unexposed animals, they have effects at their low and high doses. You know, neurotoxicity to offspring born with--and the exposures are not that high.

DR. PAULE: I don't believe those studies were reviewed in this particular effort.

DR. GOLDMAN: Okay.

DR. BURTON: Let's go over to, over on the left-hand side and then we'll come back across.

DR. ASCHER: Michael Ascher. I'm essentially following up on Mike's question about the 5 micrograms per day exposure. Has that been looked at in terms of temporal exposure?

I mean, is it two years after the amalgam has been placed? Or ten years? Do we know anything about the temporal exposure in terms of how much vapor is emitted right after the placement, or at the time of placement?

DR. PAULE: Most of the values that we have seen in the report are not immediately after placement. I don't know that--I have not seen data on levels immediately after placement.

So these are probably in place for months, weeks, if not years.

DR. ASCHER: Is there any reason to believe that perhaps two weeks, or five weeks after the placement, the levels might be a lot higher than 5 micrograms per day?

DR. PAULE: I think immediately after placement, there could be differences in levels; yes.

DR. ASCHER: Thank you.

DR. FLEMING: Just two quick questions. One is there a couple of studies looking at brains, human brains, and the variability in mercury levels in

these two studies is quite high. I wonder if you have looked at these studies, perhaps, and modeled them, and considered how high these levels might be if the entire population might be involved?

Because if you see high variability in a small number of patients, you might see a lot more variability in larger populations, and then this might explain the fact that perhaps only the outliers, as you said, the most sensitive people, are affected by this mercury process.

Have you considered the brain exposure with regard to variability and how high these levels might be?

DR. PAULE: The charge for this review was to simply look at the published literature and see what those authors presented in their conclusions.

DR. FLEMING: I'm referring to two articles.

DR. PAULE: We have not modeled and have no plans to model that data.

DR. FLEMING: Why not?

DR. PAULE: That was not the charge--

DR. FLEMING: It's a very standard pharmacokinetics, pharmacologic technique.

DR. PAULE: I think we could benefit from

someone doing that.

DR. FLEMING: Yes; okay. I'm going to come back to this issue later on cause I think that the document is very deficient, not because of you, but because the emphasis has not at all been on pharmacologic and pharmacokinetic aspects of mercury, and I think this very much needs to be enhanced in this document.

May I ask one more questions, Mr. Chair?

DR. BURTON: Certainly you may.

DR. FLEMING: Along these same lines, for example, are you comfortable looking at urinary excretion as the most valid and useful way to look at how mercury is excreted in the human body.

The reason I ask this is that there is a contention, at least, that this is only 5 or 10 percent of the total excretion, and that most of the excretion is in fact for a few biliary or fecal route, and if that's true, are we looking where the light is rather than where the excretion is going?

DR. PAULE: In my own personal view, the best metric is the number of amalgam surfaces placed, irrespective of what levels are anywhere. That is the metric that persons are exposed to and that is the issue, I think, that we are concerned with.

DR. FLEMING: And actually, modern pharmacology looks at what the exposure is in the body, in the tissues, rather than the proximate cause of these kinds of levels. I think, again, that I will recommend later on, that we do maybe even a separate paper on the pharmacology and pharmacokinetics of this issue, and again I compliment you on creating a very excellent document.

I Just think this is one area where we need a lot more data and a lot more analysis of the data that's currently presented.

DR. BURTON: Okay. Ms. Cowley.

MS. COWLEY: Filling a cavity is the largest, it's the largest number of implants ever done, and we have 166 total fillings per year--166 million total fillings per year. Of that, we probably have 5 percent, which would be about a million people, having either adverse effects, toxicity, allergy, sensitivity, hypersensitivity, or poison.

I don't think I've had definitions of any of these, other than I think sensitivity was where the gum turned blue, and then we have all of the people who have spoken to us with some incredible medical issues.

So can you help me make sense of what this

5 percent might be?

DR. PAULE: No. First of all, I have not seen that report, or the data suggesting that 5 percent of people with amalgams have--

MS. CROWLEY: Well, the people with over 5 micrograms, I believe, who--

DR. PAULE: Oh, the 5 percent over--having over 5 micrograms--

MS. CROWLEY: Who might have, you know, a problem. Let's just pretend that they have more--

DR. PAULE: I don't know the answer to that question.

MS. CROWLEY: Okay.

DR. BURTON: Dr. Taylor.

DR. TAYLOR: George Taylor from the University of Michigan. Thank you for your very concise and clear presentation and review of the white paper.

I have a question, a methodological question. In terms of your evaluation of the studies, and which you included in the report, I know there's a description of the selection criteria for those studies, and yet, did you also consider the quality of the studies in terms of weighing the evidence?

Specifically looking at case control

studies versus cohort studies versus cross-sectional studies, I didn't see that in the report to help give me some guidance in looking at a hierarchy of evidence, and how we might attribute the data and the information provided, in reaching the conclusions.

DR. PAULE: Well, I think we tried to be more inclusive rather than exclusive. For example, a lot of the work that was done with the dental professionals, we don't believe had the proper controls, and yet we included those in our report because we felt they did contribute some useful information.

With respect to the current review, since the focus was amalgam effects, we thought those EPA studies or those human studies in persons in which the metrics or amalgams were the most important.

DR. TAYLOR: I appreciate that. If I can just follow up. I think my concern, and my question to you is more about the differentiation in the design methodology for the studies and the kinds of inferences that we might draw from each of the different kinds of designs, and so that's the reason for my question.

I was not suggesting that any of the studies that you reported in the white paper need be

excluded. It was more of a concern of weighing the type of evidence based on the study designs and the kinds of inferences, and the weight to those inferences.

DR. PAULE: Yes. I appreciate that question. I think that the gold standard, in many cases, is the prospective clinical trials and two of those were done in children. So we feel that those were very well conducted studies and of the kind that we would like to see more of.

DR. TAYLOR: Just to follow up, I would argue that perhaps in some cases it would not be appropriate to administer a clinical trial in certain kinds of exposure outcome relationships, so then the gold standard, we might look at it as some other design as well.

DR. BURTON: Dr. Hughes.

DR. HUGHES: Michael Hughes.

I wanted, first of all, to concur with a couple of comments about the methodological issues behind your search strategy. I think it's potentially below quite widely accepted standards, for instance, from the Cochran collaboration, and so on.

It's unclear to me how you got from 200 studies that came out of the search, the one search

that you did do, down to 24 studies that you judged to have potentially the most significant information. And there are other potential issues there. I know you didn't do the search but I think there are question marks in my mind about that.

But the main question I would like to pursue is the issue of urine concentrations, and what are the levels that are seen in the general population.

I note in your white paper, that you mention occupational exposures which averaged about 20 micrograms per gram of creatinine as being associated with neurological deficits.

And a comment was made about a small percentage of people having levels, perhaps above five. But you don't really bring that information out in your review, and if you look, for instance, at the U.S. military study, the Kingman study, they actually showed the information for actual levels for individual subjects, and it's in a figure, it's hard to see exactly what proportion are higher than five, but I would say it's much larger than 5 percent.

There are an appreciable number of subjects with values between five and ten. A comment was made by one speaker this morning, I think it was

someone from Columbia University who had done a study, and I wrote down, I hope this is correct, that approximately five out of 500 I think had levels above ten.

So I think when you're thinking about individual subjects, I would suggest that it's quite possible that there are a reasonable number of subjects in the population who have urine concentrations which are extremely close to the levels that you're associating with neurologic deficits.

And I think then the safety issue about how amalgam fillings actually affect those levels becomes much more important, and this factor of thirty that's being talked about, that's in the context of concentrations in air, it's not in the context of concentrations in urine.

But I have a feeling that the margins are less than those being discussed here.

DR. PAULE: I think in the paper that you're talking about, the Kingman paper, there were levels that were higher, and it could very well be that that was because that was a military population, and I think we've heard from a previous speaker, that because he was in the military he had all his teeth filled.

So it could be that that particular population does in fact have a higher placement of mercury amalgam than other populations.

Dr. HUGHES: Okay. Just to pursue that, one other study that's referenced uses an NHANES dataset.

DR. PAULE: Yes.

Dr. HUGHES: That dataset, as far as I know is in the public domain.

DR. PAULE: That's correct.

Dr. HUGHES: That study focuses on women in the reproductive age range. It doesn't give individual levels, but it would be very easy to go and look in that different population as to what the levels are. It wouldn't be hard for the FDA to do that.

DR. BURTON: Dr. Rizzo.

DR. RIZZO: Yes. Thanks for the presentation. One of the interesting parts of your white paper was on page four in which you quote an adverse correlation between urinary mercury levels in dentists and dental workers with regard to neurobehavioral outcomes.

But interestingly, occupations with even higher levels of mercury, higher exposure, didn't show

those same neurobehavioral changes.

I'm wondering if that discrepancy might be explained, in part, by differences in the neurobehavioral testing procedures. How closely do those techniques compare? Is it possible that the studies in the dental workers were somehow better or that more sensitive tests were used?

DR. PAULE: In some cases the tests were exactly the same, and in most cases, they at least were tapping into the same functional domain. So I think that they're incredibly comparable, which is why it was mentioned.

DR. RIZZO: If they were comparable, were you able to put the results together, in, for example, a meta analysis, and were you able to do an added analysis, like a funnel plot or something similar, to see if there was some file-drawer effect. Perhaps data showing neurobehavioral impairments in dentists and dental subjects somehow didn't make it into the literature.

DR. PAULE: We did not do that.

DR. RIZZO: Thank you.

DR. BURTON: Dr. Honein.

Dr. HONEIN: Yes. I have one sort of editorial issue and then one question for you.

At the bottom of page 23 in the white paper, there's a summary of the New England Journal of Medicine paper on mercury in primary heart disease, that shows a correlation between toenail mercury levels and fish consumption.

But then the summary on the following page states that there was no correlation.

So I assume this is just an editorial issue but I do think it needs to be corrected.

DR. PAULE: Sorry; could you repeat that comment.

DR. HONEIN: So the last sentence on page 23, "Significant correlation between toenail mercury levels and fish."

DR. PAULE: Yes.

DR. HONEIN: And then the third line down under summary of studies on cardiovascular disease, no correlation between. I think there's just a editorial error that has occurred in there. One of those two would be correct.

DR. PAULE: We'll correct that.

DR. HONEIN: Okay. And then my question, unrelated, in the dental professional study, you raise the issue that the controls might not have been the appropriate control groups since there were no non-

dental controls and there could be other exposures.

Do you have any hypotheses about what those exposures might be, that would be of concern?

DR. PAULE: Well, since I don't know exactly what dentists do, I don't have anything for certain, but all those people were worked in exactly the same environments. I would imagine that in addition to dental amalgam, there are other chemicals, other sorts of exposures that go on in those dental clinics, that may co-occur with the placement of dental amalgam. I just don't know, so I don't have a particular hypothesis.

DR. BURTON: Dr. Goldstein.

DR. GOLDSTEIN: Thank you.

You know, the charge I think for the committee is to judge, or offer an opinion regarding the adequacy of the white paper. That is the ultimate charge here. I had a few methodologic questions that you may not be able to answer right now but maybe you can arrange to get us the information later this afternoon.

When you review a systematic literature review such as this, there are established criteria for judging quality.

One is does the clinical premise make

sense? And it gets back to the question that's being asked. I think the question makes sense. The premise was that the prior reviews were adequate, and this is now adding to it, and we obviously have noway of judging that because that wasn't done.

Does it include all the relevant randomized control trials?

Dr. Hughes mentioned some questions about the search strategy. Using just the single database is obviously an issue. Then usually these types of reviews will then involve hand searching of the article that have been reviewed, to look for other relevant papers.

Then they also will very often look for the so-called gray literature as well, and look at other systematic reviews and search those databases as well, looking for other potentially relevant articles.

The reason that I'm bringing this up is even just looking at some of the materials that some of the witnesses brought yesterday, and I did a quick search looking for some of them that might be potentially relevant, many of those references aren't included in this database, which gets to the next issue. The criteria for exclusion are well-stated, but what we don't have is the list of articles that

were excluded and the reasons that those articles were excluded.

Usually in systematic reviews those are available online, in an appendix in some way, so that way the reader can go through and say, okay, they excluded this paper because of this and I agree with that reason or not. And we just can't do that.

There's also a question as to whether there's statistical heterogeneity between individual studies.

Now when you don't have a lot of randomized controlled trials to judge, it's hard to do that, but there are very often point estimates and 95 percent confidence intervals around whatever outcome it is that you're looking at, and again that's not here.

The final thing is that, again, with systematic reviews like this, very often what we'll do at the end is say not only what we know from the data that's available, but also have a list of gaps, what we don't know, what questions remain to be answered that are potentially relevant to the topic at hand. And again, that I don't see here. So again, as we are going ahead and discussing this this afternoon, we have a series of specific questions, but the ultimate

question to us is is this adequate or not? And without answers to those questions, I don't know how we can judge the adequacy of this white paper.

DR. BURTON: Thank you.

Dr. Kieburtz.

DR. KIEBURTZ: A question about the approximate daily dose of mercury at 5 micrograms; or less than five. And then it references--this is on page 10-ATSDR-99 in the WHO document.

The WHO document says, quoting: Values generally in the range of 1 to 5 micrograms per day were the estimates in the U.S. population, although--and there's quotes of the Swedish studies. Those estimates were 5 to 9 and an average of twelve. And I'm just wondering what the process was in choosing a lower value of the WHO proposed values.

DR. PAULE: I am not certain, how that was chosen.

DR. KIEBURTZ: Okay.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: Yes. I want to start out, actually, with a comment, because I believe it may be part of what's happening here and maybe you can reflect back on this, is that in being asked--as I'm going back over the white paper, I'm realizing that

the task that you guys were asked to do was almost as if though you were being asked to set a reference dose, to come up with a limit, a regulatory limit for mercury. And it seems to me that what I'm beginning to understand is an implicit interselection of the studies. When I'm looking at the studies that I'm aware of, that you include, and then those that you didn't include, that you were looking for studies that could contribute to the identification of no observed adverse effect levels, or lowest observed adverse effect levels that might be different than the levels--or perhaps a benchmark dose approach.

It might be a different approach than the ones that had been used in the past by ATSDR and EPA, and therefore prompt the development of a different, if you may, regulatory standard.

And I think that, you know, it's a little frustrating for me, and I apologize, because I think in doing that job--this is an excellent white paper--you know, because when I'm approaching reading this, what I'm looking for is the studies that might provide information about the safety of the use of the product and management of the risks that might be there, and which would be a much broader array of studies.

It might include studies that don't

provide LOAELs and NOAELs, and don't actually inform us on that, and so it's just kind of a comment on this.

The question that I wanted to ask is, in your opinion, are any of the studies that you reviewed--do they provide solid information about peak excursions of mercury exposures during procedures such as drilling, fillings that contain amalgam, or placing amalgam fillings?

Do we have information about peak concentrations, brief though they might be, that might be occurring during those kinds of procedures?

DR. PAULE: Yes. I think it harkens back to Dr. Ascher's question, and we don't have that data. We don't know.

DR. BURTON: Dr. Zero.

DR. ZERO: In the report, as well as some of the other general discussion, I'm struggling with two terms. One is "sensitive sub groups" and what that means with populations. Are these traditionally sensitive sub groups like fetuses and children? Or does it include, perhaps, an adult population as well, that may be, due to body burden, may also be sensitive?

So that's one. Related to that is this

issue of hypersensitivities that we keep on throwing out in these reports but there's no definition of what that means. Is this a local short term, acute hypersensitivity? Is it a chronic hypersensitivity? It just seems to be so vague to me, that I don't know how to work with that.

DR. PAULE: I think in terms of sensitive subpopulations, certainly children, the elderly, the infirm, those populations are considered potentially sensitive subpopulations. The hypersensitive question I think is a totally different issue and it's not a term that I particularly coined. It's being used out there to define persons that seem to be extremely sensitive to very small levels of exposure.

I mean, beyond that, I'm not sure--

DR. ZERO: But what obvious hypersensitivities? What are the reactions? What are the presentations? There's nothing beyond that, in anything I've read, that defines those, in any way.

DR. PAULE: I think in the past, most of those have related to allergic reactions.

DR. ZERO: So it's a local reaction as opposed to a systemic reaction?

DR. PAULE: I'm not sure it's all-inclusive or not; but that's been the term.

DR. GOLDMAN: I mean, I think what he was trying to get at, how is it identified or described, or, you know, is there a case definition? Are there any of the literature that--

DR. PAULE: Not to my knowledge.

DR. BURTON: Dr. O'Brien.

DR. O'BRIEN: To follow up on a question Dr. Goldman raised, in terms of what might be really going on out there. I find, and being in dental schools for over 20 years, is that when there's a research study that has been established, people "clean up their act," the committees are notified, any kinds of problems in terms of procedure are cleaned up for the presentation.

But what might be interesting, you may have a study, there's an organization, OSHA, Occupational Safety and Health Organization. As far as I know, they regulate mercury vapor levels in dental offices in order to protect the dental assistants, and mainly the dental assistants and other people that are there, and I've heard--I haven't seen this myself--that they will, if they have tips from people, they will come and raid the lab with a Jerome meter, and they will take readings.

This is the underbelly of what the problem

might be in the dental offices, is, Did you find any studies of which levels they have found in dental labs, and how many, or that type of thing? So we might get an estimate of how far off some dental labs might be from what you report as an acceptable level?

DR. PAULE: None of the dental professional studies that we examined even talked about air mercury levels in the workplace.

DR. BURTON: When you're finished, please turn your mikes off.

Dr. Taylor.

DR. TAYLOR: I wanted to follow up on one of Dr. Goldstein's comments, and it's a struggle that I'm having as well, and perhaps you can help. The working premise was that the review would involve literature since, subsequent to the ATSDR and the other reviews.

Was there any consideration of the quality of the previous reviews in moving forward to select the new papers, and to move forward in that approach?

DR. PAULE: We made the assumption that based upon the previous reviews, had all been reviewed by expert panels such as this one, that we felt confident those reviews were good.

DR. TAYLOR: Okay. So at least from my

thinking, it is the working assumption that the other reviews were substantial?

DR. PAULE: Correct.

DR. TAYLOR: Okay; that's helpful to me. Thank you.

DR. BURTON: Dr. Olson.

DR. OLSON: In your review of these 200 articles that were originally selected out, do you remember if there were any that studied mercury effects, any kind of mercury effect on people with immunocompromised systems? In other words, any folks with immunological disorders, or things that might be considered immunological disorders, and what the burden of mercury may have on their disease?

DR. PAULE: We specifically focused on looking for and including any studies with humans involved in mercury exposure.

DR. OLSON: So there were none.

DR. BURTON: Dr. Sacco.

DR. SACCO: I concur with some of the other comments and I guess the one thing I'd ask, in looking at this white paper, is whenever you review a body of evidence, you know, you identify what's out there, you try to characterize the findings, try to come up with some recommendations. I guess what I see as missing

is--and maybe you can try to shed some light on this--is where do you see gaps in the literature? Where do you think more research would be needed? Where are the questions that aren't fully answered by literature, out there? We know what the literature shows and what you tried to digest. But it would be helpful for me, hearing what we've heard in the last 24 hours, to getting a better idea, and even to even identifying the white paper, where there may be some other approaches for the next steps and gaps in literature.

Do you have some comments to help us there?

DR. PAULE: Well, it wasn't officially part of our charge to come up with that kind of thing, and, in fact, in retrospect, I was thinking that would be part of the charge of this committee.

We can always use more information and I think that we need to continue to perhaps follow the children that have been implanted and watch them over 10, 20, 30 years. As some in the audience have indicated, it took that long for things to develop.

Those kinds of data are not available and we need that information.

DR. BURTON: Dr. Porter.

DR. PORTER: Thank you. I'd like to follow up on Dr. Zero's issue about hypersensitivity. I don't think any of us have seen what we would consider a classic idiosyncratic acute reaction or something that was special about any one particular patient here, that would suggest that there is a hypersensitivity category that we can wall off here.

I'd like to suggest the possibility, in fact, that what we're really looking at is a hypersensitivity related purely to the idiosyncratic ability of some patients to accumulate much higher levels of mercury than others, and I back this up again by the data in which there is tremendous variability in the brain levels, of the two studies in which there are autopsied brains, and these are small numbers, and the numbers which are actually out there in the tens of millions of people who have these amalgams may be much higher.

So I'm suggesting that the hypersensitivity may simply reflect those people who happen to be so unlucky as to have high mercury levels.

DR. BURTON: Dr. Luster.

DR. LUSTER: Sort of following up on that question but back to the urinary mercury levels again,

and, you know, a lot of the audience indicated that there's negatively charged amalgams and there's higher exposures.

Most of the data, the recent data that you were describing, you provided average levels of urinary mercury level, and that could be very misleading, of course, typically with large populations that might be exposed.

So do you have any feel for the range of mercury levels within the population?

DR. PAULE: I think that in my recollection, some of the highest range went up to 17 micrograms per gram of creatinine. I mean, that was an exceptionally high level.

DR. LUSTER: And that was unusual or that was--

DR. PAULE: That was unusually high; yes. There is a derivation that I think holds up, and that is for every ten amalgam surfaces placed, urine mercury goes up by one microgram per gram creatinine.

DR. LUSTER: Right. But that's still the average, so--

DR. PAULE: Yes; that's true. That's correct.

DR. BURTON: Dr. Fleming.

DR. FLEMING: I wanted to make a comment first, please, sir, and then ask you a question about your studies. The literature is replete with information that would suggest that urine mercury levels will increase, the more surfaces of amalgam that you have.

DR. PAULE: Correct.

DR. FLEMING: However, the literature is very clear that symptoms do not correlate with urine levels very well. The fact of the matter is, in my clinical experience, that seems to be the case, that urine levels, when you have them available to you, don't seem to correlate with what patients report to you in symptoms.

My question to you is, I think some of the variability in urinary mercury excretion in the studies here may be accounted for a retention phenomenon, whether the mercury's being retained and not excreted--for example, you may have mercury workers who have very large levels of mercury excretion, no symptoms whatsoever, and those who have very low excretion levels and may be replete with symptoms.

So it doesn't seem to correlate well, symptoms and urinary mercury excretion. So did you

account for a possible retention phenomena in your analysis?

DR. PAULE: No. In fact, we think that dose-related effects are important. If levels don't go up and effects don't go up, then there's no association between exposure and the effect.

DR. BURTON: Dr. Diamond.

DR. DIAMOND: Yes, sir. I want to follow up on a question that was raised by Dr. Olson. This relates to special populations.

You reviewed, one of the criteria was well-controlled trials. In many cases you have inclusion/exclusion criteria which will, you know, which will exclude patients with more complicated medical histories.

This is naturally to ensure a more homogenous population with which to study. But at the same time, you're losing a segment of the population that might show up as some possible hypersensitivity, some kind of reaction that would maybe represent 5 percent of the population, and so did you exclude isolated case reports, or case studies, where these reactions might be reported? That may be something. Did you think about something like that?

DR. PAULE: Well, unfortunately, you're

right. I think there have been very few studies where specific populations have not been looked at. Persons with kidney failure, liver failure, the other, infirm, aged persons. So that could be identified as another data gap.

DR. DIAMOND: Thank you.

DR. BURTON: Dr. Klaassen.

DR. KLAASSEN: Yes. I was going to ask about the mercury concentrations in urine. Now the method that you're using measures all mercury in urine, it does not differentiate that which came from the amalgam compared to that which came in fish, etcetera?

DR. PAULE: It depends upon the study. Some reported total mercury; some reported actual inorganic mercury. So it varied somewhat. But most of the studies, as I recall, in the white paper, were inorganic mercury.

DR. BURTON: Dr. Kieburtz.

DR. KIEBURTZ: A question about the documents. You look ed at the NGO reviews. Did you look at other Government reviews?

DR. PAULE: No; we did not.

DR. KIEBURTZ: Why not?

DR. PAULE: I was simply following orders,

okay, and was given the charge and we took it.

DR. KIEBURTZ: Fair enough. I mean, there are other governmental assessment documents. Sweden has one. There's other ones which--I realize it wasn't in the charge, but those are probably, at least from my perspective, relevant documents that have other reviews and other--

DR. PAULE: I would think that the other government reviews encompassed the literature that they could identify at the time. So, to the extent that they did or did not include other government reviews, we did not follow up on that.

DR. BURTON: Dr. Amar.

DR. AMAR: When I heard the testimony of the people coming in, what became pretty clear is that if it is the case, it takes a long period of time for symptoms to appear. It takes a long period of time, decades, two, three decades, for the symptoms to appear.

But what's important, and what the people disclose is that the minute they had amalgam removed, it took two-three weeks for the symptoms, or major symptoms to subside.

In your review of the literature, being somewhat anecdotal in the report of the literature,

have you come up with conditions that took, or that take decade for the symptoms to appear, immediately after the removal of the potential causing agent, symptoms disappear?

DR. PAULE: Well, what we know is that after you remove amalgam fillings, that the mercury levels don't necessarily decline very much, if at all, for very long periods of time. So I have no explanation as to why removal would result in resolution of symptoms over that timeframe.

DR. AMAR: Would the literature that you reviewed support a condition like that?

DR. PAULE: Not to my knowledge.

DR. BURTON: Ms. Cowley.

MS. COWLEY: I guess I keep trying to get something to wrap my arms around, this hypersensitivity issue. Do we have any percent of the total population who will be getting a filling this year, that will exhibit a hypersensitivity effect?

DR. PAULE: I don't know that number, and I don't know that that number exists.

MS. COWLEY: Okay. Another question. In the studies that we've looked at, we have looked at the maternal studies, the maternal/fetal, and we might presume that the dental assistants or dental

hygienists are all female, but I don't think we can do that. Have there been any gender studies?

DR. PAULE: With respect to--

MS. COWLEY: Effects of mercury on women versus men. Not pregnant women and fetuses.

DR. PAULE: We did not come across any articles on that topic in the current review.

MS. COWLEY: Thank you.

DR. BURTON: Dr. Ascher.

DR. ASCHER: What I learned yesterday, which I didn't know, was that the amalgams have 13 percent tin on the average, some probably more, some less, and has there been any characterization of the tin evaporation from the amalgams? Any studies on--

DR. PAULE: Not to my knowledge.

DR. ASCHER: Is there any reason to believe that there might be interaction between tin and mercury, or may offset the effects of mercury? I don't know.

DR. PAULE: I don't know the answer to that question either.

DR. ASCHER: Thank you.

DR. BURTON: Yes.

DR. O'BRIEN: In most fields of medical treatment, there's been an attempt to estimate placebo

effects, in terms of--for example, with headache medication, there have been good estimates that that could be as high as 30 percent.

Did you find anything in the literature, or anyone has tried to estimate placebo effects having to do with dental treatment, not necessarily with amalgam?

DR. PAULE: Have we come across any information on placebo effect but not with amalgam?

DR. O'BRIEN: No; not necessarily with amalgam but in terms of dental treatment.

DR. PAULE: Not that I can specifically recall; no.

DR. BURTON: That appears to be the questions at this time, which is good. I wanted to get some of this covered at this point, while you were still here. Thank you very much for your presentation.

DR. PAULE: Thank you.

DR. BURTON: And your addressing the questions of the committee.

Next on our agenda is the start of the committee discussion, which we will discuss the materials presented over the last two days. To guide our discussion, the FDA has prepared some questions

which will be given to us by Dr. Alderson.

Dr. Alderson.

DR. ALDERSON: Thank you, Mr. Chairman. This discussion, the last few minutes, has been very interesting and I think it kind of lays the groundwork for the rest of your discussions and deliberations today.

I want to emphasize to the committee the importance of this meeting to us.

In making scientifically-based decision on products we regulate, we rely on the available peer-reviewed science, other information and evaluation of all the material.

Through advisory committee meetings such as this, we ask the scientific experts, all of you, to give us your assessment of the material.

We also ask for the public comment. We are committed to improving public health and patients' concerns are important.

For the subject of this meeting, the potential health effects of mercury in dental amalgams, we have had presentations from our guests from Canada and Sweden. We've been discussing the FDA white paper and we had, by my count, 52 presentations during the open public session. That included a

presentation from a U.S. Congressperson, that being Congressman Watson from California.

We use meetings such as this to ensure we have identified and characterized the information on possible health effects of dental amalgams, in a manner that provides the best possible basis for any subsequent regulatory decisions.

In addition to the input we have already received during this meeting, and the deliberations and responses that you are about to make, we have also opened a public document for submission of additional information.

This docket will be open for 60 days and will close on November the 9th, 2006. Comments may be submitted electronically or via mail.

All comments submitted to the docket will be publicly accessible, and we will review them, in addition to the oral comments and the deliberations of this joint committee.

Again, I want to thank you all for what you've done and are about to do. You've got some tough decisions ahead of you.

And with that in mind, I want to review, with the help of our technician--they're already up there, thank you--the charge which we've given you and

the questions we want you to answer for us.

Based on the peer review of the scientific literature, the draft FDA white paper, and any other information, including the information from the 52 presentations, discuss the following topics, including issues of quality, experimental design, or other attributes of the specific studies that may affect the weight that should be given to conclusions drawn from them.

And first, discuss the direct evidence, if any exists, supporting or refuting the occurrence of adverse health effects for mercury vapor release from dental amalgam devices.

This first part is the overall impact that you see. What is the evidence? Then we break this down further. Discuss the indirect evidence, i.e., or e.g., extrapolation for higher dose studies and animal studies, if any exist, supporting or refuting a link between dental amalgam devices and adverse neurological effects at the absorbed doses received from these devices.

So now we're talking about the neurological effects in this particular point.

Third. Discuss the indirect evidence, for example, extrapolation from higher dose studies and

animal studies, if any exists, supporting or refuting a link between dental amalgam devices and adverse non-neurological effects at the absorbed doses received from these devices.

And fourth, a subject you've been discussing in the last few minutes. Discuss the indirect evidence, if any exists, supporting or refuting a link between dental amalgam devices and adverse effects specific to vulnerable populations such as children, pregnant women, at the absorbed doses received from these devices.

In the last few minutes, I think you've started this process already, of these particular points, but this is to lay the groundwork for the real questions we want you to answer.

Does the FDA draft white paper objectively, and clearly, present the current state of knowledge about the exposure and health effects related to dental amalgam?

And third, given the amount and quality of information available to the draft FDA white paper, are the conclusions reasonable?

I think we all look forward to your discussions, and I think you're ready to proceed. Thank you, Mr. Chairman.

DR. BURTON: Thank you, Dr. Alderson, for your support and guidance here.

With that charge, why don't we continue on, and we'll move on to the first of the four points, and the first question in evaluating the various types of evidence and its outcomes.

So let me pose that question, and I'd like the comments then directed toward this goal. The direct evidence, if any exists, supporting or refuting the occurrence of adverse health effects for mercury vapor released from dental amalgam devices.

Dr. Kieburtz.

Dr. KIEBURTZ: Just the way the question's framed, I don't think--and it's a two-part question--direct evidence supporting or refuting the occurrence of adverse health effects.

As some speakers have already alluded to, I don't think there's any studies in the white paper, or any have been performed with the idea of refuting the occurrence of adverse health effects, so-called non-inferiority or a demonstration of safety. All the studies have been designed to detect a certain level of intolerability or adversity. So I'm just not aware--I'd be interested if other people think that there are studies here that are designed and provide

evidence of refutation.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: Yes. I have a suggestion, I think that's an excellent comment, and I have a suggestion on how we might want to organize our thinking about all these questions, and I think that that issue is a very important, kind of, if you may, kind of a binary way of looking at this world of studies, and that is, you know, on the one hand, studies that are designed to look for specific adverse effects like poor performance on neurological exams versus studies that are designed to look at safety, which might include reactions that could occur in one in a 100, or one in a 1000, one in 10,000 humans.

And I can already tell you where I'm coming down on that. Well, we don't have any studies in that second category, at all. But anyway. The other thing that I think is worth thinking about is to, yes, split the studies in the world into kind of subpopulations.

And so we have adults who have received fillings and studies on them. Children who have received fillings and studies on them.

We have adults who have worked in dental settings, preparing and putting in and drilling

fillings, and studies on them, the occupationally exposed.

We have the fetus, who might be indirectly exposed through the womb, a transfer from the mother. And I would say those are four very different kinds of studies and that we may--at least I think we may have different conclusions about what the literature that we're looking at tells us about these, and I think that that has also implications in terms of managing risks. So I just kind of wanted to propose those, if you may, kind of almost like an eightfold way of looking at it, although I think this one column of safety studies, there really isn't very much there.

DR. BURTON: I would agree very much with what Dr. Kieburtz has said, and the fact that, again, I think we're really sort of looking at things, does the evidence support the fact that there are adverse effects. But I'm not sure that you refuted. It's really a question, can we eliminate that? You know, we're not going to refute its existence, and unfortunately, I don't think that we really got--I don't think that's the correct term or the right guidance.

Dr. Klaassen.

DR. KLAASSEN: Yes. I'd just like to add

to what Lynn just said, but a fifth category, and that is the people who have been occupationally exposed, not as dentists, but from the chlor-alkali group, which is probably extremely valuable information, that is, people that have been exposed to real high concentrations of the chemical in question.

DR. BURTON: Dr. O'Brien.

DR. O'BRIEN: Since the literature review shows that there are limits upon which adverse effects take place, notably what's known in the medical literature as mercury poisoning, and since there are many groups involved, and the amount of mercury that's used by practitioners, and how they use it, is uncertain, I would put this in a classification of an uncertain risk, similar to the risk associated with radiography, antibiotics, aspirin, penicillin, any other type of material with potential risk, but we cannot quantify it, what it is. But we do know suggestible safety limits.

DR. BURTON: Yes, Dr. Dourson.

DR. DOURSON: I'm a toxicologist, so I have a certain way of thinking about things. One of them is all chemicals are toxins. So this table is filled with toxic material, including that right there, water. We lose, yearly, in the United States,

two or three athletes to water toxicosis. I mean lose them--they die. So to a toxicologist, all things are poisons, and an important consideration is what level is safe.

And all chemicals, with maybe some exceptions for genotoxic carcinogens, chemicals that cause cancer, have safe doses, including mercury vapor, and that forms the basis of regulatory agencies throughout the world trying to establish the safe dose, and there's lots of good discussion as to whether the safe dose has been established or not. I mean, maybe we'll even get into that a little bit.

So, to me, the answer to the first question is we have evidence that both supports the safety of amalgams, and evidence that we've heard today, and we have some epidemiology studies, those of Echeverria and colleagues, that might suggest that amalgams are not safe.

What is important to me in this question is the second part of the question, is effects from mercury vapor released from dental amalgam devices, and I think what needs to be studied here is what is the mercury release, in vapor, from dental amalgam devices.

It may be true, and probably is, based on

some of the studies we've seen, that the chronic low level off-gassing to mercury vapor is at or below the safe dose, and we can argue a little bit about that, or discuss it, perhaps better.

But what I have not seen--and several people have already alluded to this, this isn't just, you know, all of a sudden. This is one person's idea, several people have said this, is what is the mercury vapor off-gassing right after the amalgam is put in. I have learned from my colleague, Dr. O'Brien, that the off-gassing peaks and slowly goes away, and characterizing that off-gassing would, it seems to me, it seemed to me to be important.

And if we have folks that have been exposed, chronically, to amalgams in their teeth, at or near the safe dose, so that they are within the safety range, and then they have an episode of amalgams removed and new amalgams put in, and they peak, which is something we need to study, they might actually be pushed above the safe concentration and therefore have effects.

That would be consistent with what, some of the evidence we're seeing. Thank you.

DR. BURTON: Dr. Fleming.

DR. FLEMING: I want to ask--we can talk

to each other, ask questions across the table. I wanted to ask Dr. Dourson about, we've been talking a lot about the dose response issues.

With respect to allergy, from a toxicologist point of view, dose response seems to me to be going out the window. In other words, it doesn't take much of a dose to see an allergic response, and based on some data that I've put together here, some data available as of 01, for example, there were 71 million amalgams placed in one year, in the United States. That amounts of 44,000 per hour being installed, as we speak.

So if there is a demonstrable risk from allergy, it seems to me the dose response is going to be--it goes out the window in the face of allergy.

Now yesterday, I think if I'm not mistaken, in Dr. Mackert's presentation, I saw a number of 6 percent.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: If I could comment on that, the actual situation, as we clearly understand, as far as I know, and I recently did a review or relooked at this question of risk assessment for allergens and dose response. Dose does not actually go out of the window. Dose is related to allergic sensitization,

but unfortunately, there are other things that are related as well, such as age and exposure, younger children are more readily sensitized than older people, and so if you're sensitized to something, a good chance you were exposed to it when you were one, two, or three years old.

And the second thing is there are genetic differences. Some of us are more readily sensitized, more readily developed, and have all kinds of allergic manifestations than others. So there are interindividual differences that are important.

But it is dose-related. But it's also age-related, and the genetics, and there's probably other factors involved as well as just co-exposure, so--

DR. BURTON: Dr. Porter.

DR. PORTER: I Just want to say that I'm not absolutely sure that we can be positive that the ordinary number of fillings won't in fact, in some patients, some unusual patients, tip them over. For example, in the Guzzi study, those patients who had greater than 12 fillings, had a range from 20 nanograms per gram of brain tissue to 500 nanograms per gram of tissue, and that was only in eighteen autopsy patients, and that subset was only six.

So I think if you look at what is possible in terms of the variability of what we're giving these patients, that we really have no idea, what the upper limit might be in terms of brain concentrations, and that's what I think most of us are interested in.

DR. BURTON: Yes, Dr. Amar?

DR. AMAR: I just want to come back to the issue of the hypersensitivity. When I looked at the literature provided, there's no sign from a medical or immunology perspective of an immunological or allergic reaction that you would see with type 4 hypersensitivity with the--and the tuberculosis. What you may see--and that's the reason I would like, if I can have the other panel members comment on this. That we should call it probably intolerance rather than a hypersensitivity.

And I'm going to give you an example. There are issues in underdeveloped countries, for example, where the water--and we heard toxicology in water--but the levels of LPS in underdeveloped countries that are higher and people do develop tolerance to LPS, or intolerance to LPS.

And I'm not so sure that we can speak from a clinical symptomatology seen in the paper's review as well as when I heard the situation. We can speak

as being a hypersensitivity or an allergic reaction.

DR. BURTON: Dr. Luster.

DR. LUSTER: I can maybe clarify that a little bit. I'm not sure why we're spending so much time talking about allergies, but I'm an immunologist, so I can allude to it a little bit. But metals are notorious allergens. Chromium, nickel, and mercury's in that group. For an occupational allergist, it's in the top ten category of allergens. The mouth is somewhat protected, however, so it doesn't occur that often with metals that are in the mouth; but it does occur.

And there's been studies done with amalgams, and approximately 20 percent of individuals that develop a dermatitis type of response within the mouth area associated with the amalgam, actually patch test positive for mercury. So that would be a diagnosis for mercury hypersensitivity.

Much of what you're discussing, though, you're confusing an immunological reaction to an undescribed idiosyncratic reaction. And that's quite different. The term idiosyncratic should be used as something that's not explained. If someone is overly sensitive to a material and gets some type of response, that's an idiosyncratic reaction. It has

nothing to do with hypersensitivity or allergy or the immune system. So we need to kind of distinguish between those.

DR. BURTON: Dr. Ascher.

DR. ASCHER: I'll try to address some of the issues in question number one, and I'm not qualified to address all of them. I think we touched upon--some of you mentioned already the methodological issues in the selection of the papers that were reviewed, and so forth, and you know a lot more about it than I do.

But walking away from the discussion of the last couple of days, in a way, I really have no problems with the way that the conclusions were addressed in the white paper.

I think what's addressed in there makes perfect sense to me. The problem that I have is that I have a lot of questions that have not been answered for me, and they relate to exposure levels, they relate to the composition of amalgams, and potential exposure to other metals, and they relate to the fact that there might be sensitive populations which we know nothing about, and I have actually a major concern about the fact that we're looking at urinary mercury to look at risk assessment, and maybe that's

one thing that the committee should discuss.

And inorganic mercury, to a certain extent, the majority of it is excreted in the urine, but some of it is excreted in the stools, the biliary pathway, and certainly methylmercury is almost totally excreted in the stool. So I think the numbers that we're looking at are really not very meaningful, and they might be actually an underestimate of the exposure.

And there's another issue that we sort of touched upon, which relates to the sensitivity and polymorphisms that might exist in terms of exposure.

It's certainly possible, that even under normal body burden of mercury, there is a sensitive population of mercury. Just because the mercury doesn't get handled the way it is in, quote, unquote, what we call normal populations, it's been seen in autistic populations, and that is no reason to believe that something like this cannot happen in people that are exposed to amalgams and mercury from other sources.

So maybe what I'm trying to say is that I think, just by looking at this paper, in a sense, we're really limiting ourselves.

I'm not sure that we're doing justice to

the topic at hand. So I'm really not sure, really, in essence--if I walk away from here, just talking about this paper, I don't feel that I've really done my job, because I think the paper is very limited in scope.

DR. BURTON: Dr. Klaassen.

DR. KLAASSEN: I'd like to kind of add to what Mike just said about--you know, using mercury concentrations in urine, or even in brain, as a good measure, I think one thing we have to remember is mercury is not mercury is not mercury.

You give inorganic mercury or mercury vapor, or methylmercury, you get completely different toxicities, you get completely different pharmacokinetics, and I think we need to be sure that we're talking about elemental mercury when we're talking about amalgams.

And so, for example, if one measures the mercury concentration in the brain, it might not have anything to do with your amalgams. It might have all to do with how much fish you eat. And it's the same way with the placenta. I mean, you know, carbon is different than carbon in different drugs. We don't talk about carbon drugs. We shouldn't be talking about mercury.

We're here talking about elemental

mercury, and I would say that our best data, that we have is the human exposure to elemental mercury from the chlor-alkali plants, because there, we know what they were exposed to, and we know what form that mercury was in. It was elemental mercury.

So I think that's one of our best clues, and if we believe in the dose response, which most toxicologists do, that as you decrease the dose, you decrease the response. So therefore what one needs to do is look at the high exposures first, and the high exposures are from occupational exposure, that has happened, quote, around the world, in various conditions, and is still occurring, and see what's happening in those people.

Okay. Then you work your way down to lower concentrations. So I guess my message is is that mercury is not mercury is not mercury. And by measuring mercury and thinking all mercury is the same is as foolish as measuring carbon, and none of us measure carbon when we measure blood levels of drugs, I don't believe.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: I'm glad you brought up that point because it's definitely a problem with all the human studies, and except for a couple where they

actually were able to speciate and look at the inorganic mercury versus the methylmercury, but usually in studies, you know, you do a total measurement of mercury in urine, you are going to see a lot of methylmercury, or blood, or any compartment. And only a few of them. Now the NHANES one did, and, you know, a couple of others did, but only a few of them did look separately at the elemental mercury.

And the same is true, actually, for the toxicology studies. The problem with the chlor-alkali worker studies, and we could certainly spend more time dissecting them--I started looking at them and they do have problems. They're not mentioned in the white paper, but the problems are problems that are kind of classic problems in occupational epidemiology, especially with healthy worker effect, lack of follow-up of retirees and people who are disabled, and all of that. And those are terrible biases, and in my view, they're more biased, actually, than the dental worker studies, which also have biases, as has been pointed out.

But we could look at them more thoroughly, but we may find also--and I could not see anything in there to show that they had excluded fish consumption, as well among some of those workers, as possibly

creating random misclassification and exposure, so I think that we have to, you know, have to be careful. To just assume that they're better because they're human studies, because, you know, like all of these studies, they're not controlled and it's up to the researchers to really carefully make sure that they don't create biases.

I wanted to go back also to something Roger said earlier about the human brain levels, and I agree that the brain compartment measurements are going to include methylmercury. There are a couple of animal studies that just look at inhalation of mercury vapor and the Danielson study, which was not reviewed in the white paper, published in '93, where mothers were exposed during gestation, mother rats, and there were measurements of the neurological performance of the rat pups, and also those rat pups were sacrificed and they looked at brain levels of mercury, and all the groups had effects, so they couldn't identify a low-effect level.

But the brain levels are in the range of the levels that we see in human brains. I mean, they are, for these pups, between 5 and 12 micrograms per kilogram.

And so that's pretty interesting, I think.

And so I just feel that, you know, one of the things that we have to conclude is that we have a major data gap in terms of the sensitivity of the fetus. I mean, every animal study that's published, of course, there could be publication bias. You know, there are major effects on offspring, including, by the way, the same group, the Danielson group, they have a subsequent paper showing at least an additive, maybe a synergistic effect between exposure to mercury vapor and methylmercury, and in the real world we have both exposures occurring, and we should be concerned about that as well.

And that's also not mentioned in the white paper but, again, it's a study that would not allow you to come up with a regulatory standard.

But I come out of this very uneasy about what we don't know, about both the exposure levels during dental procedures, what the transfer of that might be to the fetus and what the impact of that might be on the developing brain, and everything that we know about other forms of mercury, methylmercury, the time that seems to be the critical time is during brain development, in utero.

And so that would be the most important thing to know in terms of assessing safety, and we

don't know it.

DR. BURTON: One more question, and I'll make a little summary, and then we'll break for lunch.

Dr. Diamond.

DR. DIAMOND: Yes. This is more a definitional question. There it's stated as adverse health effects. We're getting very granular in our discussion with regard to causality. We're getting into a lot of the specifics with regard to hypersensitivity and some of the mechanisms of, well, potential mechanisms of toxicity. But is this definition that we're using more toward the regulatory definition that we use for adverse experiences that are common to drug devices and biologics? Because that's a very different thing.

In that case, you know, these are associated with the use of a product, whether or not considered related to the product, and are we to look at within that context, or do we need to look at it with the specific due causality?

You know, that might help to guide the discussion.

DR. BURTON: At this point, I'd just like to try to summarize what we've covered in just the last few minutes. In addressing it, it would appear

what I'm hearing so far--and Dr. Kieburtz will continue this after lunch--but at least initially, what I'm hearing, particularly at least in answer to Part A of one, is that the direct evidence, perhaps mainly because a lot of the components that we don't see in the white paper, and in the materials that are presented, that we can't see direct evidence, really, supporting, or really refuting.

We have a big question whether we can refute anything, given what we have in terms of information. But I would at least try to answer the first, that A, appears to be what I'm hearing, and if anyone, please respond to this, is that the direct evidence doesn't seem to exist that supports, you know, that at that point.

Does anyone care to comment on that?

Dr. Hughes.

DR. HUGHES I guess if you take the two pediatric randomized trials, I would consider them direct evidence of the effect of amalgam versus non-amalgam fillings. You can debate whether they support or refute the occurrence of adverse health effects. They were designed to look at adverse health effects, neuropsychological outcomes, not to look at a beneficial effect of those particular devices.

So I would say that those are as close as we get to direct evidence, looking at adverse health effects. They were designed, if you look at the U.S study, it was designed to look at, or to detect a three point difference, I think it was, in IQ scores. The paper presents a confidence interval which has its bounds within--or smaller than three point difference.

So arguably, if you accept that a three point difference is significant, clinically, arguably, they would provide direct evidence refuting the sort of adverse effect that the study was designed to detect, and if you combine the evidence from the two studies, maybe it's more persuasive. I think the caveat there obviously is that although these studies I think followed the children for five or more years, it is relatively short term in terms of how long those children, and when they become adults, might be exposed to the two different types of filling.

And secondly, one study certainly mentions this. That a lot of the fillings obviously were in primary teeth, which were lost early in follow-up. So the extent of exposure to amalgam fillings, there's clearly a difference, if you look, even at five or seven years. The extent of exposure may be

comparatively small compared with levels that are--or exposures being seen in a broader population. But I think in my mind, they provide as close as we get, some measure of direct evidence of the effect of amalgam devices, and it's hypothesized that any difference there would be due to the mercury vapor, I presume.

DR. BURTON: Dr. Goldstein.

DR. GOLDSTEIN: I agree, you know, a prospective randomized trial is always the gold standard for detecting effects, but again, I think you need to also, in addition to the limitations Dr. Hughes had mentioned, there are also other potential ones. For example, what we're doing here is looking at a given population with a standard error around it. That's not to say that there isn't a group within there that might have had divergent effects, that you couldn't detect because it's underpowered to detect it and the study wasn't designed to look for those types of things.

So you get the answer to the question that you ask. If you take this group of children, given what happens to them in an intention to treat, this is what you get.

But in terms of refuting a potential

detrimental effect in a potentially very clinically relevant sub group, you won't see that unless you look for it and the study is empowered to do that.

So with that additional caveat, I agree.

DR. BURTON: Dr. Goldman.

DR. GOLDMAN: Yes. Actually, that's almost exactly what I wrote down before we started the discussion. I even think, from those two studies, that we can even have some idea, if there is a subpopulation of that type, kind of, you know, how important it is.

I mean, it would probably--you know, I think what we're talking about is that it could be a subpopulation that is in the range of, you know, one percent, one in a 100, one in a thousand. These studies couldn't detect subpopulations and effects in subpopulations that are that small, and it's just the limitation--you know, this kind of epidemiology just wouldn't be able to. It's not a "knock" on the studies. It's just simply an inherent limitation to the kind of studies that are here.

I would also say--and I read her study and now I don't remember her name, the person who presented to us this morning, and the study that was published in Environmental Health Perspective on the

dental fillings in adults, I think also provides the same kind of evidence, even though it was not a prospective clinical trial, I was very impressed that they did a pretty good job controlling for, you know, potential confounders, had decent exposure measures, not just, you know, teeth filled, and that it does provide some information about safety, again, not necessarily that there isn't a subpopulation that's more sensitive but in the general population of safety, and I felt that that study was reassuring in terms of, you know, fillings, in the general population. Again cannot refute that there might be more sensitive groups, and that, in fact, I think to find that, you would need to go about looking for them in a completely different way, and I hope we can get to discussion on that at some point, because I think at some point, we ought to talk about what we might recommend to the FDA in terms of being able to not necessarily refute but seeing if more specificity can be put around some of these--I don't want to say hypersensitivity because I agree with what Michael said. We don't want to confuse it with allergy, because we're not just talking about allergy. But if we have sensitive subpopulations, who they are, how those might be identified, and some of the issues that

we've heard about for the last couple of days might be able to be studied.

DR. BURTON: A last comment from Dr. Goldstein, and then we'll break.

DR. GOLDSTEIN: Yes, and again, I think the way to frame our approach to all of these questions is that list that I ticked off when we had the presentation of the white paper, looking at the adequacy of the methodology that was used to produce in the papers and the studies that are actually included here.

That's the database that we're working from and I can't be assured that that's adequate or not, based on the methodological issues that I raise.

DR. BURTON: Thank you to all of you, and I'll be happy to let Dr. Kieburtz take over this afternoon and I appreciate your support, and perhaps what we should think about during our break is that, you know, one of the things I'm sort of hearing in here is that as we go through, you know, A, B, C, and D, are sort of issue raisers, but in a lot of ways they don't really answer a question.

And I'm not sure that they're framed as a question. You can say yes or no, or you could say, well, we vote one way or the other. Perhaps the

components of A through D really just give us a little guidance then to affect questions two and three. They're really contributors to that because they make up a point of whether we feel that they clearly and objectively present the knowledge that we have, and we can say yes or no, and given that, do we have conclusions, and if not, then we need to be able to go back to the FDA with why we feel that their white paper--so I guess I feel that--we can think about this during lunch--is that we really have two questions to answer, which is two and three, and then A through D really are sort of the factors or the contributors to how we feel that those two questions should be answered.

DR. KIEBURTZ: Can I just remind people to even think about it but don't talk about it. That talk happens here on the record. Okay. It's very important for the public to hear that talk. Think about it but talk about architecture.

DR. BURTON: We'll break for lunch at this time. Please be back shortly after 1:00 o'clock. Thank you.

[Whereupon, a luncheon recess was taken at 12:19 p.m., the Advisory Committee to reconvene at 1:00 p.m., the same day.]

DR. KIEBURTZ: Well, maybe, even the absence of some of folks being here, we don't have that much time to discuss these matters, so I think we will reconvene, even in the absence of the executive secretary.

So just to mention some points about this afternoon. The open public hearing is closed. This is a period of time for discussion amongst the members of the committee.

Members of the committee can address questions to each other. They can address questions basically to anyone they want to--prior speakers, members of the public. You're allowed to address questions to whom you want. The public cannot address questions to the committee. No one's theoretically supposed to ask anyone anything, unless I recognize you.

So even though Michael or Darrell are not here right now, between the two of us, we'll try to catch your eye, get a list of people. So if you want to put your hand up, put your microphone on, once Darrell or I catch your eye, we'll put your name down and make sure we have you on the list.

Try to get around, to make sure that everybody says something who wants to say something,

before we go back to someone who's already had something to say.

I think it is important for the FDA and for the public, for people to have their say. This is a chance. 4:30, we're done. We will have voted and we will have had our say. And then it's over. So this is it. There's no other information to be gathered, or timeframe in which this is going to happen. It's now.

The consultants are deputized as voting members. The only individuals who do not vote in this are the industry representative for the device panel, the consumer representative for the device panel, the patient representative from the device panel, and the industry representative from the PCNS. So those four individuals at that end of the table cannot vote. However, active members in the conversation, everyone's point of view is important and valued and should contribute as they see fit.

But when we actually do come to the vote, which will be on questions two and three, the really only votable questions, the discussion will be around question one.

I think, in fact, we'll probably, not to presage things, I think the discussion we want to

really engender around one will lead to voting around two and three.

When you vote, you vote yes or no. You can abstain, but I don't think that's so useful. In fact, in many of these things, I think for the agency Dr. Alderson can comment, he's here, if he wants to, but it's better to say no and why or yes and why than just a no and a yes. Not a lengthy discussion. And when we vote, if someone says I vote yes, and such and such, this is the reason, I won't entertain engagement of that person's statement.

So if Dr. Goldstein votes yes and says blah, blah, blah, I won't let Richard ask him a question about his reasoning. I'll go around and let everybody vote and then--so you'll have an unrestricted coda. You know, you can say your little piece about why you vote. Do people understand that, or are comfortable with that scenario? Questions about that? A question here?

Yes, please.

DR. O'BRIEN: Yes. The question regarding the vote. I was made to understand there are three categories of response, one being, I suppose, no, one's yes, and then there's qualified yes or no. Am I correct in that or am I misunderstanding?

DR. KIEBURTZ: It would be useful to vote yes or no and explain yourself, either way, because, again, this is not like--Dr. Alderson, do you want to comment at all about that, on what would be useful for the record and for the agency.

DR. ALDERSON: I would be glad to. I think you're thinking the same way we are. Any qualification that you can give us on your thoughts on these issues, we want to receive that. We really genuinely want your input on the issues we've presented before you. And it's clear from listening to the discussion, you've got a lot of issues.

So, you know, give us that feedback. And while I'm on this, there are a couple of things that we've talked about during the lunch period, that we really see you having some difficulty with and we'd like to encourage you to help us on that, and the first one is on this issue of whether to use the urine levels or not as a measure.

Yes; that's one thing we've been using. But if that's not appropriate, give us feedback on that. We will want to know how to do this the best way. So that's the reason you're here; you're the experts. Help us.

The second point that the folks picked up

on is from Dr. Porter. He has mentioned two studies regarding brain levels. We're not aware but one. So help us identify both of those, if you will.

But as you're in the discussion this afternoon, as things come up, that we're going to prod you a little, beyond maybe where you are, we will do that. Is that helpful?

DR. KIEBURTZ: Yes; thank you. I think that's very helpful.

So to reorient ourselves. Dr. Zero?

DR. ZERO: The point that was just raised, I think to me, personally, is a fundamental issue, and that is, are urine mercury levels a validated circuit, a valid circuit of body burden? Is body burden the issue here or is it--what are we talking about here? And if we're talking about body burden, are urine mercury levels a valid circuit?

Frequently, when I work on the FDA on the other end of the street, you know, when we're putting in submissions for consideration, they come back to us with the question, Is this a valid surrogate?

So I want to turn the tables here because I really think it is a pivotal and key point here.

DR. KIEBURTZ: Thank you.

Let me just frame up, at least from my

perspective, having the bully pulpit, part of where we are.

I think it's important for us to realize that we do have to come with some concrete responses to the questions, and which are--as you've already seen laid out and I won't reiterate them--but you can see that, you know, an important aspect is objectively and clearly present the current state of knowledge about the health effects of dental amalgams, and are the conclusions of the white paper reasonable.

Now one thing we may want to point out, which I've already heard articulated, is that the current state of knowledge is inadequate to fully address some of the questions. And I think that would be very important.

But a very important thing here is does the white paper, again, objectively and clearly present the current state of knowledge?

We could want the current state of knowledge to be a lot different than it is. But I just want to keep those two issues separate.

Dr. Alderson.

DR. ALDERSON: And that's an important point to us, that I failed to mention earlier. The word data gap has come out in a number of the

committee members. We need that badly. Your identification of the data gaps that exist, to help us make this decision on the safety of amalgams, is so vital to us.

So, you know, in your consideration of the questions, yes or no, you know, a qualifier is "But here's a data gap." That's critical.

DR. KIEBURTZ: So returning to some of the discussion about the questions 1A through Part D, I think that some of the things we heard--and Dr. Burton already summarized it but I'll just say it again. Some of the things we already heard, there are two randomized trials. There's the ranch hands and the New Zealand defense forces, and I'm going to forget, say her name wrong--the Factor-Litvak study, all of which are fairly large population based kinds of studies, looking at the issue of is there an association between amalgams and adverse health effects, and those relatively high quality kind of studies in terms of drawing inferences about a relationship.

To my read, and I haven't heard comment to the contrary, do not provide evidence of adversity from dental amalgams.

There are limitations to all those

studies, and I'm not aware of other studies of that quality, not just using the white paper but doing my independent searches of the literature, of other studies of that character and quality which have substantively different observations.

Is that in keeping with people's--I'm not discussing the issue of urinary measures or other--but just the phenomenological association of amalgams and adverse clinical effects.

DR. GOLDMAN: I'm in agreement with that and it's just with the same, you know, proviso that we talked about earlier, which is that these studies, by design, cannot tell you about subpopulations that have, you know, genetic susceptibilities or other special susceptibilities.

But, you know, for what they are designed to do, I would agree with what you said.

DR. KIEBURTZ: I think that brings to mind another point. Several of the articles, again, already alluded to Dr. Factor-Litvak's paper. The Kingman paper. Also with Kingman is the ranch hands, U.S. Air Force data, and the Ellingson is the chlor-alkali workers, so slightly different.

But one of the interesting things in looking at those are there are urinary concentrations

about the reference population as well as exposed populations. Also the Bellinger randomized trial.

It's interesting to see just how much variability there are in these measures of urinary excretion. I believe it's in the Kingman, there are excretions which are graphed out, you see there's tails out, but there are quite high excretions, thirty-five as opposed to the sort of lower levels, five to ten. So anyway, just picking up on that, that even with the non-exposed populations, and certainly within exposed populations, a great deal of variability in whatever measure we have of mercury exposure.

DR. PORTER: I'd just like to point out, the questions, since you're talking about urinary levels, that in the back, in the note from Dr. Boyd Haley, he makes the point--and I think that this may or may not be correct--but if it is, in part, correct, it needs to be part of the document, so that we know where the excretion of this drug comes from. At the moment it's not in the document.

"It has been published and verified that over 90 percent of mercury excreted by humans leaves through the biliary transport system of the liver and that mercury is found in the feces, not the urine.

Urine mercury levels are well-documented and do not reflect exposure under many conditions."

Now I don't know if that's a 100 percent correct, but the document, again, from a pharmacological standpoint, is weak, in that it does not address this issue.

DR. KIEBURTZ: And, you know, the WHO document is different in that it says that urinary excretion is the best measure. So there's inconsistencies amongst reputable documents, about the relative utility of these measures, of exposure.

DR. ASCHER: I would argue that urinary excretion is the best estimation of inorganic mercury excretion but it's not a very adequate measure. There are tremendous differences and especially in people that are under conditions of steady state. The amount of mercury in the urine is not a good measure of exposure of body burden.

So I don't think that necessarily having measurements of mercury in stool will give you a better estimate of inorganic exposure. Most of the mercury that's excreted in the feces is from the methylmercury because it cycles from the gastrointestinal tract to get the hepatability excretion.

And there's another surrogate measure of mercury which hasn't been used very much, and it's also riddled with problems, but one can certainly look at--couldn't do it with me but people that have a lot of hair, you can get a very nice profile of mercury exposure in those individuals. It will be more recent but it's a good measure.

DR. KIEBURTZ: Dr. Klaassen.

DR. KLAASSEN: You know, in regard to urine concentrations, you know, this is one biomarker of exposure. Is it perfect? No. And I can give a classic example. A number of years ago, Tom Clarkson, who's a big mercury expert, as most of you know, had an NIH site visit coming.

So for ten days before the NIH site visit came, the only thing he ate was fish, and measured his urine concentration of mercury and he got the $10 million grant.

So, you know. But it is an approximation--you know, there's nothing better that we have right now for measuring exposure to amalgams, that I'm aware of. But, you know, it's not perfect and, again, so much of it depends on which form of mercury people are exposed to, and are concerned about, and, you know, a lot of the information that laypeople have on mercury

is from methylmercury, and so, you know, we want to make sure that we separate the methylmercury from the elemental mercury.

DR. KIEBURTZ: Dr. Dourson.

DR. DOURSON: Yes. I have, if you don't remind, a response to an earlier question of Dr. Fleming and then I have a question myself for the panel and perhaps Dr. Klaassen.

So Dr. Fleming, you asked earlier about dose response and safe doses and safe concentrations and things like that. Our colleagues at FDA have done a very good summary of safe concentrations, the RFC or the minimal risk level in the document. I worked on the EPA's value many years ago. I'm not beholden to that value. It was done by an expert committee at one time. So it was derived by an expert committee and we just did some work inside EPA and then put it up on EPA's IRIS.

EPA's done some good work since then. ATSDR's done lots of good work, confirming that, and the Dutch, also the RIVM, which is the Dutch Institute of Environmental Protection and Public Health, has also come up with a similar safe dose or concentration for methylmercury. All of those definitions include words to the effect of sensitive sub groups are

protected, and there are certain factors used when a science is not sure and they tend to be somewhat conservative.

None of those definitions say every sensitive individual and so each of these organizations has used words on hyper-susceptible, or immune-sensitive people might not be protected, or an idiosyncratic response, which means a response that just isn't predicted.

But all sensitive sub groups are considered in those estimations of safe dose and in this particular case, the safe doses that are being used by our colleagues at FDA look to be well wrought, especially the other two, I won't talk about the EPA guy since I had part of it. They look to be very well wrought and the literature review that the FDA has done is consistent with looking at other studies that might affect these chronic, little bit every day safe doses or concentrations.

So that's the dose response question, and I hope that helps a little bit. That doesn't mean that every sensitive individual is protected but it does mean sensitive sub groups are considered.

DR. FLEMING: May I respond to that, just quickly?

DR. KIEBURTZ: Yes.

DR. FLEMING: My concern is, as I read all this literature, is there are so many expressions of probability used, which is an entire discipline in itself. For example, you see the words rare, small, isolated. So to me, I think that term needs to have some kind of definition meaningful for us, and if we're trying to say that there are no adverse effects from dental amalgam, I think we need to have some kind of definition of what sensitive means, what rare means.

In other words, is there a number we can attach to it, realistically?

DR. DOURSON: Well, the idea of sensitive sub group has been fairly well established. There are either populations of children or pregnant mothers, or elderly individuals as sub groups, that are considered in these estimations of safe dose. However, when you get into rare and hypersusceptible, those kinds of words are not defined because the science is not precise enough, the risk assessment science, to define those.

What is of more concern to me in his dose response is not whether the safe dose protects every last person on the planet--it may not; it may; it may

not--is do we have exposures that are exceeding the safe dose?

And that's when I talked about characterizing the off-gassing of inorganic vapor from dental amalgams, either acutely, you know, day one through day 14, to chronically, or long term.

And it looks like we've got a handle on the long term off-gassing; it's just a little bit. But what about acutely? And that's maybe an open question.

And actually that leads to my question to anybody on the panel, and this is prompted, Dr. Klaassen, by you. You know, mercury is not mercury, etcetera.

We do have papers in here, and I'm looking at the paper, in particular, by Dye, et al. It's urinary mercury concentrations associated with dental restorations, etcetera. They do have mean levels in the urine and also standard deviations, very good at getting to, you know, the variability in the population.

And they have in here a mean value, creatinine adjusted, of in pregnant people, 1.2, two standard deviations above that is 3.38, and this is micrograms per liter, creatinine adjusted.

And in the white paper we have an adjustment for that, to find out what would be in air. Now I can make that adjustment; it's real easy. I just divide 3.38 by 1.22 to the paper. The question is, is it legitimate to do that adjustment, because it assumes that everything in the urine is coming from the amalgams? And so that's the question. Is that a fair assumption? Is it 50 percent? Do we not know?

DR. KIEBURTZ: Dr. Goldman.

DR. GOLDMAN: And I've asked, those that come from the CDC, and I've asked them and they tell me that actually the majority, when they do speciate, the mercury in the urine, the majority of it is from methylmercury in the general population. It's not an occupational population but in the general population.

And actually, that they kind of assume, when they're looking at those levels, that they're looking at a methylmercury exposure.

Now in this paper, is it not broken down? I thought the Dye paper, they actually gave a breakdown of inorganic versus the methylmercury. I might have them confused, though.

It seemed to me that they did give the inorganic mercury level in that paper, though.

DR. DOURSON: Well, the footnote to the

table says total mercury--well, that's in blood. Okay. I'll look.

DR. GOLDMAN: There's a urine--

DR. DOURSON: Right.

DR. GOLDMAN: Yes.

I mean, you know, there are other issues as well, because as has already been said, the urinary mercury measurement is not perfect, and even less so when it's a spot measure, because there can be variability, even within a day, about excretion that has to do with metabolic state, and numerous things, and then the creatinine correction is to at least try to correct for the dilution of the urine.

But that still doesn't give you as good a picture as if you do it like a 24 hour collection, or a longer collection, but, you know, in practice, nobody's going to do that with a large population. You're just not going to be able to do that.

DR. KIEBURTZ: So two issues, I hear people identifying a knowledge gap. Is one, an accurate measurement of the exposure burden with acute manipulation of amalgams, that, for example, could be the placement or removal.

Dr. Dourson, am I hitting on that accurately?

DR. DOURSON: I believe so.

DR. KIEBURTZ: And perhaps even, but to a lesser degree, the chronic exposure from them.

And secondly is a good measure--there's tolerable good measures but perhaps with a certain degree of imprecision regarding current exposure vis a vis body burden. If I understood correctly, Dr. Ascher, there are individuals who will have different body burdens but might have the same urinary excretion just based on the chronicity of exposure.

Dr. Porter.

DR. PORTER: I just wouldn't downgrade, too much, the total body burden on a chronic basis, because we know that there's accumulation of this drug in various body tissues, and what that accumulation means right now, in my view, we really don't know.

DR. KIEBURTZ: You wouldn't downgrade body burden too much. What do you mean?

DR. PORTER: You emphasize the acute event, and nothing wrong with the acute event. I'm sure that there's a lot of mercury floating around with the acute event. But you said and to a lesser degree, the chronic exposure, and I just want to make sure we don't downgrade that too much because that may be a very important factor.

DR. KIEBURTZ: Yes. I think some of the things we saw with chelation and that transiently reducing blood levels but then they go back up, and other evidence in the white paper already suggests that there's a depot effect in storing, and an increasing body burden, and I did not see--and perhaps people are familiar with other, more direct measures--

DR. PORTER: There's a beautiful animal study that shows that there's--and in 11 days--there's tremendous accumulation in the kidney. It's the Davis study, page 231 in the white paper.

You have to be careful because the urinary levels are in nanograms and the other are in micrograms.

DR. KIEBURTZ: And this is from amalgams.

DR. GOLDMAN: Inorganic.

DR. ASCHER: It's the vapor?

DR. PORTER: Yes, the vapor page.

We are in agreement that there is a substantial accumulation of this drug in body tissues and we don't know what this means, either on an acute or chronic basis.

DR. KIEBURTZ: Actually, I guess we should be careful, Dr. Porter. There is an accumulation of elemental mercury, is what we're saying. I think

lingo is going to be very important--

DR. PORTER: Fair enough; fair enough. I stand corrected.

DR. ASCHER: Well, once it crosses into the brain, it's not elemental. It's going to get oxidized to AG plus plus. It's inorganic but it's not elemental at that point.

DR. PORTER: Inorganic.

DR. KIEBURTZ: Dr. Taylor.

DR. TAYLOR: I just had a point of clarification. In the chronic exposure where would we put the vapor that might be created with the chewing and the brushing, and, you know, as we talk about our exposure? Because we have the acute exposure with the removal of, insertion of the amalgam. Then we have the chronic exposure, if I understand, with the accumulation in the tissues.

So then we have one other potential exposure, which might be the volatile mercury that occurs with the brushing and chewing and things like that.

DR. KIEBURTZ: So there have been several things we've seen, one, mechanical disturbance, such as chewing, can increase levels. There's at least one report of nicotine gum chewing increasing level. So

there appears to be ability to increase, enhance release, a certain thing. So I don't know how--I don't think we know how those relate to the other acute perturbations.

DR. DOURSON: Let me just step in a little bit. In the risk assessment science, we've tried to keep things as simple as possible, so--not that we always succeed.

But in the case of the chronic safe dose, we're going to say--or safe concentration, we've got three examples, three different organizations giving almost the same thing for organic vapor. I'm sorry. Vapor itself; mercury vapor.

It's going to be that concentration daily, 24/7, for your whole life, and if you're below that, if you're off-gassing in your teeth, the amount of vapor that's going to be less concentration, 24/7, that's going to be considered safe, including sensitive sub groups, not necessarily every sensitive individual.

Now the other side of the coin is if you are worried about an acute event, risk assessment scientists estimate a safe concentration for acute exposure.

At ATSDR--I should have looked it up--they

also do one day and I believe ten day, or shorter, intermediate, safe doses, and a chronic value. Not surprisingly, those safe concentrations for the acute tend to be higher, just because that's how toxicology works out.

Usually you can take a larger concentration in a shorter time.

DR. GOLDMAN: Unless it's fetal.

DR. DOURSON: Unless it's fetal effect. So there are ways to do that safe dose and compare that, then, to the exposure, if you know it.

Hopefully that helped a wee bit.

DR. KIEBURTZ: Dr. Luster.

DR. GOLDMAN: People couldn't understand--

DR. LUSTER: I'm a little confused, though, Michael, because, you know, you put a lot of weight in those, the reference concentration from EPA, and it was duplicated by ATSDR and by the Dutch. You know, I don't know about the Dutch study but both the ATSDR study and the EPA study used the same data set to establish that reference dose, and, you know, the 24 hours and the uncertainty factors, it's not going to make it change that much, the differences between how the different agencies do it, and that study was a little frightening to me.

From what I understand, this is a follow-up study -- it was a good study, and probably the best at the time to do that with. But it didn't have--it was a small population, it was 25 workers, and it didn't have a no-effect level, and so you probably designed it with a--I mean, you guys have an interest in cancer, you're not interested in mini relationships, so you probably did a threshold sort of thing and drew a line. So, you know, how good is that data set at the low end?

DR. DOURSON: Well, those are good questions and that's what the reevaluation by ATSDR and RVM, and EPA, and now FDA, they looked at all the newer studies to try to replace that study, and it was, as you said, it's got some flaws. They use an uncertainty factor of, I believe three, with all three organizations. That's RVM, and ATSDR and EPA, to adjust the minimal low observed adverse effect level down to the expected no observed adverse effect level, and then a tenfold uncertainty factor for within human variability. And then EPA used some database considerations as well, which is their habit of doing.

So in all cases the uncertainty factor was thirtyfold for each of those organizations and subsequent reviews by each of these agencies has not

found something better than that study, even though it has its limitations.

DR. GOLDMAN: Could I explain that a little more? You know, the thing about risk assessment is that it's very narrow. What you're trying to do is very narrow, and that is that you're trying to kind a come up with the equivalent of what's the speed limit? What is a number that we can say is a safe number?

And only a very narrow band of studies, even animal studies, will support the development of that kind of a limit. And so there are lots and lots of studies that are quite relevant to the discussion, the questions we've been asked, you know, that we've asked, that you could not use for doing a different risk assessment.

And so when they say we reviewed the newer studies and there's nothing better to replace what we've used before, it doesn't mean that the newer studies didn't provide new scientific insights or new information about risk. That's not what it means.

What it means is there was nothing in the newer studies that would allow them to set a different speed limit. You know, very few studies are actually designed to do that.