Most epidemiology is not conducive to doing that, for example.

DR. KIEBURTZ: And I presume all the panel members read and thought about the information not with just are the reference doses and the reference concentrations accurate and good measures, but the totality of the risk.

Dr. Zero.

DR. ZERO: I'm just trying to understand where in this reference dose analysis we have the data to understand what would happen in an adult patient that has a chronic body burden from various sources of mercury. And then on top of that, we put in an acute exposure. Where is that information, in any of the analyses that we've been looking at?

DR. KIEBURTZ: I don't think we have that.

DR. ZERO: And that goes back to the open research question, is what is the off-gassing mercury vapor from amalgams, either in the acute window, which I don't think--I think there is data on that but I haven't seen it. I think Dr. O'Brien had some in vitro data for off-gassing of mercury from amalgams. So we do have data.

And in the chronic window, when it's just a little bit eking out each day, and then the episodic

increase, I don't know that we have data on that either. That seems to be a data gap.

DR. KIEBURTZ: Dr. Honein.

DR. HONEIN: Yes. I just wanted to share Dr. Goldman's concern about fetal exposures and that being a fairly significant research gap, and what we do understand is what effect it might have, especially during early development, and to that end, I was wondering if the practicing dentists on the committee could shed any light on the standard of care for pregnant women in the U.S. currently.

Is it only emergency care for, you know, things that cannot wait until after pregnancy?

Is it fairly typical to be removing and installing fillings during pregnancy?

What would be the typical standard of care?

Dr. Fleming.

DR. FLEMING: Well, I can tell you this. That, for example, to give you an example of the unique situation, it's in the hygiene department of your practice. I personally would never think of replacing, removing or installing anything in a woman who was pregnant.

So that's my personal view. The issue in

hygiene departments is that the hygienist will take a prophylaxis cup, if the patient has amalgams, and they'll polish those amalgams and the mercury release rates are dramatically increased. That's the acute "hit" that they get. Not to mention the "hit" that the hygienist gets in the field around the oral cavity.

So the big problem I think that you face with pregnant women is not so much the installation removal in the pregnant woman, but it's in the maintenance that's often emphasized during their pregnancy.

For example, dentists are very quick to recommend that they need to be cleaned because they can get pregnancy gingivitis and things of that sort.

So the cleanings are emphasized. So I think some attention needs to be given to keeping that prophylaxis cup off that amalgam.

DR. KIEBURTZ: Dr. Burton.

Are we done?

DR. FLEMING: Yes; yes. That's just my perspective on it.

DR. BURTON: I guess my comment would be a little different. I haven't practiced general dentistry for a while but I've managed large dental

clinics, both in the military and where I'm currently at, where we have both a number of hygienists and a number of general dentists.

And my thought would be that there really is not particularly, in terms of providing general dental care, which is what I would put this under, whether you're replacing initial restorations or replacing restorations, there's really not a restriction that I'm aware of, that I've ever had in any of those facilities. So at least potentially, if someone came in and they've broken a filling, they're always very acute--or during a pregnancy are more aware of their overall health and well-being, and I can honestly say I know that those are replaced.

And in our particular state, where we also take care of a number of Medicaid and Title 19 patients, interestingly enough, some of them become eligible for care because they're pregnant.

So they will come in and get large amounts of treatment done during their pregnancy because it becomes covered during that period.

So I guess I would say, you know, in answer to your question, yes, I think that the standard of care--and I'm not trying to describe what that is--but I would say I'm not aware of anything out

there that says no, you would not treat them, you limit care, those kind of things.

So they are going to be exposed to either initial restoration placement or potentially replacement during the time that they're pregnant.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: As I'm thinking about this, again, I'm not a toxicologist and I'm not a dentist, so I'm just looking at it, just standing back a little bit. You know, we're looking at these levels as if these are dichotomist variables, that you reach this threshold and all of a sudden there's risk and below this threshold there is no risk.

And these are clearly continuous variables. They're not dichotomous. So setting a, quote, level that's safe, to some degree is sort of in the eye of the beholder, and depends upon all these other factors that we've been talking about.

Is there a population that may be at risk at whatever level? Are there genetic variations that increase total body burden, that may have an effect?

And I don't know the answers to these questions but, again, as we're thinking about gaps, things that we don't know, those are things that we don't know, and as we're looking at, you know,

epidemiologic data, although they're very helpful, we all know that we can be mislead by epidemiologic data because of unmeasured confounders in all sorts of different directions.

So those, I think, are also things to consider as we're looking at the totality of the data.

There is one question I also just have, just as an aside.

One of the statements that we heard, over and over again, through the public testimony from many dentists, was that there is, was that resin don't serve as a substitute, very often, for amalgam fillings. The clinical trials that we have to review, the prospective randomized clinical trials, none of the people that were randomized were dropped because of technical reasons, that a resin filling couldn't be placed.

If you look at these things, there may have been other reasons that people were dropped, but technical reasons related to putting a filling in was not a reason for excluding any of these folks, once they were randomized, in any of these studies.

So if one of the other panel members who knows about these things could tell me, you know, is this really--you know, how big a problem is this?

Because it didn't seem to be a problem in the randomized trials.

DR. KIEBURTZ: Please.

DR. NG: Man Wai. I know something about the New England amalgam trial, although I was not involved in it. But I think it has to do with the study design, and it was purposefully designed to enroll children who are older and without medical problems.

So by those two criteria alone, would imply that the patients or the individuals would be cooperative for both types of restorations.

DR. KIEBURTZ: Were you thinking about other technical issues, or--

DR. GOLDSTEIN: Yes, some of the discussions, again, from public comment, from dentists--not being a dentist, I have no frame of reference for this--was that there seemed to be not only young kids that wouldn't sit still but other technical reasons, especially in these back teeth. All of these studies apparently did these things in back teeth, so that didn't seem to be a problem.

I know that obviously, if you've got a really young little kid that's squirming around, that that might be an issue, but, again, I don't know the

answer.

DR. NG: Oh, I'm sorry; go ahead.

DR. GOLDMAN: Clinically, as a pediatrician, I can remember very well in the clinics, I mean it's not just young kids squirming but you have, you know, you have kids who are fairly big, who are constantly seizing, that you need to treat, you know, in some cases.

I mean, you can't stop the seizures and you have to treat. So some of the situations truly are very difficult and there's just no doubt of that.

DR. NG: And in terms of the study design, again, it's looking at two different types of restorations, but that doesn't preclude other treatment options that may have been given to the patients. For example, a tooth might have been extracted because it was not restorable. A crown could have been placed on because a filling was thought not to be appropriate.

There was also mention about for anterior teeth, that the restoration of choice was composite, for aesthetic reasons.

DR. KIEBURTZ: You wanted to mention on this topic, Dr. Burton?

DR. BURTON: I just want to comment. I

mean, I think that from a dental standpoint, I mean the transition between a composite restoration and an amalgam has been primarily the fact that amalgam has always been at least a stronger material, therefore can support more load to it.

So you made a comment about back teeth. Well, yes, there's more occlusal load on a back tooth than an anterior tooth, and the fact is as you have less and less tooth structure left, you're replacing more of the tooth structure with an artificial material, you need a material which then is inherently stronger thanB it=s the difference between a plastic and a metal, if you want to look at it that way, and it would take more load.

And as dental materials have improved, that line has blurred somewhat, between that differentiation. But when I look at this, and again, dealing in that age of a pediatric population, you don't always have patients--those patients don't always require big restorations. Okay. You know, sometimes in adults, it's because they've had multiple episodes. I had a tooth, they broke part of it off, I had another filling, and that's why they end up with larger amalgam-based restorations. But there are always alternatives.

DR. KIEBURTZ: Dr. Amar.

DR. AMAR: I wanted to comment on the issue of pregnancy. Although I'm not a general dentist but I know my academy, for example, prevents us from treating pregnant women, and particularly in the third trimester where you have the placental barrier that is pretty loose and open for contamination.

And usually that recommendation goes, if there is no necessity of emergency, we should not treat pregnant patients. So that's the recommendation that we have on the American Academy of Periodontology.

And on the other issue that I wanted to comment, before addressing the white paper, I wanted to see whether the committee would be in favor of revisiting the approach of looking at the literature and making sure that the literature has been addressed properly with parameters of using two or three search engines, to make sure that we give credit to the whole situation, before addressing the whole white paper.

DR. KIEBURTZ: Can we come back to that, leave that open on the table?

Dr. Sacco.

DR. SACCO: I was going back to the

question that Dr. Goldstein raised. Having just had a wisdom tooth, mercury filling I guess, replaced with a composite, it's interesting to hear this whole discussion. But I heard in the first speaker, that there were other reasons of why amalgams may be better than composite, including recurrent caries, and bacterial infections.

So I think the risk benefit ratio between, I sense, not just the cost issues we heard about, but the amalgams versus the composite, brings up other issues, and other potential issues besides just the ability to do this in children. I'm a neurologist, not a dentist, but I did hear some other benefits of amalgams over composites.

DR. KIEBURTZ: Dr. Zero and Dr. Burton, do you want to end.

DR. ZERO: By the way, I'm a preventive dentist, so I try to avoid ever picking up a handpiece. I chair a forum called Preventive and Community Dentistry, and if we prevent disease in the first place, there's no need for restoration, so--and tooth decay, dental caries, is a totally preventable disease. We have all the knowledge base to do that. So I need to get that on the table at some point in this discussion.

And by the way, as a restorative dentist, I went to Georgetown, graduated first in my class as a restorative dentist trained, so I know how to do these restorations. The one issue that does come up with amalgam versus composite is salivary contamination, and in certain areas of the mouth it's very, very difficult to isolate the two, to place a restoration without salivary contamination.

So that's one of the issues that has come up by the speakers earlier in the session.

The other thing we need to also think about is that material science is progressing and newer and better materials are coming down the pike, that probably will equal, maybe hopefully exceed the qualities of amalgam.

So I think we have to think now and also in the future, and I think there's things coming down the pike.

DR. BURTON: I would like to agree with that. I wanted to address what Dr. Amar said, in fact, that it wasn't the thing that we advocate the care, but is there a prohibition against it, shall I say that? We do the same thing in terms of--the truth is, many times women are unaware they're pregnant during their first trimester, so again, they may have

extensive treatment done because we normally don't sedate patients during their pregnancy without clearance from their OB, things like that.

And during the last trimester, we try to stall them, because, you know, you've got some eight month pregnant female, that's really not the ideal time from positional issues and comfort and things such as that.

But again I would agree with Dr. Zero, that I think a lot of us, myself being at a dental school 30 years, believe that material science will take us past this point because the other issues you mentioned, you know, salivary contamination, but also the ability to isolate it. It produces a smoother surface, which is more maintainable from a periodontal standpoint.

There are other issues other than just strength and things such as that. But again, probably material science, bluntly, 20 years from this, may take us past this point.

DR. KIEBURTZ: Dr. Fleming.

DR. FLEMING: I wanted to address Dr. Goldstein again about--did I understand your question to be the technical differences between the placement of amalgam and composites, perhaps being a factor in

the--

DR. GOLDSTEIN: It was a more general, it was just more general question. You know, as I think about these things, I think about risk benefit, okay, and in some cases you have risk and you don't know the level of risk and there may be vulnerable populations, there may be not Then, you know, on the other side there are potential benefits, and we read about some. Maybe it's more resistance to caries, et cetera.

But then you have to also look at the other side of the coin and that's what's the potential alternative and what's the upsides and downsides to that?

And my comment was based upon all the comments we heard from yesterday and this morning, from a number of dentists, saying that there is no alternative in many cases, and then I was just commenting just based on the randomized trials that we have here, where all patients, once they were randomized, were enrolled, and got one or the other, and, you know, one answer to that was, well, it may be an exception cohort bias, in that they only took people who they could either, to begin with, although I didn't see that being one of the criteria for inclusion. But, again, I don't know the answer to

that.

So the issue about that, you know, about the saliva, if that were an issue, then I would have thought that they couldn't have done it, you know, in any of the, you know, in one group of kids or another, and they would have been selected out, because we tried doing it, we couldn't keep a dry eye, so we had to do the other. But that didn't happen here.

DR. FLEMING: Right. So what I was getting at was from a technical point of view. I do composites very frequently, and so the technical difficulties in installing them, once you've gained experience, knowledge, and understanding as to how to use them, you can use them in any indicated tooth, including a wisdom tooth. It's not difficult to do that. This business about moisture contamination, the newer rubber dam materials that we have make this--it isn't a non-issue but there are very few areas where I cannot get a composite, if I want to get on in there, with a rubber dam on.

I would just as soon have a rubber dam on to eat lunch with, if I could do it. But we use it routinely in the practice. I might add, vinyl dams and not latex dams, which is another issue entirely.

But still, the technical difficulties

become moot with experience and technical training.

DR. KIEBURTZ: Okay. I want to start to redirect our thinking back to looking at some of the questions, and I'm just going to surprise my colleagues and friend, Dr. Hughes here. You commented earlier about A, and direct evidence, and the constraints on.

Where are you coming down that? I want to make sure I understand your position.

DR. HUGHES: I guess part of the comment was to make the point that there was direct evidence in several of these studies, I think, about the issue of adverse health effects of amalgams.

Whether they support or refute the occurrence of adverse health effects I think is unclear. I don't think any of these studies were really designed, per se, to refute the question.

None of them were equivalent designs, non-inferiority designs in the context of clinical trials. But the point that I was trying to make was at least the randomized trials certainly suggest in children, that any true difference in the outcomes that were assessed are likely to be relatively small.

But I think it's important to put the caveat on we're really looking at quite short-term

effects there, and a lot of the discussion has been about the chronic long-term effects over potentially several decades.

DR. KIEBURTZ: Thanks. I know it wasn't part of the white paper but I did look at the Swedish dental assessment, which is on the dentalmaterial.gov.se, on this, and it's pretty much consistent with the FDA white paper, aside from one issue.

But I will just read a sentence. I thought it was constructed rather well, considering it was probably written by a Swede rather than a native English speaker.

But it says, "At present, it may be considered unproven, but not excluded, that subclinical psychomotor function impairment caused by mercury is demonstrable in groups at the mean exposure level for amalgam bearers."

So let me just give you that again. "At present, it may be considered unproven, but not excluded, that subclinical psychomotor function impairment caused by mercury is demonstrable in groups at the mean exposure level for amalgam bearers."

It goes on to go through a number of other clinical conditions and arrive at essentially the same

conclusion. That although there are lots of concerns and hypotheses, why it may be so, that this is the conclusion. I think there's some important things there. Unproven, not excluded, mean exposure level for amalgam bearers.

Which leads us to some of the things, that some of the designs have not been intended to exclude the possibility but it is unproven, certainly at predefined measured levels of toxicity, particularly the three IQ points, for example, but that there are at least from my read of looking at this, just the data on people who, on the studies already alluded to, there's a remarkable degree of variability on this parameter, maybe not that remarkable in the toxicologic world. Again, it's not a world that I live in that much.

But there certainly are long tales of urinary excretion levels and other things. It seems like there are potentially vulnerable subsets, not in the traditional sense, not children, pregnant women, elderly, infirm, but those who, for whatever biological characteristic, and we've seen data on some of the potential explanations for that biologic variability, there may be individuals that are poor excreters, higher body burden accumulators, or

whatever, that may be linked to some of these clinical phenomena we've heard about.

Dr. Porter.

DR. PORTER: Well, I just want to reiterate what you just said, because I've been saying that earlier, that if you look at the brain levels, there's tremendous variability, even among similar groups with similar amalgams.

Now there's also a dose response curve. The more amalgams you get, the more there is. But in the high group, there was a range from 20 to 500. So there's tremendous variability, even in small groups. This was 18 cadavers. So what this would expand to, if you expanded that or modeled it to the entire population, you might end up with a tail, as you put it, of patients who have very high levels in their brain.

DR. KIEBURTZ: Dr. Diamond.

DR. DIAMOND: He made a very important point and we see this often, you know, in pharmacologic studies, where we try to model on pharmacokinetics and pharmacodynamic parameters.

You can see efficacy in a large cohort of patients and we can construct very nice population, pharmacokinetics curves, but when you start looking at

the individual patient's data, it's all over the place.

So what you're saying about individual variability I think is very important, not just from a efficacy standpoint but also from a safety standpoint. It's important data but it's just one piece of the puzzle.

DR. KIEBURTZ: Dr. Li.

DR. LI: Yes. I would like to come back to the question itself. The challenge I'm facing, when I'm trying to answer the question, the first one particularly, is probably related to the way the question itself is stated. But it asks us for evidence, particularly direct evidence to support or dispute the possible adverse effect of amalgam.

In toxicology studies, many times you find inactive results. That means you find no toxicologic data, results, as defined by that particular test. I know there have been debates regarding how to consider significance of these inactive findings.

In 1980's, there was a discussion regarding how we consider the significance of the inactive finding in carcinogenesis study, and if we find a chemical that does not induce any carcinogenic effects, you know, particular study system, and

whether that is significant.

Logically, it's much easier to prove something that exists, like the testimonials we have heard, they experienced this suffering, they are there, it's easy to see, and it's easy to be convinced.

Now how about the result, the finding that did not find those adverse effects? Again, logically, it is very difficult, if it is not impossible, to prove something that do not exist. Now we do not find the adverse effect. There are two possibilities. One is the adverse effect, the significant adverse effect may not truly exist.

But, on the other hand, it is also possible our current technology is not good enough to detect such an adverse effect. Just like the vapor from amalgam.

When I was in dental school, we were taught--quite a few people said that--they would not emit the vapor but now we can find it. So coming back to the question, if we have to have definitive evidence that can dispute the adverse effects associated with amalgam, that would be much more difficult to do.

We need to probably consider what is the

amount of the evidence, is adequate to support either way. I think we need to take that into consideration when we try to answer these questions.

DR. DOURSON: Yes. Just, Dr. Kieburtz, to add to what you had said. If you take the safe-- again, going back to the safe concentrations that have been established by different groups, chronically, and then you go an estimate, as our colleagues at FDA have done on page ten, the range of intakes that's associated with amalgams, you find that the value of 5 micrograms per day is at, or very close to the amount that you would get from a safe concentration per day. And it therefore follows, if you're going to have some people in excess of that, and 5 percent of the people apparently are, then you're going to have 5 percent of the people in excess of the safe concentration and maybe sensitive individuals would start to exhibit effects.

That's consistent with what I believe the Swedish authors are stating, put in a little bit more quantitative way.

DR. KIEBURTZ: And if the 5 microgram daily intake from amalgams is an underestimate, if it's more likely ten--

DR. GOLDMAN: If it's an underestimate,

then--

DR. KIEBURTZ: Then the average person may be above the RFC.

DR. DOURSON: Right, and the usual interpretation of exposures above the safe concentration is effects are more likely, they're not certain, but the higher you go, the more certain they become, and the first individuals that would become, that do exhibit effects, would obviously be the sensitive individuals, by definition.

DR. KIEBURTZ: Let me be clear. I'm not suggesting that the 5 microgram number is wrong or is low. I'm just saying the state of knowledge is one that is characterized more by uncertainty than certainty, as best I can tell. But Dr. Goldman and Dr. Amar.

DR. GOLDMAN: However, one thing that I think that is important to note, and that is that we are not looking at the cumulative impacts of the amalgam-related mercury, the fish-related mercury, and other sources. There's only one paper, that we got, that attempts to look at both exposures to inorganic and methylmercury, to see if those effects are additive or competitive or synergistic, and it appears to be at least additive, if not more.

And that's, you know, another thing that needs to be factored in, which is that people are not starting out with a baseline of zero mercury. There are other sources of mercury.

DR. AMAR: I just want to come back to Dr. Hughes. Could you just comment on your readout of the direct adverse effects that you mentioned from the literature. I presume that we're talking about the two randomized clinical trials. Am I correct?

DR. HUGHES: Primarily, yes.

DR. AMAR: The conclusions are--and I'm reading what I see. None of the parameters evaluated reached statistical significance. So if we look at randomized clinical trials, we have to have statistical significance, and in the absence of statistical significance, I'm still wondering.

Unless I read you incorrectly.

DR. HUGHES: I think the point to make is if you look at the primary end point of the U.S. study, for example, it's looking at an IQ score, and they powered the study to look for a three point difference and judged that to be clinically significant.

So this is a three point difference, on average, between the amalgam arm and the composite

arm. So they didn't find that difference. There was no statistically significant difference.

Having shown that there's no significant difference, within the paper there's also a confidence interval for the difference between the two arms.

Now that confidence interval, one interpretation of it is that it gives you a range of true differences between the two arms, which are compatible with the data that's been obtained, and that confidence interval--I don't have the exact numbers in front of me--but the bounds of the interval are less than plus or minus three, if I recall rightly.

So, in other words, the true difference is reasonably likely to be smaller than the difference which they considered clinically significant when they designed the study.

So on that basis you might argue that it provides direct evidence that the adverse effect with respect to that particular neuropsychological outcome is likely to be small, at least over the short term, and not clinically significant.

DR. AMAR: But that would be, at best, for the confidence interval, as you mentioned, of three potential correlation and not direct evidence.

DR. HUGHES: Well, it provides direct evidence that the difference between using amalgam fillings and composite fillings is not producing or it seems unlikely to be producing a larger effect, on average, on neuropsychological outcomes than the three point difference that they thought was statistically significant when they designed the study.

DR. KIEBURTZ: And, in fact, looking at the data, some health outcomes are better in children who are randomized to amalgams, and in a way, these randomized studies, you know, come to the nub of the question, which is it isn't whether you're going to get a restoration or not. It's what the restoration's going to be, amalgam versus something else. You know, comparing just people with amalgams with no restorations is not as good as the pointedness of this question, at least to my read, and certainly as best as I could read from these, and I understand the difficulty in the external validity or the over-generalization from a randomized study to other populations, but at least in terms of the health effects, ignoring the urinary excretion of mercury for the time-being. There's really no difference between the two. May be too short, may be--

Dr. AMAR: That's what I was alluding to.

DR. KIEBURTZ: Yes.

DR. AMAR: That's what I was alluding, and I'm truly trying to find the evidence here. Wholeheartedly.

DR. DOURSON: Let me make sure I'm clear. What we're saying here is there is evidence from these studies that mercury vapor is not causing problems. It, like any study, has limitations. Follow-up. Okay. But that's what the studies are saying and that's the evidence.

DR. GOLDMAN: I think that we have to say that those studies are--they're well-designed clinical trials. I can't really see much to criticize in terms of the ways that they randomize the subjects, the measures that they used, the neuropsychological measures, the exposure measures that they use. The follow-up. I thought they were done very well, and I think that they were very clear, the authors, about the limits, and the fact that one, there could be effects that are smaller, but that they simply can't observe because the studies may not be powered to observe smaller effects; and two, that there could be longer-term effects, effects in other dimensions.

One area that I am concerned about here, and that these studies did not assess, and that we did

not receive anything about them, there's nothing about in the white papers, and that is the area of immune effects. Immunologic effects that have been documented in some of the toxicology literature for mercury, were not assessed, and by design were not assessed in these studies because they're newer.

And I don't think these studies tell you anything about that. But they did, and I think it's truly marvelous, they did look at cardiovascular effects, which most studies haven't done, and as you know, those were negative, or as you said, some of them even going in the opposite direction.

So I think that they did provide some evidence, and I think they're certainly very reassuring, and that this committee ought to be able to be clear, that if you have, you know, a child that's not forming well in terms of IQ, that although there is some chance that there are subpopulations that are more impacted, there's no way that we can say that, but that generally, we wouldn't expect to see an effect on IQ from children having these fillings.

I think that's a very important thing to be able to say, in terms of reassuring families, and, you know, and I think those studies do show that, even though they can't prove that there isn't some small

subset of children, you know, that aren't more impacted.

DR. KIEBURTZ: Dr. Hughes, and then Dr. O'Brien.

DR. HUGHES: I think the other major caveat with these studies is the amount of mercury exposure, at least if you look at the urine concentrations, the difference between the two arms may be relatively small. So looking at the U.S. study, the mean concentration at five years after baseline was .9 in the composite group. Sorry. Point nine in the amalgam group and .6 in the composite group. So it's a relatively small difference in terms of exposure, and obviously, if you have no difference in exposure, and you think it's the mercury causing the difference in the primary outcome, or it's the mercury that would cause any difference, then no exposure would mean no difference. So the difference in exposure is relatively small.

DR. AMAR: Do you think the "n" number, the "n" was not enough to provide sufficient power to the study, and a larger study would allow to detect minimal effect, if any? Because we're talking about here an effect size; am I correct? And apparently the effect size is minimal, to be picked up by the

approaches that we have.

So my question is, would a larger randomized clinical trial pick up minimal differences?

DR. HUGHES: You know, I work with a lot of pediatric clinical trials, not in the dental setting, but a three point difference in mean IQ score is a relatively small difference. These studies were well-powered to detect the sort of difference they were interested in.

So I would consider, at least for the primary end point, these studies were well-powered.

DR. AMAR: And the primary end point being the IQ, and within the IQ, it's reassuring that amalgam--am I getting this clear? That amalgam does not affect the IQ?

DR. HUGHES: Certainly, it doesn't appear to affect it, substantially, at the mercury exposures observed in this study and over the duration of this study.

DR. PAULE: Dr. O'Brien. I'm sorry.

DR. O'BRIEN: I'm very reassured by the studies that are in the study, especially the recent one, Journal of American Medical Association. But I think we're missing another point. In other words, words dental amalgam seems to be safe when used, from

all these studies. However, there's a wider risk in the real world and that is that mercury is ubiquitous in the environment. Recent reports that I have heard, that we are the "Saudi Arabia of coal," and especially in Wyoming, the increase in coal is going to be much higher, to make up for the lack of petroleum.

So that there is an inherent risk in amalgam that other gold alloys don't have, for example. They have a gold alloy, for example, or a composite material. You don't have to have the risk of "a perfect storm" of some individual, lives in a house where there's a broken mercury thermometer, and then eats fish three times a day. There's no risk involved with these other restorative materials. That you have potential in an amalgam because it's cumulative.

So that the studies are reassuring, there's nothing wrong with the amalgam procedures as given, but in the total environment, in the system that we live in, it has an inherent risk that needs to be recognized, and in addition to dentists telling their patients who receive a new amalgam, "Don't bite on hard food," they might also advise them, "Don't eat fish for a week."

DR. PAULE: I think it's a good point. I

think that several speakers have alluded to, that aside from amalgam which does appear to be the, or one of the two major sources of mercury, there are other sources of mercury in the environment and in the food chain which add to the total risk, and needs to be in that context.

Dr. Diamond, then Dr. Olson, then Dr. Sacco.

DR. DIAMOND: I'd like to respond to Dr. Amar's concerns. My old statistician professor had, you know, told me that--and pretty much it's widely accepted--that human beings have an incredibly variable, you know, response to any kind of stimulus or drug or any kind of treatment effect.

So in a controlled clinical trial, if you're trying to focus on one particular outcome, you have to eliminate as much of the variability as possible. So the concerns, like, for example, in the American study, they excluded any physician-diagnosed, psychological, behavioral, neurological, immunosuppressive, or renal disease as a confounder. So you try to create as homogenous a population, as possible, to permit a valid comparison of the two treatment groups, to address issues of finding any kind of safety concerns.

Those are generally, you know, even from many drug approval processes, where a lot of studies are run with very large patient populations, a lot of things you don't see until a product is released on the market and, you know, you have a much broader exposure in the population. So to pick up a safety, even blip on the radar screen, you might need, you know, tens of thousands of patients to be exposed before you might see it, and you might not get this in a well-controlled trial.

DR. KIEBURTZ: Dr. Olson.

DR. OLSON: Going along with some of the discussion about other sources, I was struck, when I first read both the Bellinger study and the DeRouen study, that in the Bellinger study the mercury from the composite group indicated that more than half the mercury in the urine is from a source other than dental amalgam, and similarly, in the DeRouen study, it was two-thirds. Well, from other than a dental amalgam, they didn't have it. So I thought this was extremely interesting data that talks about using the urine level with the creatinine that we've talked about already, that if you think about that, and being conservative, you could say okay, well, then at least half of that doesn't come from dental amalgam, and it

comes from obviously elsewhere in the environment.

So as I say, that struck me as being important, considering about the toxicity of the amalgam.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I wanted to go back a little bit to this idea of the randomized trials, and I guess "weigh in" again a little bit more heavily in terms of the weight of the evidence. I think Larry mentioned, and others mentioned, that in randomized trials we grade these as level A, there are two of them, so we have concordance between two different randomized trials, albeit given the statistical considerations that Dr. O'Brien has mentioned, they're there, but these are still important findings and I think the only thing I'd add is that we focused on the primary outcome but there are secondary outcomes that also did not show any differences, nor any differences in multiple adverse health conditions reported during the five year follow-up, that were even more frequent, including things like allergies and skin disorders.

So I weigh these trials, at least when I look at the data, as the heaviest, most direct evidence that we have, that don't show that much of an adverse health experience.

DR. KIEBURTZ: I think there is a defense force data is also, and is 20,000 people, I think it's a large accumulation of people with exposure that's also relevant, not of the same quality of evidence in terms of inferential reasoning but still a large and important accumulation of information. The same for the ranch hands and for Dr. Factor-Litvak.

Other comments?

DR. LUSTER: Not to discuss the epidemiology studies from this, but going back--and I keep on hopping back to it--again is the earlier studies by Fowler that were used to set the reference concentrations, and Michael, you went through this, so please correct me if I'm wrong, but as I see it, the average exposure level in those workers, where there was a small but observable effect, was about 25 micrograms per liter of urinary mercury, and given how much of that's from--where that comes from we don't know, I know, but--and then in the population, general population with amalgam exposure, they average up to 3 or 4 micrograms per liter based upon the number of amalgams, and can go up to 15 or 16 micrograms per liter of urinary mercury in some individuals. That's the high range. I don't know what the percent of that population would have that high level but if it's the

total U.S. population, that can get probably a goodly number.

So the argument would be that you're looking at a difference between 26 micrograms per liter in a worker population versus 17 micrograms per liter in the U.S. population, in the high range, which might be significant numbers. How much of that is contributed by amalgams, we don't know; but some of it is. And we're not that far away. I mean, we're not far away from levels that seem to have, potentially, a universal effect.

DR. DOURSON: Yes, and although I go through the numbers a little bit differently, I would agree that what we would appear to have is exposures to the general population with amalgams that are at or very close to the safe concentration. So the Fowler study was 25 micrograms per meter cubed of air, and the way EPA and others took that information is they adjusted it for continuous exposure, which was 24/7, you know, 24 hours a day, seven days a week, cause the workers didn't get exposed to that, then they took that reduced level in air and they divided it by uncertainty factor because the study was not perfect, we haven't found one yet that was, and so you've got to a thirtyfold uncertainty factor, net, and three

different federal agencies, with the Dutch being the third federal agency--all kind of characterize these uncertainty factors differently but all come up with the same end point.

And that safe concentration that's good, say, 24/7, is in the range of where people seem to be exposed from amalgams right now, on average, or I think it wasn't on average--there's 95 percent, or lower.

DR. LUSTER: So the average would be around three but there is a group--but the range goes up to seventeen.

DR. DOURSON: Right, and then the question then becomes, is how do you track those urinary levels back to, you know, what is due to vapor itself, which is a question, that when you've got that determination, what level is that consistent with in air? Once you have that determination, you compare it to the safety concentration, and you say you have a problem or you don't. And that's the basic concept.

DR. KIEBURTZ: I think, you know, if we were talking about an intervention that might encompass 10,000 or a 100,000 people, we would not be having the discussion we're having, because we're talking about the very tales of distributions, but

we're talking about an intervention that has hundreds of millions of people, and the tales constitute maybe tens of thousands of people.

Is that fair?

DR. GOLDMAN: I think there's, you know, there's so many problems. I mean, one is these numbers, when you dig into these numbers, for example, the occupational numbers, the urinary numbers. Well, I'm not sure that those numbers really are representative of what the exposures were in those work environments, looking at those studies, because the studies were done at a certain point in time, and probably many years earlier, many of those workers had higher exposure levels that were not measured, you see?

So just because, as I said before, just because it's an occupational study and it's a higher level, it doesn't mean that the data are done accurately, and the effects could be from higher levels earlier in those studies, but we don't have any way of knowing that, looking at those. So it's hard to do, kind of what is the MOE between those people and people today, because those people weren't maybe measured, you know, at times when they were more highly exposed.

DR. KIEBURTZ: MOE.

DR. GOLDMAN: And that margin of exposure. And then the other thing that we see sometimes, despite use of uncertainty factors like thirty--is this an uncertainty factor? Well, we use uncertainty factors because we're uncertain, and one of the things we're usually the most uncertain of is uncertainty, or I think Yogi Berra said something about, you know, the only thing I'm sure about are the things I know that I don't know; or something like that.

But one thing where we've been very far off on uncertainty factors in the past, and why I keep going back to this fetal exposure thing, is with the gap in where we observe effects in the fetus and where we observe effects in adults.

And those levels have sometimes been much farther apart than thirty, sometimes, you know, hundreds or even a thousandfold difference between a level that causes an adverse effect during exposure to the fetus and a level that causes an adverse effect to an adult. So in my opinion, you see that thirtyfold factor does not take that into account at all, and I'm sure there is a way to take that into account. I think you need to directly observe what's going on, and that the studies that are available really don't

do that.

DR. KIEBURTZ: Just thinking of question, part sub C and D, getting to that, I mean indirect evidence, I think there's no direct evidence of impaired fetal outcome or gestational outcome in amalgam-exposed people versus not, although there's a lot of indirect evidence from animal data, and just reasoning about mercury's ability to interfere with the developmental process.

But just sort of the difference between direct evidence--there is some direct evidence Swedish workers exposed to mercury but include a number of professions, including leather workers and other things, associated with small for gestational age, but I don't think there's any direct amalgam.

Dr. Goldman, then Dr. Fleming.

DR. GOLDMAN: Yes. I mean, I think we can look at it more carefully, but I actually think that there are some birth outcomes that have been examined in humans, not with studies that are as good as the studies, as high quality as the studies that have been done, that we discussed earlier, about the actual effects on, directly to people with fillings. But there have been some birth outcome studies. There have been some reproductive studies that did provide

some evidence. But there have not been studies to look at that specific issue with developmental neurotoxicity, kind of like the Bellinger study, but the design instead would be the mothers, whether the mothers had mercury fillings or other kinds of fillings, and then doing the same kinds of assessments, the neuropsychological tests. There are no studies like that, at all.

DR. KIEBURTZ: Neuropsychologic tests of the subsequent delivered children?

DR. GOLDMAN: Yes, of the children, and following them through grade school, and so forth, as has been done, you know, for methylmercury and lead, and some others.

DR. KIEBURTZ: Thank you. Dr. Fleming.

DR. FLEMING: Briefly, I just wanted to introduce another confounding factor to this whole business of exposure. One of the things that we have to consider is the juxtaposition of other metals next to amalgam or over amalgam, which would increase the release rates dramatically.

So if you have a pregnant woman who has a gold crown, or perhaps a nickel crown, or amalgams adjacent or underneath, you're going to have a much higher level of exposure, potentially, than you would

in, say, a child in the amalgam trial who may have only a few amalgams.

So it is a confounding factor in our understanding of what the daily dosage would be. It can be much higher in some individuals, very small in others, and variable in the same individual from day to day, hour to hour, meal to meal.

So that's another confounding factor in risk assessment.

DR. KIEBURTZ: We're about to take a break, which we will break shortly, I mean for a short period of time when we break.

I just want to sort of summarize. We've talked both about direct and indirect evidence, the paucity of direct evidence showing any adverse health effect of amalgams, the lack of information, the uncertainty about the actual exposure from amalgams, both the acute and, to a certain extent, in the chronic setting, how to best measure body burden, and apparently, a great deal of variability among individuals in the exposure they experience from amalgam use. I'm trying to think of what else we said we didn't know much about.

DR. GOLDMAN: Can I? That last point that was made, we heard a lot about that kind of thing in

the cases that we heard about over the last couple of days, the testimony that we heard, and if anybody on the panel has factual information they can contribute on that, I mean is there really something that can go on with juxtaposition of these metals, and so forth? I mean, I don't understand that, and so--

DR. KIEBURTZ: And a particular concern about the possibility that the ratios between what is relevant for an adult occupational exposure to what might be potentially fetal toxic, we don't have a good handle on what that ratio might be.

Dr. O'Brien.

DR. O'BRIEN: It's well-established that if two metals are in contact in the mouth, with the saliva as an electrolyte, their electrolytic cell will be set up, and this is a common occurrence. In fact, dentists will come and we get calls over the weekend, in the course of a year. In the case of the amalgam versus the gold, for example, the amalgam will be the end note and will dissolve, electrolytically, rather than just by solubility.

Well, dental schools, we warn the students about that quite a bit. But I doubt if any of these, what I call uninformed dentists, would end up in one of the studies that you find published in the journal.

So that when we look at these published studies, they're done under the best conditions.

DR. GOLDMAN: These cases that we heard about, that could be a possible thing going on with some of these--with, you know--

DR. O'BRIEN: Yes. It can be the effect that it's been reported in the news and actually verified, that the electrical currents produced can produce radio signals and the patients can hear radio stations, and they get a buzz. But the common thing is when an amalgam is put in, for all patients, if they happen to touch the amalgam with a fork--this is universal--they get a shock, or aluminum foil that might be in some of the food that they're eating. So that is another hazard but really is not, wouldn't be a concern for the use of amalgam, but, rather the correct use of it.

DR. KIEBURTZ: Very briefly.

DR. DOURSON: Very briefly.

Okay. Indirect evidence that we've, I think all talked about, I just kind a clarified in my mind, was the testimonies from the public, some of which would probably be characterized as indirect evidence, and also the Fowler studies which were mercury vapor studies but not amalgams, and then

taking that information and sifting it down into the estimation of a safe concentration would be obviously indirect, since it's not an amalgam study itself.

DR. KIEBURTZ: Right, and that in addition to the other animal work we referred to for--okay. Ten minutes. That means ten minutes from right now. Thanks.

[Whereupon, the above-entitled matter went off the record at 2:37 p.m. and resumed at 2:49 p.m.]

DR. KIEBURTZ: Dr. Alderson.

DR. ALDERSON: Mr. Chairman, let me raise an issue for you and the committee, in listening to your discussions, and this again relates to the urinary level issue. We think we heard a number of committee members raising the issue of the acute impact of mercury vapor from amalgams as it relates to urinary levels.

The question we have for you, we're having difficulty understanding the relationship of that concern with the end points or markers of toxicity that are followed through the term of the studies, and clarification on your concern for that would really be helpful.

DR. KIEBURTZ: So let me make sure I understand. Why are we interested in what the acute

levels are, and how does that relate to the later clinical effects?

DR. ALDERSON: That's right.

DR. KIEBURTZ: Why would we be interested in it, for example?

DR. ALDERSON: Or how does it help us assess the risk?

DR. KIEBURTZ: Right.

DR. ASCHER: I would say it doesn't help you, necessarily, to look at the risk, but theoretically, if you have a fetus that is exposed to 30 micrograms per day, for example, then you look two years later, because of the redundancy in the CNS, you might see nothing. It will take 20 or 30 years to see an effect.

So I would have liked to know what the urinary levels or the exposures are at the time of placement of the amalgam, because there may be a cumulative effect of exposure to very high levels of mercury that may not be manifest until decades later, especially--

DR. KIEBURTZ: I'm just looking to see who we're missing before we go too terribly much longer. Not too many. Okay. People are filtering in.

I think the other issue, at least as I've

heard, is that if you get a spike up in concentration for some brief period of time, and that happens to happen at a critical part of fetal development, that could be not a long-term consequence but a very short-term consequence of two things happening at once that will critically affect one another.

Other--if you want to speak to the issue of acute level changes with manipulation and how--or what the concern is as how that might relate to clinical phenomena.

Dr. Diamond.

DR. DIAMOND: Yes. One thing, it might provide some kind of insight into some of the situations where people have developed some sort of reaction very shortly after placement of the amalgam. You know, in studying that, you know, it may be able to provide some insight into it, even though the people who might be studied may not react at all, but at least it might provide some exposure level that could possibly be used as a benchmark for individuals who may be found to be susceptible for that sort of acute response.

DR. KIEBURTZ: Go ahead. Did you want to speak?

DR. DOURSON: Yes. Right to your

question. I would think it's reasonable to ask our colleagues at FDA to search for safe concentrations of mercury vapor after an acute or short-term exposure. I would expect that such safe doses are either at the chronic level or higher; most likely higher. And I think that would be fruitful.

I've checked the ATSDR Web site, which is an agency that has a habit of doing that, and it wasn't there. But that doesn't mean someone hasn't done that worldwide, or maybe--and our FDA colleagues are quite adept at doing that.

DR. KIEBURTZ: Some of the toxicokinetic studies involved short-term eye administrations in normal volunteers too.

DR. DOURSON: That's true. There is one that was in the literature on that.

DR. KIEBURTZ: So inhaled. So you get some sense of what--

DR. DOURSON: Right.

DR. KIEBURTZ: Well, I don't see anyone eager to contribute, to comment right now. So I think we have discussed question one. Does anyone else want to comment on question one?

DR. AMAR: Just I heard from the FDA, asking for surrogate markers other than urinary

excretion of the mercury, and I was wondering, particularly in a complex toxicity problem such as the potential mercury exposure, could we suggest to add a salivary content and exposure of mercury, similar to what we do with clinical trials where we use two or three surrogate markers that are converging towards the same issue? I think that we should suggest other surrogate markers. And one of them could be for the acute, or later on, the salivary content of mercury.

DR. KIEBURTZ: I don't know about salivary mercury measures.

DR. AMAR: I have it in front of me, so it's in the literature.

DR. KIEBURTZ: Dr. Honein.

DR. HONEIN: I have a question, I think for FDA, which relates back to sort of the first day's presentation on mercury being up-classed to Class 2 instead of Class 1, and my recollection of what was said about devices is that special controls could be put in effect for that, and I was wondering if 1D, and sort of the issue of reproductive outcomes--I think that's 1D. Anyway, the possibility of looking closer at people who are occupationally exposed to dental amalgams for reproductive outcomes, if that's an example of something that could be a special control

for the future, because I feel like that data gap is huge, and perhaps at the highest levels of exposure, which I assume would be the occupational exposures, we might gain more insight on the reproductive outcomes.

DR. KIEBURTZ: Let me just draw a distinction between occupational exposure monitoring and the device. So you're talking about those with occupational exposure; is that correct?

DR. HONEIN: Correct.

DR. KIEBURTZ: Do you want to comment on that, Ms. Rosecrans?

MS. ROSECRANS: Susan, will you see if you can find Linda Cantu, too, please. Just see if she can come in.

Obviously we regulate devices, and OSHA does the OSHA part of it. Special controls can be a guidance document, it can be a patient registry, and then the law gave us "Other," and whatever the circumstances fit for a device, if we can identify and they can provide reasonable assurance of the safety and effectiveness of that type device, then that allows us to keep it in Class 2, cause we try to make it the least burdensome level of control needed to provide that assurance of safety and effectiveness.

So I think the overall answer is yes

because we have that category of Other.

DR. KIEBURTZ: Let me just caution the committee--our question is about the white paper, and the task of drafting regulatory language and labeling things, and special controls takes a lot of time and effort. We have not talked about that nor have we been charged with that. So we may make a recommendation to the FDA that they should think about that, but I don't want us to start getting into a discussion about what we think the right labeling pathway or special controls are for the device.

Dr. Alderson, did you--

DR. ALDERSON: I totally agree with you, that is a whole other, probably advisory committee meeting.

DR. KIEBURTZ: Dr. Goldman.

DR. GOLDMAN: While you're up here, cause in the course, over the years, of regulating this product, do you have data on the exposure levels that are achieved when the product is used, either applied new or drilled through in patients?

MS. ROSECRANS: I'm afraid I wouldn't be the person able to answer that question. Dr. Alderson?

DR. ALDERSON: I seriously doubt that we

have that data at all. I'm not aware of it, if we do.

DR. KIEBURTZ: Dr. O'Brien.

DR. O'BRIEN: Do you have a name at OSHA who's interested in mercury? I'm not going to get into the issue. Just these links between the agencies are very hard to find. Is there a mercury person over there?

MS. ROSECRANS: I don't know about a mercury person but we do have a person at OSHA that we speak with.

DR. GOLDMAN: Actually, NIOSH has a person and they've written a recommended standard, and so forth. Over the years, they've worked on mercury alot.

DR. KIEBURTZ: Dr. Dourson.

DR. DOURSON: Yes. Just a small addition to my prior statement about, you know, estimated, a safe short-term concentration. That ties into Dr. Goldman's prior point about reproductive or developmental toxicity. So, in utero exposure from when you are pregnant, and then at a high short-term exposure, and if you've got a safe dose on the basis of a short-term exposure, it should look at those kind of studies, and use those kind of studies, in part, for determining such a safe concentration.

DR. KIEBURTZ: Dr. Klaassen.

DR. KLAASSEN: Yes. I'd just like to come back to the adults exposure, and ask a question of the dentists in the room, and that is, have you ever made amalgam fillings for a patient and the patient really truly had what you would expect from elemental mercury poisoning?

And from occupational exposure, we know that one of the most easily measured things is trembling. So has that been experienced in your practice, or has this been indicated frequently, or even a few times in the literature?

DR. KIEBURTZ: So I take it the question is does anyone have a personal, sort of clinical experience of after setting mercury-containing amalgams, of someone looking like they have classic mercury poisoning?

Dr. Taylor.

DR. TAYLOR: I've not seen that, and I'd also add that I'm comfortable to say that we wouldn't, in dental schools we wouldn't even be taught to look for that. So we wouldn't even ask about--if we were to call a patient, and other practicing dentists chime in--if we were to call a patient as a follow-up, say we had an extensive procedure and we did a large

amalgam, and we were concerned about how the patient was doing, that would not be on the check list.

DR. KIEBURTZ: Dr. Diamond.

DR. DIAMOND: Yes. I'd like to respond to just the question about standards, is that in industry what we do, we look for various standards, I guess the ASTM or ISO, and if none exists, then we look to the literature to see if there's some established levels, or sometimes to proceedings that, to decisions where insights that come out of meetings such as this, for some kind of guidance with regard to that, and then that's discussed with the FDA. But there's always a scientific basis behind that.

DR. KIEBURTZ: Dr. Zero.

DR. ZERO: Part of my question earlier about hypersensitivity was to understand this 6 percent and what that meant, and what was the full range of the expression of that, and the reporting of that. So I'm not sure if this is included in that, I have no way of knowing because I don't know what that means.

DR. ASCHER: Right. You know, what I was getting at there is there are some things that we know for sure, that elementary mercury will produce. And then there's these hundred other things that people

think it might be associated with. The one thing that everybody agrees with is how steady your hand is, and if no dentist has ever heard of that, or experienced that, then it's not a problem for the adult. Correct? Or is my logic wrong?

DR. TAYLOR: We wouldn't know. We wouldn't know.

DR. ASCHER: If you can't hold your hand still, you're going to go to somebody.

DR. KIEBURTZ: It may happen two days later.

DR. TAYLOR: That's okay.

DR. ASCHER: They may not associate it with--it doesn't sound like anyone has seen a clinical standard phenomena of tremor after placement of amalgams.

DR. KIEBURTZ: I guess I would then say we don't have one example, from what I've just heard, of anyone ever being poisoned by a classic example of what happens with elemental mercury exposure; is that correct?

DR. TAYLOR: Well, we have a limited set of practitioners here at this table, for one thing. But we have a huge opportunity to get a many of these unknowns. NIDCR has established three very large

practice-based research networks, and where the questions that have come up from the testimony here, these past couple days, as well as the questions that we are raising, we have the exposure going on daily, and we also now have an organized network from which we could develop, suggest topics to discuss. The turn-around time could also be potentially very quick, to get at some of these unknowns that are important. For example, the question about trembling, and acute manifestations of mercury toxicity.

We certainly have a network in place. When I say "we," that is the people of the United States has a network in place to be able, to potentially be able to get at some of those issues.

The sample of practitioners here could answer questions but I certainly wouldn't draw any inference on our experiences as they would be generalizable to the population.

DR. KIEBURTZ: Dr. Fleming.

DR. FLEMING: Yes. I'll try to address the issue of the tremor. The first comment I would make is it's not like our patients drop dead over the hitching post when they leave.

So what I think the issue is is that very often, the first person they call when they have a

problem of that magnitude or that sort, there'll be accompanying symptoms of anxiety, sleeplessness, perhaps excessive sweating, urination, things like that, which I have seen in my practice, reported by patients who were treated elsewhere.

The issue there is, again, the patients are more likely to call their physician, not the dentist. They're not going to call a dentist and say I am sick, I am anxious, I cannot get out of bed, and it may happen the next day, the next week, it may take many, many months, or perhaps years of accumulation, which doesn't fit the classical pattern of an acute mercury exposure such as in the chlor-alkali industry, for example.

DR. KIEBURTZ: Ms. Cowley, did you want to add something?

MS. COWLEY: Yes. I can only say amen to what Dr. Fleming said. One of the hardest, shall I say perhaps the most dangerous situations we have in this country, is this incredible gap between dentistry and medicine, and speaking from the TMJ perspective, our implant patients are treated by the dentist, they get implants by the dentists, and just like examples we heard from the patients yesterday, the dentists do not address any of the medical health issues. It is

totally out of their realm.

But then, when you go to a physician with these incredible sequelae, there is absolutely no understanding of what you have just gone through, or a year later, and the implant is in your brain, and so forth, and so on. So if anything this, the FDA has done, is to bring together neurology with dentistry in this room today. I think you have done a heck of a service to the American people and I applaud you.

DR. KIEBURTZ: Dr. Rizzo.

DR. RIZZO: From the point of view of neurology, we frequently see patients with tremor. I'm not aware that it's common, or, really, even occurs, that we see people who have tremors as a result of amalgam restorations. When we see people with tremor, it's generally from exaggerated physiologic tremor, Parkinson's disease, inherited disorders.

From the perspective of a neurologist, when we evaluate tremor, amalgam isn't even on the radar screen. So that's a different perspective.

DR. KIEBURTZ: Dr. Burton.

DR. BURTON: I guess I just have to, as an oral max facial surgeon, have to answer Mrs. Cowley's comment about dentists, and I've been fortunate

enough, I've worked with her for many years on the dental products panel. But I wouldn't say that the dentists are clearly "quite off the screen." There are large numbers of us, both in oral medicine and in oral max facial surgery, and oral pathology, and probably other specialties. I mean, I've worked in a hospital for 25 years, and most of my dental colleagues, at least the dental school I work with, most of them claim I'm not more a dentist than the guy who cleans the hallway, at this level of education.

So I guess I would defend the dental profession, a little bit in this arena, in the fact that I'm not sure that we're quite that unaware, nor that unobservant, or perhaps unconcerned to not pay attention to the symptoms. And I will tell you that there are many disease processes that are picked up by the dental profession, because of the fact that those patients do bring symptoms that are somewhat inexplicable at times to them, that they've taken to their family physician, internists, etcetera, and have not had answered.

DR. ZERO: Just a comment regarding the availability or line of health care exposures for neurotoxins or other toxins that we deal with in dentistry. My particular practice, we can identify

neurotoxin effects with a temporal pattern. I think the discussions I've heard, these last two days, would again maybe take amalgam, proposed mercury toxicity out of that exposure, so we may not see that because-- or we may not see, or there may not be an existing acute pathology or toxic effect.

So in my practice, as well as in our dental schools= exposures, we just don't, I just have not seen that, in particular.

DR. KIEBURTZ: Dr. Goldman.

DR. GOLDMAN: Yes. I mean, I think it's important to understand, in terms of the way the clinical world has looked at this issue, that I mean, I've been involved in a number of exercises to come up with just environmental history questions for physicians to use, and triggered by different indications, and most of us were taught, I was certainly taught that exposure to mercury from amalgam is minimal, and that one shouldn't think about mercury toxicity from amalgam.

I have never included a question about recent dentistry on an environmental exposure questionnaire that I've worked on. It's never been suggested.

Now I will have to say there is something-

-I was recognizing this, and I appreciate your asking that question, because there is something that's happened in the last couple of days in these discussions, to kind of at least move me a little bit further over into being a little more concerned than I was before, and I will tell you the two things that concern me.

One is that some of these exposure data, the range of exposures then--and there is a lot of new science, even though the white paper kind of implies there's not. But then it uses the studies, and there are a lot of new studies that do show, that do document an association between, you know, amalgam and levels of mercury in urine, and more than I would expect, given what I was taught. And I'm sure that that's true for the others who were taught what I was taught, because we were all taught that at one point.

And so I'm taking it more seriously, that there could be exposures, A. Two, that there could be acute exposures and that there could be symptoms associated with that, and that maybe it is worth inquiring about whether there's symptoms. We haven't done that inquiry, and I just took a quick look at PubMed, just to see, you know, if someone's published on that question, and there are no publications, other

than, you know, the Kingman study included a question about tremor in the questionnaire, and that's about it.

You know. So I think this is an area where I don't think we can make a conclusion based on the literature, you know, it's kind of silent, but I will say on an indirect basis, I am more concerned about this today than I was last week. Whatever that means.

DR. KIEBURTZ: Movement disorder neurologists, of which I am one, do ask about metals, but we don't tend to ask about dental work. So there's an association--you know, we think about occupational and industrial exposures more than we would think of--because of tremor.

DR. RIZZO: And when you suspect, you check, and you do a 24-hour urine for heavy metals, and the condition is also related to the company that it keeps in terms of signs, and there can be evidence of neuropathy, and so forth. So we do look but we don't ask about mercury amalgam restorations.

DR. KIEBURTZ: No.

Dr. Sacco.

DR. SACCO: I would just caution about the use of registries, like we've been hearing about, try

to look at these questions, or even questionnaires. I think if we wanted to look at this, we would do studies, probably a little larger scale studies, and some of them designed, perhaps like the Factor-Litvak study, and perhaps like the Kingman study, which did show us, in very well-documented outcomes, with an exposure of interest, that there wasn't at least a dose response relationship.

A registry with just questionnaires attached to it on dental patients may not give us the answer.

DR. KIEBURTZ: Okay. Question two.

Does the draft FDA white paper objectively and clearly present the current state of knowledge about the exposure and health effects related to dental amalgam. We're going to go around.

Dr. Porter.

DR. PORTER: If you're going around, you can start over here.

DR. KIEBURTZ: Very good. Yes or no?

DR. PORTER: No, and I'm only going to stick to the one area in clinical pharmacology that I think that I've certainly emphasized in this meeting, and that is that I think that there is a very great lack of a good PK and pharmacologic analysis of the

data in this paper. There's enough data here, that you could almost consider a second paper.

I think that it should include absorption distribution, excretion, metabolism I'll leave out, although it's important to note, as somebody did, that it doesn't stay elemental mercury in the body.

It should include an evaluation of the two human studies which are autopsy studies, looking at brain levels, with an emphasis on the variability of these numbers as well as the outliers, and preferably with some modeling.

It should look at the issue of accumulation for which there is some very good animal data, at the very least. It should conclude the dentist study, the Woods et al study, that shows that there are high urinary levels in some of these patients, or at least in some of these groups. It should address the issue of excretion. Is this urinary or it is mostly fecal? And is the urinary technique that we've been using really the best technique to use, to judge what kind of exposure a patient has? I'm personally very doubtful of that.

Those are just the highlights, I think, of what a good pharmacologic summary would be, and I would guess that Dr. Larry Lesko's group is still here

at the FDA. If it is, he would be an ideal person to contact and work with, to generate such an addendum or a section, or whatever you would like.

But I would say that in this regard, the white paper is deficient.

DR. KIEBURTZ: I'd just note for the record that our first four votes don't technically count but I still want to know what you think.

Dr. Jang, who is a member of the PCNS Advisory Committee, who's the consumer rep from the Advisory Committee, who, on our committee is a voting member, was scheduled to attend. She couldn't attend because of a personal emergency, so she's not here.

Dr. Diamond.

DR. DIAMOND: I have to agree with Dr. Porter. I don't think it reflects--let me qualify that. Taken as a whole, it doesn't. From a perspective of reflecting the current state of knowledge with regard to controlled clinical studies, it does, and I think it does an excellent job at pointing out the benefits as well as deficiencies of all of these studies.

So from that perspective I think it does. Where I think it does not is in a broader picture, by not looking at the studies, by excluding a lot of

studies you're missing some of the potential insights that may reflect, that might provide some insights into some of these other reactions that, you know, would not necessarily be seen in some of the more controlled studies.

DR. KIEBURTZ: Dr. Fleming.

DR. FLEMING: I would go with no. The two reasons that I would give are the tremendous data gap in the methods of risk assessment, and connecting that to symptomatology, very difficult to do, but we still lack that information. And then secondly, allergy. Frank allergy is simply not quantified.

DR. KIEBURTZ: Okay. I just want to reiterate to the committee, does it present the current state of knowledge, not whether the current state of knowledge is adequate, but does the paper adequately state what the current knowledge state is. So just taking your comments at face value. I'm not asking you to change what you said, but just bear in mind, it's not a fault of the paper if there's uncertainty. It is a fault of the paper if it inadequately addresses a question or a knowledge state.

Ms. Cowley.

MS. COWLEY: Not being the scientist on

this panel, I don't think I can adequately assess that, so I will pass.

DR. KIEBURTZ: Thank you.

DR. ASCHER: I have to agree with what was said. I just think that the paper is way too focused and not broad enough in considering a lot of other things that have been published.

DR. KIEBURTZ: That's a no.

DR. ASCHER: It's a no.

DR. KIEBURTZ: Dr. Klaassen.

DR. KLAASSEN: I would say yes, I think it does state and summarize the current knowledge. I don't think it tells us everything that we would like to know because it's basically not known, and it doesn=t give and suggest data gaps but I'm not sure that that was part of the question.

So as far as going back to the original--you know, does it state and summarize the current knowledge? I think it does that very well.

DR. KIEBURTZ: Dr. Rizzo. Please turn on your mike.

DR. RIZZO: I agree with Dr. Klaassen. I think yes, it does a good job summarizing existing evidence. I think that it could have done a better job in terms of grading. I think that it could have

given reasons for excluding studies that weren't included in the data tables.

But, on the whole, I think it does a very good job at summarizing what is known, and most of the fault with what is not known is that the research hasn't been done.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I think there are deficiencies, so because there are deficiencies in clearly reviewing the literature, I'm going to vote no, and the deficiencies are some things that people have already outlined. I think the literature search strategy may be an issue. Weighing of the evidence. I'd like to see a little bit more weight and adjustments of the evidence, addressing vulnerable populations, and I think as mentioned, I think gaps in the literature do need to be identified, even though it may not have been the remit of the paper.

DR. KIEBURTZ: Dr. Taylor.

DR. TAYLOR: I'd vote no, very consistent with Dr. Sacco's comments. I'd also include a concern for assessing the quality of the previous reviews from which this was based.

DR. KIEBURTZ: Dr. Li.

DR. LI: I would vote yes, although this

white paper is not broad enough, and having some deficiencies, but based on the two new studies that have recently published, that was carefully reviewed, and I would have to think about the evidence pointing to the results of it.

DR. KIEBURTZ: Dr. Olson.

DR. OLSON: I would vote yes. It asks about the current state of our knowledge, and certainly we know there are gaps, there are big deficiencies of our knowledge that we don't have, especially about subsets of vulnerable populations, namely people who may have this substrate upon which a mercury burden would give them additional, or give them de novo problems.

But, on the other hand, when one looks at the recent articles, especially the two in the JAMA, that were well done, and even with their deficiency, that we would like to see them go out longer in these folks, and I assume that perhaps they would do that, I think it gives us some good insights into the effect of these devices.

DR. KIEBURTZ: Dr. Honein.

DR. HONEIN: I would say yes on number two. I think it is an objective and clear presentation. However, I would agree with the

comments that it would be helpful to see an expansion of the white paper to include a broader range of papers, and both other research strategies as well as potentially including more of the original 200 papers, or a clear rationale for why each was excluded.

DR. KIEBURTZ: Dr. Luster.

DR. LUSTER: I have to say no. I felt that the neurological issues were very well covered. There were other issues, maybe not so much as frank allergic responses, but there's been a lot of issues with autoimmune disease and publications that weren't included, and given I don't know the literature, I don't want to make any specific comments on them. They may not be that strong, papers, but it would have been a more balanced presentation if it was included as well, so we could at least see it.

DR. KIEBURTZ: Dr. Amar.

DR. AMAR: I have to say no for the reasons that I alluded, really, to the searchers. Most importantly, if a position paper is here to give the current knowledge, it should be all-encompassing, including the whole breadth of the literature, and there is still some literature missing in the white paper.

DR. KIEBURTZ: Dr. O'Brien.

DR. O'BRIEN: I would say yes, but with a caveat, and that we add to that sentence. Does the draft FDA white paper objectively include, present the current state of knowledge about the exposure and health effects related to dental amalgam? And I would add "used under clinical research conditions," because in terms of the public, they should know that there's a vast difference of what goes on in a research clinical study and the average practitioner's office.

DR. KIEBURTZ: Dr. Dourson.

DR. DOURSON: I find that the FDA white paper clearly and objectively presents the state of knowledge on the health effects from chronic exposure related to the dental amalgams. I would like the white paper to emphasize, estimating a short-term safe dose and a short-term concentration, and better characterize case studies, which they specifically did not, were asked not to do.

In contrast, I think that the characterization for the exposure was deficient and that in what should be done is to determine or find the release of mercury from amalgams as it ages in vitro and in vivo, giving both average and upper bounds, and for different amalgam types.

DR. KIEBURTZ: That was a no, I think.

DR. DOURSON: I think because--

DR. KIEBURTZ: Or is it a yes?

DR. DOURSON: --the sentence--because the sentence says "exposure and health," I suppose the answer would be no.

DR. KIEBURTZ: I don't want to--I was interpreting. I should have asked you. I don't want to--

DR. DOURSON: Well the sentence does say exposure and health. I think the health is well-characterized; the exposure is not. The word is "and" and so therefore the answer has to be know. I'm sorry.

DR. KIEBURTZ: Thank you.

Dr. Goldman.

DR. GOLDMAN: My answer would be no and I do think that the paper was written clearly, and I do think that it was written from an objective point of view. So if you just read the question literally, it would be hard to say no. But the fact that the criteria for selection of studies is never laid out and the criteria for ranking or rating studies are very unclear, and in some cases I don't agree with some of the things that were said about studies in terms of, you know, it's implies, for example, that

occupational cohort studies always have to have a non-occupationally exposed cohort as well, and which is not the case, and there are other things like that.

So I think that there's some problems. I felt that there were some deficiencies on the outcome side, in terms of a lot of studies related to immune effects, cardiovascular effects, developmental neurotoxic effects, just a few of those were not reviewed, most of which I think came about because of the choice to use the ATSDR and the EPA reviews as a starting point, which I think may have been the wrong decision to make, because the question that they asked us, and that they seemed to be asking, were different questions than the questions that EPA and ATSDR were asking.

The exposure data is also not complete, and I could easily find what I considered to be relevant and important exposure information online, that is not reviewed in this, and so there may have been criteria that were used to not include those data, but I don't understand what those criteria were, on what the basis was for certain studies to be picked out and others not. Then I have to say that it was not objective and clearly presented.

DR. KIEBURTZ: Dr. Zero.

DR. ZERO: I would say no, based on many of the points raised, particularly, in my case, would be lack of identifying the limitations of the available data. I think that just reporting data and giving it as it is--although there were some qualifications of the data in terms of generalizability, that I think there needs to be more discussion about the limitations of the outcome measures that are currently being used, and I think a very important thing is the completeness of the data in terms of the research strategies, which was also raised earlier.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No, and again, just based upon the generally accepted criteria for a quality systematic review, does the clinical premise make sense? I think we've had a big discussion about, questions about even the underlying premise and some of the underlying assumptions. The search strategy was given but, again, we have major deficits in terms of the way the search was carried out, methodologically. There were exclusion criteria but we don't have the list of papers that were excluded, or the reasons why they were excluded, and again, just looking at some of the materials we have, and as was

stated, there seem to be other papers available that may directly be relevant. There's no statistical analysis of the data, looking at odds ratios or risk factors, etcetera.

So from those standpoints alone, I'm concerned.

DR. KIEBURTZ: Lynn, could you turn off your mike.

DR. GOLDMAN: Yes. Sorry.

DR. ZERO: I would vote no. The primary reason was, in at least my opinion, the sample strategy, again, was concerning. A single search engine sample would exclude possible other sources, especially within other divisions, departments in the agencies, or within the Government, Federal or local, that could help provide more information on mercury exposures as well as in relationship to the primary concern, and I too would feel that the lack of the information regarding why exclusions of some studies deferred from a full evaluation.

DR. KIEBURTZ: Dr. Ng.

DR. NG: I think that the paper is fairly well-written but I would also vote no, for the same reasons that have been reiterated, particularly with the limited literature review and the data gap that I

think exists.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I would vote no, for a lot of the methodological reasons that have been given with respect to doing a systematic review. I think they fall short of the sort of current gold standard. Even if it doesn't identify the papers, I think it really affects the credibility of the white paper. I would question the presumption of--I'm assuming that the older reviews are still complete and that the standard that we might expect today, and I would consider reevaluating older studies as well in the context of newer knowledge.

And I would look to see more consideration to collation of information across the studies. I think the draft paper really goes study by study, individually, and doesn't really think, particularly from a quantitative point of view, about the information across studies.

The other big issue that I have with the paper is that it's very focused on comparison of mean levels in exposed, non-exposed populations, and I think it's absolutely critical to think about the distribution, whatever marker you look at, whether it's urine mercury levels or any other marker, it's

critical to look at the distribution of those markers in the population that might be exposed to amalgam fillings, and obviously with the dental talking about essentially a general population. I think there's a lot more information in these papers about the distributions of exposures, and I think when you start looking at information, you raise the concern that there are some subjects in the population that may be getting levels which are not too dissimilar from levels which have been associated with neurologic deficits, and so on, in certain studies.

I would also, I think--maybe this is going beyond a white paper--but many of the recent studies, it wouldn't be hard to contact the authors and get relevant data which would help address the questions at hand.

DR. KIEBURTZ: Dr. Burton.

DR. BURTON: I'll vote no, because of the, really, as the last person--everybody else has sort of said everything. I have to be very honest, though, that I think it's sort of a semantical answer, because I think that those--I have to be honest--I thought I would vote yes because I think that the people who did looked at the question and I think that the white paper does, within limitations, objectively clear

that, it clearly presents the state of knowledge, but I think that we're all drawn to the various shortcomings, whether it's search design or other portions of that, that make us not support that, I guess like I said.

So it's a no but it's a bit of a semantical no, and I think those who voted yes voted that because they answered the question, and I think that, really, I think this is an important vote but I think more of our concerns really are addressed in the next question in terms of that, but I will vote no.

DR. KIEBURTZ: We have a procedural dispute between the executive secretary and the chair. In my committee I vote, as chair of the device committee you don't vote unless there's a tie, but I'm going to vote anyway, so--

[Laughter]

DR. KIEBURTZ: Using my prerogative. I actually vote yes. I acknowledge the concerns about the inadequacy in terms of a systematic review of the data but I think I--this is an unusual circumstance. Usually, in drug approval, where I mostly work, you would get a document from the sponsor and a document from the FDA, and they nicely play off one another with different interpretations of the same data,

different bodies of data being brought in in those documents.

Here, it was a little bit of a challenge in that we basically had a solitary document, so I took it upon myself to act like the devil's advocate, to go out and find everything they didn't find. In fact, there are many things that were not noted here and it was impossible to know why they weren't here. But the substance of them was no different, in my opinion. Now, that's not something one should need to do, theoretically, in a systematic review, it should be all laid out so that you can decide whether you agree with the decisions that were made, or not.

But I think the findings were objectively presented, I think they were clearly presented about the knowledge.

I think though--but--yes, but--there was not a sufficient categorization of the un-knowledge.

There is a significant, a fairly clear and objective statement of what we do know, but it is balanced by a great deal of, a lack of knowledge, and I think it is worth, in this kind of setting, quantifying what relevant un-knowledge there is, even though it is not the FDA's task, at least in my understanding, to go about conducting that research.

It is part of understanding the exposure and the health effects, to be able to clearly identify what is not known and is potentially relevant. So it's a yes, but. I would say that the, if you count my vote, it's thirteen to six. Whoop. Thirteen to seven. So it's for the record, for question two, thirteen no, seven yes. Deep breath.

Question three, which you see on the screen.

Given the amount and quality of the information--mind you, you could vote no to two and yes to three.

So given the amount and quality of the information available for the draft FDA white paper, are the conclusions reasonable? I would say Roman numeral six, the final paragraph, would be taken to be--it says "update slash review, conclusion." I could read that, just--"Based on an evaluation of the extensive literature reviews conducted by ATSDR and EPA, and an assessment of the health effects based exposure reference values for elemental mercury derived by those agencies, and WHO and ACGIH, no information was found that would change the comprehension of health risks for inorganic or elemental mercury and mercury in dental amalgam.

An effort to obtain new information that might improve understanding or change risk estimates for the use of dental amalgam, 24 peer-reviewed scientific articles, published primarily since the reviews conducted by ATSDR and EPA, and 10 peer-reviewed articles from ATSDR and/or EPA reviews deemed to contain important and relevant information were critically reviewed. Period.

Compared to previous analyses performed by USPHS, Public Health Service, no significant new information was discovered from the review of these 34 articles, that would change the risk estimates by FDA for the use of dental amalgams.

No significant new information was discovered that would change the risk estimates by FDA for the use of dental amalgam. That's the conclusion.

The question is: Based on the information in the white paper, amount and quality of information available for the draft white paper--available for the draft white paper, not necessarily in it--are the conclusions reasonable?

So I'll go in reverse.

Dr. Burton.

DR. BURTON: I'm going to vote no, and like I said, I feel that more of the issues revolved

around this question because I think that it's in the conclusions where the shortcomings of the white paper really come into play. It's because the gaps in knowledge that we've all discussed for the last couple of hours in the white paper, and in the information that we have available to us at this time, raises questions, in my mind, whether those conclusions are reasonable, because those conclusions really make you feel that you're pretty comfortable with the outcomes and there really are not any potential risks.

And in my mind, I'm not sure that those risks have been quantified out, where I'm comfortable with those either, but I guess that that the draft came to conclusions of safety, at least in my mind, are not fully verified from the information that was made available to us in that.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I would say no, and it's primarily driven by the fact that I think there are marker levels in the population which may be consistent with modest risks to the subjects concerned.

DR. KIEBURTZ: Dr. Ng.

DR. NG: I would also vote no. I think that with additional information, the conclusions may

still be the same, but without that additional information, it's really hard to make that determination.

DR. KIEBURTZ: Dr. Zuniga.

DR. ZUNIGA: I would vote yes, the primary reason being the level of some of the prospective studies were convincing enough to me, that within the confines of the 34 articles I read, it supported the conclusions.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I think a qualified no. I think if you just read what it says, no new information was found that would change anything, I think that that's factually correct. They didn't find any new information that would necessarily change anything. But I think the spirit of the question is is there something here that we or the public needs to be--or health professionals and the public needs to be concerned about because of a lack of information and that was not addressed, and those are all the issues that we were talking about.

DR. KIEBURTZ: Dr. Zero.

DR. ZERO: I also vote no and I'll leave it there.

DR. KIEBURTZ: Dr. Goldman.

DR. GOLDMAN: I'm also voting no, and on two bases. One being that the levels of exposure, the newer studies indicate that they're higher than FDA had once thought, and second, that there really isn't evidence of safety for the fetus.

DR. DOURSON: I have a hard time distinguishing these two questions but I'll try.

I agree with the FDA white paper, again, that the review of the prior information that focused on the chronic health effects is adequate and well done, and does not change the chronic health values. I'm agreeing with that.

However, because the FDA talks about comprehension of health risks for amalgams, and that includes not only the toxicology but the exposure information, I find the exposure information not adequate, in my opinion, the way it's now stated, to be able to say that it is with or without risk.

I'd just like to see the exposure information and compare that to the chronic health values, which I think are well wrought, and as I said before.

The last part, it says the review of the 34 articles. I don't see any of those articles changing the chronic health risks that we now have,

but, again, I'd like to emphasize the inclusion of case studies which were specifically excluded, and the development of a short-term health risk value which might give us a handle, once we have the proper exposure information in hand, to quantify whether we're expecting health risks from the acute and episodic episodes.

DR. KIEBURTZ: Dr. O'Brien. I'm sorry.

Dr. Dourson, could you just reiterate what your summary is.

DR. DOURSON: I think overall would be still a no.

DR. KIEBURTZ: You just said no, qualified.

Dr. O'Brien.

DR. O'BRIEN: I'll just say no, briefly.

DR. KIEBURTZ: Dr. Amar.

DR. AMAR: No.

DR. GOLDSTEIN: Based upon the charge that FDA people had, which was to review the data, post '97, and look at the--I would have to go back, to say yes, the conclusions are appropriate. However, on the other hand, when I look at the earlier data and where the really reference exposures were established and looking at the current levels of potential exposure

from amalgam, I'd basically be scared to death, to say that--not to be rethinking about how to evaluate this data. But based upon what has been reviewed, there isn't, I don't see very much evidence that would require that there's a concern here right now.

DR. KIEBURTZ: Dr. Honein.

DR. HONEIN: I would say no to this question because I think it's critical to identify the research gaps before drawing conclusions about whether or not there's additional concern.

I think that there is serious research gaps, particularly with respect to reproductive outcomes and fetal exposures, and I think the occupational studies that were included in the 34, while they are not perfect, do suggest levels of exposure that could be of concern, both directly to those adults and for any reproductive outcomes.

DR. KIEBURTZ: Dr. Olson.

DR. OLSON: Again, reading the question rather literally and straightforwardly, I would say ye, because, again, it asks us to consider the information since 1997, and that goes to the amount and quality of the information available.

I am troubled by the fact that articles were excluded that may shed light on this. However, I

also heard that other information was looked at and doesn't change anything from what we have already seen. Therefore, I will stay with yes.

DR. KIEBURTZ: Dr. Li.

DR. LI: My vote is also yes, although there are a lot of deficiencies and not broad enough, the information presented, the second question was adequate. I also did some readings, reviews of those papers, not including, including this review, and I cannot find the information that would change this vote.

DR. KIEBURTZ: Dr. Taylor.

DR. TAYLOR: I'd say no and I'd reiterate the concerns expressed about methodological shortcomings as well as perhaps not sufficiently recognizing the gaps in knowledge.

So with those omissions and shortcomings, I would think the conclusions are not reasonable.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I'm going to say a qualified yes, based on, again, literally reading the question, which is given the amount and quality of the current information, I think the conclusions reached are is that there is no real change in the older recommendations, based on what--I recognize there are

gaps, but I think given what we have in front of me, and given some of the quality of the data reviewed in this, I don't think that the health risks have changed, in my mind.

DR. KIEBURTZ: Dr. Rizzo.

DR. RIZZO: I would vote yes. I think that the review of the available evidence since 1997 doesn't show any objective new reasons to be concerned. There are clearly deficiencies in the way the review was conducted with regard to exclusion of some papers, which probably, however, wouldn't change the conclusions.

There are gaps in the research but that's not the fault of this white paper. So I vote yes.

DR. KIEBURTZ: Dr. Klaassen.

DR. KLAASSEN: Yes. I would also vote yes and I would like to explain maybe why. In regard to, you know, looking at the literature, and if they use the appropriate search engines, and what have you, is a potential concern. However, I guess one thing that minimizes that concern, I haven't heard a lot of papers that have been announced here, that they have missed major papers.

I recently have reviewed the literature for a textbook in pharmacology, and at the present

time am editing a book for toxicology, and I'm not aware of any major papers that would alter the conclusion, even though they maybe should have done it. So it might be an academic exercise. In regard to exposure, yes, I would like to have more information on exposure, but they were supposed to review the literature, not do experiments, so I can't criticize them on that.

I think a question about fetal exposure is very interesting and is an area that more research needs to be done. Again, it wasn't their job to do experiments to solve this problem, and I think, you know, the other major problem is, you know, the gaps in knowledge, and, again, I don't think it was these people's responsibility for this white paper, and therefore I think the conclusions are reasonable and the amount and quality of the information, I think is quite good.

So the answer is yes.

DR. AMAL: I think the paper is objective and my problem is, though, that we're looking at the keys under the light. There's just too many things that we don't know, too many things that have been excluded.

I think this was an opportunity to go back

and look at some of the issues that we talked about, for example, what does urinary mercury excretion mean? What does mercury levels in hair mean? And how can we take those together and come up with a reasonable exposure assessment and opportunities to look at susceptible populations, to look at variability, and none of those were done.

So although the conclusions are based upon what's presented, I have no problem with that, I think it's very limited, and I vote no.

DR. KIEBURTZ: Ms. Cowley.

MS. COWLEY: I would vote no, if I had a vote, particularly based on the absence of information on the vulnerable populations, and those vulnerable populations that we have yet to identify in the future with genetic testing, and so forth.

It's as though everything is just fine and yet we know there are specific risks, we don't know how to manage the risks from this, so the semantics say yes, the conclusions were reasonable, but we, I think if anything, this shows us how much we need to know to make reasonable decisions as patients and consumers.

DR. KIEBURTZ: Dr. Fleming.

DR. FLEMING: I would vote no. I cannot,

for two reasons, vote yes. One is I don't think that we have, as I said earlier, considered the data gaps with respect to risk assessment and how we quantify that, and secondly, my conscience won't let me vote yes.

I've treated thousands of patients through the years and my assessment of this is that it--and I must vote no.

DR. KIEBURTZ: Dr. Diamond.

DR. DIAMOND: Yes. I would vote yes, based on the power of the studies and the quality of the studies, and, you know, personally, I don't think that--I agree with the statement that the risk probably would not--the risk estimates would probably not change, but I'm voting no, primarily for one reason, and part of the charge was to obtain new information that might improve understanding, and it's that particular statement and the absence of that other information that might provide whatever modicum of broader understanding is deficient.

So that's why I'm voting no.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: My nonvoting no is expected, of course, and I think that it's purely on the fact that although the health effects analysis is not bad,

and the outcome will unlikely change, I think that we owe it to the public to have a decent clinical pharmacology analysis, without experiments, just an analysis of the available data, and we don't have that.

DR. KIEBURTZ: I think I would also vote no. It's a complicated no, in the sense that I think the conclusion that the risk estimates haven't changed is probably right, but the uncertainty of the risk estimates is one of the important things to state, which is not stated, and I think particularly in potentially vulnerable populations, and the subset of individuals who seem to be able to accumulate or have higher levels with what would be considered a standard exposure is not well understood.

I think that risk, at this point, is not easily quantifiable, but parameters could be put around it. I think the vast majority of populations, of the population that receives dental amalgam, is extremely unlikely to have any ill health effects from it. But it is impossible to exclude that there's--well, it's not impossible.

It's always impossible to exclude but it's hard to even accurately quantify what subset of the population may be at what risk of problems.

So I think that's where the precautionary principle comes in and some of the concerns about pregnant women and children need to be better laid out in the context of this document.

For the record, the vote was thirteen no, seven yes, to question three. Is that right? Very good. We have a few more things to do after voting on these questions. There's the opportunity for each of us to say something, in summation, after the vote on this panel. Not in my panel.

[Laughter]

DR. KIEBURTZ: So I'm just going to look at you as I go around the table and see if there's any summary comment you would like to make.

Dr. Luster. Dr. Amar.

DR. AMAR: Yes. I think the major thread, or the take-home message that I have, is that the Federal Government, and the agencies, need to force dentists to provide informed consent to the patient, and making sure that the patient is going to be well-informed, and making their appropriate decision towards the use of this material.

Having said that, I don't know what would be the mechanism, whether ADA has to step forward, or the federal agencies. I leave it as a question open

at this point. But something has to be done. I'm a periodontist. I do a lot of--and the oral surgeons must also do that. I do a lot of bone grafting, and any time that we implant something, we must have an informed consent.

So I think it's a must at this point, particularly in populations such as younger children, pregnant people, and immunosuppressed patients.

DR. KIEBURTZ: Dr. O'Brien, would you care to say anything?

DR. O'BRIEN: The literature supports that dental amalgam is generally safe, as we can see. However, there are unknown risks involved in the handling of dental amalgam. I, for example, I was asked by a dentist what he should do. Plus he accidentally swallowed a little white cup that had water in it, had amalgam in the bottom of it.

And so the fact that it's around, and it's a toxic material, would put this in the category of a risk, maybe in the area as antibiotics, aspirin, birth control pills. But it's in the risk space. However, we use all of those things, and so it isn't that we don't use things without risk, but it has to be, you need a lot of care and careful attention to it.

DR. KIEBURTZ: Dr. Dourson.

DR. DOURSON: Okay. Some research opportunities for our colleagues at FDA, cause someone said that they wanted them. So I have three. First of all, I think it would be useful to continue to follow-up the children in these existing epidemiology studies. If the study is over and you can't do doubleblind, okay, then do singleblind.

And if you can, within these studies, characterize the polymorphisms, if possible. These really are great studies. We should continue to use them.

The second is a study of polymorphisms in relationship to the use of the uncertainty factor of ten, that we use for risk values.

It is standard operating procedure now to replace these default factors with actual data. There are ways to do it, codified by the World Health Organization, and also used by different federal agencies and other countries' federal agencies, and if you study the polymorphisms, you can get data-based uncertainty factors that may be greater than ten or less than ten. This is doable.

And then finally, I would encourage our FDA colleagues to listen well to our public commentators, and ask the public commentators to, best

as possible, quantify their exposures, so if they have a case, individually, or know of someone that has a case, try to get quantification of the exposures or potential exposures, because without this quantification, it's difficult to use the case, as we all know. Thank you.

DR. GOLDSTEIN: I agree a lot with Michael. I also would like to see some data on exposure level estimations within the population and not the use of median values, and I'd also like to see somebody, some regulator take it on and not accept this ATSDR and EPA early reference values, and look at the newer data, or see if they can develop some newer data to reestablish reference doses based upon inclusion of susceptible populations, genetic polymorphisms, etcetera.

DR. KIEBURTZ: Dr. Goldman.

DR. GOLDMAN: Yes. I want to recommend that FDA consider kind of a broader strategy be taken, that might include collaborating with, at the other agencies, in addition to picking up on their work. But it occurs to me that, for example, some of what we suggested could be very much remedied with a little more toxicology lab work, which NCTR could do, but through the national toxicology program, maybe some

other parts of the government, like the NIEHS could get involved.

Also that it's been suggested that some additional epidemiology could be done. I think that's a good idea, doing more follow-up on the existing cohorts. But it also occurred to me that--I mean, NHANES would support that most adults in our country don't eat fish at all.

And so there are a lot of women of child-bearing age who do not eat fish, therefore, their only exposure to mercury, by and large, would be through dental mercury, mercury amalgam, and that might be a way to try to begin to get a handle on what's happening very directly to the fetus. But that's the kind of thing that FDA wouldn't generally do by itself but perhaps NIH, if they could be interested, you know, could fund that kind of research.

It just seems to me like that kind of a--that the occupational data--I have residual concern about the dental workers, even though those studies are not perfect studies. But, you know, why not get NIOSH involved with that, and get their help picking those studies apart, and what can we do to find out what's going on with those workers, because I think there is a possibility that those are positive

studies. It's just very hard to say, with the kind of time that we had to review them.

DR. KIEBURTZ: Dr. Zero.

DR. ZERO: I'd first like to say I came here, kind of neutral, thinking that there wasn't much of a concern with this issue, and now I'm sort of leaving it, that there may be a concern. So that's where I'm at. And I also want to sort of thank the panelists around the table from other fields, that I don't normally get a chance to interact with, for all I've learned from them, I think that's been a very educational process, as well as from the audience, and the public, that have contributed so much to this meeting.

In terms of gaps, in addition to the one related to fetal development, I really, I have the concern, in the adult population, that has been raised in terms of a research agenda, of adults that have an existing body burden, and then get acute exposure from dental treatment, which will be referred to as removal of amalgams and placement of additional amalgams. That acute exposure needs to be understood a little bit better and the implications of that on health. I think that has to be looked at, from what I've learned at this meeting.

I also, you know, as a dental professional, you know, feel that as a professional we always have to put the interests of patients first, and regardless of any other issues that are out there, and that's really our obligation, and I think this has been an excellent exercise in really looking at and addressing the needs of patients, going forward.

DR. KIEBURTZ: The worm turns. We have twenty minutes. So I'm going to stop you after you talk for one minute, everybody, from now on.

So Dr. Goldstein, you have a minute.

DR. GOLDSTEIN: Well, again, I think, you know, there's no question from a neurologic standpoint that mercury is toxic and I think that it's a continuous risk, not a dichotomous one. So having said that, I think in the next version of the white paper, that only should it consider the risk side but it also needs to consider the alternatives.

That is, I tried to question quite a bit about this. Is there an absolute reason that only this could be used, given all the gaps that we have and all of the issues? The answer may be yes, that there are situations where this is the best alternative for a patient. But given what we've heard in other countries as well, and from these trials,

given the inception cohort bias, that the alternative may be as good, if not better, in many circumstances, and then you don't have to deal with even this potential risk.

DR. ZERO: Having been a lifetime educator in dentistry, this has been a very fruitful experience, and from the providers, both on the panel, as well as the audience, this has brought to light a new level for us, and as an educator in dentistry, I would like to recommend that the FDA work with the dental communities and the dental sponsorships, to bring this to the next level, and I would like to echo your comments regarding the redo in the white paper.

DR. KIEBURTZ: Dr. Ng.

DR. NG: I would like to thank the FDA for putting this meeting together. It was a very worthwhile experience for me and I learned quite a lot from the public as well as from the panelists around the table. My personal view is that amalgam is going to go away, it's just a matter of time, but I think that we need to get more data, do more research, and find some answers.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I guess I would just reiterate a comment made earlier, that I think there

is more information out there in these existing studies, and I think that the FDA or a collaborating agency should reach out to some of these studies, and try and use the information that's there to answer the specific questions of interest.

I think equally, it sounds like there's a lot of activity in Scandinavia, and perhaps other countries, and reaching out to hook into that would be useful, I think.

DR. KIEBURTZ: Dr. Burton.

DR. BURTON: As with Dr. Zero, and as a dentist for 30 years, I came here thinking that there was potential, that there were a few individuals which I hate to say, were idiosyncratic, who were potentially at risk, but I think that this at least provided me some information that raises a level of question in my mind, that there may be more people who are at risk than we can fully understand.

The data that we had presented, I hate to say, supports what we already knew, but what we found out was that there are gaps in what we knew, particularly in regard to special populations, that raises questions about the use of this material in the long term.

I agree very much, the technology, within

10 or 15 years, or perhaps even less, will make what we're talking about probably moot. But the truth is that in that interim period, we need to be aware of what the shortcomings are and try to protect our patients, and I think that the FDA needs to look at this in a broader sense and look into some of the issues that we've raised, and revisit this issue, either again as a white paper, or through a joint panel, or the dental products panel.

DR. KIEBURTZ: As I said before, I think the population-based information is pretty clear. There's very little to no risk. But the tails of those populations, there's already data on individuals who had very high and very low levels.

One of the advantages of population-based research is you can sample at those tails and see if there's any characteristics of the individuals, from the data already collected, that are predictive of being very good or very bad handlers of mercury, as the case may be, and those data from those studies may be available already to look at that kind of analysis.

Dr. Olson.

DR. OLSON: Yes. I think it's very important to have informed consent and I think there should be a change in the labeling of these amalgams

to, if you will, silver mercury, or mercury silver amalgams, so people really understand what is being put in their mouth. I think also, as other people have said, what from I can understand, these are going to go away, and go away fairly soon.

So I would recommend also that women who are of child-bearing age, especially the pregnant women, and also children, really be especially counseled on getting these in their mouth.

The other thing I would like to see is clearly studies of mercury in people who are immunocompromised, people with immunological disorders, not just for what the mercury may do, but it may shed some light on their underlying problems.

DR. KIEBURTZ: Dr. Li.

DR. LI: I also appreciate opportunity to be part of this meeting, which has been a great learning experience for me, and I just want to point out that my votes were based on the current available information, and I think the future for further studies are really necessary to further define the potential risks. And one area we mentioned quite a few times, that was the allergic reaction. When I was a dental student, I was told the allergical reaction in the population was less than one percent but we

have seen, recently, during this meeting, it was presented as 6 percent. So there has been a dramatic increase.

On the other hand, there are alternative materials available, and I would encourage dentists to consider those available alternative materials for those high-risk populations, although we do not know what, exactly, the risk is yet.

DR. KIEBURTZ: Dr. Taylor.

DR. TAYLOR: This was a tremendous learning experience and an honor to work with the colleagues around the table today and yesterday.

I was particularly struck by the testimony, like Dr. Zero, from the public. Like Dr. Zero, I came, having read the white paper and felt that I was pretty set and it would be a pretty easy decision to assess questions two and three.

So the testimony struck me in this way. It led me to think that perhaps there are a constellation of symptoms, a constellation of experiences that may be related to the provision of dental care, that we have not paid close enough attention to and need to focus on.

In that regard, I come back to the practice-based network as a potential vehicle to be

able to address many of these questions, not only a registry, Dr. Sacco, but a few other study designs that could be done, and we could possibly look at the model of osteonecrosis of the jaws, where, actually, the practice-based networks have been engaged to address that issue.

So I see a need, and I see areas in dental education as well as in dental practice.

I was also struck by colleagues, in terms of technique and methodologies, with the use of materials, and we've selected an approach for using amalgams in those difficult restorations, if you will, and perhaps there are ways that we might be able to seriously look at technique, teaching our dental students new methodologies--or new methodologies but more focused methodology on those difficult restorations.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Thanks for allowing me to participate and I learned a lot, and opinions were changed a bit as to what I heard here. I think the recommendations to the FDA are we need to advocate for more well-designed, namely, epidemiologic studies, to better qualify the exposure-risk relationship. I would say studies are difficult in this day with

funding, funding being diverted where it has been, and it makes it more difficult to do research, but it's clear research is needed.

And the only other thing I'd say, maybe to the public, though, is I'd hate to see an overreaction and a panic, and I think having all their dental amalgams pulled at this point in time, when we don't have enough information, could also be just as deleterious.

DR. KIEBURTZ: Dr. Rizzo.

DR. RIZZO: Thanks for letting me participate today. It's an honor to be here and to hear from the public as well. I think that because there is uncertainty, informed consent is essential, and I think that before anyone has mercury amalgam replacements, there ought to be some discussion and informed consent.

I think the white paper has good bone structure. I think it's not broad enough and I think that we need to increase the scope of the review, including different databases.

I think it's especially important to explain why studies were excluded, especially some potentially important studies that were mentioned by the public.

Maybe they are up to snuff and maybe they're not, and if they're not, I really want to know why. I think there are lots of opportunities to point to, directions for new research. We could probably sit around all day, and think about what we might do, and we could include some ideas in the white paper. There are potential populations that are at risk and we need to know who they are, and we need to know what the effects are of acutely elevated levels, with dental procedures like polishing amalgam, and so forth. Thanks.

DR. KIEBURTZ: Dr. Klaassen.

DR. KLAASSEN: Yes. I too found this an interesting experience, and I think as I look back at it, when I came here, and what I thought the question was, and what I see it now is quite different, is when I came, I thought we were to look at the current available information, and if that's adequate or not adequate. But basically what we're saying, I think, is what has been done is not adequate, which is a very, very different question, and may be a very, very important question.

We are now saying we don't--or at least as I see it, we don't disagree very much but we think there's more that should be done. And I think we all

agree with that, that more research needs to be done.

It's unfortunate, at this time in history, it's very difficult to find money to do research. But we've got to find it and if the public wants more research on this, we have to find money to do it.

DR. KIEBURTZ: Dr. Ascher.

DR. ASCHER: Like the other members of the panel, I'd like to thank everybody, I've learned a lot, I'd like to thank the public at large, and there's a couple issues that I want to address.

The first one is I know we're charged with looking at the white paper but I think we should think in broader terms, and like our colleagues in Sweden, and other countries in Europe, perhaps we should consider the issue of mercury within a broader perspective, environmental impact, and other issues, that are not part of the discussion today.

The second message is actually for the FDA, and maybe I'm talking now more as a citizen than a scientist. But knowing what I know about thimerosal, for example, and that six injections of thimerosal will result in exposure to the child of about 30 micrograms, so a total of 180 over a two year period, I'm asking myself how is it that six times 30 micrograms over two years is unacceptable and 20

micrograms per day is acceptable.

DR. KIEBURTZ: Ms. Cowley.

MS. COWLEY: Thank you for the honor of representing the patients. I think we need a definite renewed emphasis on informed consent. People need to understand what is going into their bodies. I think an awareness campaign would not be a bad idea, to alert the public to the fact that there are alternatives, and the presence of mercury within amalgams. To me, the most important issues are to try to understand what happened to the people who talked to us yesterday and today.

Do they have something going on that is totally unrelated to amalgam? Is what is happening to them related to amalgam? And we won't know until we look. So that is the focus that I would like to see, among all of the others.

When I went to Congress in 1992, and the visit resulted in a congressional hearing on how are FDA and NIH ignoring the dangers of TMJ implants, the legislative staffer looked at me and she said, How many people have these devices? I said I don't know, I'm in my house getting phone calls. I have no idea. And she said, You know what? if it only happened to you, it's worth an investigation. So if it only

happened to one of those people, I think we need to look at it and find out why.

Along the research lines, FDA, working with NIH, NIBIB, NIDCR, to develop new materials, would be terrific.

I know the dental division has tremendous interest in the biomaterials division, bioengineering. We ought to be looking to autoregeneration. We're doing an awful lot in other areas and this is a whole new field that is opening up. I think that's it. Thank you, again.

DR. KIEBURTZ: Dr. Fleming.

DR. FLEMING: Well, for me, words can't express the honor that I've had serving with this distinguished panel. There are two issues that I have to lay before you. One of them is could it not be that we are on the verge of one of the greatest medical discoveries in the last 150 years? Could it be? Just could it be? Sometimes, I entertain the thought.

I think secondly, informed consent is an absolute given. I think that it needs to be given, prior to the installation of amalgams or any dental material that we use, any dental treatment that we perform.

And lastly, I would like to ask the FDA to consider restrictions on the use of amalgam in high-risk populations, which would include pregnant women and children under six. If that is within the scope of the regulatory authority of the FDA to do so, I think until we have adequate methods of risk assessment, until we have established what the risk is, it seems to me not to make sense to continue doing something that's going to add to the burden that we'll have to treat later. Thank you, again.

DR. KIEBURTZ: Dr. Diamond.

DR. DIAMOND: As this is my "baptism by fire," I'd like to say that I am honored to be a member of the dental panel and to be a part of these proceedings. Give the understandably emotionally-charged nature of this issue, I am struck by the dignified, respectful, and productive interactions between all the participants at this meeting.

To me, this says that we're all focusing on our purpose here, communicating our views and learning from each other.

I believe that we have all gained a broader perspective from where we can move forward toward an objective and more accurate understanding of the risks, which is in everyone's best interests.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Although I hope I've introduced some concepts of clinical pharmacology that will take in the device part of the FDA, I really want to say that it was a great meeting, I really enjoyed it, it was a pleasure to be a part of it, and I think the FDA did a great job in organizing it.

DR. KIEBURTZ: We're not done yet, so hang in there. I just want to reiterate for the committee and for the record, and for the press, what we commented on was the draft white paper. There are no official recommendations on any kind of change in regulation labeling, or otherwise. The last little bit that went on was a personal reflection on the part of individual committee members.

The charge was to comment on the white paper, the vote is what the vote was, and now it's FDA's task to take that vote and the contents of the discussion into their consideration.

In that regard, I'd like to ask Dr. Alderson to give us any closing comments or questions to the committee. We're at your service.

DR. ALDERSON: Do I have the last word?

DR. KIEBURTZ: No. I do.

DR. ALDERSON: That's okay.

Ladies and gentlemen, you're all to be congratulated. We are elated with the input you've given us. We're elated with the assessment of this very, very difficult situation, both from a science and a regulatory perspective. This is not an easy situation we find ourselves in.

Your input, the last two days, the input of the public, is very critical to our process of making decisions relative to the public health of products we regulate.

The expertise and science that you have brought to this issue is so critical to us. We make our decisions based on the best science that we can bring to bear on the issues that face us.

Certainly, your contributions are great to us. You heard input and opinions from 52 members of the public. You heard from a U.S. congressperson, Congressman Watson from California. This is part of our process. We want it to be as transparent as we can make it, from both the science perspective and also the public's perspective. So we're going to take your recommendations, your comments, and we will start evaluating the next steps in what we do, both with the white paper and this whole issue of dental amalgams.

So I can only say thank you for all you've

contributed the last two days. I do want to provide some additional information about the process of sending comments to our docket.

Everything that's submitted to docket will be publicly available through FDA's Docket Office. However--and this is very important--because of legal concerns about privacy, FDA does not normally post comments from individuals on the Internet. We will have them internally but we don't post them for the public.

If you want your comments to be available for electronic access, please include as a cover to your comment a signed statement saying that you understand that if the comment is posted on the Internet, it will not be redacted but will be posted just as you submit it to us.

If you want to delete some personal information like your home address or telephone number, please make those deletions before you provide the write permission to have that comment placed on the public Internet.

The transcript of this meeting will also be posted to the Web site. If you have comments you would like to submit to the Agency for consideration, we encourage you to make those comments to the docket

that we previously provided the number to.

And with that, Mr. Chairman, I'll leave you the closing comments.

DR. KIEBURTZ: Thanks, Dr. Alderson.

I just want to thank my co-chair, Dr. Burton, all the committee members, the public who testified, a great contribution on everyone's part.

I particularly want to thank the FDA staff. The FDA professional staff, scientific staff, sometimes take a hit in the public, I would say almost inevitably. They do a terrific job. They arranged a terrific meeting, organized things, got people the chance to speak. So I thank you for doing that and it benefits the public. This meeting's adjourned. Thank you very much.

[Whereupon, at 4:25 p.m., the meeting of the Dental Products Panel was adjourned]