MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

TOM BRADLEY INTERNATIONAL HALL

UNIVERSITY OF CALIFORNIA, LOS ANGELES

417 CHARLES E. YOUNG DRIVE, WEST

LOS ANGELES, CALIFORNIA

FRIDAY, DECEMBER 5, 2008

8:00 A.M.

LINDA KAY RIGEL, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 13196

APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Stanton Glantz

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison

Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Dr. Melanie Marty, Chief, Air Toxicology and Epidemiology Section

Dr. Bruce Winder, Staff Toxicologist

Dr. Martha S. Sandy, Chief, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Dr. Rajpal S. Tomar, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

ALSO PRESENT

Dr. Mary Lou Verder-Carlos, Department of Pesticide Regulation

I N D E X
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P R O C E E D I N G S

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CHAIRPERSON FROINES: Can we get started? If we can get started, that would be good.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY : All right. We have --

CHAIRPERSON FROINES: Wait. You're jumping the gun.

First, everything -- everything is okay. Everything is just fine.

PANEL MEMBER GLANTZ: But he'll find something to criticize.

CHAIRPERSON FROINES: No. Everything today is going to be just fine because Elinor Fanning just walked in.

(Laughter)

CHAIRPERSON FROINES: And therefore, nothing can go wrong no matter what I or Stan or anybody else tries to do.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No pressure, Elinor.

CHAIRPERSON FROINES: The second thing I wanted to say in the form of a proposal, is the process that I want to follow today, Melanie, is as follows:

First, we're going to have Stan and Joe make a

presentation -- presentations -- about the process that has been underway since the last meeting so the panel knows what's actually happened.

Then we're going to ask you to make your presentation.

Third, we're going to ask the panel to not ask questions unless they are for purposes of clarification. They are not going to have an open debate during the presentations.

Fourth, we're going to then turn to the Leads of the panel who will then make their presentations after you have made yours.

And fifth, we'll go around the room, and we'll then have open discussion.

And that's the procedure that we're going to follow here, and that's the procedure that we're going to follow in the future as well so that we maintain -- so we keep the sort of Pandora's box closed, as it were, on the discussion. And I think it shows more respect for your staff.

So unless anybody objects or has other alternatives, that's how I'd like to proceed.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I have just one question. We have the Reference Exposure Levels to finish off because you

guys had a few questions that we researched.

CHAIRPERSON FROINES: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So I assume that's going to go first, and then the cancer document.

CHAIRPERSON FROINES: Yes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: And the other thing that I want to do at the outset, and this should be on the -- all this is on the record. We've formally opened the meeting of whatever -- what day is today?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: December 5th.

CHAIRPERSON FROINES: December 5th, of the Scientific Review Panel.

Before you start, the one other item I wanted to pursue is to introduce Marylou Verder, who is our new representative from the Department of Pesticide Regulation. And if Marylou could come up and tell us a little bit about herself so that everybody feels that we have met.

DR. VERDER-CARLOS: Thank you, John.

I'm Mary Lou Verder-Carlos. I am with the Department of Pesticide Regulation, Assistant Director

for Pesticide Programs Division.

I am actually a veterinarian by profession and took my master's in epidemiology and in public health at UC Davis.

I was working with DPR for 13 years, and I went to and I worked for OEHHA for a year and a half; and then I am back in DPR, actually just started the middle of November.

And I'm happy to be here. It's nice to meet everybody, and I'm looking forward to working with the panel.

CHAIRPERSON FROINES: Great. I had actually written down Verder-Carlos, and I left it out, so I apologize.

Well, thank you very much. Anybody have any questions for Marylou? Thank you very much.

DR. VERDER-CARLOS: Thank you.

CHAIRPERSON FROINES: Okay. As we said, we're going to start out with -- I believe the Lead person at this point is Stan Glantz or Joe? Who is first?

PANEL MEMBER GLANTZ: I thought we were going to finish these RELs.

CHAIRPERSON FROINES: No. We're going to -- oh. You want to finish the RELs before we go to cancer. Okay, fine. Let's do that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. We had a few things to add and a couple questions to answer based on the last October 30th SRP meeting, so I'm going to ask Bruce just to walk through.

We have five slides, and the copies are coming, so I apologize for leaving those in Oakland. Those are the only ones I left in Oakland. The rest of them are coming.

So Bruce why don't you start with the few things that you did in manganese? You have these slides, and then we can ask if that satisfies the concerns of the panel.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. I'm Bruce Winder with OEHHA.

As you can see on this slide, we have expanded table particle sizes from the Singh, et al. 2002 study to -- and included a statement that we need more study of manganese and ultrafine PM. These are -- the table that I'm making reference to is on the --

CHAIRPERSON FROINES: Am I reading the wrong -- I'm sorry. For clarification --

OEHHA STAFF TOXICOLOGIST WINDER: We'll get to that --

PANEL MEMBER BLANC: He's not on this yet.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I'll get to that particular part a little bit later.

Also in response to questions of the panel, wherever the studies presented information we're including the ages of the experimental subjects, the size of the particles used in the exposures, whether it's experimentally determined, and some discussion of the effects of particle size and uptake at site of deposition.

There's also additional discussion regarding sulfhydryl binding as a mechanism of action for manganese toxicity.

And then we've talked a little bit about the neurotoxicity potential from extended exposure to Maneb either by itself or in conjunction with other subsequent neurotoxic exposures.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So all of these are underlined in the document that you guys received.

CHAIRPERSON FROINES: And you haven't dealt with thiolate versus thiol.

OEHHA STAFF TOXICOLOGIST WINDER: No.

CHAIRPERSON FROINES: You might put a sentence in there that talks about what the pKa of these things are in terms of their relative ability to bind

proteins. Do you know what I mean? You know what I mean.

OEHHA STAFF TOXICOLOGIST WINDER: Somewhere in that discussion of sulfhydryl binding. Okay. We can do that.

A question arose regarding the prevalence of iron deficiency in the discussion of manganese being more of a problem for individuals with iron deficiency, and here we have the data. This is presented in a -- in that paper you're talking about there. This.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The handout.

OEHHA STAFF TOXICOLOGIST WINDER: -- paragraph is in italics. This is an addition we want to make to that on page 8, section 4, where we talk about how infants one and two years of age have a nine percent prevalence of iron deficiency whereas adolescent girls and young women of childbearing age, the prevalence is nine to 11 percent. But compared to males, teenagers through about 50 years of age, it's only one percent.

So the iron deficiency differentially affects children and women of childbearing age. This is from an NHANES III study by Looker, et al. So that's in the text as well.

PANEL MEMBER BLANC: Okay. So Bruce, a couple

things about this wording here.

One thing is that I think following the word "infants" I think you need to say "of both sexes" since you go on to talk about women only --

CHAIRPERSON FROINES: Excuse me, Paul. The recorder is asking for panel members to speak close to their microphones.

PANEL MEMBER BLANC: So Bruce, I think the words "of both sexes" should be inserted after "infants" because the next sentence is about --

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER BLANC: And secondly, I'm assuming that the way the NHANES data were presented was infants less than two years of age. It's very strange wording to say infants of one and two years of age.

OEHHA STAFF TOXICOLOGIST WINDER: That's what is -- well, I don't know what NHANES says, but this is the way Looker reports it.

PANEL MEMBER BLANC: You mean you didn't go to NHANES?

OEHHA STAFF TOXICOLOGIST WINDER: No. This is the -- a paper by Looker, et al. in -- I think this was JAMA.

PANEL MEMBER BLANC: Analyzing NHANES?

OEHHA STAFF TOXICOLOGIST WINDER: Yes.

PANEL MEMBER BLANC: Can you just double-check that? It's just such strange wording.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER BLANC: It may be "one to two" years of age, but not "one and two." It seems very strange.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

PANEL MEMBER BLANC: And then finally, I think, to be consistent, your last phrase should say infants represent a more susceptible population.

OEHHA STAFF TOXICOLOGIST WINDER: All right.

PANEL MEMBER BLANC: Because you actually haven't presented data that show that children --

OEHHA STAFF TOXICOLOGIST WINDER: Per se, okay.

PANEL MEMBER BLANC: -- you start talking about. Or you could say infants and adolescent women.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER BLANC: Or adolescent girls or whatever you want to say.

OEHHA STAFF TOXICOLOGIST WINDER: All right. Any other --

PANEL MEMBER BLANC: Or female adolescents.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

Now this is referring to that second paragraph in the handout that you have. This goes back to our presentation of two studies, one by Dorman and one by Guilarte, looking at rhesus monkeys.

And in the Dorman study, these monkeys were exposed by inhalation to manganese sulfate; and the levels of manganese accumulation in the caudate, putamen, globus pallidus, and white matter were reported.

Guilarte, et al. also exposed rhesus to manganese sulfate but by injection, a rather different protocol. They too measured manganese levels in these brain -- same brain areas.

Using the data from Dorman, we extrapolated what the air concentrations would have been in the Guilarte study to see that same level of neurotoxicity. That same number that we're presenting along the side of the screen is in the text of that second paragraph on your handout.

What this is showing is that the air concentrations -- 75, 98, 150, et cetera -- are all roughly in the same order of magnitude, same general area, as that reported by Lucchini, et al. in his LOAEL for a human occupational study of 97 micrograms per meter cubed and is similar to 72 micrograms per meter

cubed that we're using as our point of departure from the Roels human study.

So this paragraph on the screen is the last part of the paragraph in front of you where we're saying that all these differences in exposure regimens among these studies prevents us from using this to derive a REL.

We think that it is a significant part of our study, part of our results, that this range overlaps what the human studies have also found; and so for that reason, we think these studies are supportive of the effect level upon which our REL is based.

PANEL MEMBER BLANC: You know, this may seem a little convoluted, but if Dorman had not simply reported the brain levels but had also reported a biological effect or described a biological effect, then you could just use that study directly.

But, of course, frustratingly, he didn't. He only -- he didn't say there wasn't; he just didn't look at it. He only looked at concentrations.

So you have to use both primate studies in conjunction because the latter study, which used injection, reported levels and correlated negative biological impacts, neurological impacts.

So even though this -- that's why this

paragraph is worded in the way it is. But I looked at it closely, and this reflects some edits I made or suggested that they make; but I think there's an easier or more straightforward way of saying it because of the nature of the extrapolation.

But I thought it was important that they -- if you'll remember at the meeting, this was in response to my suggestion they not completely ignore the nonhuman primate data since it is a rich source of information.

So it's kind of like if A equals B, and B equals C, then A does equal C to some extent. But that's the exercise they have to go through.

PANEL MEMBER GLANTZ: Actually, I think A equals C.

PANEL MEMBER BYUS: In that analogy.

PANEL MEMBER BLANC: Yeah, that's what I'm saying. But it was more like if A approximates B and B approximates C is more like it. But anyway.

OEHHA STAFF TOXICOLOGIST WINDER: And those are the changes we have for the REL document.

PANEL MEMBER BLANC: I do have one tiny question about this paragraph. Is where you say Lucchini 96.71, is that a typo in any way?

OEHHA STAFF TOXICOLOGIST WINDER: That's what he reported.

PANEL MEMBER BLANC: He went out to that many?

OEHHA STAFF TOXICOLOGIST WINDER: He did.

PANEL MEMBER BLANC: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But we rounded.

PANEL MEMBER BLANC: Rounded from what?

OEHHA STAFF TOXICOLOGIST WINDER: From the 96.71.

PANEL MEMBER BLANC: All right.

CHAIRPERSON FROINES: Where the 97?

PANEL MEMBER BLANC: It says Lucchini, et al. of 96.71.

OEHHA STAFF TOXICOLOGIST WINDER: On this screen, I've rounded it to 97 for purposes of presentation here.

PANEL MEMBER GLANTZ: I would round it in the document too.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah. Okay.

CHAIRPERSON FROINES: Especially when all your other numbers are rounded.

OEHHA STAFF TOXICOLOGIST WINDER: All right. Like I said, that's what I have for the revisions to the manganese document. Now I have -- if we're ready to move on, I have some for formaldehyde as well.

CHAIRPERSON FROINES: We talked about there

being some clarification on manganese with respect to the Cory-Slechta data in terms of the outcome going back to normal after a week.

And did you address that?

OEHHA STAFF TOXICOLOGIST WINDER: Yeah. It looks like page 21. We've added to that paragraph there that describes how these experiments, you know, talked about enhanced neurotoxicity associated with these experiments are partially a function of the design.

For example, we say these experiments also do not address the potentially enhanced neurotoxicity associated with more continuous exposure to manganese as Maneb during prenatal to adult development.

We say that the:

> Long-term exposure to Maneb among adult farmworkers has been associated with the development of symptoms in Parkinson's disease characteristic of manganism.

And we say:

> It should also be noted that while this experimental design emphasized the neurotoxicity of the sequential exposures to Maneb, then paraquat, it is possible that the deleterious effects of

exposure to other neurotoxic substances during development or adulthood would also be enhanced by early life exposures to manganese-containing pesticides.

CHAIRPERSON FROINES: Not to make an aside, but if the panel agrees, I would like to invite Cory-Slechta out here for a morning's discussion with some other scientists who are doing neurotoxicity.

Because I think that there are some interesting science and policy questions about how do we view early-life exposure, and what are the implications of that outside of cancer?

Because we haven't really addressed that issue, and Cory gave a very good talk at the Air Pollution meetings recently and raised some doubts about some of the rush to judgment on some of this.

So I was thinking that we might, next time we have a meeting, maybe we could have her and perhaps other colleagues give us a little perspective on where they're at with this whole issue.

OEHHA STAFF TOXICOLOGIST WINDER: That sounds --

CHAIRPERSON FROINES: Because it's very -- it's -- when we get into SB 25, we're looking for differential toxicity.

But this kind of early-life effect is in effect different than that in some respects in terms of the criteria that have been used. So that needs to be sorted out over time, I think.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

CHAIRPERSON FROINES: Do you disagree?

PANEL MEMBER BLANC: No.

No, I think it's very healthy when we bring in outside expertise for discussion that's not linked necessarily specifically to a single chemical that addresses the class effect and helps inform our discussions going forward.

CHAIRPERSON FROINES: Is that okay with you, Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: Melanie says yes.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. Now that --

CHAIRPERSON FROINES: That's the last joke I'll make on that.

PANEL MEMBER BLANC: Thanks.

OEHHA STAFF TOXICOLOGIST WINDER: This next slide represents the changes to the formaldehyde REL document.

In response to some comments regarding the role of the respiratory tract lining fluid, we've introduced some discussion of that and described the potential role of this fluid in neonatal susceptibility.

There is also a question regarding the clarification of our Lang study which we're reporting he came up with a similar LOAEL/NOAEL as the study upon which the REL is based. There is clarification now what these modifying factors were with respect to the negative affect.

This study was describing how personality effects will tend to influence perceptions of irritation. So it's -- this is in the document to clarify it.

We -- also in response to concerns of the panel, we've indicated that if there's a need to re-eval- we'll look at the need to reevaluate the REL if there is evidence of a developmental effect for formaldehyde in, well, like I said, in development.

And throughout, we've changed sensitization type of responsive -- responsiveness in response to the panel's concern that we were misusing the term.

And that's pretty much the changes to the formaldehyde document.

PANEL MEMBER BLANC: So when you -- we had a brief discussion about the data available and the NIOSH or health hazard evaluation data set. Did that prove to be unrevealing?

OEHHA STAFF TOXICOLOGIST WINDER: Pretty much.

What NIOSH did is they've -- they've come up with a level which pretty much overlaps ours, but tracing back the basis for that level has been fairly unproductive.

CHAIRPERSON FROINES: It was what?

OEHHA STAFF TOXICOLOGIST WINDER: Unproductive.

Now we've -- I'm sorry; I did have one more slide here. We reevaluated the uncertainty factors with respect to the infant neonatal glutathione pools.

Those data talk about how GSH levels tend to be high in normal neonates at birth but they're low in premies. This may suggest that individual premies may be a more susceptible group.

However, unlike the studies for ozone and environmental tobacco smoke, there's very little data which address formaldehyde's effects in lung development.

So at this time, we're leaving uncertainty factors unchanged but recognize that if data do become

available we want to go back and reevaluate our uncertainty factors and consequent RELs.

CHAIRPERSON FROINES: Remind me, I'm sorry, what you did in terms of reevaluation with respect to GSH pools.

OEHHA STAFF TOXICOLOGIST WINDER: We were looking at -- the concern was what role do GSH pools play in the susceptibility of small children -- in this case, neonates -- to formaldehyde exposure.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And this is particularly in the lung lining fluid and lung tissue with respect to that.

CHAIRPERSON FROINES: Well, the reason I ask the question is: The other thing that's important in lung lining fluid, of course, is ascorbic acid. And there's vast amounts of ascorbate which is also a good electron source.

So it's not just GSH. It's GSH and ascorbate that I think are important. So you might just note that ascorbic acid issue.

Because most people -- you know, when you -- most people think that they go out and drink their orange juice every day, and it's a wonderful antioxidant, and it's going to provide them wonderful health; and yet they don't really realize that it's a

very strong electron source in lung lining fluid and therefore may have some counter -- more negative effects to the degree that you have oxidative stress issues.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

Well, we can include -- we can address the ascorbate. I didn't find much data with respect to -- especially in neonates -- looking at this -- these effects. But I can look at that for adults.

CHAIRPERSON FROINES: I don't know what -- you know, the GSH ascorbate, I don't know if one might include what the relative -- so it may be that GSH overwhelms everything. I just don't know.

OEHHA STAFF TOXICOLOGIST WINDER: I didn't find -- in the studies I was examining for GSH levels, I didn't find much data that referred to ascorbic level -- ascorbic acid levels per se. So I'm not sure the data are out there.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll bring up the point.

CHAIRPERSON FROINES: Look at Fred Kelly's work.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So there's one more thing that I wanted to

bring up, and that is when we -- last time, when the panel was discussing the acetaldehyde REL --

CHAIRPERSON FROINES: Frank Kelly.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sorry.

When the panel was discussing the acetaldehyde REL, there was a question of whether the 95 percent confidence interval that was reported about the mean was geometric or arithmetic.

So we contacted the author again, and he assured us, no, that is the geometric mean and the geometric standard deviation.

So just a reminder, we've used a lower confidence limit on the mean of the 20 percent drop in FEV1 as our starting point for that reference exposure level. I just wanted to let you know we actually did go back and talk to him.

PANEL MEMBER BLANC: Can I ask one other question about formaldehyde before we leave that altogether?

It's very helpful that you have this secondary analysis not to derive the REL but to show that it falls similarly, the one based on the guinea pig study on page 29.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER BLANC: But can I just ask for the sake of understanding the mindset: You do, as with the previous one, use the intraspecies tenfold uncertainty factor for the toxicodynamics because of questions of asthma in children.

Since the study was done on adult guinea pigs, when you do the intraspecies uncertainty factor corrections, you have a sixfold toxicokinetic adjustment. That's based on exposure-related factors of the guinea pig lung or something?

OEHHA STAFF TOXICOLOGIST WINDER: Yes. It addresses the differences with respect to the guinea pig lung versus --

PANEL MEMBER BLANC: Right. And that's your standard adjustment factor when you go from guinea pigs to --

OEHHA STAFF TOXICOLOGIST WINDER: With a HEC adjustment.

PANEL MEMBER BLANC: Right. Why, when you do the toxicodynamic adjustment, since these were adult guinea pigs and not childhood guinea pigs or infant guinea pigs, is there no adjustment for that?

OEHHA STAFF TOXICOLOGIST WINDER: Okay. I'm sorry. I see. It's been pointed out that that was a typo. The 6 actually represents a 2 for toxicokinetic

and 3 for toxicodynamic. Is that combined --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's a typo. It should -- toxicokinetic is 2 with a HEC adjustment.

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's the standard because you haven't accounted for all of the kinetic factors with the HEC adjustment.

The dynamic should be 3, or root 10, not 1. So the total is 6. Sorry about that.

PANEL MEMBER PLOPPER: Oh, okay.

PANEL MEMBER BLANC: Good. All right.

PANEL MEMBER BYUS: You earned your hundred dollars.

(Laughter)

PANEL MEMBER BLANC: At least.

PANEL MEMBER BYUS: That's a joke.

(Laughter)

PANEL MEMBER GLANTZ: It's not a joke.

(Laughter)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So that's all we had for the RELs.

CHAIRPERSON FROINES: Good.

PANEL MEMBER BLANC: Can you -- since we're

done with these, can you -- and since we've been efficient in time so far, could you wax reflective for a couple minutes about the process, as you see it, for these five RELs?

These are the second five of the childhood RELs. This was an incredible amount of work, which I think will help inform you going forward for other ones, but also I think may have implications, public policy implications, in a variety of different ways.

But do you see this process as being proportionately productive to the amount of effort it takes? Is there some way in which it could be made more targeted?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, these are good questions.

What we did was we went back to the original prioritization document, which was I think finalized in '01 or '02, and we looked at chemicals that didn't quite make the top five.

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If you remember, initially we were restricted by the statute to naming just five to start with.

And then go back, evaluating TACs to make sure that they were protective of kids, and during that

evaluation pull out chemicals that might differentially impact and should therefore be on that list of TACs that disproportionately impact children, so we went back to the ones that hadn't quite made the top five to start with and developed these new RELs.

And yes, it's very time-intensive, and we have been thinking about is there a way to streamline that; and, you know, it's really -- you're caught between a rock and a hard place because the science review demands that there be lots of detail and you be very careful.

So it's always -- you know, it's always a tension between the time it's going to take to do this, get the document through public and peer review and get things listed, versus doing some sort of streamlining.

So we're thinking about it and thinking about a way where you could have a scientific justification for the streamlining and then be able to go faster.

CHAIRPERSON FROINES: Well, can I ask you a question about that? This may be what Paul's referring to in part.

And that is, we've now gone through ten chemicals -- 11, if you include environmental tobacco -- and within the context of those 11 substances, there were criteria that were used to make

the determination.

And my question would be: Can one define at the policy level the criteria that were used to make that determination and then put that in stone so that those criteria become in a sense the starting point when you look at compound in the future?

In other words, have you set in motion a process that has some stability associated with it over the long term. So you say that in the past we have used these criteria for this determination, and we're using that same criteria for chemical X.

In other words, can you -- not simplify, but can you define criteria that you can use more often in the future?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. In a way, we actually already have. In that prioritization document, we brought up the issue that there are certain toxicological endpoints that are red flags for differential susceptibility between a developing organism and a mature organism.

And we have used those red flags. One of them is neurotoxicity. The other has been asthma exacerbation. And the chemicals we just dealt with naturally fell into that because that's what we were looking at when we did that initial prioritization.

So we intend to continue using those. It's easier said than done because you still have to look at all of the data for that chemical when you're doing these evaluations.

CHAIRPERSON FROINES: I don't want to interrupt Paul because I know he wants to follow up, but I would just say that it might be worth putting together a one- to two-page document that spells that out so you can provide that to a wider audience who might benefit from seeing how OEHHA is approaching this whole issue.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. It actually is pretty well spelled out in that prioritization document.

CHAIRPERSON FROINES: No, but I'm talking about a two-page document that's --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, a two-page document.

CHAIRPERSON FROINES: -- something that somebody will read.

(Laughter)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure. We could definitely do that.

PANEL MEMBER BLANC: This actually does tie in to a related issue which is the formalization of the

findings of the committee.

I know we've had a draft circulating in terms of these RELs, and one of the -- I think one of the challenges with that draft is that it comes off as seeming more haphazard than the actual work product that underlies it is.

And perhaps with some work, there might be a way of concluding this by having a concluding piece of the findings which at least summarizes the consistent issues that are reflected in the five individual chemicals, which would include issues of chemicals which aggravate asthma and for which not only presumptively is there data that, you know, that the presumption is that more children have asthma but in fact there is some data for those specific chemicals which suggest more of a problem in younger persons.

And with, I think, the neurodevelopmental also, it's both a generic supposition, but also there are specific data for those chemicals that argue for potential greater susceptibility.

And I think one thing also that comes into play came into play with manganese, and I'm trying to think of with another metal -- or with metal sometimes it's the issue of iron deficiency. It's certainly an issue with lead.

And I'd have to think carefully, and then I think the protective mechanisms against oxidative stress is a sort of generic issue, too, with younger organisms.

So I think it might -- I mean maybe part of the burden falls to us to have some phraseology in the findings that pull out from here because there is no -- given the structure of this document, there is no way to do that.

You don't have an introduction to the document that says here's why these five things -- here are the things that these five chemicals share in common. You just do -- and after all, it's written by committee; different people in your group had responsibility for each chemical, so there isn't one unifying introduction or conclusion.

CHAIRPERSON FROINES: Melanie, I would propose the following: First, if the panel has any verbal comments on the findings that they have seen now, they can --

(Cell phone interruption)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sorry.

PANEL MEMBER GLANTZ: Are you going to start dancing, Melanie?

(Laughter)

PANEL MEMBER GLANTZ: That was a joke in response to her cell phone.

CHAIRPERSON FROINES: So besides Paul, if anybody has any verbal comments about the findings, they can raise them right now.

Second, I -- my guess is that they don't have any verbal comments, although I don't know that.

PANEL MEMBER GLANTZ: Well, let's ask.

CHAIRPERSON FROINES: I'm going to, but let me finish what I'm saying.

If people then want to from the panel provide me and you any written comments, that would be useful for after the meeting. And then we're going to take Paul's comments that he's made, and I'm going to work with you, and you and I are going to work together to come up with the final document for that -- that is -- that we'll send forward.

PANEL MEMBER GLANTZ: I think that's too complicated. I'd like to adopt the findings at this meeting.

So what I would suggest is see if anybody has any comments on what's been written. I don't.

Then I think what Paul said, I agree with. I think it was a good suggestion. But I think what we

ought to do is finish the discussion of what's in front of us, then during the -- you know, table this, write up the short paragraph Paul described, present that to the panel, and then vote on the whole package and then be done with it.

CHAIRPERSON FROINES: I'm sorry. As the Chair, I don't think these comments -- this document is ready for prime time. I think it needs more work.

PANEL MEMBER BLANC: The wording of the findings?

I think in the past we have actually been able to approve the RELs, and we have separately as a group signed off on the language of the findings. So I don't think, Stan, what you're suggesting -- I think both things are possible at once.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER BLANC: And that's what I would support. In fact, I would move that we accept the -- approve the RELs as presented to the panel.

CHAIRPERSON FROINES: And the letter that follows, we can get --

PANEL MEMBER BLANC: Consensus.

CHAIRPERSON FROINES: -- consensus on -- out of the meeting, and then we can send it forward so that there is no contradiction.

PANEL MEMBER GLANTZ: I'll second that.

PANEL MEMBER BYUS: I have one question about glutathione. Is that --

PANEL MEMBER BLANC: Can we --

CHAIRPERSON FROINES: It's an important molecule.

PANEL MEMBER BYUS: I'm just saying, it's not really -- it is low in premies, but it's not higher than adults in neonates. It's normal.

I mean it's just low in premature infants, and then it reaches what you would call a normal level which is pretty much the same for adults and neonates. It is very low in premature infants.

OEHHA STAFF TOXICOLOGIST WINDER: All right. The information I was suggesting that in neonates, at birth in neonates it was relatively high. I think higher than --

PANEL MEMBER BYUS: Higher than adults?

OEHHA STAFF TOXICOLOGIST WINDER: And then it dropped.

PANEL MEMBER BYUS: Higher than children?

OEHHA STAFF TOXICOLOGIST WINDER: It dropped relatively quickly after birth.

PANEL MEMBER PLOPPER: Yes.

PANEL MEMBER BYUS: Okay.

PANEL MEMBER PLOPPER: It goes through a very rapid time phase shift.

PANEL MEMBER BYUS: Shift down?

PANEL MEMBER PLOPPER: Shift down.

PANEL MEMBER BYUS: Okay.

PANEL MEMBER PLOPPER: So right before birth, it goes up. Then it's high at birth. Then it drops. And it's not really clear how it's maintained and whether the maintenance is the same. That's -- it's not complete, but that's what's out there.

PANEL MEMBER BYUS: Okay. Thanks.

CHAIRPERSON FROINES: I think it's worth stating that, given the high concentrations that you find, that GSH depletion is a measure of oxidative stress --

PANEL MEMBER PLOPPER: Mm-hmm.

CHAIRPERSON FROINES: -- and that connection being made explicit because it's -- people don't really understand. Everybody uses the word oxidative stress, and nobody has any idea what they mean except for a bunch of ROS. Which is wrong, scientifically.

So I think having one or two sentences that say oxidative stress and GSH levels are related, and that's important. Charlie, do you agree with that?

PANEL MEMBER PLOPPER: Yes.

PANEL MEMBER BLANC: I believe there was a motion on the table that was seconded.

CHAIRPERSON FROINES: Did somebody second?

PANEL MEMBER GLANTZ: I did.

CHAIRPERSON FROINES: Is there discussion? All those in favor?

(Ayes)

CHAIRPERSON FROINES: The vote is unanimous that the OEHHA document on the five noncancer compounds are adopted. The RELs are adopted.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Great.

Just a note that these findings go to the OEHHA director, not ARB, because that's who establishes the list.

CHAIRPERSON FROINES: Just for curiosity's sake, when you have a REL -- for example, acetaldehyde is not exactly a trivial chemical when it comes to the air, since we're putting ethanol as fast as we can into gasoline and we're generating acetaldehyde; and so as far as I'm concerned, we've got an issue that is emerging, to be euphemistic.

And so when a new REL for acetaldehyde, for example, becomes accepted by this panel, what happens with ARB?

Do they then take notice of that REL? And does that become part of their regulatory process? Or is it just like they say, oh, what a nice thing OEHHA has done, and we'll go on with business as usual?

In other words, what's the driving force, if any?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, they do use our Reference Exposure Levels. The program was set up to look at the Hot Spots program --

CHAIRPERSON FROINES: Sure.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- was the stationary part of it, and so the districts all use the RELs and risk assessments.

But ARB also uses any RELs and slope factors that we generate when they're looking at measures and trying to figure out: What's the risk; and if we do this measure, does it go down?

CHAIRPERSON FROINES: Well, will Joan then send a note to Mary to say we now have five new RELs that need to be considered at ARB?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We've actually sent the note in the past to the secretary and -- secretary of Cal/EPA -- and cc'd the Air Board. And actually, I think all the other boards.

CHAIRPERSON FROINES: Because these RELs -- like manganese may not be the most important REL of all. But acetaldehyde and formaldehyde, these are hot topics.

And so it's not that we should just say, well, there's AB 2588, and we've now done our Hot Spots work, and let's go on with business as usual.

We really do need to have follow-up at some level from --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: There's lots of follow-up, especially at the staff level. The ARB staff is always asking us where are the RELs? Where are the RELs? You know, where are you in the process?

So they're very aware, and those are the people that actually use them at the staff level. It's almost like a courtesy just sending them to the Chair so now she knows. But really it's the staff that --

CHAIRPERSON FROINES: Theoretically, should it be that those compounds now reenter the 1807 process?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: They don't need to. Because they've been identified, and now we've produced the health effects assessment piece.

So a lot of those -- a lot of the chemicals

that we're looking at were a hazardous air pollutant. That's how they got onto the TAC list. They didn't have any health values. So we're -- that's what we have been doing.

CHAIRPERSON FROINES: That's exactly my point.

If they now have risk assessment values, which is required under the Act, don't they then go into the regulatory framework that's established under 1807?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think you'd have to ask the Air Board that. Once the chemical gets onto the list of TACs that may disproportionately impact children, that triggers a needs assessment on the part of the Board.

So they have to -- if there is already an airborne toxic control measure, they have to go back and look at it and make sure it's as good as it can be.

If there isn't one, they have to generate a needs assessment which looks at concentrations that people in California are exposed; is there something that we can do to ratchet that down?

So they've been in the process of doing that for the last batch.

CHAIRPERSON FROINES: I'd just say, even though this panel is not supposed to deal with risk management issues, obviously we're concerned about what

happens with our findings once we've made them, and is there anything that goes on besides being put in some bible that, you know, lasts till the end of time and that -- you know; you understand exactly what I'm saying.

PANEL MEMBER BLANC: Well, should we take a five-minute break before we go on to the next thing?

CHAIRPERSON FROINES: Sure. Let's take a five-minute break, and then we'll go on to cancer potency.

(Recess)

CHAIRPERSON FROINES: So Stan Glantz is going to begin by discussing the process that's occurred since the last meeting up to today, and then he'll obviously embellish that with other thoughts, but -- so let's -- and then Joe will follow.

So Stan, why don't you start off?

PANEL MEMBER GLANTZ: Okay. Well --

CHAIRPERSON FROINES: Ready, Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER GLANTZ: So I'd like to just preface what I say with: The document in front of you, it looks very different, but the substance of it is the same as before.

And as people recall from the meeting, the last meeting, there was a lot of confusion about what the document was trying to say; and there have been a lot of revisions, but none of them are substantive. They all have to do with presentation and trying to present the ideas in a way which is clear.

And so I think it's important for people to not think that the results of the process I'm going to describe to you were substantive changes because they weren't substantive.

And from my perspective, and the things I know about, I'm happy with the document as it is.

Now I'm sure other people who have other expertise may raise issues that I didn't think of; but, you know, in terms of the things I know about, I would vote to approve the document right now.

Now I may change my mind based on other discussions.

So the process that we went through, which was slightly different than what we discussed at the meeting just because of scheduling problems, is I had two long meetings with Melanie and Sandy and Rajpal and a few other people. And the idea was that Joe would be there, but we just couldn't schedule it, so they had separate discussions with him which I'll let him talk

about.

The first meeting went on for about three hours, and we went through their presentation one slide at a time. And I went from a state of total confusion to actually understanding what they were trying to say.

Then we spent a lot of time talking about how to say it differently. And the changes that were made in the presentation --

CHAIRPERSON FROINES: Is it to say it differently so others would understand it better?

PANEL MEMBER GLANTZ: Yes, or even so I can understand it.

PANEL MEMBER BYUS: Anyone.

PANEL MEMBER GLANTZ: Anyone.

PANEL MEMBER BYUS: Anyone.

PANEL MEMBER GLANTZ: Anyone, even the Chair of the Committee.

And so the changes that we made were the following; and if you want, I can also give my understanding of sort of how things -- what their analysis was trying to do.

CHAIRPERSON FROINES: I think you should do that.

PANEL MEMBER GLANTZ: Okay.

The first thing is: Before, the document

basically presented a couple of conclusions and referred everyone to Appendix J which is very dense and very detailed and was very confusing. And that's also been rewritten to parallel the document.

The main elements of the analysis now appear in the document itself, and the appendix is an appendix. So if someone reads the document and they want more details, they can go to the appendix.

But I think that the approach that they have is now discussed in enough detail in the primary document that you don't actually need to read the appendix unless you want lots more details.

The second thing that they did is that the process of -- I thought the nomenclature that they were using was very confusing because they were using the term age -- what's the S stand for?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sensitivity.

PANEL MEMBER GLANTZ: Sensitivity factor, ASF, to mean three different things. And that was a great source of confusion.

So now in the revised document, the term age sensitivity factor only refers to one thing; and what it refers to is the multiplicative adjustment that you apply to an adult potency to compensate for exposure at

different points early in life.

And the age sensitivity factor is the result of two components which are multiplied together, one which is the effect of exposure at different times in life, the fact that if you're exposed, say, as a juvenile, that's different than being exposed as an adult for some of the chemicals.

And then the second part is the duration of -- the effect of duration of exposure. And I can't -- we had a lot of discussion over what to call these, and I frankly don't remember.

But those have two -- are called three different things, and the age sensitivity factor is the product of the first two, of the two separate elements.

And I think that clarifies it.

Another change in the presentation that I thought greatly clarified things is there was a lot of discussion in Appendix J of the details of the distributions of the potencies.

CHAIRPERSON FROINES: Can I ask a question?

PANEL MEMBER GLANTZ: Yes, sure.

CHAIRPERSON FROINES: Melanie, this is a question.

Stan was talking about the timing of exposure and when the exposure occurs. Is there a place -- and

I'm sorry for interrupting -- but is there a place where the issue of the reversibility of chemical change actually becomes an element?

Because if you have an irreversible change that occurs over a long period of time, you have to grow new proteins before you can get revitalization of that protein, and so reversibility and irreversibility are part of the --

PANEL MEMBER GLANTZ: Okay. I want to just impose your own rules, so let them answer that later.

CHAIRPERSON FROINES: I'm just asking for -- that's a clarifying question.

PANEL MEMBER GLANTZ: No -- well.

PANEL MEMBER BYUS: No, it's not.

PANEL MEMBER GLANTZ: No, it's not.

(Laughter)

PANEL MEMBER GLANTZ: I'd like to request we come back to that. Let me finish my little spiel.

CHAIRPERSON FROINES: Sorry.

PANEL MEMBER GLANTZ: That's okay. I don't have to be as nice to you as they do.

(Laughter)

PANEL MEMBER GLANTZ: So in any event -- now I lost my train of thought. Okay. I remember now.

The basic idea of what they do is that they

compare, they take experiments -- you know, there's a couple of different ideal experiments, which Craig is going to ask about which I'll let him bring up when it's his turn.

But, you know, the basic idea is you expose the animals, say in the juvenile phase, and you look at the potency at that point; and then you expose a different group of animals as adults, and then you look at the ratio of those potencies.

And that's the first part of the age sensitivity factor, and there's uncertainty about what those potencies are.

Now, in the usual way these things are presented -- and in fact, the way they are presented in the first part of the document -- is to get a benchmark dose which is a single point with some uncertainty around it.

And what they did in the analysis in the second part of the document, which is what we're talking about, is they estimated the actual probability distribution of the potency. Okay? And I'll let them tell you how do it.

But instead of getting a point, they actually tried to estimate the distribution. And these distributions have different shapes; and then when you

have situations where there's several different relevant tumors, they add the potencies together so you can get some fairly weird-shaped multimodel distributions, and in the previous version of the paper, they really talked a lot about the shapes of those distributions.

Well, in meeting with the staff, that's really not important, that important. The thing that's really important is the cumulative density function. That is the -- you know, how does the risk increase with dose?

And so another really big change in the document was instead of focusing on the probability density functions, like the normal, the bell curve, is to look at the cumulative distributions because that's really, after spending all this time with them, what they're really talking about.

So when you look at the chapter -- or at the document, you'll see there is a whole bunch of new figures which are presented as cumulative distributions, and all the little bumps and wiggles, which are actually embedded in those, don't even get talked about because they're not important.

And then the other thing which is -- in changing the way it was presented -- is another source of variability is different chemicals behave

differently.

And what they've done in presenting the cumulative distributions, you'll see that there is variability within chemical, but then the chemicals themselves are different, and the overall curve looks like the pile of boxes, it's sort of S-shaped, you know, that is describing the differences between different compounds.

And the overall kind of default values for these adjustment factors is at some percentile point on that distribution.

So in the end, the idea -- the final result is pretty straightforward, at least from my point of view. So I think that the process of getting that is now much better described.

The effect of exposure at different points in the life cycle is treated and called one thing. The effects of the duration of exposure is a separate thing which has got another name. And then you multiply those two together to get the age sensitivity factor.

So that's the presentation, and the basic idea.

And the first meeting was three hours of going through slide-by-slide and having me ask fifty million questions until I could finally figure out what they

were trying to say and then giving them suggestions on how to say it in a way that I thought was understandable and talking about reorganizing the document.

Then we had another meeting about a week and a half or two weeks later to review the revised document and made -- I made -- that was completely on presentation, and that's where we came up with the idea of calling these things different things and some more edits, and then that's how the document ended up.

There's one other little change to it that isn't in the document that's before you which we'll just present. It's just a minor wording change.

So that's -- and then the other -- so that's what I did. And then they met separately. All this was reviewed by Joe, too. I'll let him talk about that.

The one other, in terms of the larger document -- I mean the great bulk of the energy was focused on this issue.

The one other substantive suggestion I made to them had to do with the discussion of the criteria for evidence and causality and things like that, and this document had not reflected the changes that we made in the REL document.

And so those were pretty much verbatim. The changes we made about how you judge evidence and criteria for causality of power and all that other stuff that we spent a lot of time talking about in the REL document have now been put into this document in place of what used to be there which pretty much followed the REL document before we changed it.

So that's the one other kind of substantive change in the document. So I hope that's what you wanted from me.

You guys have any questions?

CHAIRPERSON FROINES: Questions for Stan?

PANEL MEMBER GLANTZ: Okay. I think it's much better. And my criteria for that is I actually understand it. Which before, I was just completely befuddled.

So Joe, did you want to?

CHAIRPERSON FROINES: Please.

PANEL MEMBER LANDOLPH: Yeah.

So the first time I worked with Melanie and Dr. Salmon and their crew, I wrote about a ten-page critique of the things that I thought should be changed. I thought a lot of the document was written very well.

I had some reservations about the use of the

factor of 10 to account for the susceptibility of early life in humans zero to two ages and the factor of 3 for humans age two to 16 years old based on the Barton paper.

The Barton paper shows us a differential susceptibility of .12 to 111 which is a 3 order of magnitude span. So we discussed that.

In general, I thought the first document was written well, but I thought they could have condensed it about ten percent just by more concise writing.

Obviously, nine different scientists and three senior reviewers reviewed the document, so I went through and tried to make the writing style a little more uniform by making the sentences shorter throughout.

I thought that the cancer risk methodologies assessment -- assessment methodologies -- was written very well. I had two or three pages of small comments, and toxicokinetics benchmark dose methodologies, linearized multistage model, selection site, and tumor type -- they were all written pretty well. I had a few small comments.

And the early lifestage cancer potency adjustments, I went through for them. And I asked them to put in some standard things that -- the National

Toxicology Program routinely uses newborn animals in carcinogenesis studies. That's just the way it's done, and they have to make that clear.

And then I went through the Barton article and had some more comments about that.

I liked a lot of the discussion that they had about early life susceptibility based on metabolism of carcinogens, et cetera.

And Appendix J I thought was technically competent and could have been clarified a little bit. I had a number of comments on it.

I like the -- three of the figures were very illustrative, and those were the three that, Stan, I believe, and I had them move forward.

So that was the first go I had, and I wrote about ten pages of comments, and Melanie and Andrew and I discussed that as well. And they amended the document --

CHAIRPERSON FROINES: Who?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Andy Salmon.

PANEL MEMBER LANDOLPH: Andrew Salmon; I'm sorry.

So they revised the document, and then Stan went after the document again with them, as he just

indicated. And I was supposed to come up for the second meeting, but I had to be in Washington to sit on the NRC perchloroethylene risk assessment committee, so I couldn't make that.

But after Stan worked with them a second time, then Dr. Marty and Dr. Salmon called me on the telephone. We had a conference call that lasted about an hour.

And they FedEx'd me the final revised document and explained what was done in that document, and I agreed with everything that was done. And I liked the document a lot. I agree with Stan.

So I just had a few comments, that I like the Executive Summary, and I completely agree with OEHHA's position -- this is all written down, so you don't have to take any notes -- that they use a factor of 10 for exposure from early life and a factor of 3 for exposure from two to 15 years of age.

And I completely agree with their applying this to all carcinogens regardless of purported mechanism of action unless chemical-specific data exist to the contrary.

So I think their position is very health protective. It's different than EPA's; and I have to admit a conflict of interest because I sit on some EPA

committees, and I disagree with that mutagenic mode of action business that they are trying to impose. I think OEHHA has the right way to look at this, just do them all the same.

And also, there's a very important statement in there which Dr. Marty and her colleagues wrote which is: OEHHA will use chemical-specific data on this issue of age susceptibility where it exists.

Obviously, it doesn't frequently exist. Where it exists, they'll use it. And that's a pretty good policy too.

And I agree with their position to use the benchmark dose methodology with the cancer potency factors and to use scaling based on body weight of three-quarters power and to generally follow the IARC guidelines on the carcinogenicity of chemicals.

And they put that IARC language in the document which strengthens it.

And I thought that they had some very good new statements. OEHHA's going to follow the recommendations of the NRC in describing a set of clear and consistent principles for choosing and departing from default cancer risk assessment options. This will make the procedures more clear, justified, credible, more acceptable to all the stakeholders.

The hazard identification section was written well, and they imported all the criteria from Bradford Hill, so that makes it very clear and makes the document defensible.

And I found it very interesting in their figure 7 that the mean of the prenatal ASF cumulative distribution frequency profile is 2.9, the mean of the juvenile ASF distribution frequency was 4.5, and the mean of the postnatal distribution frequency was 13.9.

So it looked to me like the later lifestages are more susceptible to carcinogenesis which I found interesting -- just based on means -- which was counterintuitive for me, but that's the way it is.

So I agree that they should apply the ASFs to all carcinogens, regardless of the mechanism of action. And I agree with using a juvenile ASF of 3 and postnatal ASF of 10 and deciding the prenatal ASF on a case-by-case basis on page 49.

CHAIRPERSON FROINES: Joe, can I interrupt just for -- I do mean this as a clarifying question.

PANEL MEMBER LANDOLPH: No. One more sentence.

CHAIRPERSON FROINES: No matter what Stan says.

(Laughter)

PANEL MEMBER LANDOLPH: One more sentence.

And I thought Appendix J was also significantly improved by addition of various clarifying figures and substantial revisions and importing the figures forward.

There were a couple of figures where I'd asked Dr. Marty and her colleague, Dr. Sandy, to show where you'd divide one distribution frequency by another to get the resultant ASF, and that clarified it really well.

So I agree with Stan. I think it's substantially improved, and it's easy to read now, and I can understand it too. So that was about the sum of the work I did.

So now you can ask your question.

CHAIRPERSON FROINES: Well --

PANEL MEMBER GLANTZ: He forgot what it was.

CHAIRPERSON FROINES: No, I know what it is. I'll just raise it for everybody else on the panel, and I'll be the last --

PANEL MEMBER BLANC: Just clearing my throat.

(Laughter)

PANEL MEMBER GLANTZ: What did you say?

PANEL MEMBER BLANC: I was just clearing my throat.

CHAIRPERSON FROINES: Okay. I'll just ask a quick question.

Melanie, obviously there has been analysis done by Sander Greenland and Ken Rothman on the Hill postulates. And they don't take the Hill postulates, as you know, as being, you know, set in stone. There are lots of things to consider.

Do you have any place in the document at this point where you actually acknowledge some of those critiques that Greenland and Rothman have made? Because I think they're important because otherwise it becomes like the Bible again, you know, that everybody just sort of bows down to.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I knew you would bring that up, particularly since I forgot to put it in. So I do have -- it's a 2008 paper, I think, 2007, where they nicely summarize the issues around the fact that they really aren't criteria, they are not set in stone, and some of the arguments around it.

So I will add a sentence referring to that paper since it's nice and concise and some similar arguments that they made in the last version of their book, except for condensed. So I'll put that in there because it is true that --

PANEL MEMBER GLANTZ: Well, actually, I think that the document -- I mean, I think the Hill postulates are taken too seriously, and I think they're actually out of date.

But I think that the -- if you look at the way that the report has been -- the REL report was revised, and then which has now been pulled into this report, that -- we put in there, I think, the appropriate modernization of the Hill criteria.

I agree with you that those things have become biblical in scope. And I mean we know a lot more than we do now -- than we did then. You know, we have the whole area of molecular epidemiology. We have -- we know a lot more about mechanisms than we did.

PANEL MEMBER BLANC: No, hold on.

I think that in each section, you have appropriate caveats. But I would support doing what you propose, and I think the obvious place is just following your lengthy quote from Lilienfeld and Lilienfeld, and that's the place where that should go.

I think the other thing that we've talked about in the past, although not necessarily in the context of this section, is some comment as to where meta-analysis or meta-analytic techniques fit into either the question of consistency or strength of

association. We were never clear. It sort of is relevant to both things, but I think that there's an obvious place for you to make the comment.

And you really should just carefully review your edits, the underlying edits, for typographical or grammatical errors. I'd just point out one sentence that struck me:

> Since it is more difficult to detect, i.e., read statistical significance, a small magnitude risk, they are just as likely to be causal as larger magnitude risks.

That's not in English, that sentence. I mean the "they," for example, "they are." So just make sure you read -- just take a quick look.

And also you've a nice -- another example of a nice caveat is where you talk about the temporal relationship. But once again, when you talk about, use example of an acute irritant exposure, and you say:

> For example, respiratory irritation immediately following exposure to an irritant vapor is temporally consistent, whereas effects noted years later may not be.

What you mean is where effects only noted

years later may not be, right? Because you certainly could have residual -- you could have irritant-induced asthma, but you should have had some acute effect, right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Exactly.

PANEL MEMBER BLANC: Let me ask a question I think for Joe.

In their discussion about data that are available for differential age effects, is there data that are relevant that should be invoked for secondary tumor risk following chemotherapy in children treated with the same chemotherapeutic agents as compared to adults, taking into accounting latency?

PANEL MEMBER LANDOLPH: I'm thinking of data with Adriamycin and secondary leukemias. I don't know if -- I don't think you've used that data in there, have you? I don't recall seeing it.

PANEL MEMBER BLANC: Because I look at table one on page 38. I don't see any of those chemotherapeutic agents. Nitrogen mustard -- I mean, I don't know if there are data or not. You don't say that those are animal studies.

DR. SANDY: Right. Table one is only -- this is referring to the chemicals in our animal study

analysis.

PANEL MEMBER BLANC: Well then, you should say animal studies on the table. And then is there somewhere else where you do discuss the data that may be relevant from carcinogenic chemotherapeutic agents?

DR. SANDY? We do not. In Appendix J, we give some examples of -- from clinical and human epidemiology literature of examples of early age effects.

But we were not able to get the -- we needed the actual data from human studies, and it was very difficult. We did try to look at that literature, but in order to do the type of analysis that we did with the animal studies to try to get some --

PANEL MEMBER BLANC: Slope or something?

DR. SANDY: Slope. We would actually need the raw data, and that's very hard to get and we weren't successful in that.

PANEL MEMBER BLANC: Nobody else has done that analysis that you could just cite; is that correct?

DR. SANDY: I'm not aware that it has been done, no, on a case-by-case basis.

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: I'll tell you -- I mentioned this last time, I think. I saw a curve at

another meeting I was at on radiation carcinogenesis, and I just about fell out of my chair. It was so stunning.

The curve looked like this (indicating) as a function of age. It was exponential. So it really dramatically showed that newborns and the earlier lifestages are much, much more sensitive.

In fact, it's dropped -- the curve dropped so fast that one questions whether the older animals are at all affected. It's such a dramatic drop.

So if you could ever find that curve -- and I'm sorry; I can't remember --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER LANDOLPH: If you could find that and put it in the appendix, that's -- you just look at it, and immediately you see that that must be a true statement.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Those analyses have been done by tumor type, but the curve is different for each tumor type.

For example, lung cancer, there does not seem to be any difference, for example, from the Japanese atomic bomb survivors.

PANEL MEMBER LANDOLPH: Any difference versus

age?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Versus age.

PANEL MEMBER LANDOLPH: Well, that's interesting in its own right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That other tumors there are.

PANEL MEMBER LANDOLPH: In fact, that's interesting in its own right, and it even informs you at a deeper level that it's not such a simple thing.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Not a simple thing.

PANEL MEMBER LANDOLPH: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We did refer to -- on pages 32 and 33 briefly -- to these other evidence in humans. We could expand that discussion. We had more discussion of this issue in our prioritization document in 2002. We could pluck more from that and put it in here if you thought it was appropriate.

PANEL MEMBER LANDOLPH: I think it would be useful. I don't know what the other members think.

Because radiation is so relatively easy to get the symmetry on, and you don't have to worry about metabolism. It's relatively uncomplicated compared to

some of the chemicals, I think, particularly the curve you mention on the lung, would be very interesting compared to the others.

PANEL MEMBER BYUS: My question was related -- I had a comment totally related to that, and that would be smoking. I mean, there's got to be -- there is; I know -- a lot of data about smoking at early ages. I mean there's an enormous amount of information.

So you really should try and comment on that. If you start smoking when you're five years old, at whatever dose, when do you get cancer? When do you see it? Do you see more? Are you more sensitive in a sense, dose-response-wise? Or is it a latency phenomenon and you see cancer earlier? Or does it still show up later?

I mean, there's got to be a lot of data on that. Or some.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. I think we have to be careful not to have an exercise in, you know --

PANEL MEMBER BYUS: No, but --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- writing a whole another document.

PANEL MEMBER BYUS: No, no, no. Here's the point. What you really want to do is -- you know, you

were trying to develop a whole procedure here, which is great, based on the animal data.

But now you need to take your results, in a sense, and apply them back to some human data, if it exists, to show that it's in fact valid.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, that's --

PANEL MEMBER BYUS: You know what I mean? So I'm not saying -- it's not a useless exercise. I mean it's very important.

And so if there's some limitations, like you just pointed out about tumor specificity, which you don't really -- which is another critique I have of the overall approach, is that you really didn't deal much with different tumor types and differences in tumors between young and old --

CHAIRPERSON FROINES: We're supposed to be commenting on Joe's presentation, and you're right into the substance which is to come after the presentation.

Why don't we hold this for now and come back to it?

PANEL MEMBER BYUS: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Could I just make one comment? The purpose of the analysis was to get a default policy in place where

you did not have the data to do an actual analysis of potency by age at exposure for specific chemicals or mixtures.

So that's the purpose. And if we had those data, and we were analyzing that chemical, we would use the data, not the default.

So just to get -- that was the purpose, the analysis. So --

PANEL MEMBER BYUS: I'll comment later.

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: I just want to thank Dr. Marty and Dr. Sandy and all their staff because they addressed every criticism I made, you know, which was two revisions and over 13 pages' worth. And I'm sure they took my name in vain doing it, but they did it. And I appreciate that.

And number two, I just want to say to the rest of the panel, other than Stan and I, what helped me was reading that Barton document, which I know John didn't want the panel to do, as he stated last time.

But I read that and analyzed it very carefully, and my research group did too. And that made it easy for me to get into the game and understand this document. Without that, it would have been difficult for me. So that -- if you want to get

educated real fast to what they're doing, to read the Barton document will help you.

PANEL MEMBER BLANC: Joe and Stan, do either of you have any specific comments on the response to public comments that OEHHA makes towards the end?

I think it would be useful to have that on record, or perhaps you already addressed that at the last meeting? Do you feel that was appropriate or --

PANEL MEMBER GLANTZ: Oh, yeah.

I reviewed the response to comments and, you know, before the last meeting, and I thought that OEHHA responded appropriately.

My big problems with the documents were not the things any of the commenters brought up, just the stuff we've been talking about.

But I don't remember the details because I read it before the last meeting, but I thought they were appropriate in responding.

And they did make some changes to the document in response to the comments. I don't remember the particulars, but that's -- when I read these documents, I always start with that, actually.

PANEL MEMBER LANDOLPH: So I also read through the public comments and OEHHA's response. And their responses are consistent with responses they make

historically on other documents.

They seem to me to be fair. They read what the public comments are, and they do answer them fairly and honestly. Sometimes there are differences of agreement, you know, differences, points of difference. And that's just the way it is.

And occasionally there will be people that don't want them to use default factors or want them to use smaller default factors.

But I think their choices of default factors are clearly health protective, and I can support them. I think those were some of the biggest issues of difference, but they weren't that big, I didn't think.

So I think they did a good job over all, as usual.

PANEL MEMBER GLANTZ: But it wasn't, as I recall, just defending the document. I mean there were things where the commenters brought up points that were reasonable, and they said this is reasonable and made changes to the document.

Probably Melanie's got that as part of the presentation. But, you know, I don't -- I think they handled that fine.

CHAIRPERSON FROINES: Well, I'm a little concerned from a procedural standpoint. Melanie, maybe

you can add to what Joe and Stan said.

Joe and Stan have just finished saying yes, we read the comments, and OEHHA's responses appeared adequate. But that doesn't really give enough in the way of substance of those comments. And so it leaves -- it doesn't -- it leaves it a little bit in a vacuum, I think.

So if there are specific technical comments that would be good to have on the record in terms of your response, I think you should mention them.

I want a well-defined record on the panel's evaluation of the written comments so that everybody knows that we're doing an adequate review.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I could go through some of the major points.

PANEL MEMBER GLANTZ: Why don't you do that? You know, typically though, when you make these presentations, you address that at the end.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER GLANTZ: So I think -- and I think that's the right way, even though I always read them first. But I think it would be best in terms of clarity and appreciating the context for the, you know, for the comments to have -- to go through the report

first, and then she can address -- present the more salient comments.

CHAIRPERSON FROINES: Do it as you think best.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. I can do it at the end. But I have to say we were surprised that we didn't get more comments than we did.

And there were only really a few major issues that were brought up that we disagreed with the point of the commenter, so I can go over that. I don't have slides, but --

PANEL MEMBER BLANC: That's fine.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- you know, take me five minutes. So why don't we do that at the end.

CHAIRPERSON FROINES: Another question about this.

What I don't understand at this point -- and this is a little bit offline -- but this now represents the position of the State of California that will be used in the future for cancer risk assessment.

And I would like you maybe to spend three minutes toward the end of the discussion today about how does this document relate to what US EPA is doing, which is different, as we know. And are we going to be

in a position where there are contradictions or conflicts that are problematic?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I can answer that in two sentences now, if you want.

CHAIRPERSON FROINES: Please.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The default uncertainty factors that we chose and that EPA chose are the same, and the application to those in risk assessment is the same.

The difference is that EPA decided to only apply that to carcinogens with, quote, a mutagenic mode of action, end quote.

They then decided to try to define what they meant by a mutagenic mode of action, drafted their report, put it out for peer review, and the peer reviewers pretty much kicked it back and said this is not adequate.

And part of the major problems with that was they had defined mutagenic mode of action very narrowly. For example, the chemical would have to have induced mutation directly in the DNA, so that kicks out any indirect mutagenicity or even any other kind of DNA damage, and that that would have had to have happened in an early stage of the carcinogenic process.

You don't have data for any chemicals about where that happens in the process and whether that early stage is more important than later stages.

You have multiple mechanisms of action for many carcinogens, if not most. You don't know whether those -- which of those modes of action predominate over the life of the person. You don't know whether some are more important in early lifestages than later lifestages.

And so the upshot is we just don't agree at all with limiting to those chemicals with a mutagenic mode of action, particularly since they can't themselves define a mutagenic mode of action at this point.

CHAIRPERSON FROINES: And so you're -- I'm looking at that -- and so what I'm really asking is:

You're satisfied with your approach to this particular issue at this particular time, and you would ask the panel to say that they feel that your actions are consistent with good science?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: I can address that even more specifically because I was on that panel, and

I think the EPA's approach was very messy. It was widely criticized by almost every member of the panel, this very narrow definition of mutation they took, and I think they are locking themselves into a box.

I think the position Dr. Marty and her staff are taking is a much more rational, more conventional, generally accepted scientific position.

I think what the EPA is doing is a little bit unusual, and I don't think it's going to be accepted. And we basically told them to take the document back and redo it and come back to us at a later time.

So I can clearly support Dr. Marty and OEHHA's position as opposed to the EPA's position in this matter.

PANEL MEMBER BLANC: Joe, can you point out to us where in the document it explicitly says: And this will be applied without regard to mechanism, just so we see the wording clearly?

Sorry not to be facile enough to know where it is.

PANEL MEMBER LANDOLPH: Let me see if I can find it.

CHAIRPERSON FROINES: Does everybody understand where I'm headed on this?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Page 48.

PANEL MEMBER BLANC: I think what you're implying is that our findings should be explicit rather than implicit in this regard.

CHAIRPERSON FROINES: That's right.

PANEL MEMBER BLANC: So it's that added paragraph now, the underlying paragraph?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER GLANTZ: I would be happy to add that paragraph to the findings.

PANEL MEMBER LANDOLPH: I would second that.

CHAIRPERSON FROINES: Melanie, did you hear that?

PANEL MEMBER GLANTZ: What I just said was I would be happy to add that paragraph to the findings. I think the suggestion Paul's raised is a good idea.

PANEL MEMBER LANDOLPH: And I am in concurrence. I agree.

PANEL MEMBER BLANC: And the critique that you alluded to that your committee provided back to EPA: Is that a citable document in some way?

PANEL MEMBER LANDOLPH: I don't know the answer to that. I mean, we gave it to them.

PANEL MEMBER BLANC: I mean is it on the EPA

website?

PANEL MEMBER LANDOLPH: I don't know whether it is or not. The meeting was held in public.

PANEL MEMBER BLANC: So there is a record of it.

PANEL MEMBER LANDOLPH: Yeah.

CHAIRPERSON FROINES: I think if there is a record, it should go --

PANEL MEMBER BLANC: Melanie, if there's some way of citing that, I would do it if you can, if it doesn't drive you nuts.

PANEL MEMBER LANDOLPH: And Kate Guyton of EPA would know where to get it.

PANEL MEMBER BLANC: John, can I suggest that we go back to Craig's, let him lead off in terms of the nonreviewers?

CHAIRPERSON FROINES: We were going to go to the presentation by OEHHA.

PANEL MEMBER BLANC: Oh, you're going to do your presentation first.

PANEL MEMBER BYUS: Then we'll come back.

CHAIRPERSON FROINES: Can we take a short break?

PANEL MEMBER BLANC: Please.

(Recess)

CHAIRPERSON FROINES: Let's go. Naphthalene.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: What I wanted to do -- I have about eight slides just running back over what John presented last time, kind of hitting the highlights of what changed in this document.

Then I have two little handouts to make a couple points. One is a wording change that is not in the copy you got that I worked out with the two Leads, Drs. Landolph and Glantz.

And the other is some examples of the difference in potency that you get when you use the linearized multi-stage model versus the newer default.

So the whole purpose, again, of this document was reevaluating our cancer risk assessment methodologies to incorporate new developments in risk assessment methodologies since the previous Hot Spots risk assessment guidelines were developed and explicit consideration of infants and children under SB 25.

So to me, the key changes are: Updating the hazard identification criteria, emphasizing IARC, which includes the supporting data more explicitly than has been done in the past; that the default for low dose extrapolation is going to be benchmark dose rather than the linearized multistage, but to point out that the

data -- tumor data in the observable range, curve fitting of that is still the same in both methods, using the multistage polynomial primarily, although you do have options of other models if they fit the data better, but at the -- when you go to extrapolate beyond the observed range in the low dose, we're going to use the benchmark dose method.

Then the other big change is the age sensitivity factors, which we just talked about, to weight risk for exposures in infancy and childhood.

So I just mention that the new guidelines emphasize the benchmark dose empirical models. So step one, choose the mathematical function providing the best fit to the observed dose response data for curve fitting, and the multistage polynomial is generally chosen. We always try that first, anyway.

Then step two is the linear low dose. And in this case, using the 95 percent lower confidence limit on the dose producing a specified tumor response.

And then linearized multistage model is still usable and will be used, for example, where you have time-to-tumor data, which we'll have a lot from NTP studies.

So for most carcinogens, the data support an assumption of low dose linearity, and we're sticking to

that.

And in these cases then, the potency is simply the slope of the line, the linear extrapolation, from the nine percent lower confidence limit on the dose that produces usually a ten percent response rate; but if you have better data you can get lower, to zero. So that line is the slope of the dose response curve, and therefore the cancer potency.

PANEL MEMBER BLANC: Just to clarify, what happens in the hypothetical situation where you have very good epidemiologic data and no experimental animal data? Does that then become a benchmark approach or some kind of -- what happens in that case?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, you could use the same -- you could use the same approach.

And if we have occupational data, we generally use that in preference to the animal data because you don't have to do the interspecies extrapolation process.

PANEL MEMBER BLANC: So this theoretically, either way could --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It could --

PANEL MEMBER BLANC: -- be used.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER BLANC: And do you say that explicitly somewhere?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Hopefully, somewhere in here.

PANEL MEMBER BLANC: Because the way the slides are, it's only for animal --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER BLANC: -- information.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If it's not in here, I'll make sure it's in here. But I'm pretty sure it's in here.

PANEL MEMBER BLANC: Is that -- Joe or Stan, is that -- do you remember seeing something about that?

PANEL MEMBER LANDOLPH: I don't remember seeing it. Because I think most of the data was centered on extrapolating the animal data to humans; huh, Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: For the age-specific factors, yes.

PANEL MEMBER LANDOLPH: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But we routinely use epidemiologic data for

risk assessment. I know we say that in here.

PANEL MEMBER LANDOLPH: You might want to highlight it, maybe, give it a separate title or something to make it stand out.

PANEL MEMBER GLANTZ: Yeah.

PANEL MEMBER LANDOLPH: Because I'm not recalling it.

PANEL MEMBER GLANTZ: I mean I don't remember because -- I mean, that's just so standard in the way they do everything. So I can't remember if they said it or I assumed it.

But I agree that explicitly making the statement, if it's not there --

CHAIRPERSON FROINES: What's the explicit statement?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That we use occupational data when we have it.

PANEL MEMBER BLANC: In other words -- or I'd just say it differently.

I'd say that these methods, although the examples being using are animal bioassay data, they could equally be applied to using epidemiologic data if it exists. Or some phrase.

Because it could be not occupational epidemiologic data too, theoretically, I suppose.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It could be. And generally when we use epi data, we have typically used different models than the LMS, although we have used all of the above.

So there -- you know, our cancer guidelines document, the '86 version, has a whole bunch of models, and so does the US EPA version 2005 which we allude to.

We didn't go into lots of detail in all of those models. You could potentially apply this, but --

CHAIRPERSON FROINES: Well, I just want to avoid the knee-jerk reaction.

That is, yes, occupational epidemiologic data may be valuable and useful. That doesn't necessarily make it better than a good animal bioassay from NTP.

PANEL MEMBER BLANC: I wasn't trying to say that though.

CHAIRPERSON FROINES: And we need to not -- if we have -- if the -- obviously, if there is epi data that has limitations, we cannot sort of take out the bible which, as the epidemiologists like to do, and just use that and forget the fact that the animal data may be superior in quality.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

When we do a chemical-specific assessment,

we're looking at all the data, animal, occupational. Sometimes the occupational data is not particularly usable because the exposure assessment is so problematic.

PANEL MEMBER PLOPPER: Mm-hmm.

PANEL MEMBER BLANC: Okay.

CHAIRPERSON FROINES: Just so that all of this is made explicit --

PANEL MEMBER BYUS: I have a related question.

So if you used epidemiology data, would you then use -- oh; sorry -- would you then apply the age sensitivity factors for children, if the epidemiology data was not generated in children?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER BYUS: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Most of time, it's not. I mean there is a --

PANEL MEMBER BYUS: That's fine.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- few examples.

Allan Smith's analysis of the arsenic data in Chile. He actually could use exposures in kids and showed a very highly statistically significant difference in lung cancer risk and bronchiectasis when

exposure occurred as children.

So there is a great human example.

PANEL MEMBER BYUS: I mean I think you really need to say that. Because I didn't pick up on that. I assumed it, but I didn't pick up on it clearly.

CHAIRPERSON FROINES: Use the reference to that paper of Allan's because it's so good. Just reference it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: All right. Okay.

So one of the major focuses of this document was dealing with early life exposures and potential susceptibility and the impact on cancer risk.

So there are essentially two things you've already heard about: That in general risk is proportional to time to exponent, and the exponent is generally 3 which agrees with -- it's pretty well established and based on a lot of data, and it applies to most carcinogens.

So just from the fact that you have a longer time to expression of the tumor when exposure occurs early in life, there is automatically a disproportionate effect on lifetime cancer risk from early life exposures.

The second point is that young animals and

humans show enhanced sensitivity to some carcinogens relative to exposure as adults -- and Martha Sandy will provide a lot of information about this in a minute -- and that's what that whole analysis of all that individual data was all about.

And it essentially shows that early lifestage exposure to carcinogens is frequently more potent than later lifestage --

PANEL MEMBER BLANC: Could you --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- being adult, mature.

PANEL MEMBER BLANC: Rather than forcing you to abandon the use of the word "sensitivity" and therefore having to call it something other than ASF --

PANEL MEMBER GLANTZ: No, no. They still call them ASFs. It's just that the ASF is the final result of combining these two other things.

PANEL MEMBER BLANC: Yes.

PANEL MEMBER GLANTZ: So that's --

PANEL MEMBER BLANC: Let me just finish what I was going to say, which is: Could you please put a footnote or a parenthesis that explicitly says you are not using the word "sensitivity" in the immunologic sense?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay.

CHAIRPERSON FROINES: In what?

PANEL MEMBER BLANC: In the immunologic sense.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

So in a nutshell, we developed in this document default age sensitivity factors for use where you don't have chemical-specific data such that:

When the exposure occurs from birth to 2 years of age, there is a tenfold weighting factor or adjustment factor.

For exposures from 2 through 15 years of age, there's a threefold adjustment.

And at 16 years of age, it's just 1X.

These age sensitivity factors then will apply when you're estimating lifetime risk estimates, using the standard calculations, standard potency values.

And for exposures that are shorter than lifetime in the general population, but we'll make the assumption that there are infants and children present, and so they will be -- those factors will be used, and --

PANEL MEMBER LANDOLPH: And these are based on your geometric means of the ASF, close to them.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Close, right.

PANEL MEMBER LANDOLPH: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And we will apply these factors, as I mentioned earlier, to all carcinogens except where there's contrary evidence and regardless of the purported mechanism of action.

This slide just gives an example, which is in the document, for a lifetime risk assessment, what the impact of the age-specific factors are, age sensitivity factors, on the actual lifetime cancer risk.

So with a hypothetical carcinogen of -- with a potency of one milligram per kilogram day and exposure of what's on the slide, .001 milligram per kilogram day, and this is with -- without considering differences in exposure now, just what is the effect of the age sensitivity factor. And so you can see it's about a factor of 1.7 in this case.

So you note that you weight that range from zero -- for birth to 2 by a factor of 10, but that's only 2/70 of the total lifetime risk.

You add that to the -- what you might call 3 to -- or 2 to 16 year period, which is 14/70 of the -- fraction of the 70-year lifetime. And then add that again to the risk for 16 to 70.

PANEL MEMBER BLANC: Now Melanie, one thing we had talked about briefly the last time, and then there was -- I think you said that there was no accepted way of dealing with it -- would be the in utero period, and that that wouldn't come into this sample calculation. Is that correct?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. We actually --

PANEL MEMBER BLANC: I mean it would make some --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- are leaving that a little open-ended.

Because we could do that. And if you added it, it would be three-quarters of an additional year times that 10. So it would be 2 point -- or 2.75 years. Nine months? 9/12? We could do that to account for --

PANEL MEMBER BLANC: Well, I think -- I probably would suggest not doing it formally because it would make you vulnerable for a bunch of criticism.

But what you might do is put a footnote and say: Although we did not do it, were we to have done it, this is the value you would get.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We could do that. And also, we left it open

for case-by-case analyses.

So if we have data that we're pretty sure in utero exposure's seriously problematic for that chemical, we would use that.

PANEL MEMBER BLANC: Mm-hmm.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And we would actually even use the adjustment factor if we couldn't figure out a slope factor.

CHAIRPERSON FROINES: Melanie, I'm comfortable with what Paul said, but I'm also a little worried because that may be a particularly sensitive period and that, to the degree that we don't acknowledge that, we may be underestimating risk.

PANEL MEMBER BLANC: I think you could say that in the same footnote.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We actually do say that.

We say that data point to in utero exposures as a sensitive time period, particularly for specific chemicals and that we could be underestimating by not including it.

CHAIRPERSON FROINES: Well, we're going to -- it seems to me that we're going to have to, over time -- we don't have to resolve it now. But over time, we're going to have to figure out how we're going

to take that into consideration on a quantitative basis.

PANEL MEMBER BLANC: I think that the important argument in favor of some kind of footnote is that it lets the reader know that you didn't miss -- this isn't something you overlooked; this is just because of the challenges of on various levels it couldn't be formally incorporated, you recognize and in the future it may.

I think also, just algebraically, it will show that it doesn't change it very much. And if you wanted to, you could even say: And even were we to assign a factor of 20 instead of 10 for that period, here's what it would be under that scenario.

Because it's still going to -- I imagine it will go up from 1.7 to 2.1 or something, you know, at the most. I mean I can't imagine it would change a lot.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: Yeah, but --

PANEL MEMBER BLANC: Algebraically.

CHAIRPERSON FROINES: -- it's also an ideological issue.

PANEL MEMBER BLANC: I know. I know. That's

why you don't want to -- I think that's why you want to say we're not formally doing this, but just to acknowledge.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, that's fine.

PANEL MEMBER LANDOLPH: Yeah, I like this calculation in the document. It's very transparent. It segmentalizes each of the compartments. And the end result is not an enormous difference. It is fine. I think it's great.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. That's --

(Blank slide displayed)

PANEL MEMBER BLANC: I like that slide.

(Laughter)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's all I was going to talk about.

There's a couple of other slides on the handout just in case there were questions; but I think you're all familiar with how the benchmark dose method works now and the multistage polynomials, so I didn't think it was necessary to go over that.

And I wanted to let Martha start on her slides.

I could talk about the response to comments

now, if you want a brief interlude between me and Martha?

CHAIRPERSON FROINES: It's your call.

PANEL MEMBER BLANC: Yes, why don't you do that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. We did --

PANEL MEMBER GLANTZ: Can I just do one thing before that? Just this one change that was handed out --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, gosh, yes. Thank you.

PANEL MEMBER GLANTZ: Yeah. The piece of paper that says starting at the bottom of page 38.

I just want to explain what this was about. And the way I read the document --

CHAIRPERSON FROINES: Excuse me a minute. I'm going to go out. But I have been through at least half a dozen e-mails on this topic, so I'm well-prepared.

PANEL MEMBER GLANTZ: Okay. This is just a point of clarification.

The way the document was originally written, I thought it made it sound like that the basic curve-fitting models used in the first part of the document for the general benchmark dose analysis, and

then the model that was used for the -- this age sensitivity stuff were different. And they are not.

So all this is is a rewrite of that paragraph to make it clear that they're not using different models. They're being applied in a slightly different way, but the basic models are the same.

So the whole point, there's again no substantive change here. It was just that I found the original wording of the document confusing. And after a bunch of back and forth, this was how we agreed to clarify it just to show how the second half of the document -- that the general approach of the second half of the document which deals with this age stuff is consistent with the way the first half was done.

It's the difference between just getting a point estimate for the benchmark dose and getting these -- basing it on the full distribution. So that's -- I just wanted to clarify that before she goes on to the public comments.

So I don't see this as substantive at all. It's just a point of clarification.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. And then there was the other handout I --

PANEL MEMBER GLANTZ: Although the e-mails

about where we're working out the language, John almost had a stroke over it, thought it was very substantive, but it's not. We can pick on John because he's not here.

(Laughter)

PANEL MEMBER BLANC: And the other handout?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The other handout, I asked staff to give me a few examples of risk assessments that OEHHA had already conducted which compares the slope factors derived with the benchmark dose and the linearized multistage.

And that is what these three tables are. One is for naphthalene with various tumor sites and species and genders. One is for MTBE. And one is for trichloroethylene.

So when we do these analyses, we generally conduct both methods and present them, and you can see that it's pretty unusual to have much of a difference in your response. I'm sorry; in the result of the model in terms of determining a slope factor.

PANEL MEMBER LANDOLPH: And given the uncertainty on those estimates, they're the same numbers I believe? They look almost identical --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We view them as the same numbers.

PANEL MEMBER LANDOLPH: -- to me. Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If you use two different models, and you get within a factor of 2 or 3, it's pretty good for risk assessment.

We got comments basically from four individuals, organizations.

We got comments from the American Chemistry Council that they believed the current cancer risk assessment methodology with linear low dose extrapolation is conservative enough and that we did not need additional age sensitivity factors to apply for evaluating exposures early in life.

And essentially, we disagree. There is really nothing in current risk assessment methodologies that adequately or even explicitly addresses the potential susceptibility of early lifestages.

So just most of the time we're using data in either mature animals or in adults from human occupational epi studies. So we disagreed that there was not a need for those factors.

They also thought that --

PANEL MEMBER BLANC: Earlier, I think the record would indicate that Joe said that animal studies typically begin from early age of the animals.

Did I misunderstand what you said?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, they typically start when the animals are somewhere between six and eight weeks old for the traditional bioassay.

PANEL MEMBER BLANC: Uh-huh.

PANEL MEMBER LANDOLPH: And the reason for that is if you wait until they are adults, you won't get any tumors so you don't have anything to report. So that's why everybody has done it that way.

PANEL MEMBER BLANC: But they're not adult animals.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Actually, they're sexually mature animals. You generally get them after they've been weaned and then acclimated to your laboratory.

So that is really the reason that they've always used about seven- to eight-week old animals.

PANEL MEMBER BLANC: I'm glad you said that because otherwise it would appear contradictory, the two comments.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It might be equivalent to older teenagers.

PANEL MEMBER BLANC: So they would be beyond the age equivalent of the age at which you no longer

use an age adjustment.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BYUS: Sexually mature, but not really mature.

PANEL MEMBER BLANC: Couldn't get a driver's license yet.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So then they also had in their comments that the data were insufficient to say that there was increased sensitivity for early lifestages because it's only based on a subset of all the carcinogens.

And we recognize that. But we disagree that they are insufficient or don't say that early lifestages are more sensitive, and we pointed them to the analysis that OEHHA did in our response.

They also provided their own little analysis. And they just picked a few of the chemicals and said, well, it looks like 55 percent of them are equally or less sensitive and 45 percent of the chemicals we chose are more sensitive, but we did -- we looked at a lot more data than this particular comment which was not from a published study.

And they also don't account for time to expression, so there's another issue.

PANEL MEMBER LANDOLPH: So you're basically agreeing with them when they want case-by-case data, and you're saying --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER LANDOLPH: -- when the case-by-case data exists, we'll use it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes. That was another big point.

They misunderstood, and they thought we weren't going to use chemical-specific data; we were just going to always do the default. But that's actually not what we say.

So then we have a few more comments, one asking for references, to add references from Ken Bogen.

Then the US Army provided a whole bunch of little specific edits that they requested and typos, but they also -- which we put in -- but they also had a little bit of a misunderstanding, thinking that we were talking about childhood cancer. So -- and no, we're not. We're talking about cancers that primarily occur as adults.

And then finally the Western States Petroleum Association actually liked that we were doing some of

the similar things to EPA, and a lot of their commentary was about risk management which, of course, is not addressed in the risk assessment document.

So that's it in a nutshell.

CHAIRPERSON FROINES: You owe 25 cents to my office because "in a nutshell" classifies a colloquialism for which there is a 25 cent charge.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Uh-oh.

(Laughter)

PANEL MEMBER BLANC: And is there a charge for using a phrase, "it seems to me that"?

CHAIRPERSON FROINES: I never say that.

(Laughter)

CHAIRPERSON FROINES: Is it Martha?

DR. SANDY: Yes.

Okay. So as Melanie is getting that up, I was going to give you a review of what we covered at the last meeting and discuss again the purpose of this analysis and our approach that we took and then briefly review the mathematical and statistical approaches with the highlights on how we estimated cancer potencies.

And then using the new terminology -- and I'd like to thank Stan for all his insight into helping to make this clearer -- our multi- and lifestage exposure

studies. That's the bulk of the analysis. Those are the studies used to come up with these default values which we call age sensitivity factors, or ASFs.

And then we also did an analysis of single lifestage exposure experiments to show you how you might approach using this type of data for deriving a chemical-specific value. And we used two examples, DEN and ENU, using only data from the mouse that we had.

And then I'll discuss the results focusing on the lifestage potency ratio which looks at inherent susceptibility of the young.

And then the age sensitivity factor. That's the second step.

And then some conclusions.

So again, the approach was to come up with values to apply to chemicals for which we don't know -- we don't have evidence or data on early life sensitivity -- to come up with a modifier for the potency.

When we do have such data, we will analyze that and use that to come up with a chemical-specific potency for early life exposure.

But this approach was: Let's see what data are out there, and can we look at all of it across the many different chemicals? We know that carcinogens are

variable, and some will have -- there will be different sensitivities for different lifestages. How can we find enough data to get a robust data set and come up with a default?

We do review examples of -- known examples of enhanced sensitivity in humans, but we did not have access to the data, the actual individual human data, to allow us to do the type of analysis that we thought we needed to do.

PANEL MEMBER BYUS: So as a clarification for the purpose, because I think it was confused -- slightly confusing to me. I'm sorry.

So if you said derive default measures for early life susceptibility to make age-specific adjustments to cancer potency, so are you mainly focusing on lifetime cancer potency risks?

Or do you want these numbers to be used for shorter-term risk calculations that are age-specific?

Because I think it's really an important difference.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. That's a good question that we get all the time. We are definitely applying them to entire life risk calculations.

However, we do in the facility-specific risk

assessment process allow for consideration of how long people actually live near the facility.

And from previous documents, we have allowed people to estimate risk for nine years, which is about the average that someone lives at any one residence; 30 years, which is about a 90th percentile; and a full lifetime.

So for those nine-year exposures, we want them to use zero to age nine. So that's what we're doing now.

And there is some additional discussion because our methods get applied to other programs too.

So people are asking us, well, we have this site mitigation going on, and we have to bring in diesel equipment or it will cause a release of, you know, chemical X from the soil as a vapor but only for a year or two.

That issue, we're trying to grapple with. If they decide -- again, it's other agencies; not us -- if they decide to do it, we're going to at least make sure they use zero to two.

PANEL MEMBER BYUS: But that's what I'm saying. You need -- I mean I would hope that you could define that purpose more completely than you just did. It's too general.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, it's pretty hard --

PANEL MEMBER BYUS: I mean if you want to do the lifetime -- when I first read this, I thought it was more a lifetime risk potency value.

But then the more I thought about it, the more I looked at, and the more I read it, it seemed that you might -- or if not you, someone else -- might use it for a shorter-term exposure.

And so you really need to -- because I think it has to do with how the experiments are done, how the animal experiments were done, how you might design animal experiments to address this, which I'll get to in a minute.

But I think you need to make it clear.

And again, you're writing the document, and so you're going to use it for your purposes. So you should make it clear that you're doing this analysis for this purpose and not necessarily another one.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. On page 50, we do have a statement and a table showing what it looks like if you're going to do the typical Air Toxics Hot Spots Program nine year scenario. But --

PANEL MEMBER BYUS: What I'm getting at:

Suppose someone came to you and said, oh, my child was exposed for two years only to some chemical, some environmental condition, then will you use the age-specific value for that two-year-only exposure, assuming then they were removed from it later on?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER BYUS: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We definitely do that.

PANEL MEMBER BYUS: So I think you really want to be little more clear about it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: A little more specific in here.

PANEL MEMBER BYUS: Yeah.

PANEL MEMBER BLANC: And perhaps one way of doing that, just to amplify what Craig just said, is your example of the impact of using the ASF that you presented in your slide of the 70-year lifetime exposure. It seems to me you should follow that with an example of a nine-year exposure, and what would it be like as a nine-year adult exposure versus a nine-year --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We actually did at the last meeting.

PANEL MEMBER BYUS: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And I debated putting that second slide in, and I didn't. So I probably should have. We did have that in the last set of slides.

PANEL MEMBER BLANC: Is it in the document?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's in the document.

PANEL MEMBER BLANC: Are both of them in the document?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, it's on page 50 --

PANEL MEMBER BYUS: Again, I think -- and I know other people use your data and all of our data for other purposes, but I think you really need to define what you think it should be used for.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BYUS: Not necessarily what it shouldn't be used for, but what it was intended to be used for.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

And this issue of short-term exposure to carcinogens comes up all the time, and it's very

difficult to answer because the slope factors --

PANEL MEMBER BYUS: I know.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- are based on chronic exposure.

PANEL MEMBER BYUS: That's the point.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER BYUS: So if you think it can be used for short-term, then you should say so.

But if you don't, then don't say that it can't be used for it, but say what you intended it to be used for.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BYUS: And that's your decision, really.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

CHAIRPERSON FROINES: But I think it's very clear -- very important to make clear that there are different agendas that you are pursuing, that you don't want to turn this into every chemical we have to look and see how long a person was exposed to it.

We need to have policy considerations drive this as well as short-term exposure issues. Otherwise,

it's -- you're really going to get into constant battles over what numbers you use for duration of exposure and you'll never escape that issue.

There is a reason to use 70 years. For comparative purposes, for any number of reasons. So we can't give up what we use risk assessment for in the broad sense relative to the narrow context.

PANEL MEMBER BYUS: I don't disagree.

But I think the -- it's implicit here on these age sensitivity factors that you're talking about now exposure for shorter amounts of time and a specific age period. It's implicit in it.

PANEL MEMBER BLANC: Also, the proportionate impact --

PANEL MEMBER BYUS: Yes.

PANEL MEMBER BLANC: -- of applying the -- although in your table it's a very small proportional impact when you're talking about a 70-year cumulative risk.

But if you're talking about what is the relative impact of nine years from 0 to 9 versus nine years from 50 to 59, it's proportionally quite a bit different, right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Exactly.

PANEL MEMBER BLANC: So I think you need to -- I couldn't find it on page 50.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Table 3.

DR. SANDY: This is on the technical support document.

PANEL MEMBER BLANC: Oh.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: You're in the appendix.

PANEL MEMBER BLANC: Sorry.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Page 50, up front. That's where it is.

CHAIRPERSON FROINES: I just want to avoid the slippery slope. Do you understand?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, I do.

PANEL MEMBER GLANTZ: Let's let them make their presentation.

PANEL MEMBER PLOPPER: I thought we were going to wait till we were done to ask questions.

DR. SANDY: Okay. I'll continue then.

So realizing that this is for coming up with default values to apply to those early ages in calculating lifetime risk, we needed data.

We considered human data and decided we didn't

have access to enough human data to do an analysis that would be robust enough, and we looked to the animal bioassay literature and used that data.

We came up with our perfect studies that we could analyze that we call multi-lifestage exposure studies -- and I'll go into detail more later -- and we focused primarily on chemicals that were listed under Proposition 65 as carcinogens.

Here is the time frame, this green bar. This is in the rodent, the typical bioassay dosing period. So as we just spoke about, dosing usually starts between six to eight weeks of age and ends after 104 weeks or a little past two years and -- let's see --

CHAIRPERSON FROINES: Martha?

DR. SANDY: Yes?

CHAIRPERSON FROINES: The 2Bs are -- fall under Prop 65, don't they?

DR. SANDY: Yes. Yes.

So in Appendix J on page 15, we have the table which I showed last time with the definitions of lifestage by species.

And for female rats, they are adults by our definition; they are sexually mature, of breeding age. At eight weeks, mice of both sexes are sexually mature. At seven weeks, it's the male rat that's a little

longer -- is sexually mature at ten weeks.

So in general, for male and female rats and mice, in the standard NTP model bioassay, they are young adults when they are dosed. So we are missing dosing during the juvenile period, which is shown here, and the postnatal and the adult period.

So those are the three early lifestages that we defined in our studies here.

Now this slide depicts the two steps that Stan was referring to. The first step is to get a sense of the inherent susceptibility of different lifestages.

And the example we have in that first bar is for postnatal exposure. You see the dosing starts just after birth and goes for a certain period during the postnatal period, and then the animal is allowed to live for a while for observation and then sacrificed and assessment of tumors.

The second bar labeled adult exposure, you have dosing for about the same length of time, and then observation for about the same length of time, and sacrifice. But as you see, those adult animals were at an older age when they were sacrificed.

So comparing potencies from the first experiment, that first bar, with postnatal exposure to the adult exposure, that second bar, you're getting a

sense of the inherent susceptibility of the postnatal lifestage.

But then you need the second step to account for time for cancer to manifest when exposures occur during different lifestages. For the dotted line that goes down to the early exposure, you have a longer time for cancer to manifest from the time the dosing occurred until the end of a life.

And then -- and I realize my dotted line is a little bit shifted to the left. I apologize. It should be right up against that adult exposure, that blue bar on that second line. When I transferred it to the slides it changed. It's correct in the document.

You can see that the older, exposed group, there's a shorter time there to manifest as cancer. So we account for that. And I'll go through this in more detail as I go through the methods.

So I was now going to give a brief review of the methods. And here, this is what the dose response data look like. You have dose on the X axis, and tumor response on the blue line is the -- an example of prenatal exposure, and you've got an increased slope, more tumors seen than when exposure occurred in the adult.

PANEL MEMBER BYUS: As clarification, your

tumor response: Is it tumor multiplicity or tumor incidence?

DR. SANDY: Incidence.

PANEL MEMBER BYUS: So it's percent of animals with tumors, not the number of tumors?

DR. SANDY: It's number of animals with tumors per group -- per animal in the group.

PANEL MEMBER BYUS: So it's incidence.

DR. SANDY: Incidence.

PANEL MEMBER BYUS: All right. Use the right -- that's important. So it's just -- so no matter how many they have, if it happens to be -- I mean they're sacrificed, so it could be they had five tumors, but --

DR. SANDY: This is just incidence.

PANEL MEMBER BYUS: Incidence. Okay.

DR. SANDY: Number of animals with tumors.

PANEL MEMBER BYUS: Percent of animals in the group with tumors.

DR. SANDY: Yes.

PANEL MEMBER BYUS: Okay.

DR. SANDY: And we do this specific to a certain tumor site. Okay? Lung tumors. Let's assume this is a graph of lung tumors.

CHAIRPERSON FROINES: It could change, which

tumors you're looking at.

DR. SANDY: Yes.

PANEL MEMBER BYUS: Okay.

PANEL MEMBER PLOPPER: So -- I have a another question.

So it really doesn't matter then whether that curve is that way because during the developmental phase the cancer has more impact, or it's just that those animals live longer?

What would happen if it was not -- let's say that exposure in the first two weeks of life was that the animal biologically was not more susceptible to tumors than it would if they were adults, say, or juveniles or whatever. How would that -- would that curve look the same then?

DR. SANDY: Yes.

PANEL MEMBER PLOPPER: Because of the -- it's just because of the duration until --

DR. SANDY: No.

PANEL MEMBER PLOPPER: -- they die.

DR. SANDY: These -- this example, and for most of the studies that we're looking at, they look like this model here on this slide where there is a roughly equivalent period of dosing --

PANEL MEMBER PLOPPER: Okay.

DR. SANDY: -- between the early life and the later life groups and roughly a comparative or equivalent time of observation.

CHAIRPERSON FROINES: So you are saying --

DR. SANDY: So it is not accounting for --

CHAIRPERSON FROINES: -- duration is about the same.

PANEL MEMBER PLOPPER: So what you're -- but at the bottom, you have something different which says longer time to manifest cancer --

DR. SANDY: Right.

PANEL MEMBER PLOPPER: -- so how does that apply to this graph?

DR. SANDY: It's not taken into account in that graph.

PANEL MEMBER PLOPPER: Okay. Great. All right.

DR. SANDY: Assuming that that graph represents this model up here where the sacrifice of the postnatal-exposed animals occurs 100 days earlier than the sacrifice of the adult.

PANEL MEMBER PLOPPER: Okay.

DR. SANDY: Okay.

So these are the types of data we're working with. We calculate a slope, a cancer potency, from

that type of data. And to do that, we fit the dose response model. We're focusing on the observable range of the data. It's the linearized multistage model that we use.

And there's widespread use of that model in cancer risk assessment. It's very flexible. That's why we chose it. It can fit different data sets, linear and nonlinear, dose response patterns.

And we focus on the linear term which is q1, the slope parameter. It's representing potency. And we compare the slope. So this is just reminding you of where the q1s are. It's the slope that we calculate. And we do a comparison.

And instead of focusing on a point estimate, as Dr. Glantz was saying, we have actually come up with a distribution of the value of q1. And this is just to represent that.

And now to address if -- oftentimes a carcinogen will cause an increase in the incidence of tumors at two different sites. In this example, the same carcinogen given at the same time, lifestage, produced lung tumors, an increase, as well as liver tumors.

And we want to get a measure of the total cancer risk in that with that -- associated with that

exposure to that carcinogen, and so we sum these potency distributions statistically, using Monte Carlo methods, and we come up with a multisite potency distribution shown here to represent the total cancer burden in that experiment.

PANEL MEMBER BYUS: Another clarification. I brought this up briefly last time.

The spontaneous tumors. So if -- where do they fit in this? Because in a sense, if you were looking at the spontaneous tumors that showed up with no treatment in the animal, maybe the treatment increased the number of spontaneous tumors. It would not be by the same mechanism and so carcinogen-related, so it might not be appropriate.

So that was my question.

DR. SANDY: Let me -- so if it's a spontaneous tumor that occurs in older ages, but it's not treatment-related, then, if that's the case, you should have equal numbers of tumors in the older controls and the older treated.

There's no difference with treatment; therefore, we're not -- we're not going to look at that tumor because we're going to say there's no treatment-related increase.

PANEL MEMBER BYUS: But --

DR. SANDY: What if there's something like liver tumors in the mouse which are known to increase with age, okay? And that occurs all the time in NTP studies.

And you may have at the end of their two-year studies in the controls 20 percent incidence in the controls of liver tumors. You may have 75 percent incidence of liver tumors in the treated group, the high dose group.

We will then calculate a slope factor. We use all the data points. We use the tumor incidence seen in the controls, in the low, in the mid, and the high dose group, and that takes that into account. And it just -- if you have the incidence in the controls is up here, 20 percent and not at zero, it just shifts the curve up, and we're still getting --

PANEL MEMBER BYUS: But I'm talking mechanistic -- I'm talking -- I agree, and I think that's fine.

I'm just worried about it mechanistically. In other words --

DR. SANDY: That's --

PANEL MEMBER BYUS: So I mean when you do this kind of -- since I didn't see all the total data, if -- let's assume liver tumor -- liver tumors are a good

example where there's a spontaneous incidence that could be relatively high meaning 20 percent, 30 percent of the animals, if you do nothing to them, get liver tumors --

DR. SANDY: Mm-hmm.

PANEL MEMBER BYUS: And so you -- one wonders why that is.

And even though it may be treatment-related, having an increase in that number, it might not. I mean it might in fact be by a different mechanism --

DR. SANDY: Mm-hmm.

PANEL MEMBER BYUS: -- that those, quote, inherent spontaneous tumors are increased in number over the -- by some treatment.

And it might not be the same mechanism as say, more likely, like a lung tumor would occur where there were no spontaneous ones.

So I'm saying when you look at the bulk of this data in terms of your distributions and where the high and low factors fell, if for example the biggest age sensitivity factors were occurring in those tumors that were spontaneous, even though they were treatment-related --

DR. SANDY: Mm-hmm.

PANEL MEMBER BYUS: Am I making myself clear?

Then I might have some worry about that. Do I make that clear? Okay.

DR. SANDY: I think so.

PANEL MEMBER BYUS: It's hard to -- this is great stuff. It's just --

DR. SANDY: In the general picture of things -- not our data set, but in general -- these questions are looked at, for example, in the NTP bioassays.

And they will look at: Is this little increase we saw, or this big increase, in incidence of a spontaneous tumor rate, do we believe that it's -- is it unique to this model animal we're using? Or is it due to the chemical?

Now if it's due to the chemical, then they will conclude that that's evidence of carcinogenicity.

And all carcinogens -- almost all carcinogens we've looked at, Group 1 IARC carcinogens that are known to cause cancer in humans, they act by multiple mechanisms. They do multiple things.

PANEL MEMBER BYUS: I know, I know.

DR. SANDY: And it's often the case where we think that perhaps one mechanism is predominant in one tumor site, and another mechanism in another site is predominant.

So these are -- they are very interesting questions. I'm not sure it's critical to this analysis because the chemicals --

PANEL MEMBER BYUS: I'm just asking, isn't there some -- I mean I understand all this, and I thank you for educating me here. It's very nice.

But I'm just asking: Is there anything unusual because you're looking at so many and so much distribution, and so if this were to be predominant in your analysis, the spontaneous tumors that were treatment-related accounted for a significant percentage of the age sensitivity factor, then I would worry about it.

DR. SANDY: I do not think that is an issue.

CHAIRPERSON FROINES: I think we should move on. This is way beyond the concept of clarifying questions.

DR. SANDY: Okay.

So we defined an experiment -- these are just definitions to help straighten out what we're doing. An experiment is a study component consisting of a control group and then some treated groups; and they're exposed during the same lifestage using the same experimental protocol such as route of exposure, strain of animal species, and laboratory. So you can have

multiple experiments in a study.

Our multi-lifestage exposure studies are indeed multiple experiments in the same study. And we require there be at least one experiment with exposure in an early lifestage -- could be one of the three listed, the prenatal, the postnatal, or the juvenile lifestages -- and another experiment with exposure in an older group, preferably adults.

We do have, if you recall, several chemicals and several data sets where they exposed animals as juveniles, not adults. They started the exposure as juveniles.

CHAIRPERSON FROINES: Can I ask one question just for clarification?

DR. SANDY: Yes.

CHAIRPERSON FROINES: Where you have cancers that derive from estrogenic types of responses, breast cancer and ovarian cancer, there it gets a little bit complicated because, depending upon when you start your adult study, you can be -- you can overlap in some respects.

Is that an issue for you? Or do you think that your adult study begins early enough where you don't have mixed missed estrogenic exposures?

DR. SANDY: Well, you know, our data sets that

we had available to us, there are very few that we know are acting by an estrogenic mechanism.

But it is interesting in the juvenile multi-lifestage studies. We have a couple chemicals that cause mammary tumors, the DMBA and MNU.

And in the MNU data sets, there was actually a very interesting study that we have where they exposed animals at different times, a couple different periods, just for I think it's a week or ten days, during the juvenile. So one was early juvenile, one group, and followed, and one was later juvenile.

And then they have an early adult and then a later adult life group. And looking at that, even within the adult lifestage, you see that the earlier exposed, in the early adult lifestage, they're more susceptible to mammary tumors than the later -- the older adults when they were exposed.

CHAIRPERSON FROINES: That's interesting.

DR. SANDY: So it's not -- you know, these demarkations of lifestage are not perfect. There's -- there can be a continuum.

And I don't know -- but because the mammary gland is the target, you have to wonder if there's something going on indirectly affecting estrogen with these genotoxic chemicals.

PANEL MEMBER LANDOLPH: There was a fascinating study, I'm remembering, which addresses that. And it was by Sara Sukumar and Mariano Barbacid. And when they treated -- it was Buf/N rats. And they treated them with MNU.

And when they treated them at an earlier lifestage, they got mammary tumors which had the typical mutations in the rats' oncogene, so it was all clear.

When they treated them in adult life -- and I believe it was later adult life -- they got zero. This was the point I was trying to mention earlier.

So clearly, it's a mutagenic mode of action, but if you don't -- oh, and if they ovariectomized them, then they did not get tumors, so it was purported to be a hormonal influence early in life.

So there's a big difference, you know, in those studies if you treat them early versus treating them late.

DR. SANDY: Mm-hmm.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think it's safe to say that for an estrogenic compound, if you're starting exposure as a sexually mature adult, you're going to miss a lot of the sensitive periods for mammary and reproductive organs.

CHAIRPERSON FROINES: Well, it just raises the larger question of homeostatic changes over time which is central to all of this. So it's -- I just use that as an example, but it is a very interesting question which -- we should go ahead.

Thanks for the comment.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

DR. SANDY: So I guess I should finish what I was -- so this, just visually, you can imagine that when you look at -- and I'm talking about prenatal multi-lifestage experiments or studies.

I'm going to be talking about groups that were exposed prenatally, so you have a control and treated groups and we calculated a potency for that experiment.

And then we also had a group in the same study exposed as an adult, and we calculated a potency.

And the same -- similarly, we do the same thing for some -- the postnatal and an adult and the juvenile and an adult.

And what we're doing is we're taking the ratio. We call this the lifestage potency ratio. And it's a ratio of the distribution. So we see the early life potency -- could be prenatal or postnatal or juvenile -- divided by the adult potency distribution

to get that LP ratio. We did that for each multi-lifestage study.

And then -- so we have many different chemicals. We have 55 data sets, for example, and 18 carcinogens that had prenatal multi-lifestage studies. And we can line them up, and I'll show you that in a minute.

Our point was to come up with some value or some sense of what all this data looks like. And we call this an LP ratio mixture distribution. We came up with a way -- and I'm here using the prenatal as an example. We combined all the prenatal LP ratio distributions from each of those studies into a single distribution.

So we're combining across chemicals. We used Monte Carlo sampling to do this from -- that's sampling from each of the distributions. And we equally weighted each chemical. Because sometimes we have five or six studies on ENU, for example, and only one on benzidine, let's say. We want to -- we don't want to over-weight one chemical versus another so we equally weighted the chemicals.

And in those cases where we have multiple studies on a chemical, how do we gather that distribution? We created a single distribution for

that chemical, and we equally sampled from each of the studies on that chemical to come up with that distribution.

So that was our rationale and our approach, and the LP ratio mixture distribution, therefore, will reflect the range of inherent susceptibilities of the prenatal lifestage in this case to the carcinogens that were studied.

So you've seen this slide before, but now I've labeled this first step. That result we call the LP ratio. And then when we take into account the time for cancer to manifest, we call that the ASF, the age sensitivity factor. And to get the ASF, we take the LP ratio, and we multiply it by a time of dosing factor.

We're assuming, as Melanie mentioned, the cancer risk increases by age to the power of 3, and this is a generally accepted assumption. In some cases, we have data saying cancer risk increases by the power of 6 of age. But we're using 3.

And I've given the time of dosing factors here for the different lifestages. And then -- so we can do that for each of our studies, our multi-lifestage studies, come up with an ASF.

We can also mix them together to get this ASF mixture distribution just like we do for the LP ratio

mixture distribution to get one representative distribution across these chemicals.

And now switching gears, we had -- if you don't want me to go into this, I won't. These are the chemical-specific case studies where we used single lifestage exposure experiments. Let me know if you care to hear about that or you would like to move on.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We can jump to the results of the multistage -- or multi-lifestage studies.

PANEL MEMBER GLANTZ: Let me just add one detail. You notice that they sampled for each chemical equally. They looked at two other sampling strategies, which are in Appendix J, and showed that the sampling strategy didn't make much difference.

DR. SANDY: That's right. Those are referred to as sensitivity analyses, and they are in appendices of Appendix J. We moved them out of the main document.

PANEL MEMBER GLANTZ: Oh, good.

But they were very compulsive about it. That's the important thing. They didn't need to tell us about how compulsive they were, except if you want to read the appendix to the appendix.

But it's an important detail which is mentioned in the main text, that there were several

different sampling strategies, and they were all about the same.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER GLANTZ: Okay, go on; I'm sorry.

PANEL MEMBER BYUS: What do you mean by controlled and treated animals exposed within a single lifestage? Were the control animals exposed?

DR. SANDY: No. No.

PANEL MEMBER BYUS: That's why I can't understand that.

DR. SANDY: Okay. It's my -- if we go back, I'm trying to capture this definition of an experiment.

It's a study component where you have a control group and treated groups, and the exposed -- treated groups were exposed during the same lifestage.

And if you have a vehicle, you know, then you have a vehicle control with IP or --

PANEL MEMBER BYUS: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sorry.

DR. SANDY: It's hard to cut this in fewer words on a slide here. Hopefully it's more clear in the document.

So for the single lifestage exposure

experiments, it's just that: A control and treated animal, treated groups, exposed in a single lifestage. We don't require that there be any other lifestages in the same study.

Okay. And we said okay, let's do some chemical-specific case studies DEN, ENU. We have a lot of data on in our -- that we have identified. There is -- many of which are single lifestage exposure experiments.

So the same carcinogen, different experiments, different laboratories. What can we do about -- how can we use that data and see what the numbers look like?

PANEL MEMBER BYUS: So really, and in those cases, there's just unexposed and exposed single group?

DR. SANDY: Correct.

PANEL MEMBER BYUS: Okay. So that's the way I was thinking. It's basically unexposed and exposed.

DR. SANDY: Okay. Thank you.

PANEL MEMBER BYUS: It gets to the control.

DR. SANDY: Yeah.

PANEL MEMBER BYUS: Obviously, there's a vehicle control, I'm sure, that was -- okay.

DR. SANDY: Okay.

So we do have these examples in the document

looking at DEN and ENU, and we derived cancer potency distributions for each single lifestage experiment, and then we created a mixture potency distribution for all of the experiments in a certain lifestage, and we equally sampled across individual distributions. And we also had some sensitivity analyses, but the sampling didn't matter that much.

And so for these two chemicals in our report here, the analysis was limited to experiments in mice. We did not find adult-only exposure experiments for either DEN or ENU in mice where it was just exposure starting as an adult.

So we used the juvenile lifestage as the referent group, so we have come up with a sort of new term, the LPJ ratio mixture distribution, and that's the ratio prenatal to juvenile.

And we have the same for the postnatal LPJ ratio.

And then we can derive an ASF J mixture distribution as well, and it's the same approach as I discussed earlier.

So now to get to the result of the multi-lifestage studies, which are what we have used to look for default values to apply to chemicals for which we don't have information on early lifestage

susceptibility.

So here we have a graph of -- it's a cumulative frequency profile of each of the prenatal multi-lifestage exposure studies ordered by the ASF distribution.

So we have 22 different studies, and you can see that some animals -- or some experiments, some carcinogens, there is less sensitivity because they're below the value of 1.

If something is 1, an ASF of 1, that means there's equal sensitivity between the prenatal lifestage and the adult and many experiments with different chemicals where the ASF is greater than 1.

And here's where we have this cumulative mixture distribution, both for the LP ratio which is the line on the left --

CHAIRPERSON FROINES: What page is that last slide from?

DR. SANDY: Just give me a second here. It is on page --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Page 43 in the --

DR. SANDY: No, 45.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- main, and it's also in the appendix.

DR. SANDY: It's on page 39 in the Appendix J.

CHAIRPERSON FROINES: No, but in the text.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Page 43.

CHAIRPERSON FROINES: 43? It looks like 45 to me.

PANEL MEMBER PLOPPER: There's two of them.

PANEL MEMBER BLANC: Go to the first part. You're too far back. Go to the first section where there's another page 43.

DR. SANDY: John, are you asking about this slide right here?

CHAIRPERSON FROINES: No, the previous one.

DR. SANDY: The previous one. So that's figure number 7 in the TSD, page 43.

CHAIRPERSON FROINES: The only reason I'm asking is I just want to make sure that in the document itself that it's readable because I can't read the slide.

DR. SANDY: I know. And because the document is in revision mode, it's --

PANEL MEMBER BLANC: It's smaller.

DR. SANDY: The print is much smaller.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We could -- I see now. We could make this

figure bigger and put the legend on the next page. That would help a lot.

CHAIRPERSON FROINES: Just as a general matter, this stuff is complicated, as you know, so you want to make sure that people can actually see what they need to read. And it may be my age, but it probably is not.

DR. SANDY: It's also having it in revision mode that makes it -- shrinks it.

PANEL MEMBER BLANC: It's smaller.

CHAIRPERSON FROINES: Yeah. I just want to make sure that everybody can read it that needs, wants to read it.

PANEL MEMBER GLANTZ: All copies of the document will be distributed with a magnifying glass.

(Laughter)

DR. SANDY: Now in Appendix J, it may be a little easier to read. And that's -- this figure is on page 39.

CHAIRPERSON FROINES: That's okay. You answered my question. I don't want to prolong it.

DR. SANDY: Okay.

So back to this slide that's up. This shows the cumulative LP ratio and ASF mixture distributions for the prenatal experiments, and we've shown you where

the mean and median of the ASF mixture distributions fall for the prenatal studies.

Okay. And here we have the postnatal ASF cumulative frequency distribution. We have 55 studies on here, and I know it's impossible to read.

In Appendix J, it may be a little more readable. We also have presented it, as you saw it at the last meeting, grouping the studies by chemical. And you'll see there is variability, even among a chemical such as EMU or benzidine that, depending upon -- oftentimes, it's either gender differences or the time of exposure within a given lifestage.

So if we go back to the prenatal, just a second -- going forward -- the prenatal lifestage window, you know, the sensitivity, we're looking at a certain group of carcinogens here. You can see that some of them, the ASF factor is a hundred, and some of them is less than one. There is a great range of variability.

And for some chemicals that require some metabolic activation and are not long-lived enough to be activated by the mom and get to the baby, those enzymes in the in utero period may only be coming up in the last couple days before birth.

So if the dosing occurred early in gestation,

then you're not going to see an effect. If it occurs at the last couple days of gestation, then you may see effects. And so that's how we have some variability.

PANEL MEMBER BLANC: And so this point about chemicals which have more than one study or not only being weighted as one, only being weighted once?

DR. SANDY: Each chemical is weighted equally in our -- in coming up with our cumulative distribution.

PANEL MEMBER BLANC: Right, so since like, for example, benzidine or safrole will appear twice here.

How exactly -- and you're showing something which wouldn't weight something -- which weights something disproportionately because you're showing a distribution -- maybe I don't understand what you mean.

If a chemical could only contribute -- I'm sorry. If a chemical could only contribute its weight once, and you're looking at a frequency distribution and the median value of all of the observations, isn't the chemical contributing its observation twice?

DR. SANDY: No. In this particular graph, we haven't done any weighting. We've only just plotted each of the studies for you in the cumulative frequency profile.

PANEL MEMBER BLANC: But then, if you go on to

your next slide --

DR. SANDY: And as we go to the next one, this one, we have weighted those two studies in safrole. Those two studies got equal weight to the five studies on ENU.

We weighted each chemical equally. So we have 22 -- or, sorry -- we have 22 studies, and we have 14 chemicals. We've weighted each chemical equally, and for those --

PANEL MEMBER BLANC: Can you translate "weighted" --

DR. SANDY: Okay.

PANEL MEMBER BLANC: -- into what you mean --

DR. SANDY: Yes.

PANEL MEMBER BLANC: -- because I could think of a mathematical way of weighting it. I could think of taking the average or the median value of the five studies and using that as a single point in your cumulative thing.

DR. SANDY: I should say that we sampled from the distributions equally.

Here. Let me go back to the methods, and hopefully this will help clarify this. To develop, for example, the LP ratio mixture distribution, if you go to that second -- well, the first bullet says we

have -- each chemical's equally likely to be sampled.

So we have all these distributions, and we're equally likely to sample from a distribution, you know, chemical X --

PANEL MEMBER BLANC: Okay.

DR. SANDY: -- we'll sample from one distribution. Chemical Y, one distribution.

PANEL MEMBER BLANC: Yeah.

DR. SANDY: We'll take one sample. We'll do that repeatedly but equally sampling from each chemical.

But when you have multiple studies for a chemical, we have an intermediate step where we create a single LP ratio distribution for that chemical.

PANEL MEMBER BLANC: Well, then, why isn't your -- why have the chemical appear more than once in your cumulative chart? Why not just show us what its distribution is for that chemical for the one time? I mean it's very misleading.

DR. SANDY: I was asked by Dr. Glantz, and Cathy Koshland liked it. They wanted to see, could you please order these?

PANEL MEMBER GLANTZ: Yeah, the idea -- remember that the idea here is to just get a sense of what the distribution of values is. And so some of the

studies were in males, and some were in females, for example, and --

PANEL MEMBER PLOPPER: Different species too.

DR. SANDY: That's right.

PANEL MEMBER GLANTZ: And different species. And remember, what they're trying to do here is come up with a default value, not a value for a chemical.

PANEL MEMBER PLOPPER: So the idea is to just sample all of these and --

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER PLOPPER: -- try to understand what would be the most protective default is what you're saying.

PANEL MEMBER GLANTZ: Well, or not necessarily the most protective, but some percentile in the distribution. I mean you don't have a random sample of chemicals here.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So -- but to answer Paul's question, this cumulative frequency profile is before they have created the mixture distribution.

PANEL MEMBER GLANTZ: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So this is the individual studies that had a prenatal component. And you'll see that some chemicals

appear more than once because there are different studies. They haven't yet created the single distribution to use in the mixture distribution.

PANEL MEMBER GLANTZ: Right.

The reason we did this, if you go back and look at the earlier draft, there was a presentation of the things ordered by chemical. And it just looked random, and I found that hideously confusing. That is still in the report in the appendix.

And I just think, in order to get some sense of kind of what was -- you know, was the ASF bigger than 1 or less than 1 most of the time in most of the studies? That was the idea of this.

And what this is showing you is that if you just look at all of the studies without their sampling thing that, you know, there were some that actually it seemed -- that the chemical seemed to be protective in a few.

But in most of them, most of the studies showed a ratio above 1, and it was, you know, and the median was around 10 or whatever it is from this chart.

That's all that this is trying to do.

Then the next graph that they want to show you -- I think it was the next slide -- is when they go back and they weight all the chemicals equally by

randomly selecting one value for each chemical.

PANEL MEMBER BLANC: Okay. That may very well be, but if you look at the way figure 8 is presented --

PANEL MEMBER GLANTZ: Which one was figure 8? The other one?

PANEL MEMBER BLANC: They're all similar.

DR. SANDY: In the technical support document.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: This is figure 8. It's the postnatal.

PANEL MEMBER BLANC: Look at this. Okay. There is the unweighted, raw observations.

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER BLANC: Right, with a 50 percent line drawn, a dotted line, at a value of 10.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER BLANC: And with a notation, the dotted line represents a default ASF for weighting risk for carcinogen exposure between birth and two years of age, see next section.

So I'm not saying you not have this figure, but I think that you could make it a bit more explicit in the title of the figure or in the legend of the figure that this is unweighted.

Because it -- otherwise, why are you showing -- if I just look at this, I see the 50 percent

median cutoff, and you're giving the value that you eventually arrived at.

I mean you could see why it's confusing.

PANEL MEMBER BYUS: I wouldn't show the 50 percent value at all.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's not a 50 percent value.

PANEL MEMBER BYUS: It's meaningless.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's not -- all we did here was show you the default, where the default lies.

PANEL MEMBER BLANC: Eventual default.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: Which you haven't come to yet, which you're going to come to in the future, after weighting.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right. Of course, we were asked to put this in.

PANEL MEMBER GLANTZ: I actually thought it was helpful to put it in.

PANEL MEMBER BLANC: I'm not saying -- all I'm saying --

PANEL MEMBER GLANTZ: All he's saying -- he's

not saying take it out. He's just saying explain it a little bit better. That's all.

PANEL MEMBER BLANC: Well, you could even just put the words postnatal ASF cumulative frequency profile prior to weighting by chemical or without weighting by chemical. Or something, you know, just to make it clear that you're about to --

PANEL MEMBER GLANTZ: The reason I asked them to put the dotted line on there was to show you that all the weighting doesn't really change things very much. But I think what he's suggesting is a good point of clarification.

PANEL MEMBER BLANC: Don't change the figure. Just change -- add a word or two to the title and a word or two to the legend so that --

PANEL MEMBER GLANTZ: I think that's a good idea.

PANEL MEMBER BLANC: The old -- you know the old schtick about the figure should stand on its own, blah, blah, blah.

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: I think that's actually very important because what you need is, whether it be lengthy or brief, but needs to be -- you need to be able to understand it on its face.

PANEL MEMBER GLANTZ: Right. I think this will clarify it. I think that's fine.

I mean I was the one who proposed to put the dotted line in.

CHAIRPERSON FROINES: Otherwise the reader doesn't know what to take from the chart.

The question is: What do you want -- what are you trying to tell the reader? And that's where -- and if you're giving different messages --

PANEL MEMBER GLANTZ: I think --

CHAIRPERSON FROINES: -- at different times -- let me just --

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: And to the degree that there are mixed messages, or rather that you want them to take different notions away, it just needs to be specific.

PANEL MEMBER GLANTZ: Well, no, I don't -- actually, I don't think there are mixed messages.

CHAIRPERSON FROINES: Right. That was a poor use of --

PANEL MEMBER GLANTZ: Okay.

I think that the point -- the reason I asked them to put the dotted line on was to make the point that if you just look at the raw studies, and if you

do -- then do their fancy weighting, you get about the same answer.

PANEL MEMBER BLANC: And I wouldn't be opposed to the footer saying the reader will note that even prior to weighting that the value comes out similar.

PANEL MEMBER GLANTZ: Actually, the dotted line is the weighted estimate.

PANEL MEMBER BLANC: But it's coming very close to the 50 percent cutoff.

PANEL MEMBER GLANTZ: Right. That's the point.

PANEL MEMBER BLANC: So you could certainly say that if you wanted to.

PANEL MEMBER BYUS: Do you know what I get from reading this figure? I look at it, and what it looks to me, what I get out of it is there's an enormous variation in values, particularly for things like DEN.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER BYUS: Enormous variation. So I start to think, per chemical there's an enormous variation. And -- particularly for certain chemicals.

So then I begin to wonder about the accuracy of the method in what you're doing because if you look

at DEN, for example, on this figure 8, it goes all the way from -- I don't know if this is a log scale, but if you look at the top versions are over a hundred all the way down to less than one.

So I don't know how -- so even though you mathematically weight these studies, they're so variable that I would wonder --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's --

PANEL MEMBER BYUS: I mean if I were criticizing this method -- say I was hired by someplace, which I'm not; that was a joke -- that's what I would say.

STAFF TOXICOLOGIST TOMAR: I would like to make a point about DEN and ENU. Because DEN requires metabolism. And the enzyme start around day 18 of gestation, and this process is complete on day 30, and we have seen what time is the exposure. Day one is different than day 15. Day -- gestation day 16 is different than 17 and 18 and 19 and 20.

ENU on the contrary does not -- it's simply hydrolyzed. There, it depends on how good the DNA mechanism is made.

CHAIRPERSON FROINES: I completely agree with everything you just said. I think it's very helpful in

terms of clarifying Craig's remarks.

I would suggest that maybe, without -- if it doesn't take too much work, to put a couple of case studies, a couple of tables in where these issues -- that is, metabolism and the differences between species are -- where you actually use the example and suggest this -- some of these characteristics may be the basis of the variability.

So that a reader who's pretty dumb can actually look at something and understand with a clear example of why there may be the variability. Because otherwise, it's left to their imagination.

STAFF TOXICOLOGIST TOMAR: I that think once Dr. Sandy started talking about DNA studies, it all will become clear. But since the question came, I thought --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We do have those case studies there right now in Appendix J, and we can easily take these same kind of figures and move them up into the main body of the report.

CHAIRPERSON FROINES: Don't you think that would be helpful? It would be helpful for me because the word metabolism, you know, grabbed me, and all of a sudden I thought to myself, oh, I know about that.

DR. SANDY: And in Appendix J, in addition to these figures, we left in, as Stan mentioned, the other box spots we showed you where you want to -- you guys want to find a pattern.

But for us, we look at it and say, oh, because it tells us the sex. It tells us the strain and the species. There are differences, and the dosing window too. So that's in the figure legend. We'll -- those are the clues that may explain some of the variability.

CHAIRPERSON FROINES: Well, there are some slight -- you know, I mean Stan's a statistician; I'm a toxicologist. And so the way I look at it is a just a little different than what he understands.

So I am just trying to make sure that we both understand pretty much --

PANEL MEMBER GLANTZ: Right, but I think -- I mean we spent a lot of time talking about this when I met with them.

Because when I looked at the figure presented the other way, where they were grouped by chemical, I kept trying to figure -- and they had all the different shapes, symbols, and colors and all that -- I was looking at that, trying to figure out exactly what you're asking about.

And really pressed them on why do we see these

differences, and why is this -- I mean they had a few things, like the one you just heard where people had some idea; but for a lot of it, it's like we don't know. This is -- this is just variability that exists that nobody quite knows why it's there.

CHAIRPERSON FROINES: Yeah, but --

PANEL MEMBER GLANTZ: Wait, let me finish. Let me finish.

CHAIRPERSON FROINES: So -- I'm sorry. I'm sorry.

PANEL MEMBER GLANTZ: And so the point is, and the reason I wanted it presented this way, is because this emphasizes the variability. Okay?

And that there is this variability, and that is what then leads you to, you know, saying okay, we're taking this default value when we can't explain all this other stuff.

Because when you can explain all the other stuff, then you're down to doing a chemical-specific analysis.

CHAIRPERSON FROINES: But I just would say one thing, and everybody else, I think, wants to talk.

All I would say is the -- having a study like he's talking about, which is already in there, and a conclusion that says we don't know, I'm perfectly happy

with that "we don't know" because that illustrates the complexity of the issues we're dealing with.

So anyway, who else wanted to comment?

PANEL MEMBER BLANC: I just want to suggest that we speed up and finish these slides so that our transcriptionist can take a break, and we can take a break, because clearly we're not -- clearly there's a discussion to be had, but I want -- it's 20 to 12:00. If you could finish.

CHAIRPERSON FROINES: Melanie, and -- we just need to --

DR. SANDY: We're almost done.

CHAIRPERSON FROINES: How long do you think it will take to get through these slides now?

PANEL MEMBER BYUS: If everybody is quiet.

(Laughter)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If everybody is quiet, Martha says five to six minutes.

CHAIRPERSON FROINES: Okay, because --

PANEL MEMBER GLANTZ: In other words, three hours.

CHAIRPERSON FROINES: Then we want to break and come back for general discussion. But I have to teach at 2:00 which means I have to leave here at 1:30.

And I would like us to come to a vote --

PANEL MEMBER GLANTZ: We can.

CHAIRPERSON FROINES: -- about that.

PANEL MEMBER GLANTZ: We can. So we'll all be quiet for five to six minutes. We'll take a pool on how long John will stay quiet.

DR. SANDY: One last point.

What this slide tells me -- I know there are -- there's variability among -- for the same chemical in different experiments. But the majority of the experiments are showing that there's enhanced sensitivity when exposure occurs postnatally. And whether it's by a factor of 7 or a factor of 17, there is increased variability.

So we also have the juvenile. We had fewer studies. These are plotted as the others were, and that dotted line is just the default factor.

That is 3, to show where that is.

And there's the cumulative LP ratio and ASF mixture distributions and the mean and median of the ASF.

PANEL MEMBER BLANC: So why -- I have to ask this question. Why is it 4.5 and not 3?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Because the -- I think there is some confusion.

The default ASFs are a policy choice. And we have some discussion in the document.

What Martha is showing you is what the data that we have are telling you about where the median and mean lie in their mixture distribution.

PANEL MEMBER BLANC: So for one it's 10; that's coincidence. And for the other it's 3.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Actually --

DR. SANDY: It wasn't --

PANEL MEMBER GLANTZ: The 10 is actually -- the median is 13 in that case.

PANEL MEMBER BLANC: Okay. Thank you.

DR. SANDY: So to summarize these results, we have studies with 23 carcinogens, 20 of which act primarily via genotoxic mechanisms, and 15 of those require metabolic activation.

We see that carcinogens vary in age susceptibility, and there is variability among studies of the same carcinogen. We talked about this quite a bit.

And it has to do with timing of exposure within a lifestage. There's gender differences and strain differences and species differences and other differences we're sure of that we haven't

characterized.

Here, this is a different table than what Melanie's shown you, the same idea. We have one column, no adjustment for ASF.

So this is what we do, with no adjustment, ASF of 0 for in utero and 1 for each of the other lifestages, and you -- with our example here, you've got a risk of 1 in 10 to the minus 4.

If we take the 50th percentile from our analysis for each of those lifestages, so you have an ASF of 3 for in utero, 13 for birth to 2 years, 5 for 2 to 16 years, and 1 for the remainder of life, you get 2.2 times 10 to the minus 4.

So it's -- you're increasing your cancer risk estimate by a factor of 2.2 if you use the 50th percentile.

If you use the 70th percentile from our analysis for each of these lifestages, it increases by a factor of 3. If you go up to the 95th percentile, it's a factor of 16.

So this just shows you some of the ranges. So we're not presenting the policy. We're presenting what our analysis showed.

PANEL MEMBER BLANC: Is this table in your document?

DR. SANDY: Yes, it is. It's in the Executive Summary, and it's also in --

PANEL MEMBER BLANC: I suggest you change it from 1.6 to 10 to the 3rd to 16 to 10 to the 4th so that somebody can follow that because, believe me, people are not going to catch that. Too subtle.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

DR. SANDY: I'll do that. Thank you.

Then I can present the results of the case studies very briefly, and Dr. Tomar can answer any questions you have.

Here, for DEN, we plotted the potencies and -- the distribution of the potencies for each of the studies. And we have grouped them by experiments where the exposure occurred during the prenatal lifestage, the postnatal, and the juvenile.

And then we created LPJ ratios which we're showing here. The green is for the prenatal LPJ ratio, so prenatal to juvenile. And the postnatal to juvenile.

So you'll see that the prenatal, based on the data sets we have, looked like they're much less sensitive than adults to DEN.

But as Dr. Tomar just mentioned, DEN requires

metabolic activation, and many of these prenatal studies, exposures occurred early in gestation when there's no enzyme to activate DEN and that's why you're not seeing any effect.

But a few of them, you do start to see an effect because the exposure occurred in the last couple of days of gestation when the enzyme is just starting to come up.

So what can we conclude? Well, animals exposed to DEN in utero are considerably less sensitive than those exposed as juveniles based on this analysis, and animals exposed to DEN during the postnatal period are significantly more sensitive than those exposed as juveniles.

We did the same thing for ENUs, so here are the potency distributions for ENU with the different lifestages. ENU does not requires metabolic activation.

These LPJ ratio mixture cumulative distributions look very similar. The postnatal one, prenatal, when they're graphed like this, equal sensitivity.

But when you actually look at the distributions a little more closely, you see in the second bullet here that the prenatal exposure's

associated with greater sensitivity to ENU than postnatal exposure over all. But both lifestages are sensitive.

So we conclude that early lifestages are generally more sensitive than the adult lifestage to carcinogens; and in the absence of chemical-specific data, age-specific adjustments to potency are justified, and that age-specific adjustment may vary with lifestage.

Thank you.

CHAIRPERSON FROINES: Thank you. Great.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Time for a break?

PANEL MEMBER GLANTZ: Do you want to take a break, or do you want to keep going?

PANEL MEMBER BLANC: Yeah, what about our --

PANEL MEMBER GLANTZ: Oh.

CHAIRPERSON FROINES: Should we break for lunch at this point?

PANEL MEMBER BYUS: If you want to get done by 1:30, why don't we just take a break and not break for lunch?

PANEL MEMBER BLANC: We can bring our food back.

PANEL MEMBER BYUS: Oh, okay.

PANEL MEMBER BLANC: Let's take a 15-minute break, bring our food back to the table, and start again.

(Recess)

CHAIRPERSON FROINES: So we're going to start again.

And the way we outlined it in the beginning was at this point we're going to give the two Leads the opportunity to say anything further they want to say before we open it to the rest of the panel.

PANEL MEMBER GLANTZ: I don't have anything else to say.

PANEL MEMBER LANDOLPH: Just a short comment.

In your page 35, where you talk about the NTP bioassay, you might just want to add a short sentence there stating if you use the NTP bioassay for risk assessment alone, you can miss the prenatal, the postnatal, and the juvenile stage.

So those are actually underestimates which then gives you even more justification to use these adjustment factors.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: I'm sorry. Peter was talking to me.

PANEL MEMBER LANDOLPH: If you use the MTBE bioassay, which starts about week 6 to 8 which is just at the end of the juvenile or just at the beginning of the adult, you miss the exposure for the juvenile and the postnatal, so any calculations made using that are underestimates because you don't have that early life exposure, so this is even more justified.

CHAIRPERSON FROINES: Do you want to raise your point now?

PANEL MEMBER BLANC: First Craig, I think, was in line. No?

PANEL MEMBER BYUS: Well, I'm -- I started out being highly skeptical, and now I'm completely convinced of the quality and the excellence of this approach.

So I think Leads and you all did a wonderful job since improving the readability -- it was never in the methods; it was just the readability of trying to understand it. It is very complicated.

And again, I would just emphasize that you state clearly what the purpose of the analysis is. Because I think it's very important whether the overall lifetime exposure, short-term exposure, what you really want to use it for.

Because you're doing the analysis, and so even

though the numbers -- this may be used for other purposes, you need to state clearly what in your mind it's best used for.

And if there's limitations, you should perhaps state that. But clearly, why -- what you think it could be used for the most.

I'm particularly concerned about long-term exposure versus short-term. Because the data was really generated from the animal short-term exposures. It wasn't generated --

STAFF TOXICOLOGIST TOMAR: Not all of them.

PANEL MEMBER BYUS: Not all. But the majority of it from long-term exposure. And there may be some mechanistic distance in terms of sensitivities is all I'm saying.

And my only other comment would be the smoking data with humans. I still think there has got to be -- now again, I don't know whether it is directly -- it is in fact applicable and analogous with your radiation experiment showing marked increase in sensitivity, if there is, for human population, something that's very large numbers.

I can't probably think of anything else more -- with a bigger data set than that.

But other than that, I think it's very well

done, and I think it's not just clever but it's very good science, and obviously lot of thought went into it.

PANEL MEMBER BLANC: All right.

CHAIRPERSON FROINES: Paul?

PANEL MEMBER BLANC: I have a biological question.

Day zero to day 21 in the small rodents from which your data are based would be the equivalent of what age period in the human?

STAFF TOXICOLOGIST TOMAR: That's the million dollar question. Not too many people have answer for that, but I'll try.

You have to divide the whole gestation proportionately to rat or mice. But the thing is, the different organs' still different in human.

PANEL MEMBER BLANC: Well, I'm not talking about just gestation. I'm talking about from birth to day 21, and day 22 to day 49.

STAFF TOXICOLOGIST TOMAR: That would be, in my best guess -- there's no real data -- would be up to 10 or 12 years, and then from teens, from 12 to 18 or 12 to 21.

CHAIRPERSON FROINES: 0 to 21 days.

PANEL MEMBER BLANC: Like from birth to age 12

or so.

CHAIRPERSON FROINES: Is what -- at what human age?

PANEL MEMBER BLANC: You just said 0 to 12, didn't you?

STAFF TOXICOLOGIST TOMAR: Proportionately because it's very difficult to --

PANEL MEMBER BLANC: Roughly.

DR. SANDY: I think what we're looking -- we've looked at -- sorry -- is the functionality.

So day 21 is the age of weaning, and we're thinking -- I think this is in humans up to age 2 of -- for end of weaning time.

It's sort of what EPA has done. It's a general assumption that you could -- that period when the animal is still drinking milk.

CHAIRPERSON FROINES: So postnatal and 0 to 2 in humans.

DR. SANDY: That's what we have applied.

PANEL MEMBER BLANC: And adolescent is from -- and juvenile humans are from age 3 to age 16?

DR. SANDY: Yeah. That's what we've --

PANEL MEMBER BLANC: Well, I have to say that that at face value is -- completely flies in the face of what any sort of lay reader, but let's just say

anybody else would think reading the thing.

And I have to say that as I heard the presentation I was completely flummoxed as to how you could -- if you're talking about 40 percent of the lifespan of the animal up to adulthood is 0 to 21 over 0 to 49, like 40 percent, right?

So unless there's something very biologically strange about rodents -- maybe there is; I don't know. But this age of weaning is only one -- is only one thing.

I mean actually children in very primitive societies may actually be nursed quite a bit beyond two. I mean what in primate -- you're a primate guy, aren't you?

PANEL MEMBER PLOPPER: Mm-hmm.

PANEL MEMBER BLANC: How -- what is the primate weaning age?

PANEL MEMBER PLOPPER: Well, it's done experimentally, just like it is for --

PANEL MEMBER BLANC: In the wild.

PANEL MEMBER PLOPPER: So it's usually six months, six months of age.

PANEL MEMBER BLANC: In the wild?

PANEL MEMBER PLOPPER: Oh, in the wild? No, that could go on for years. I mean that's sometimes

even what would be considered juvenile or young adults in some species are still nursing, so.

PANEL MEMBER BLANC: Uh-huh.

PANEL MEMBER PLOPPER: It's like humans. I mean, some places it's a long time. Sometimes it's a short time.

PANEL MEMBER BLANC: So I have to say that I don't want throw a monkey wrench in your entire edifice here. That's a mixed metaphor, but this two-year --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: 25 cents.

PANEL MEMBER BLANC: You know, up to two years and then 3 years to 16.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. I know.

It's entirely a policy call to how you want to use those weighting factors. And there is not a nice little chart that says at day 22 that's equivalent to whatever age in a human. It's very difficult, and in fact it might even go by organ system rather than just the whole animal.

So, you know, I know what you're saying. And there is not an easy way to deal with it, and that's why we just decided to do a step function: Zero to 2, we're weighting by 10; 2 to 16, we're weighting by 3;

and above that, we're weighting by 1.

PANEL MEMBER BLANC: But you're asking us as a Scientific Review Panel to say that the science behind that finding is -- meets --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think we're asking you to say the science behind assuming there is increased sensitivity by use of these default weighting factors, that the science behind that is -- justifies using a --

PANEL MEMBER BLANC: Some type of weighting factor, yes. But obviously that's not -- our finding, doesn't our finding have to go beyond that?

You're actually proposing numbers, and you're proposing ages to apply them. Is that not part of your document?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But it's a policy call. So, you know, if you want to comment on the policy call, that's fine; you can do that. It's okay with me.

But it is a policy call.

PANEL MEMBER BLANC: What's the science behind the policy?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The science is that exposures early in life --

PANEL MEMBER BLANC: No, no.

What's the science behind using a two-year human equivalent?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, there's not. I just said there wasn't.

There's not a perfect answer to that. There's not a perfect way to apply the uncertainty factors and decide what number to use.

So that is why we said, okay, if there's infants and toddlers up to two, that, you know, clearly those are pretty early postnatal. So let's use that 10X for that age group.

Then we wanted to encompass puberty somehow, so we went up to 16.

CHAIRPERSON FROINES: But your actual numbers that you come up with -- the 13.16, I think it is, or something like that -- is not 10.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's right. It's not 10 because 10 is a policy call. 13 is a median of the weight that the data were analyzed.

And we also discuss in there that it's not easy to take a number from that data analysis in part because of the limitations in the data themselves.

PANEL MEMBER BLANC: And if your median had been 7, would you then have chosen the value of 10

because that was a policy decision?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We may have, yes.

DR. SANDY: You may wonder, do you want to pick the median? Do you want to pick something else?

PANEL MEMBER BLANC: Well, why did you emphasize the median so much if you weren't going to use it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We didn't really emphasis it. We just showed it as part of the distributional analysis.

The little thing that you were looking at was the policy call. And it -- maybe it shouldn't be in that graph. But it was because we were asked to put it in there.

PANEL MEMBER BLANC: No, no, okay. But I'm trying to -- you see the position you're putting me in, a little bit, which is you're asking me, on the one hand, to approve -- to say use the best science, and I want to echo the other comments that were made. I think it's a very diligent, creative, and important approach that you took.

And at the same time, you're asking the panel to say and then when you get to a certain point in the document, don't think about science; that's policy.

And you can either like the policy or not like the policy.

That to me is very different than other things we've been asked to comment on where it has seemed less -- your whole effort has been usually to avoid the substance or appearance of being arbitrary in a way.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, it's somewhat analogous to uncertainty factors. Why do we pick half logs and logs?

Because there's a lot of uncertainty, yet we know that there are these differences that need to be accounted for. If you can't account for them with data, you have to do something.

PANEL MEMBER BLANC: No, but you've also given us good rationales for this is what standard we'll use, this is what others have used, that if you use this you get values which seem to make sense with observable data.

I mean I think you're not doing yourself justice. You've actually given us quite cogent arguments why you used the uncertainty factors that you've used.

PANEL MEMBER GLANTZ: Well, I think -- I mean here's what I would suggest you do.

First of all, I think to say 13.16 is

ridiculous. I think -- I mean the way I interpreted it is they rounded things off to one significant digit, you know. If you take 13 and round it off to one significant digit, given the uncertainties that --

PANEL MEMBER BLANC: Then why doesn't 3 round to 0 or 1?

PANEL MEMBER GLANTZ: Well, I'm just telling you the way I --

PANEL MEMBER LANDOLPH: Well, 3's kind of a half a log of ten.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Exactly.

PANEL MEMBER LANDOLPH: That's justified.

And I agree with Stan. I mean the 13, I would say given the uncertainty, which stands a couple orders of magnitude for one chemical, 13, you might as well drop to 10. It's reasonable. I could support that.

CHAIRPERSON FROINES: But I think, just to support Paul on this, this notion of 0 to 2 as this weaning period in humans, and then 3 to 16 relative to the animal data leads you to -- it's -- it is a policy decision to make those determinations. It's not science.

PANEL MEMBER GLANTZ: Well, I think that there's two different issues --

CHAIRPERSON FROINES: And I think what the question becomes, Stan, that how is this going to be phrased in the document?

Because do we really think that 0 to 2 and 3 to 16, you know, leads you to where you end up? And that's -- or how does it lead you to where you end up? It can't be argued on the basis of some scientific merit, I think.

PANEL MEMBER GLANTZ: Well, I think that there's two different issues that are getting mixed up here that I think need to be treated separately.

One issue is: Why did you pick 10 instead of 13.28734? Okay? And I think that we've given you what you can say. You know, the median is 10; given the uncertainties, we're picking something to one significant digit, the half log.

I think that's -- if you take your pre and postnatal and juvenile periods that you presented, I think you can very logically argue why you picked the numbers you picked. That's one question.

Paul's raising a different question really, which is: Why did you call -- you took juvenile rodent studies, and how do you come to the ages that you correspond those to humans?

So those are really two different -- the why

you use 10, I don't think that's problematic.

I do think this other thing, you know, he's raising a good point. This is an area where I, you know, just assumed there was a good logic for it because it's not something I know.

But, you know, are you saying that there is nothing in the literature that gives you some, you know, rationale for why you -- you know, what you would call a juvenile period in a human versus a rat?

PANEL MEMBER PLOPPER: I think what Melanie said exactly what the problem is, is that there is plenty of those sorts of comparisons for different organ systems. And the problem is nobody has done it for the whole organism.

And what I was going to suggest is that -- I mean you've already got this very sophisticated statistical expertise -- is to try to accumulate the four or five -- obviously the two most important organ systems would be respiratory system and nervous system. That's where you focused most of the rationale so far.

And there's also one for lymphatic system, whole lymphoid system, and try to come up with a derivation based on what those -- the target organs that you think are important for doing these analyses and making these susceptibility measurements and look

at what's there.

I mean the one I know -- I've published four or five for the respiratory system that compare all kinds of species. They're all over the place. They're in all the reviews.

So that -- and it's not -- and it's been used -- it turns out that brain, nervous system in general, respiratory system, and lymphatic system have almost the same time frame. So it might be easy to do it that way.

In fact, the same regulator's apparently involved in postnatal developmental growth issues in all three organ systems, and the time frame is almost the same.

So maybe that would be -- and it's not that far off of what you've got, but I would be picking different time points knowing what happens with those target systems.

That would be my suggestion. Then you don't have this argument because you've already made the argument you're going to use nervous system and respiratory --

PANEL MEMBER BLANC: I think you're confusing the noncancer health effects. I wouldn't necessarily say here these are brain tumors and lung tumors.

PANEL MEMBER PLOPPER: Well, that's -- I'm just giving this as an example. And I would suspect that if you identified the three or four organ systems that are the main tumor targets, that you'll find those for those. That would seem to me to be a better --

PANEL MEMBER BYUS: Use that as a rationale. I think that's an excellent idea.

PANEL MEMBER PLOPPER: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: There is some logic to that.

Here is part of the issue, that again we have a subset of carcinogens people focused on back in the '70s and '80s, these sort of prototype carcinogens, so --

DR. SANDY: '60s and '70s.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Or '60s and '70s.

So in terms of what tissues these particular subset of carcinogens target is not necessarily representative of the universe of carcinogens to which we want to apply the default factor.

That is one reason we had issues and trouble

with using the distributional analysis that we did to pick the actual policy number.

So even if you could do that, I'm not sure -- you know, then would you pick a different number depending on which tumors were produced by that specific chemical?

I mean, I think it would get pretty contorted, and that's why we stepped back, looked at the whole picture, what it's saying, and said okay, we have to do something to try to account for this susceptibility of early life exposure.

PANEL MEMBER BLANC: Melanie, is an unstated issue here that were you to apply your uncertainty factor of 10 to age 0 to 7 you would be diverging from the EPA, not only in the mutagenicity issue but in the age range to which they apply their numbers?

Is that an --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It is true that we would be diverging, although we didn't really think about that specifically when we were looking at this.

Pretty much everyone has talked about the postnatal as really being most applicable to humans at -- from birth to 2.

PANEL MEMBER BLANC: Who -- and they're

talking about that in writing, in articles that can be cited and invoked with a rationale?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, it's pretty much the risk assessment community.

And I don't remember that EPA provided any very specific justification when they did their document, and I was actually on that SAP panel, so.

CHAIRPERSON FROINES: It does seem, if I'm hearing Charlie and Paul correctly, that 0 to 2 may not be the best number that should be selected.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well then, I don't think there is enough science to pick another value.

PANEL MEMBER BLANC: Well, there is -- sure there is. You could say 40 percent of the preadult lifespan of the rat is what this group of studies applied to, so we're going to apply our finding to 40 percent of the preadult lifespan of the human. I mean that's science.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But it would make -- the assumption there is that the organ development and tissue differentiation and cell proliferation is identical in rodents and humans in that time span, and it is definitely not.

So we did not want to specifically --

PANEL MEMBER BLANC: Do you have evidence that --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- make that statement.

PANEL MEMBER BLANC: -- 40 percent of the rat is equivalent to 10 percent in the human?

I mean that's the decision you have made.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No. And I think also you have to realize that when we're talking about postnatal studies the mixture distribution is a distribution because the studies aren't all done with the same protocols, so some of the exposures were day 5. Some of them were day 15.

PANEL MEMBER BLANC: I know, but you took that into account by analyzing the data in the way you did by doing the Monte Carlo, by being so meticulous. And then --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: -- at a certain point you take this 90-degree right turn and make, you know, a fiat to --

PANEL MEMBER BYUS: I have a comment that may be an alternative. That's why I said about picking the

purpose.

If the purpose of your analyses is lifetime exposure, calculating the potency and accounting for these early stages, then it doesn't make any difference because it's just lifetime.

However, if you want to use these age-specific factors then in other studies to define other human applicable or comparable exposure scenarios, then you're going to have to get into this question.

So for lifetime, I don't think it much matters other than if it's between rats and mice and humans. So you don't have any problems with it. But if you want to then apply to specific windows in human exposure, then you're going to have to come up with some rationale.

And I like Charles's idea of the comparable organ-specific maturity factors, whatever you want to call them, comparable relative to the tumors that you're seeing a lot of.

And again, it doesn't really -- the fact that it's carcinogen-specific doesn't matter because your data is based on these carcinogens. So whatever tumors you see a lot of, make the comparable organ maturity calculations.

CHAIRPERSON FROINES: Craig, what I hear --

and Charlie should correct me if I'm wrong.

What I hear Charlie saying is if you look at the neurologic system and you look at the respiratory system, it doesn't appear that a 0-to-2-year period is adequate because there is development occurring within a longer time frame.

Am I getting you accurately?

PANEL MEMBER PLOPPER: There is a variety of things. There's rates of proliferation, there's rates of differentiation, there's initiation that go in stages. And it seems like for now the nervous system and respiratory system sort of track each other.

So there would be -- the same time frame will have higher proliferative rates and lower proliferative rates.

CHAIRPERSON FROINES: So does that mean --

PANEL MEMBER PLOPPER: Metabolism will be functional and not functional.

CHAIRPERSON FROINES: So based on what you're saying -- and presumably there are references to that effect?

PANEL MEMBER PLOPPER: Yeah.

CHAIRPERSON FROINES: Could you, Melanie, come up with some estimate that would help you not have to make your argument solely based on a policy decision?

I don't know the answer to it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think --

CHAIRPERSON FROINES: I'm just trying to help.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I'm guessing no. I'm guessing no.

I mean one of the other issues that Martha just reminded me about is that there's not necessarily tissue concordance between species for specific carcinogens. So then --

PANEL MEMBER PLOPPER: Oh, yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: You know, then you're getting into -- like if you're trying to base your age grouping by a specific maturation of a specific system that was more predominant, for example, in determining the postnatal distribution, you still don't know whether that carcinogen would impact that system in a human.

So it's pretty -- there's a lot of twists and turns, making it pretty difficult to --

CHAIRPERSON FROINES: What do you think, Paul? What would you propose?

PANEL MEMBER BLANC: Well, I think there's two ways of going.

One would be for you to stick with the 2, and

then I'm going to urge the panel in its findings to reject that and say that it should be applied to a different age range.

Or for you to change your age range and come to some age range that's more convincing.

And that -- the former might be a better way because it would put you less at direct loggerheads with EPA, and that might be a more advantageous situation to be in.

I do think that this is one situation in which, as opposed to our discussion this morning, I don't think it's going to be possible to disentangle the approval of the document from the draft -- from a very close read of the text of the findings of the panel.

So I don't think that we could come to an approval of this document at this meeting because it will for me depend on what the findings look like.

And although I think Craig's point is well taken that in your calculations, for example, of the 70-year-old person the proportion -- the actual numerical value changing from 0 to 2 being 10 versus 0 to 5 being a 10 or 0 to 10 being a 10 is not going to amount to very much if indeed one of the applications of this will be for nine-year exposures for risk

assessment. Then the proportional change, of course, will be quite a bit more. So it does have implications.

So I'm sensitive to the sort of difficult situation you're in, you know, the sort of middle ground between science-based estimates that support the conclusion and then the more obvious policy decisions.

But if they are just policy decisions, then I think we -- the panel could discuss among itself what we think the policy should be or what -- actually, that's not our role either.

We need to comment on whether the science supports that part of the document or not.

DR. SANDY: The way I have thought of the postnatal period in the animal and then in the human from 0 to 2 is the rate of rapid growth that occurs from birth until age 2. And presumably, you have that with the rodents as well and also have this whether the animal or human is still nursing. Age two is a rough --

PANEL MEMBER BLANC: Well, the human is nursing in a western society until age two. Primates, we've just heard, will be nursing quite a bit longer than that, and the human in the different -- so biologically, why humans stop nursing at age two in Los

Angeles isn't, you know, is not a purely biological thing.

And one of the reasons why I would suggest a kind of step back from the precipice here is because, you know, we may all be wrong and there may be actually very obvious data out there that very strongly support the two-year age human translation, and you'll find that quickly, and everybody will be happy, and you'll be able to insert a paragraph as to the pros and cons and why ultimately you chose that, and everybody will be ecstatic.

PANEL MEMBER LANDOLPH: And maybe also a figure on page 35 below the mouse, maybe have a human? This is not perfect. You just do the best you can.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's not doable.

PANEL MEMBER LANDOLPH: If it's not doable, or there are other --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. It's not doable.

DR. SANDY: Especially for the prenatal period. There are so many -- each organ system, the brain, the lung --

PANEL MEMBER BLANC: Well, the prenatal is not an argument because you've never used that ultimately

anyway.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But even in the postnatal, it is still organ-dependent, species to species. There's not a nice little correlation. So -- and, you know, I think that we can look at the --

CHAIRPERSON FROINES: But Melanie --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- the EPA's document, but I'm -- you know, I'm not going to be able to tell you what their rationale was.

CHAIRPERSON FROINES: Melanie, you're right about that. You may be right about that.

What Paul is simply asking for is: How do you justify that 0 to 2 then?

Am I correct? Isn't that what we're really talking about? Because it's the underlying justification that he's asking for, not -- and so that seems to me to be the cutting edge.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. The way it's been described when the EPA did their document in 2005, as Martha just pointed out, they looked at it as a period of rapid growth and differentiation, 0 to 2. And obviously, there's not a cutoff.

CHAIRPERSON FROINES: Did they have references to that effect?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, there's -- I mean you can -- we'd have to look. I'm sure they had some references to it.

And then a relative --

PANEL MEMBER BYUS: It had nothing to do with weaning. It has nothing to do with weaning, does it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No.

PANEL MEMBER PLOPPER: No. Weaning is not part of that.

PANEL MEMBER BYUS: Weaning is not part of any of that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: A slower period of development until puberty, and then at puberty all kinds of things happen. And that's why we wanted to also include puberty in that second-fold factor.

CHAIRPERSON FROINES: That starts basically, the juvenile period, at a relative early age.

PANEL MEMBER GLANTZ: Can I ask just one point of clarification?

Would it be accurate for me to say that except for this issue everybody's happy with the rest of the

document? Is there anything in the rest of the document that people still want to talk about?

PANEL MEMBER BLANC: Well, I want to come back to your rounding off. I'm going to buy the 13 to 10, but the other value was 4 point what? What was the other median value?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It was 4.5.

But I will point out that we -- when we -- there's a section in the document, selection of the default age sensitivity factor. And in that, we discuss --

PANEL MEMBER BLANC: What page?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Trying to find it. Page 48.

PANEL MEMBER BLANC: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So the second sentence is really kind of the key sentence:

> In view of the variability shown --

With those which Dr. Byus brought up earlier with those distributions -- and the:

> Uncertainty in applying conclusions from a relatively small set of chemicals to the much larger set of carcinogens that

are out there, it is probably unreasonable to specify a default ASF with greater than half-log precision.

So that is what we've got in there now: Therefore, in the absence of chemical-specific data --

Blah, blah, blah.

PANEL MEMBER LANDOLPH: You know, I would accept that, particularly given that some of the specific chemicals have a hundredfold range. That's reasonable. I wouldn't want it any more -- that's a rationale that's justifiable, and you can't get any more precise than that.

I would accept that rationale.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We didn't look at the numbers and then round them down. We just said --

PANEL MEMBER BLANC: The nearest half-log. We'll go to the -- you rounded to the nearest half-log. Is that what you mean?

PANEL MEMBER GLANTZ: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. If you look at -- yeah. 10 is somewhere around the median. And so let's go half-log, you know. It's just you can't --

PANEL MEMBER GLANTZ: So are you happy --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- use the distributions --

PANEL MEMBER GLANTZ: -- with that, Paul?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- to pick a number is what we're trying to say. You can't use the distributions to pick a number.

PANEL MEMBER GLANTZ: Are you happy with that?

PANEL MEMBER BLANC: Not happy, but I understand it now better.

PANEL MEMBER GLANTZ: Okay. So here's the practical --

PANEL MEMBER BLANC: And I probably would say we rounded off, therefore, to the half-log.

Because I actually had to think through what do you mean by half-log precision? What you mean is you rounded off to the nearest half-log so why not just say we rounded -- therefore, we rounded off to the nearest half-log?

That's what you did, right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We actually viewed them more as like an uncertainty factor at half-log.

PANEL MEMBER GLANTZ: Well --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: But yes.

PANEL MEMBER GLANTZ: You can say what Paul says. That's fine.

(Laughter)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. I mean if it were --

PANEL MEMBER GLANTZ: I'm trying to help you.

CHAIRPERSON FROINES: As a practical issue, live with it. This is counting angels on the head of a pin.

PANEL MEMBER GLANTZ: Okay. So here's the question -- so I have the following question for Melanie:

So basically, the only outstanding issue is this issue of where do you draw the line between postnatal and juvenile and juvenile and adult.

And I think the question is -- I mean the point I think Paul raises is reasonable in that you're not -- we're supposed to be approving science, and you're just saying that there isn't science, or it's all mushy and complicated.

So it seems to me that we have a couple of options that we could have.

One thing is for us to not approve -- to say that we don't -- that where you made that is a policy

decision, and so in approving the document we're not making any comment one way or the other on the policy decision because we're supposed to be approving science, not policy.

CHAIRPERSON FROINES: No, I think we might say something more affirmative and say we are -- we find that the scientific information available is inadequate; therefore, we recognize that OEHHA needed to make a policy decision on this issue.

I don't know if Paul could live with that. Am I being too Pollyanna?

PANEL MEMBER GLANTZ: Well, let me just finish what I was -- that's one choice.

The other choice is to give it to, at the risk of prolonging the torture here, is to let you guys go back and look at -- I mean I guess a second option is to say this is what the EPA did, and we're doing the same thing they did, and cite the EPA.

The third thing would be, you know, to leave this open and let you go back and see if you can come up with a rationale for whatever -- and which may involve changing those cut points, I don't know, but something that addresses the issues that Paul is raising.

I think those are the three options. I mean I

can live with any of those. What would be best from your perspective?

CHAIRPERSON FROINES: This is not something to ask Melanie right now. This is something to ask the committee.

PANEL MEMBER GLANTZ: Well, except I think that --

CHAIRPERSON FROINES: No, this is a decision how the committee wants to approach the issue, not how Melanie wants to approach it. No disrespect to Melanie at all.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: My approach is thank you very much, we're done.

(Laughter)

PANEL MEMBER GLANTZ: Well, we can do that. Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That was a joke, by the way.

(Laughter)

PANEL MEMBER BYUS: That's a joke.

PANEL MEMBER BLANC: I've already stated my preference. My preference is to come to consensus, which can't be done today.

And we have previously always found ways to not have our findings contradict or undermine in any

way the documents that have come forward but have always taken the approach of trying to amplify and strengthen.

And I would not blithely want to diverge from that, and I don't see logistically a way of solving that at this sitting. And I don't see such great urgency if this, as you point out, is the only thing that's sitting between us. It would mean our next meeting would be a very brief item of business.

I don't know that there's an administrative reason. Perhaps Jim could tell us that there's some deadline that's been missed --

CHAIRPERSON FROINES: There isn't.

PANEL MEMBER BLANC: -- in terms of a legislative mandate.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We missed that deadline a long time ago.

(Laughter)

PANEL MEMBER BLANC: Also, by the way, just from a purely practical point of view, seeing a document, the majority of which was no longer in track changes, would make the thing a lot easier to look at.

And also, I would recommend that if we have the opportunity that the Leads, working with our Chair, come up with draft findings well in advance of the

meeting so that the committee can link closely the wording of the findings to the wording of the document, bearing in mind whatever version is coming forward to us. Because I think the proof will be in the pudding in terms of the findings.

That's my own personal view. I want to avoid that kind of -- and it may, again, it may be that a cursory review of certain written documents will come up with a straightforward rationale that's supportable.

PANEL MEMBER GLANTZ: Are you doing a rapid literature search, Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I'm looking at EPA's document.

PANEL MEMBER BLANC: Maybe Joe, because you're the other Lead along with Stan, it would be important for me to hear what you have to say.

PANEL MEMBER LANDOLPH: You know, with Stan, we've worked through two revisions of the document, transmitted a lot of changes. I agree with all the work Stan had done.

So I think the document's in reasonably good shape. But I would like to make you satisfied as well, and I agree with your criticisms.

I could suggest that Charlie, who is really an expert in this area, might work -- I'm making a

suggestion, and Charlie's looking irritated already.

But why not have Charlie work a little bit with OEHHA?

CHAIRPERSON FROINES: I would say that Paul was being very strategic. He said that you and Stan and I -- I'm the new body. I would work on the findings. And if that were the case then, given my authority, whatever that may be, I would go to Charlie and ask for his input.

PANEL MEMBER LANDOLPH: That's fine. And I'm completely in agreement with that. Charlie's not unhappy.

PANEL MEMBER GLANTZ: Well, are you saying -- so is what you're saying, John, that we would basically approve, as we have before, approve the document subject -- no. So you're just saying -- okay.

CHAIRPERSON FROINES: What's Paul saying?

PANEL MEMBER BLANC: No, I'm not saying we would approve the document because I don't know what the document will be. There are two or three forms it could be in.

One could be staying with 2 and with no further justification, staying with 2 with a justification that's convincing, or saying, okay, it's going to be 7 or 5 or 9.

CHAIRPERSON FROINES: The tension that everybody feels is that Paul's scientific points are clearly correct.

We also, however, want to be sympathetic and supportive of OEHHA, and so delaying it makes everybody uncomfortable.

My sense is that we will, if we do delay it, we will come out with -- we will take a half hour to finalize it at the next meeting, and we will all feel satisfied with the outcome.

PANEL MEMBER GLANTZ: When is the next meeting?

CHAIRPERSON FROINES: I mean we're trying to be sensitive and supportive, but we also recognize that there is a fundamental technical issue that needs comment on; and Paul's said twice now three different options that would work to resolve it, and we'll just have to -- we might have to see which way we ultimately agree would be the best outcome.

PANEL MEMBER LANDOLPH: So would you like Stan to start working on the findings and send them to me, and then I'll work on --

PANEL MEMBER GLANTZ: Well, we actually drafted some findings up that you approved.

PANEL MEMBER LANDOLPH: Right.

PANEL MEMBER GLANTZ: But this point wasn't addressed. The findings are quite simple, basically part of it -- these were given to John, but this point that Paul's raising wasn't in there.

But the findings were basically -- the first part was just lifted verbatim from the REL document about causality, that stuff that basically said we concur in this two-step estimation and these default values.

It didn't address -- this last point wasn't addressed?

PANEL MEMBER BLANC: And I apologize. You know at the last meeting we had, I had to go -- I was there for the REL part but left before the concluding discussion of the cancer document.

PANEL MEMBER GLANTZ: Did you find what the EPA said?

CHAIRPERSON FROINES: Melanie, did you want to make a comment at this point?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I have -- not really. I mean, you know.

I'm looking to see what EPA said in their document. It's a 250-page document. I can't find it right this second.

But, you know, in all the presentations I

heard from them, the primary justification for the age groupings were this rapid cell proliferation differentiation 0 to 2, and then a relatively quiescent period, as they termed it, up to puberty. And then puberty --

PANEL MEMBER GLANTZ: And I'd like to make the following suggestion to avoid having Melanie's head explode: We don't have any other business. It's a quarter to 1:00. You don't have to leave till 1:30, right?

Why don't we stop for 15 minutes so Melanie and the others can look through this EPA document without us all sitting here staring at her and then come back and see if we can't come to some closure on this that everybody's happy with.

And if not, then we'll just put it over to the next meeting.

CHAIRPERSON FROINES: But the thing that concerns me Stan about that suggestion is that's -- what you're assuming is that the basis for resolving this issue is going to be what EPA says.

PANEL MEMBER GLANTZ: Well, that --

CHAIRPERSON FROINES: And I'm not sure that that's --

PANEL MEMBER GLANTZ: No, not necessarily --

CHAIRPERSON FROINES: -- as a matter of science --

PANEL MEMBER GLANTZ: No, no.

I think I'd like to hear -- it would be interesting to hear what they said and what the rationale was. And it may be that if we hear that, given the general difficulties that several people have been talking about around the table, that we'll listen to that, hear how they did it, and then say, you know, that's probably the best you're going to do.

CHAIRPERSON FROINES: Melanie, is this -- if there is something in the document, EPA document, is it in your document? I think the answer to that is no.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No. It's not in our document.

CHAIRPERSON FROINES: So that raises the issue of the timing of whether we're not -- we can resolve that.

PANEL MEMBER GLANTZ: Right. But why don't we give them a little time where we're not sitting here and let them just look, and come back in 15 minutes or 20 minutes and just see what they can find out.

CHAIRPERSON FROINES: Is everybody comfortable with that? Paul, are you?

PANEL MEMBER GLANTZ: We don't have to vote on

anything, but I would like to hear what -- if they can get this information, I'd like to hear it.

PANEL MEMBER BLANC: I am certainly in favor of doing whatever will make the group that worked so hard writing this not feel blind-sided or overly frustrated due to the circumstances.

PANEL MEMBER GLANTZ: Why don't we recess for 20 minutes?

CHAIRPERSON FROINES: Okay.

(Recess)

CHAIRPERSON FROINES: We will reconvene right now.

PANEL MEMBER GLANTZ: Give her ten minutes.

CHAIRPERSON FROINES: She just said she found it. I thought she was asking to speak.

Melanie, are you asking to speak right now?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I actually need five minutes.

CHAIRPERSON FROINES: Five minutes, we'll reconvene.

(Recess)

CHAIRPERSON FROINES: Melanie, it's your call.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

This is from the US EPA's Supplemental

Guidance to Assessing Cancer Risk From Early Life Exposure. And what they have in here is a little different than what I remembered, but I can understand now or remember a little better now what they were talking about. And there was actually a lot of discussion by the SAB about this and about the age groupings.

Anyway, in here they describe that the adjustments reflect the potential for early life exposure to make a greater contribution to cancer risk.

The adjustment of tenfold is applied for the first two years of life when toxicokinetic and toxicodynamic differences between children and adults are the greatest.

So that's work done by Gary Ginsberg, Dale Hattis, Renwick, and others. And you can see, in fact, in some of our other work where we looked at kinetic differences, they are largest at infancy relative to adults, and they drop off.

So they're focusing on both kinetic and dynamic differences.

So then they didn't really have additional data like Ginsberg and Hattis had put together for choosing a good rationale for going from 2 to 16; but they wanted to include that middle adolescence where

there is a more rapid period of development including the physiologic changes in puberty, so that's why they went up to 16.

And they didn't think that the full 10 was applicable after the age of two because of the slowdown in -- well, actually because there's not as large differences in kinetics and dynamics.

So that's the rationale.

And there was a lot of discussion at the SAB meeting about, you know, how do you pick an age group and what -- how do you -- for sure to include puberty, but should it be more than three at puberty or -- and that's what they ended up settling on.

CHAIRPERSON FROINES: And is the Ginsberg/Hattis work peer-reviewed?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. And in fact, there is more work now besides what is on --

PANEL MEMBER BLANC: Well, Melanie, I would say that that's a very generic argument, and I would think that -- I think your data analysis actually contradicts that and is more supportive of the broader early age range.

So I would kind of throw the whole thing on its head. I think that the very important analytic

work that you did actually argues against the two-year cutoff, unless there's something about the first half of the life span of a rat up to adulthood that I am missing.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, if you assume -- okay.

If you look at the toxicokinetic differences, basically Ginsberg and Hattis looked primarily at drugs and drug clearance and looked at metabolic pathways. And you can see that in an infant chemical clearance tends to be slower, so the half-lifes range -- and we also did the same stuff looking at environmental chemicals -- and the half-lifes can be up to, you know, 10-or-greater-fold for infants relative to adults.

Dynamic differences, they're going to be all over the map because as you're growing and developing you have different targets for toxicity.

So I don't think that the data that we analyzed show anything particularly different in that and certainly don't provide a cutoff point for humans.

PANEL MEMBER BLANC: Well, I would argue contrary to that because in fact if you, by choosing this period of time of day zero to day 21, were diluting your effect which would have mostly been between day zero and day 6, then why would you have

come up with a median that was not less than 10 but actually greater than 10?

It should have been, if you were diluting out the effect of this equivalent period of 0 to 2 -- which it's hard for me to accept the argument that that's the same as 0 through day 21 in the rat -- then you should have come up with something considerably less than ten if all the effect is really -- would have been partitioned had you had studies which you didn't have that were only from day zero to day 5 or day zero to day 7 or whatever the argument is you want to make.

Does that make sense algebraically, what I'm saying?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And again, you know --

PANEL MEMBER BLANC: Let me ask another --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I don't think you can compare a rodent's -- you can't make specific age comparisons readily between humans and rodents and their various lifestages.

PANEL MEMBER BLANC: Well, let me ask you a different question, theoretical, coming back to something else we've talked about in terms of indirectly supportive data, radiation data, that Joe referred to before and my question about cancer

chemotherapy, delayed, secondary cancers:

If you have data that showed Adriamycin administration in childhood leukemia between the ages of three and 12 was associated with a hazard ratio of 10 for lymphoma, and the hazard ratio in adult-onset cancer treatment with Adriamycin was a hazard ratio of 2 versus a hazard ratio of 10 -- and these are not in two-year-olds; these are in three- to 10-year-olds -- would that -- how would you interpret that?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Again, that's a chemical-specific example. And if we had the chemical-specific data, we'd use it.

You can see that some of these chemicals, the hazard ratio is more like 1000. So it -- there is --

PANEL MEMBER BLANC: I was just making the argument about whether three to 10 was the same as being an adolescent or not.

I mean what you're placing people between three and -- you're saying people between the ages of three and 10 are the same as people between the people between the ages of 11 and 16. And I would say --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, we're lumping the groups. Yes.

PANEL MEMBER BLANC: Right. And I'm saying I think people between the ages of -- children between

the ages of three and 10 are probably more like children between the ages of one and two for the purposes of what you're talking about here.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, actually, I'll give you a flip example.

If you take girls treated for Hodgkin's with radiation, it's 10 to 16 that's the much more important age group and not three to 10. So there's a flip side, and that's for breast cancer, and the risk ratios are huge.

PANEL MEMBER BLANC: Mm-hmm.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So we're lumping that whole group together, knowing that there's going to be differences across chemicals for susceptibility by early age.

PANEL MEMBER BLANC: But you're not comparing two to 16 to one to two for Hodgkin's.

I'm just trying to make the point that, biologically, if you ask anybody out there how they tend to divide up youth and adolescence, they don't do it one to two and three to 16.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: For sure.

PANEL MEMBER BLANC: So why -- what is the rationale other than the EPA saying that's what they

like to do?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, it's not necessarily what they like to do. I mean there are larger differences between infants, toddlers up to two, and adults than there are by the middle time period in adults for -- certainly for drug clearance. That's pretty clear. And also clearance of other chemicals.

CHAIRPERSON FROINES: There is a danger that we're beginning to go a little bit around in circles on this argument.

What's the -- what do we think is a compromise solution to this?

PANEL MEMBER BLANC: I think the compromise is for you guys to take a time-out to make an internal decision. You have three different pathways you can go down. Give us what your final decision is, and we'll respond accordingly.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So tell me what the three pathways are again.

PANEL MEMBER BLANC: One is you stick with zero to two and don't provide any other supplemental justification, other than this is policy.

One is that you --

CHAIRPERSON FROINES: And EPA does it.

PANEL MEMBER BLANC: And EPA does it.

One is that you stick with zero to two and you have a pretty convincing rationale, a scientific rationale or argument.

CHAIRPERSON FROINES: As good a rationale as --

PANEL MEMBER BLANC: I would say tactically, by the way, if you do that, also with some caveats like we recognize that with additional data this may be extended, you know, to age ten, and here's what it would look -- here is how it would change, you know, in a very small way, the cumulative life risk, some kind of throw-out to that.

Or the third possibility is that you come up with some widened age range.

I don't think any -- I'm certainly not --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: With an appropriate rationale.

PANEL MEMBER BLANC: With an appropriate rationale.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We right now don't have a rationale for going up to five or six or seven.

PANEL MEMBER BLANC: Well, you could say we based this data on rat studies that represent

40 percent of the maturing period of the rat, and so we're using 40 percent.

That to me is a more convincing argument than anything you've said about one to two, frankly.

PANEL MEMBER BYUS: The other alternative is using the approach that Charles suggested of organ development.

I mean the reason there's a big difference at two years old and drug clearance is because of renal development. Strictly renal development -- and clearance, renal capacity. Not the proliferative capacity but --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's also hepatic --

CHAIRPERSON FROINES: That's Paul's second alternative.

PANEL MEMBER BYUS: Oh, that's the second one?

PANEL MEMBER BLANC: Well, yeah, they come up with a rationale. And it may be or two or it may be three or it may be four or whatever. And then we can respond to it appropriately. I mean I think it's --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll be back in a year and a half.

CHAIRPERSON FROINES: What?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: No, I just said we'll be back in a year and a half. Fine. That's what we'll do.

PANEL MEMBER BLANC: I think you've got a really important document here.

I think it's important because it's original. It's important because it's not the EPA. It's not mouthing what they're doing.

To the extent that it's diverging from them, you have excellent rationale for doing so. And you haven't painted yourself into the corner that they have with this mutagenesis stuff.

So if it takes another two months to shore it up in a particular way that makes everybody happy, or whatever it is, all the better. As frustrating as it is.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll look and see what's out there.

DR. SANDY: I was just going to say that I don't think it's appropriate to say that zero days or day one to 21 in the rodent is 40 percent of, you know, this period of their life, and then we're going to apply that to 40 percent of the human lifespan.

It's not a direct correlation. We just can't do that. The animals are maturing earlier, and organ systems and enzyme systems are changing. It's not

simple, and we can't just apply that.

PANEL MEMBER BLANC: Well, that's conservative. If they are maturing earlier even, then it goes to a higher age equivalent.

CHAIRPERSON FROINES: I have two comments.

One, does the panel -- I mean Paul's making a recommendation which is up to us to vote. Another alternative is to vote to approve the document right now. So there are different potential options.

So at this point, I'm not going to phrase it different options to vote, but is there general agreement on his proposal, or do you want to continue the discussion?

PANEL MEMBER GLANTZ: Well, my concern, you know, based on talking to a couple of people in the audience who know about these things who I said, well, why don't you come up and address the panel and they said no.

But I think that -- and listening to the discussion here, my concern is that I think that this is an area where there just isn't much data that leads to a clean decision. So my concern is that we could end up delaying without substantially improving the document.

So I would, you know -- I mean I -- my bias

would be to approve it with the following -- well, no. You asked what we thought; I'm telling you what I thought.

Okay. I think we should approve the document but, you know, with the -- subject to this section being rewritten a bit to say that this is an area where there is no clear bright line available to say that this is what the EPA has done and their rationale, that there are other rationales that we have talked about that lead you to generally a similar conclusion, but that this is an area where there is just -- the data simply don't exist to draw a bright line. And that's the best you can do.

CHAIRPERSON FROINES: I think that's a reasonable argument with one -- where I would disagree with you is I would prefer his proposal because it gives us a chance to look a little bit more into the science.

What I'm concerned about is having an important section that says we're doing this because it's our policy to do it, and that puts the panel in a position of not being able to comment on the science.

PANEL MEMBER GLANTZ: No, I'm saying to take the "it's our policy" out and rather replace it with an explicit statement that this is a very different issue,

that there's not a clear answer; this is what the EPA has done and why, but there's other -- you know, the kind of stuff that has been discussed in the transcript of, you know, this is a reasonable thing to do but, you know -- but it is -- that's all it is, and that there isn't some sort of bright line where things suddenly change.

CHAIRPERSON FROINES: Well, I agree with you, except I'm not prepared to vote on something that I haven't seen yet.

PANEL MEMBER GLANTZ: Well, then what I would hope we could do is have another meeting soon to bring this to a conclusion.

CHAIRPERSON FROINES: We could have it a week from now as far as I'm concerned.

Joe?

PANEL MEMBER GLANTZ: I mean I agree that this is an important point. And I agree with what Paul is saying, is that it is a very good document. It's better than what the federal EPA has.

And we don't want to leave a loose spring hanging that could undermine the whole rest of the document. So I mean I do agree with that.

Just based on the discussion and talking to a couple of the other people who are here, I think it's

going to be hard to come up with a nice clean argument.

CHAIRPERSON FROINES: Sure. This one isn't going to be clean. We know that.

PANEL MEMBER LANDOLPH: I'm happy with most of the document. I think it's an excellent document. I wanted to congratulate you guys and gals for working so hard on it.

CHAIRPERSON FROINES: Speak to the issue on the table.

PANEL MEMBER LANDOLPH: Well, I want to put that issue in context.

And I think I would go along with, for my own personal point of view, a conditional approval of most of the document, you know, what we've already reviewed which is pretty good, and it's not going to change except for the small comments they all make, and then deal with the issue of Paul at the next meeting, that he brought up and maybe have Charlie help EPA or however they want -- OEHHA -- or however they want to do that.

And I agree with your comments; it's difficult to make these determinations, but lay that out cleanly.

It doesn't have to be a long section. I would say three or four paragraphs would do it. Two pages would be fine, overkill maybe. You don't have to make

a tome out of it.

PANEL MEMBER BYUS: I don't think it's such a big issue, personally. I think it's important, but I don't think it's a big issue. It's going to be up to however people want to look at it, and I don't have a strong feeling one way or the other.

But I would like the panel -- I think it's important the panel reach a good consensus and everybody feel good about it. I think that is very important.

CHAIRPERSON FROINES: Charlie?

PANEL MEMBER PLOPPER: I agree with what you guys have said. I think it's a great document, and that my main concern would be that there isn't some little systematic problem like this that can then be used to undermine whatever findings you come up with the next time somebody says yeah, well, they picked the wrong time so it doesn't matter.

Let's just have a rationale, like Paul said, and we don't have to worry about it.

CHAIRPERSON FROINES: Can -- everybody's tiptoeing around the bush.

As the Chair, I am taking the position at this point that we won't take a vote on the document at this point, and we'll take the vote at the next meeting when

we have seen the document and everybody can unanimously approve it rather than sort of saying, well, we'll give it a tentative approval.

I think we should be clearer in our articulation than that. But I'm -- I can be beaten to death by Stan and others on this issues.

PANEL MEMBER GLANTZ: Okay. Well, the only thing -- I'm happy with that. But I just want to make sure as one of the Leads on this that the rest of the document is finished --

CHAIRPERSON FROINES: Yes.

PANEL MEMBER GLANTZ: -- subject to the few comments that were made here.

CHAIRPERSON FROINES: Yes.

PANEL MEMBER GLANTZ: So I'll work, and Joe -- we can work with Melanie to double-check all the last-minute little corrections, but that's put to bed.

The only outstanding issue is this point that Paul raised.

CHAIRPERSON FROINES: And --

PANEL MEMBER GLANTZ: And we'll have -- we had had drafted findings which, I guess, didn't get circulated. But we will also prepare a set of findings that will include this point that will be circulated to the panel well before the meeting too.

I just hope we can put this -- not have to wait months and months and months.

CHAIRPERSON FROINES: Everybody around this table -- I want to be clear -- everybody around this table wants this to be over. And there's no doubt about that.

(Laughter)

CHAIRPERSON FROINES: And secondly, I -- as the Chair, I strongly apologize to Martha and Melanie for delaying it one more time.

But I think in the long run everybody will feel better about the outcome if we can make one more half-hour-to-an-hour stab at it, and we'll be done with it.

And I'm really sorry that it didn't get done today, but the arguments that Paul raised I think have merit, and we should address them and then go forward.

I want this to be seen in the most positive light possible, if we can do that. Martha is nodding, so I get a little positive --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It depends on how extensive a justification you want. I mean we could do this in a year.

PANEL MEMBER BYUS: Two paragraphs.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Two years.

PANEL MEMBER BYUS: Two paragraphs.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Two paragraphs?

PANEL MEMBER BLANC: First you have to decide -- what I do want is a commitment in good faith that you are going to have an open mind that it might not be two years.

I don't want you just to walk out of here and write a de facto justification for why you're sticking at two years. I want you to look at it and to make your argument.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: When I said two years, I meant it could take two years to do the analysis.

PANEL MEMBER BLANC: No, no. Nobody is saying --

PANEL MEMBER BYUS: No, no, no.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Or, you know, we can look at -- I can tell you that lots of people have tried to make nice little charts comparing --

CHAIRPERSON FROINES: Melanie, I would like you to work out a meeting in two weeks to finish this, if you can.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

CHAIRPERSON FROINES: Two weeks to a month.

PANEL MEMBER BYUS: Take you maybe two days.

PANEL MEMBER GLANTZ: Okay. Well, I think Joe and I have this good sense of what people are looking for, you know. We'll work with Melanie. We'll bring in Charlie who actually knows what he's talking about, and we'll come up with something.

PANEL MEMBER PLOPPER: Uh-oh.

CHAIRPERSON FROINES: And I'm going to be reading the document as the person who signs it. So it's not just the two of you and Charlie. If you don't mind -- no disrespect intended, but I have to sign the thing.

PANEL MEMBER GLANTZ: Okay. So are we all done?

CHAIRPERSON FROINES: Are we done?

PANEL MEMBER BLANC: I move that we adjourn.

PANEL MEMBER LANDOLPH: Second.

* * *

(Thereupon the AIR RESOURCES BOARD SCIENTIFIC REVIEW PANEL meeting adjourned at 1:19 p.m.)

CERTIFICATE OF REPORTER

I, LINDA KAY RIGEL, a Certified Shorthand Reporter of the State of California, do hereby certify:

That I am a disinterested person herein; that the foregoing AIR RESOURCES BOARD SCIENTIFIC REVIEW PANEL meeting was reported in shorthand by me, Linda Kay Rigel, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this December 15, 2008.

LINDA KAY RIGEL, CSR
Certified Shorthand Reporter
License No. 13196