

MEETING  
STATE OF CALIFORNIA  
AIR RESOURCES BOARD  
SCIENTIFIC REVIEW PANEL

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## 1 P R O C E E D I N G S

2 --o0o--

3 CHAIRPERSON FROINES: We will formally start  
4 the meeting. This is the meeting of the Scientific  
5 Review Panel on toxic air contaminants. It's the  
6 meeting October 30th, 2008.

7 We have some problems with classes today.  
8 Stan has a class at 10 o'clock, I'm told; and Paul has  
9 to leave at 1 o'clock. So here's what we're going to  
10 do today.

11 We're going to start with the cancer potency  
12 factors so Stan can be here for the first hour. Then  
13 when he leaves, we'll switch over to manganese and  
14 acetaldehyde and formaldehyde.

15 And then Stan will be back for the afternoon  
16 discussion on the cancer potency factors.

17 PANEL MEMBER GLANTZ: I should be back around  
18 noon or a little before noon.

19 CHAIRPERSON FROINES: Talk into the  
20 microphone.

21 PANEL MEMBER GLANTZ: I'll be back by noon,  
22 probably a little before noon.

23 CHAIRPERSON FROINES: So we're all set,  
24 Melanie, for this major undertaking.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Okay. This is Melanie Marty from OEHHA. And  
2 this morning you're going to hear a presentation on our  
3 air toxics hot spots risk assessment guidelines going  
4 over the technical support document for cancer potency  
5 factors.

6 This is a revision of a document that already  
7 went through the public and peer review process and was  
8 reviewed by this panel several years ago, and what  
9 we've done now is updated the methodology a bit and --

10 CHAIRPERSON FROINES: Could you use the mic?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Sure. There we go.

13 We have updated the methodology a bit and come  
14 into compliance more with SB 25, which is the  
15 Childrens' Health Protection Act.

16 So I'm going to let staff take over. John  
17 Budroe, to my right, is going to be giving the overview  
18 of the presentation; and then, depending on time,  
19 you'll hear from Martha Sandy who is Chief of the  
20 Cancer Hazard Assessment Section in OEHHA.

21 Martha's group also had a statutory mandate to  
22 look at risk assessment for carcinogens and determine  
23 whether it's adequate to protect early life stages.

24 So the two programs dove tailed, and then  
25 this, the document you guys are reviewing, is the

1 result. So John --

2 CHAIRPERSON FROINES: I want to just make one  
3 comment at the outset for the panel's benefit. And  
4 that is, if you will remember, we originally selected  
5 five chemicals as representing substances that had  
6 increased risk for children.

7 And those -- I won't go through the chemicals,  
8 but I asked Melanie on the telephone yesterday, is  
9 there any reason why we now at this point have to limit  
10 the number of chemicals to five again? And the answer  
11 is no.

12 So to the degree that there is an evidentiary  
13 basis for identifying as having increased risk in  
14 children that we can proceed as we so choose. And so  
15 whether or not we limit ourselves to five is up to us.

16 So Melanie, go ahead.

17 STAFF TOXICOLOGIST BUDROE: Good morning. My  
18 name is John Budroe. I'm with OEHHA. The presentation  
19 title is Air Toxic Hot Spots Program Risk Assessment  
20 Guidelines: Technical Support Document For Cancer  
21 Potency Factors.

22 The timetable so far in the document, the TSD,  
23 or technical support document for describing available  
24 cancer potency factors, is being replaced by a new  
25 document, the technical support document for cancer

1 potency factors.

2 The draft was reviewed by Stationary Source  
3 Division of the Air Resources Board and CAPCOA in May  
4 and June of 2008.

5 There was a 60-day public comment period from  
6 June 23rd to August 22nd, 2008; and two public  
7 workshops on August 14 and 15 were part of the public  
8 comment process.

9 There's two main sections to the main part of  
10 the document, a section on selection of cancer potency  
11 factors of all the possible --

12 CHAIRPERSON FROINES: Can I just say one  
13 thing? I want to emphasize the fact that you had two  
14 public workshops. Because that question got raised in  
15 the comments with respect to an open forum with respect  
16 to the SRP.

17 But there have been public comments meetings,  
18 and I want that on the record.

19 STAFF TOXICOLOGIST BUDROE: One in northern  
20 California, one in southern California.

21 The main part of the document, first section,  
22 is selection of cancer potency factors. And this  
23 describes how, if there were several cancer potency  
24 values available from different programs, how a  
25 specific value was picked, and the cancer risk

1 assessment methodology section.

2 The major subsections under this were hazard  
3 identification, dose response assessment, early  
4 lifestage cancer potency adjustments, and the other  
5 source documents for cancer risk assessment guideline  
6 put out by US EPA and OEHHA.

7 There are also 11 appendices contained within  
8 the document. Appendix A is a lookup table containing  
9 unit risk and cancer potency values.

10 Appendix B is composed of chemical-specific  
11 information summaries.

12 Appendix C describes the toxicity equivalency  
13 factors, or TEFs, for determining unit risk in cancer  
14 potency factors for polychlorinated dibenzo-dioxins,  
15 dibenzofurans, and dioxin-like polychlorinated  
16 biphenyls.

17 Appendix D is a listing of toxic air  
18 contaminant documents.

19 Appendix E is a description of IARC and US EPA  
20 carcinogen classifications.

21 Appendix F describes asbestos quantity  
22 conversion factor from converting asbestos  
23 concentrations expressed in mass per volume of air to  
24 fibers per volume of air.

25 Appendix G lists procedures for revisiting or

1 delisting cancer potency factors by the program of  
2 origin.

3 Appendix H lists the exposure routes and  
4 studies used to derive cancer unit risks and slope  
5 factors.

6 Appendix I is a reprint of the paper assessing  
7 susceptibility from early life exposure to carcinogens  
8 by Barton, et al. from 2005, from Environmental Health  
9 Perspectives.

10 Appendix J is the document In Utero and Early  
11 Life Susceptibility to Carcinogens, the Derivation of  
12 Age-At-Exposure Sensitivity Measures. This document  
13 was authored by OEHHA's Reproductive and Cancer Hazard  
14 Assessment Branch, and Dr. Martha Sandy will be  
15 speaking to this later on in the meeting.

16 And finally, Appendix K is additions and  
17 corrections from prior document versions.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: This is Melanie Marty. I just want to make  
20 sure that everybody understood that there were no  
21 changes from Appendix A through H.

22 So you folks got what was new compared to the  
23 last document; that's why you're missing all these  
24 appendices. So we put that in the cover letter, but  
25 who reads cover letters?

1           PANEL MEMBER GLANTZ: That was a joke.

2           STAFF TOXICOLOGIST BUDROE: This document did  
3 a reevaluation of the risk assessment methodologies.  
4 It was intended to incorporate scientific developments  
5 in cancer risk assessment methodologies since the  
6 original guidelines were developed.

7           The previous guidelines were based on previous  
8 sources, the DHS cancer risk assessment guidelines from  
9 1985 and similar documents from US EPA in 1986.

10          US EPA produced new cancer risk assessment  
11 guidelines in 2005, and also in 2005 included  
12 supplemental guidance on children's cancer risk.

13          The changes in general guidance principles in  
14 this document, there is a revised hazard identification  
15 criteria. This is made more explicit than the previous  
16 version. Benchmark dose methodology is preferred over  
17 the linearized multi-stage model.

18          This document introduces age-dependent  
19 adjustment factors, or ADAFs, for exposures in infancy  
20 and childhood and suggests the use of models and  
21 case-specific data whenever possible, the use of  
22 mechanistic data when available and appropriate, and  
23 the preferred use of pharmacokinetic models for inter-  
24 and intraspecies extrapolation.

25          The previous guidelines mostly relied on the

1 linearized multi-stage or LMS model. It's assumed to  
2 be biologically based, and extended forms of the model  
3 can accommodate variable dosing and time-to-tumor data.

4 That's just a representation of the general  
5 form of the linearized multi-stage model. The potency  
6 estimate  $q1^*$  is the 95 percent upper confidence bound  
7 on the fitted value of  $q1$ .

8 The new guidelines will instead emphasize  
9 empirical models, primarily the benchmark method.

10 CHAIRPERSON FROINES: May I ask you a  
11 question? When you report values, risk values, are you  
12 going to report both the benchmark calculation as well  
13 as the linearized calculation so one can actually look  
14 and make comparisons between the two?

15 This is an extremely important policy change  
16 that you've made, and a lot of us have some queasiness  
17 about this process. And so we -- I think you need to  
18 be careful to fully demonstrate the efficacy of the new  
19 approach and the values therein.

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: We've reported both methods of derivation in  
22 full in all the cancer potency derivations which you've  
23 seen recently.

24 For instance, the nathalene and the  
25 ethylbenzene and things like that, we've made points of

1 presenting both of the methods for those.

2           There may come a point at which you or we  
3 decide that it's no longer necessary to do that, but we  
4 have currently a policy of presenting both.

5           CHAIRPERSON FROINES: Thank you.

6           PANEL MEMBER GLANTZ: Could I just pick up on  
7 that? I actually -- and maybe this is too detailed for  
8 right now -- but the report's actually a little  
9 ambiguous on that point.

10           CHAIRPERSON FROINES: Stan, can you put your  
11 mic closer?

12           PANEL MEMBER GLANTZ: Oh.

13           The report is a little ambiguous on that.  
14 Because if you -- I mean, I had the same concern. And  
15 if you look on page 24 of the report, the version that  
16 we were sent most recently in the green binder, in  
17 there you say that the multi-stage model isn't very  
18 good at low doses.

19           STAFF TOXICOLOGIST BUDROE: Mm-hmm.

20           PANEL MEMBER GLANTZ: And then on page 49, you  
21 say you're using it, and it's the preferred way.  
22 Unless I misread something.

23           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
24 SALMON: I think that -- tell me what's page 49, would  
25 you?

1 PANEL MEMBER GLANTZ: Here.

2 And then while you're looking at that, I had  
3 another question.

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: Oh, okay. I know what -- I think I know what  
6 this is.

7 The -- excuse me, the page 49 description is  
8 a -- is in the section where we're describing the  
9 different historical sources of potency numbers which  
10 are in the database of numbers.

11 And what we're saying on page 49 is that the  
12 Proposition 65 numbers have had, and in fact still  
13 have, the linearized multi-stage model as their  
14 preferred method.

15 So that section at the end is not saying what  
16 we are recommending as our current policy. It's  
17 describing what the existing programs have used and  
18 those programs, the sources of most of the numbers  
19 which currently appear in the database.

20 So that's why there's a difference between  
21 what's said on page 49 and what's --

22 PANEL MEMBER GLANTZ: Okay. Well, I think you  
23 want to clarify --

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

25 SALMON: We may need to clarify that somewhat in the

1 introductory section where we start describing the  
2 historical sources.

3 PANEL MEMBER GLANTZ: Yeah, you might, since  
4 there's -- it's just, when I read it, I thought there  
5 was a direct -- you might want to --

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
7 SALMON: Yeah.

8 PANEL MEMBER GLANTZ: -- make that point again  
9 when you're writing that.

10 CHAIRPERSON FROINES: And on my page 49 is an  
11 October 2008 version?

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
13 SALMON: Yes.

14 CHAIRPERSON FROINES: Is that the same one  
15 you're talking about?

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON: Yes, I think it is.

18 PANEL MEMBER GLANTZ: Yeah.

19 CHAIRPERSON FROINES: What -- where are you  
20 referring this? What paragraph? I'm missing it. I'm  
21 sorry.

22 PANEL MEMBER GLANTZ: You can tell him.

23 CHAIRPERSON FROINES: Sorry.

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
25 SALMON: Okay. Wait. I've got the wrong page 49.

1           Page 49 in the main document is what we need.  
2   And there's the statement in the middle of page 49.  
3   There's the statement of the standard multi-stage  
4   equation where the probability of cancer is one minus E  
5   to V, minus  $q_1$ ,  $q_0$  plus  $q_1 D$  et cetera, et cetera.

6           And the statement is made that the Crump  
7   linearized multi-staged polynomial was fit. And, you  
8   know, this -- the statement is, this is the linearized  
9   multi-stage model that's being used. So that's the  
10   statement which Stan was saying, hey, but you just said  
11   this isn't so good.

12           But I point out that on the -- you know, this  
13   section in fact starts on page 47 where it's described  
14   as the methods used in the Proposition 65 expedited  
15   cancer risk assessment derivations, which is a large  
16   group of potency values which were produced in fact by  
17   Martha Sandy's group, the Proposition 65 cancer group,  
18   several years ago.

19           But it's an important resource because it's --  
20   a large number of those potency values are actually in  
21   our table, so we need to describe how they were done.

22           And if you want more detail and exactly how  
23   all of that was done --

24           PANEL MEMBER GLANTZ: Well, I'm not -- I don't  
25   think you need more detail on how it was done, but I

1 really do think you need to clarify again right there.  
2 I mean most people are going to read this sort of the  
3 way I did, and it just seemed like a frank  
4 contradiction now that you explain it.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: Yeah.

7 PANEL MEMBER GLANTZ: You know, I -- but I  
8 think at this point right here you need to make that  
9 point again.

10 CHAIRPERSON FROINES: But I think, Stan, I  
11 think you and I are right insofar as there needs to be  
12 presented here or December 5th, whichever, the  
13 intellectual basis for the decision, not simply the  
14 procedural basis.

15 PANEL MEMBER GLANTZ: Yes. I agree.

16 The other thing -- and then -- we can come  
17 back to this later, but the other thing that sort of  
18 dawned on me as I was reading this is you say the  
19 linearized model is at low doses, but then some of  
20 these studies are done at high doses.

21 So when you get to it, at some point, I'd like  
22 to have some discussion, some explanation of when you  
23 can use the linearized model because the doses are  
24 quote low and when you have to use the full nonlinear  
25 model. You don't need to do that right now.

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: We can perhaps go into those details --  
3 perhaps John can run through what we have here, which I  
4 hope will introduce the idea, you know, why it is that  
5 the benchmark method is being proposed as a default at  
6 this point.

7 And we can go into more detail about that once  
8 we've --

9 PANEL MEMBER GLANTZ: No, I -- you can come  
10 back to it later.

11 CHAIRPERSON FROINES: Because there's also a  
12 literature that we are familiar with, that everybody in  
13 the room is familiar with, that Dale Hattis has written  
14 about low dose extrapolation as well. So that all this  
15 needs to fit together is all I'm really saying.

16 STAFF TOXICOLOGIST BUDROE: The new cancer  
17 guidelines will emphasize empirical models, primarily  
18 benchmark method, whereby you choose a mathematical  
19 function that provides the best fit to the observed  
20 dose response data.

21 A multi-stage polynomial is usually the best  
22 fit, and in this default case results tend to be very  
23 similar to the LMS method.

24 More plausible biologically based models have  
25 also been considered but are seldom used in practice.

1 Sample was cell proliferation models.

2 And the LMS method can still be useful,  
3 especially in situations where you have time-to-tumor  
4 data that can't presently be handled well using the  
5 benchmark method.

6 And this is a graphic representation of the  
7 benchmark dose method. This was done with US EPA BMDS  
8 software.

9 As said previously, the choice of model was  
10 based solely on the quality of fit. We frequently used  
11 the multi-stage polynomial. This graph, BMD is  
12 essentially ED10. That is the effective dose per ten  
13 percent tumor response. And BMDL is the LED10 or the  
14 lower 95 percent confidence interval on the ED10.

15 CHAIRPERSON FROINES: John, do you think --  
16 we're talking about cancer here, and we all know what  
17 the nature of chronic animal bioassays have  
18 historically been used for testing chemicals.

19 Is it your judgment that you're going to have  
20 a number of data points to be able to satisfactorily  
21 carry out these -- the benchmark approach? Because in  
22 traditional practice, the amount of data that you have  
23 to work with is so very limited that it worries me a  
24 little bit. Do you know what I'm saying?

25 STAFF TOXICOLOGIST BUDROE: Yes. And if the

1 benchmark dose method didn't fit well, then --

2 CHAIRPERSON FROINES: Then you'd defer to --

3 STAFF TOXICOLOGIST BUDROE: -- the backup  
4 default would probably be the LMS.

5 But there's been a number of recent documents  
6 turned out, for example, by Public Health called the  
7 PHG program where they have done -- analyzed tumor data  
8 sets using both methods, and the results done by the  
9 two methods tend to be pretty close.

10 I don't think there's been many, if any,  
11 examples where they've deviated greatly.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
13 SALMON: Yeah. The quality or quantity of data issue  
14 is exactly the same for the benchmark dose method as  
15 for the LMS method, and I would be the first to agree  
16 with you that the extent to which typical bioassay data  
17 actually constrain the shape of the dose response  
18 curve, you know, to say we know what it is, that's  
19 quite limited.

20 And we actually did do some studies. You  
21 know, we looked at that, for instance, when we were  
22 worrying about DHP and things like that.

23 We said how much does even a well-conducted  
24 bioassay which was specifically designed to  
25 quote/unquote demonstrate a non -- you know, a

1 nonlinear type of dose response, how much does that  
2 really constrain the shape of the dose-response curve?  
3 And the answer is not very much.

4           So this is one of the problems, and it's the  
5 reason why people have been in effect reduced to either  
6 applying a biologically based model on grounds  
7 completely unrelated to the actual data in fact, just a  
8 supposition that this is how cancer goes; or,  
9 alternatively, using a default which has been found to  
10 make a decent job of fitting most cancer data sets, and  
11 then apply the linear extrapolation procedure as  
12 specified in this version of the benchmark dose models  
13 who deal with the low dose case.

14           So in that sense, I agree with you. But we're  
15 not doing anything which is either better or worse than  
16 the previous case in this respect.

17           PANEL MEMBER GLANTZ: I agree.

18           PANEL MEMBER BYUS: I have a question in that  
19 regard. It just may be my incomplete understanding.  
20 But is the quality of -- the poorer quality of the data  
21 in animal bioassays is at the lower dose, correct? I  
22 mean, there is just usually less numbers of tumors?

23           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
24 SALMON: Yes, it's essentially a statistical --

25           PANEL MEMBER BYUS: And so -- so my question

1 is: In the linearized versus the benchmark dose,  
2 doesn't the -- does the benchmark dose rely more on the  
3 lower dose values than the linearized? That's my  
4 question.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: Not really, no. No. Both of them are  
7 designed to provide a --

8 PANEL MEMBER BYUS: Because it seems to me if  
9 you extrapolate from the linearized, it's less  
10 important because you're extrapolating to the lower  
11 doses so the lower dose data is of less importance in  
12 moving the curve from the extrapolation, whereas if you  
13 do it from the benchmark dose you're --

14 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

15 SALMON: No.

16 PANEL MEMBER BYUS: -- you're valuing that  
17 data equally. That's just my perception.

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: The linearization procedure also weights the  
20 lower end of the curve.

21 PANEL MEMBER BYUS: Equivalently.

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: Not necessarily exactly the same. But  
24 somewhat similarly.

25 PANEL MEMBER BYUS: Just my perception then.

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: I mean, what the linearization process does  
3 essentially is it doesn't throw out -- it minimizes the  
4 attention that you pay --

5 PANEL MEMBER BYUS: Exactly.

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7 SALMON: -- to the higher order terms --

8 PANEL MEMBER BYUS: So it --

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: -- which are the ones which provide the --

11 PANEL MEMBER BYUS: Right.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: -- differential phase of the higher dose.

14 PANEL MEMBER BYUS: Well, it's almost -- I  
15 mean my -- the way I -- the holistic way I'm looking at  
16 this, which is nonmathematical. If I look at the math  
17 long enough.

18 It just seems like, though, in the benchmark  
19 dose that the weaker data is weighted -- weaker meaning  
20 the lower dose data -- is weighted more than in the  
21 linearized.

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: No. That isn't in fact the case.

24 PANEL MEMBER BYUS: All right. You do see  
25 what I'm -- do you guys get what I'm saying?

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: The lower dose region of the fitted curve is  
3 determined by all the points in the data.

4 PANEL MEMBER BYUS: All right.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: It's not a Safarjan fit-fit.

7 PANEL MEMBER BYUS: Okay.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: It's actually a -- you know, it's one of these  
10 likelihood fits across all the data. So all the data  
11 are included in the fit.

12 PANEL MEMBER BYUS: Okay.

13 PANEL MEMBER GLANTZ: I'm sitting here  
14 listening to this and -- I mean it's hard for me to --  
15 I mean I don't see why you're saying one end of the  
16 curve or the other is more heavily weighted.

17 Because you use the linearized multi-stage  
18 model to get the curve and generate the confidence  
19 interval. So I think all the data is weighted equally.

20 PANEL MEMBER BYUS: That isn't what I mean. I  
21 guess I think that in the linearized model I just think  
22 about extrapolating from high to low doses.

23 And so -- perceptually then, the high dose  
24 defines the curve more. But that's just maybe the way  
25 I'm thinking -- you follow me? Because a high to low

1 dose extrapolation --

2 PANEL MEMBER GLANTZ: Well, except that --

3 PANEL MEMBER BYUS: Whereas with a benchmark,  
4 it isn't.

5 PANEL MEMBER GLANTZ: Well, I don't know. I  
6 mean, it's just -- it just seems to me that you're  
7 using the -- and correct me if I'm wrong, but my  
8 understanding of this is that you're using the low dose  
9 range and the linear multi-stage model to get the  
10 overall curve and the confidence interval, and then  
11 you're taking the confidence interval at the low dose  
12 that was determined based on the full range of the day,  
13 and you're simply saying from there down, I'm assuming  
14 it's --

15 PANEL MEMBER BYUS: Okay.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: Yes. That is correct, yes.

18 PANEL MEMBER GLANTZ: I don't know. It's not  
19 obvious to me which is getting weighted more. Maybe  
20 Gary has something.

21 PANEL MEMBER FRIEDMAN: Well --

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: Just as a matter of detail, the model which is  
24 fit in the benchmark dose method is the multi-stage  
25 model, not the linearized multi-stage model.

1           The linearized bit is the actual procedure of  
2 pulling out the q1 term and developing an upper bound  
3 on it and calling that the low dose slope.

4           So the linearized bit is the actual process of  
5 making a model-based extrapolation to zero. So what  
6 you're fitting for the benchmark dose, in terms of  
7 being nitpicky, it's the multi-stage model as  
8 opposed --

9           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: But I think that --

11           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

12 SALMON: Mathematically, the effect is the same.

13           PANEL MEMBER GLANTZ: Of the polynomial --

14           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

15 SALMON: Yes.

16           PANEL MEMBER GLANTZ: Oh, okay.

17           PANEL MEMBER BYUS: That's better.

18           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: The benchmark is actually set using the fitted  
20 polynomial, not just the q1, and that is --

21           PANEL MEMBER BYUS: I got it.

22           PANEL MEMBER GLANTZ: Okay.

23           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

24 SALMON: -- actually the significant --

25           PANEL MEMBER BYUS: You're right. Thank you.

1           CHAIRPERSON FROINES: But the next slide is  
2 going to -- I mean, obviously, the concern is  
3 nonlinearities, and you actually address the linear low  
4 dose issue coming up. Am I correct?

5           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: Yeah.

7           STAFF TOXICOLOGIST BUDROE: You are in fact  
8 correct.

9           For many carcinogens, data support the  
10 assumption of low dose linearity. For carcinogens of  
11 unknown mechanism, low dose linearity is assumed as a  
12 policy default, and in putative nongenotoxic  
13 carcinogens may exhibit low dose linearity.

14           In these cases, potency slope is estimated by  
15 linear extrapolation from the LED10 to zero. For  
16 carcinogens where threshold mechanism has been shown,  
17 an uncertainty factor is applied to the LED10 to  
18 estimate a safe level.

19           However, I'm not aware of any carcinogens that  
20 have been evaluated by OEHHA yet where this has been  
21 shown.

22           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: There are a couple of examples where we've  
24 used that for comparison.

25           CHAIRPERSON FROINES: There are? Could you

1 give one example?

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: One is the carcinogens for which a threshold  
4 approach was developed for comparison is butylated  
5 hydroxyanisole. And in fact, that calculation was also  
6 done for MTBE, for comparison purposes, not saying this  
7 is the way it should be done.

8 CHAIRPERSON FROINES: Okay. Go ahead.

9 STAFF TOXICOLOGIST BUDROE: The new guidelines  
10 will assume that potency scales between species as  
11 three-quarter power of body weight. This used to be  
12 the two-thirds power body weight that was used, but  
13 most regulatory programs have changed.

14 This change is based on metabolism  
15 considerations and some data on chemotherapeutic drugs.  
16 Data on range of carcinogens show body weight index  
17 varies between 0.5 and 1.3 depending on the type of  
18 chemical and the mechanism involved.

19 With regard to risk in infants and children,  
20 risk is proportional to the exposure duration to the m  
21 power. The time exponent, or m, is three or above.  
22 This applies to most carcinogens, although the less so  
23 for some late-stage carcinogens.

24 But this part of the multi-stage model is  
25 pretty well established and based on empirical data;

1 therefore, exposures early in life have a  
2 disproportionate effect on a lifetime cancer risk.  
3 This has been called by some the shelf-life effect.

4 CHAIRPERSON FROINES: Could you go back.

5 PANEL MEMBER BYUS: I -- sorry.

6 CHAIRPERSON FROINES: Go ahead.

7 PANEL MEMBER BYUS: You mean constant exposure  
8 rather than intermittent time?

9 Because the whole -- there is this whole  
10 interesting field of what happens when you stop  
11 exposure to the cancer risk vis-a-vis cigarette smoke  
12 and other things, which is an other interesting  
13 phenomenon. So you mean constant exposure to the --

14 STAFF TOXICOLOGIST BUDROE: Correct.

15 PANEL MEMBER BYUS: Okay. Not like a sum over  
16 some amount of time. Okay. Assuming constant  
17 exposure.

18 CHAIRPERSON FROINES: We're going to talk more  
19 about this particular issue, aren't we? Over time,  
20 today and --

21 STAFF TOXICOLOGIST BUDROE: Yes.

22 CHAIRPERSON FROINES: -- at the next meeting?

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: I'm sorry. Ask that again?

25 CHAIRPERSON FROINES: This issue is going to

1 get greater attention later.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Absolutely.

4 CHAIRPERSON FROINES: Because it's really  
5 quite crucial.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: In gory detail.

8 CHAIRPERSON FROINES: Because this is your  
9 overview, and then we're going to get into the science.

10 STAFF TOXICOLOGIST BUDROE: Yeah, the  
11 presentation by Dr. Sandy will cover this in great  
12 detail.

13 CHAIRPERSON FROINES: I think this is a  
14 fundamentally important issue that you're raising here.

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
16 SALMON: I think one of the things also is that we're  
17 needing to make a distinction between what Dr. Sandy  
18 can present in -- you know, it's the science which  
19 you're going to hear soon, which is an exploration of  
20 what data are out there versus what we have to come up  
21 with in this present document which, you know, the main  
22 document which is essentially a policy-based default  
23 which is consistent with that science.

24 But of course one of the problems, as you will  
25 hear, there isn't an enormous universe of data

1 available to evaluate that.

2 But we think that what we recommend in the  
3 main document as a policy default is consistent with  
4 what data are available that are out there. So that --  
5 to some extent, there's two sides to the discussion  
6 that we need to have about these effects.

7 STAFF TOXICOLOGIST BUDROE: Young animals and  
8 humans do show enhanced sensitivity to some  
9 carcinogens. This is independent of the shelf-life  
10 effect, may target --

11 PANEL MEMBER FRIEDMAN: Excuse me. Could you  
12 explain what you mean by shelf-life effect?

13 STAFF TOXICOLOGIST BUDROE: The shelf-life  
14 effect applies to the fact that risk is proportional to  
15 exposure duration.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON: So exposure --

18 STAFF TOXICOLOGIST BUDROE: So if you have an  
19 exposure early in life, you have a greater effect, more  
20 time for that effect to become manifest.

21 But there's -- infants and children have  
22 susceptibilities to carcinogens, greater  
23 susceptibilities compared to adults, that go beyond the  
24 shelf-life effect in some cases.

25 Different sites are targeted, they have

1 differences in metabolism or cell proliferation  
2 compared to adults, and the later stages of fetal  
3 development can show special sensitivities.

4 CHAIRPERSON FROINES: Can I ask Gary a  
5 question? Are you happy with the term shelf-life?

6 PANEL MEMBER FRIEDMAN: No. I was going to  
7 say, if you could use the words that you use to explain  
8 it, that would be helpful. I mean that's sort of  
9 jargon that I didn't understand, and I don't know how  
10 many people understand.

11 It sounded to me like it meant that somehow  
12 this carcinogen is kept in storage for a while; and  
13 then after it's been there a while, it's more effective  
14 so . . . Shelf-life always seems to apply to things  
15 before they get into the body rather than after.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
17 MARTY: Okay. It's definitely risk assessor's jargon,  
18 so we can purge it if you want.

19 Martha just told me that she has four slides  
20 on this issue of time, the probability of tumor  
21 increasing to the third power of time. So if you want  
22 that now or later -- Joe?

23 PANEL MEMBER LANDOLPH: Yeah, you know, I  
24 could make a suggestion because I feel the same way. I  
25 don't like that word at all.

1           If you called it expression time, then  
2 automatically it pops into my brain the expression time  
3 for mutagenesis curves and all, and it's much more  
4 clear what you're referring to.

5           So if you call it a lengthened expression time  
6 rather than shelf-life, I think that makes it much more  
7 clear for me.

8           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
9 MARTY: It came about from discussing it with people  
10 who are not necessarily at the level of sophistication  
11 as this panel.

12           But in terms of saying -- if I'm exposed to a  
13 carcinogen today, it doesn't matter nearly as much as  
14 if a one-year-old is exposed to the same level of  
15 carcinogen. So because I'm not going to be around to  
16 manifest the tumor whereas the one-year-old will have a  
17 long time to live before the --

18           CHAIRPERSON FROINES: You want my opinion? My  
19 opinion is similar to everybody else's. Which is I  
20 think 20 years from now when we're making -- we're  
21 still going to be getting questions. Which is I think  
22 20 years from now when we're meeting you're still going  
23 to be getting questions about what is the damn  
24 shelf-life.

25           And when you have something that never becomes

1 understandable, then that's a term that you probably  
2 want to discard for something that human beings  
3 actually can connect to.

4 PANEL MEMBER GLANTZ: I had the same reaction.  
5 I finally figured out you probably meant how long the  
6 cage with the rat was sitting on the shelf.

7 (Laughter)

8 PANEL MEMBER GLANTZ: It really -- I was  
9 wondering, is this like a technical term of art? But  
10 if it's jargon, I mean.

11 STAFF TOXICOLOGIST BUDROE: We could revise  
12 the document to provide a better descriptor.

13 PANEL MEMBER GLANTZ: You can call it the  
14 Froines Number.

15 PANEL MEMBER BLANC: Wait, wait, wait, wait.  
16 Just one small point.

17 There are two separate issues. One, if this  
18 is a jargon term that hasn't appeared in print and that  
19 you are inadvertently promoting by putting it in print;  
20 and I would say -- and I would not have it appear  
21 repetitively in the document.

22 However, if there is in print use of the  
23 jargon term, I would refer to it in one sentence, just  
24 so that the reader knows that you are aware of that  
25 literature, so you won't be using the term: Some have

1 used the term blah, blah, blah; we won't be using that  
2 term.

3 Because you do want the reviewers to know that  
4 you're aware, but that's only if it's out there. If  
5 it's not out there, just don't use it.

6 CHAIRPERSON FROINES: Joe?

7 PANEL MEMBER LANDOLPH: Yeah. In fact of  
8 clarity, if you said expression time or latency, I  
9 think that would make it really clear to us.

10 PANEL MEMBER GLANTZ: Yeah. I like latency,  
11 actually, better than expression.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: I'm not sure. Latency --

14 PANEL MEMBER GLANTZ: Better term.

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

16 SALMON: -- has been used in different ways by  
17 different people. I would regard that as a bit of a --

18 CHAIRPERSON FROINES: Andy --

19 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

20 SALMON: Weasel word.

21 CHAIRPERSON FROINES: -- I don't think latency  
22 is exactly what you're implying.

23 PANEL MEMBER LANDOLPH: I think it's lifetime  
24 of life years available for the carcinogen to take  
25 effect.

1           PANEL MEMBER GLANTZ:  It's the time -- I guess  
2  it would be the time at risk.

3           PANEL MEMBER BLANC:  It is two things.  It is  
4  latency in part.  If the exposure is not continuous.  
5  And it is duration of exposure plus latency if it is  
6  continuous, so it's got two aspects to it that I'm sure  
7  will be explained.

8           PANEL MEMBER HAMMOND:  I agree.  I think the  
9  problem is it actually has different meanings; and  
10 that's not a good term to have then, to have these  
11 different meanings.

12           Shelf-life to me implies some of these  
13 chemicals will just decay -- and maybe you mean that --  
14 and others won't.  Because it's like shelf-life, a food  
15 thing, you know.

16           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON:  Absolutely not, no.

18           PANEL MEMBER HAMMOND:  So I do think the  
19 discussion here points out that it's a term that  
20 doesn't have a clear meaning.  Think hard about what  
21 you mean by it so that you're conveying that.

22           CHAIRPERSON FROINES:  Peter, are you ready?

23           MR. MATHEWS:  Yes.

24           CHAIRPERSON FROINES:  Then we should take a  
25 ten-minute break because the court reporter has

1 arrived.

2 PANEL MEMBER GLANTZ: I'm going to have to  
3 leave in ten minutes.

4 CHAIRPERSON FROINES: Then no. Then let's  
5 wait till Stan has to leave. I'm sorry. Let's  
6 continue. Good point.

7 Go ahead, John.

8 STAFF TOXICOLOGIST BUDROE: Okay. This  
9 document will introduce the use age dependent  
10 adjustment factors, or ADAFs, for exposures. Exposures  
11 before two years of age, a tenfold adjustment will be  
12 implemented. For two through 15 years of age, a  
13 threefold adjustment will be implemented. And at  
14 16 years of age or more, no adjustment.

15 And I have an example on the next slide of how  
16 these factors are actually used. The adjustment  
17 factors applied to lifetime risk estimates using  
18 standard potency values for exposures during the  
19 specified time periods.

20 One major difference in use between us and  
21 US EPA: US EPA applies these for carcinogens acting by  
22 a mutagenic mode of action only; OEHHA applies these  
23 factors for all cases except where there is contrary  
24 evidence.

25 PANEL MEMBER BLANC: And do you mean from

1 birth to two years of age?

2 STAFF TOXICOLOGIST BUDROE: Correct.

3 PANEL MEMBER BLANC: And so in utero exposures  
4 are handled how?

5 STAFF TOXICOLOGIST BUDROE: They are not.  
6 They are currently totally ignored by US EPA. We're  
7 looking into this, but we can't recommend a default  
8 approach at this time.

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
10 SALMON: There's some more data on specific examples of  
11 what happens with in utero exposures in Martha Sandy's  
12 presentation.

13 PANEL MEMBER BLANC: That means you won't be  
14 using any adjustment at all for in utero exposures, so  
15 it will be treated as an adult exposure.

16 CHAIRPERSON FROINES: I'm sorry; I'm missing  
17 what Paul's saying.

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
19 SALMON: They're not considered.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
21 MARTY: It's actually not even considered in risk  
22 assessment. So we are looking at ways to adjust that.  
23 I mean, if you applied a ten X to the nine months which  
24 is an option that, you know, we could consider, in the  
25 end it doesn't make a huge difference in the final risk

1 number anyway, as you'll see in a minute.

2 But it is definitely an issue.

3 PANEL MEMBER BLANC: It will have to -- let me  
4 ask another question then in a different way. How do  
5 you handle -- is there a place in the document where  
6 that limitation is acknowledged?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Yes.

9 PANEL MEMBER BLANC: And perhaps at some point  
10 you could present the wording just so we see that, or  
11 tell us the page number so we don't miss it, and see if  
12 it's appropriate.

13 CHAIRPERSON FROINES: Melanie, this is  
14 actually quite an important issue when you think about  
15 it. Because one's homeostasis changes with time,  
16 obviously, and the assumption -- and so you're trying  
17 to get at changes that are occurring by various  
18 adjustment factors. And I guess you simply don't have  
19 the data to do better than that.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Well, that's pretty much it in a nutshell.

22 When you see the data that Martha and Claire  
23 and Rajpal will be presenting, you'll see that it --  
24 the postnatal exposures, it's a little clearer that you  
25 have for many chemicals increased sensitivity,

1 increased susceptibility.

2           It's a little less clear for prenatal  
3 exposure. And it's really very complicated because it  
4 depends on metabolism capability of both the mom, the  
5 placenta, and the fetus. It's really very complex.

6           So we have chosen at this point not to weight  
7 prenatal exposures when we're doing these risk  
8 calculations. To date, no one really considers  
9 prenatal exposure when you do the routine risk  
10 assessments that we've been doing. It's a 70-year  
11 lifetime starting at birth, so.

12           CHAIRPERSON FROINES: Yeah. We can't continue  
13 with that approach in the future, obviously.

14           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
15 MARTY: But we will have more discussion on that.

16           CHAIRPERSON FROINES: It's scientifically so  
17 invalid.

18           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
19 MARTY: We'll have more discussion of that so you can  
20 see. And, you know, if you think we should be doing  
21 something different, please tell us.

22           CHAIRPERSON FROINES: Okay.

23           PANEL MEMBER BLANC: We're going to come back  
24 to it, so we'll see.

25           STAFF TOXICOLOGIST BUDROE: Okay. On this

1 slide is an example of ADAF use. Given the  
2 hypothetical carcinogen with a potency of 2 mg/kg day,  
3 exposure of .0001 mg/kg day. If there's no adjustment  
4 for age factors, lifetime risk is potency times dose  
5 for a 70-year lifetime risk. You'd be looking at a  
6 risk of two times ten to the minus four with the use of  
7 ADAFs where the lifetime risk is potency times dose  
8 times the appropriate ADAF times the appropriate  
9 fraction of lifetime. The 70-year lifetime risk would  
10 be 3.3 times ten to the minus four. So for a 70-year  
11 lifetime risk, you're looking at approximately 1.5-fold  
12 higher risk.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: I'd like to add in a comment here, and that is:  
15 On the exposure side of things, we'll be presenting a  
16 document to you later on in -- well, 2009, that looks  
17 at age-specific exposure factors that play into the  
18 final risk calculation.

19 So in fact, in the end, it is going to be more  
20 than a 1 1/2-fold increase in lifetime risk because  
21 infants especially tend to have higher intake rates of  
22 air , food, water, dust, breast milk, et cetera.

23 PANEL MEMBER GLANTZ: So are you saying that  
24 next year we're going to come back to this and tweak  
25 the whole approach?

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: No. We're just going to talk about the  
3 exposure side of the equation rather than just the --

4 PANEL MEMBER GLANTZ: Oh, okay.

5 PANEL MEMBER BLANC: Can you go back to that  
6 slide for just one second? Thanks.

7 PANEL MEMBER LANDOLPH: You know, while we're  
8 on this slide, I just want to say I really like this  
9 slide. It's so clear, and I want to congratulate you  
10 on it. I would recommend you put it in the document  
11 somewhere. It's brutally clear. Very nice.

12 PANEL MEMBER HAMMOND: I would point out we  
13 all know there are uncertainties in all of these  
14 things, and I wonder if it's worth -- although it's  
15 supportive of what you've been doing, I wonder if it's  
16 worth going to all that effort if it doesn't increase  
17 the factor of two and even, despite the exposure things  
18 you're adding, that would make any difference. I mean  
19 that's still going to -- I mean the exposures still  
20 will be there.

21 CHAIRPERSON FROINES: Kathy put your mic  
22 closer.

23 PANEL MEMBER HAMMOND: Should I say that  
24 again?

25 CHAIRPERSON FROINES: I just can't hear.

1           PANEL MEMBER HAMMOND: Do you want me to say  
2 that again?

3           CHAIRPERSON FROINES: Please.

4           PANEL MEMBER HAMMOND: Given the concerns and  
5 trying to make estimates about this, which are always  
6 challenging and we understand there are errors around  
7 them, I sometimes think in a situation like that, going  
8 to all that trouble, if it makes less than a factor of  
9 two difference, it's going to -- is it really worth it?

10           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
11 MARTY: Well, there's a couple of issues there. One is  
12 that we really wanted to see what difference it made.

13           PANEL MEMBER HAMMOND: Right.

14           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
15 MARTY: So that you can't know that till you do it. So  
16 that's one issue.

17           The other issue is, we feel it is important to  
18 include that. Right now, we're just proposing policy  
19 defaults. Hopefully research centers will be  
20 stimulated, will get some more specific data which will  
21 help in the long run be a little more accurate in our  
22 estimates.

23           Then the other issue is we have, in terms of  
24 the application, many times an air district will say,  
25 well, I have a project that's going to go on for five

1 years.

2           So we used to say, well, you have to do a  
3 70-year exposure estimate and a 70-year cancer risk  
4 because we didn't want them compacting 70 years' worth  
5 of risk into five years.

6           So now, we're actually going to make them look  
7 at it as if you have children, because usually you do.  
8 It's next to a residential area; that's why a district  
9 is worried about it.

10           And so we're going to apply the cancer  
11 weighting factors from zero to five years, zero to two,  
12 and so that risk assessment will be considerably  
13 bigger.

14           STAFF TOXICOLOGIST BUDROE: So OEHHA's cancer  
15 risk assessment guidelines will follow US EPA's  
16 guidance in general. You may consider using additional  
17 adjustment factors. For example, for reproductive  
18 system cancers during adolescence on a case-specific  
19 basis.

20           CHAIRPERSON FROINES: Can I just make one  
21 comment? Without going into great detail. This slide  
22 makes me very nervous. When you say that you are  
23 following EPA's guidance in general, that makes my  
24 heart flutter.

25           (Laughter)

1           CHAIRPERSON FROINES:  And I don't have to  
2 explain that to anybody in this room.

3           PANEL MEMBER GLANTZ:  Fortunately, the people  
4 who deal with arrhythmias are in this building.

5           CHAIRPERSON FROINES:  What?

6           (Laughter)

7           PANEL MEMBER GLANTZ:  I said fortunately the  
8 people who deal with arrhythmias are in this building.

9           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
10 MARTY:  Let me qualify that.

11           We looked at their analysis of the available  
12 data on potency by age and exposure, and Martha Sandy's  
13 group under Lauren Zeise did their own analysis.  So we  
14 ended up coming to the same general conclusions, that  
15 we should be weighting for age at exposure.  So in that  
16 sense, we are on the same page with US EPA.

17           But as you'll see, we're applying it to all  
18 carcinogens; and they have dug themselves a deep hole  
19 trying to apply it to carcinogens that quote have a  
20 mutagenic mode of action, which they are finding it  
21 impossible to define.

22           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
23 SALMON:  I hope we will by the end of the presentations  
24 have made it clear that when we say we're following  
25 US EPA we mean we agree with them rather than we're

1 doing what we're doing because it's what they're doing.

2 Is that a reasonable distinction?

3 CHAIRPERSON FROINES: I might have done this  
4 strategically differently. I might have gone through  
5 the science and then drawn whatever conclusions you  
6 wanted to make rather than starting out with we're  
7 following EPA.

8 And you realize what that can -- you know what  
9 everybody's going to worry about. So that Martha's  
10 work -- the science is really what we want to see so  
11 that we're not left with a high degree of insecurity on  
12 whether or not --

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
14 SALMON: We aim to fill that deficiency.

15 CHAIRPERSON FROINES: Yeah. It's very, very  
16 important, because we don't want to be in lockstep.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
18 SALMON: That's absolutely not what we're saying.

19 We're saying we've come to a similar  
20 conclusion to US EPA, not that we're doing it because  
21 that's what they're doing.

22 PANEL MEMBER HAMMOND: Right. But I think  
23 what John is saying is that the way that it's presented  
24 sounds like you start with EPA and then you make a few  
25 modifications.

1           But in fact, what I think I'm hearing you say  
2 is you started with science, you did this  
3 independently, came up with ideas; and in the end,  
4 then, you went back and looked at how that compared to  
5 EPA and those were quite similar.

6           But those really have very different  
7 implications.

8           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Mm-hmm.

10          PANEL MEMBER HAMMOND: Which is that route.

11          STAFF TOXICOLOGIST BUDROE: Okay. ADAFs will  
12 be applied to risk assessments except where the data  
13 specifically show otherwise. This will not be  
14 determined -- repeat, not -- of mode of action  
15 determination.

16          For example, a quote mutagenic mode of action.  
17 And as stated earlier, with regard to exposures in  
18 utero, which are currently ignored by US EPA, OEHHA is  
19 looking into this but cannot recommend a default  
20 approach at this time.

21          And to summarize, application of infant- and  
22 children-specific factors, the risks from lifetime  
23 exposures are not greatly changed; however,  
24 implementation at the ADAFs could substantially  
25 increase cancer risk from limited duration exposures

1 where children are present.

2           Increased intake rates for infants and  
3 children will also increase calculated risk, and this  
4 will be coming in the forthcoming exposure risk  
5 assessment TSD.

6           With regards to methods for calculating  
7 potency factors, the methodological changes outlined in  
8 this document probably won't make a big difference.  
9 What would be more likely to make a major difference  
10 would be new tumor data sets.

11           And finally, potency factors will not change  
12 immediately, but SB 25 reviews are ongoing.

13           That includes concludes the presentation.

14           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
15 MARTY: Okay. I think because of the time constraints  
16 that we discussed earlier we should probably segue over  
17 to the RELs now after further questions.

18           PANEL MEMBER LANDOLPH: Just one second before  
19 you do that. That discussion on the benchmark dose  
20 method versus the linearized multi-stage method I  
21 thought was very good that the panel had with you.

22           If possible, I would recommend that you try  
23 and capture the clarifying points in maybe a half a  
24 page, less than a page, just so it's very, very clear  
25 to anybody that reads this document all the

1 ramifications of that discussion. Thank you.

2 CHAIRPERSON FROINES: Kathy?

3 PANEL MEMBER HAMMOND: Were you planning to --  
4 based on the comments here, were you planning to add  
5 into the document the example you gave for the  
6 lifetime?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
8 MARTY: Yes.

9 PANEL MEMBER HAMMOND: So if you do that, I  
10 would suggest that you have two examples and one that  
11 you work through that's the 70-year one and the other  
12 one where the exposure is just to a child for five  
13 years, and make that very explicit.

14 STAFF TOXICOLOGIST BUDROE: That's an  
15 excellent suggestion.

16 PANEL MEMBER BLANC: Just some quick algebra  
17 or multiplication, actually.

18 When I did it as a 70.9-year individual and  
19 with 2.9 years of tenfold increased risk, then the  
20 potency factor, instead of going from 2 to 3.3, it went  
21 to 2 to 3.5. In other words, a 150 percent increase.

22 Just so it -- one person's trivia might not be  
23 another's. Just so you know.

24 CHAIRPERSON FROINES: Gary.

25 PANEL MEMBER FRIEDMAN: Are you suggesting

1 that we defer questions that we have about other parts  
2 of this document till later, or do you want to deal  
3 with them now?

4 CHAIRPERSON FROINES: I think Stan's gone, and  
5 he's the Lead person with Joe on this topic, and so we  
6 were going to take this up after we did the REL  
7 discussion when Stan comes back.

8 PANEL MEMBER BLANC: So we're still going to  
9 have a ten-minute break now.

10 CHAIRPERSON FROINES: Yeah. We're going to  
11 take a ten-minute break because also, Gary, I don't  
12 think you were here yet, but Paul also has to leave in  
13 the afternoon so that we've kind of got -- I think we  
14 really do want Stan here for the discussion. Because  
15 he's the most -- he and Joe are the most familiar with  
16 it.

17 PANEL MEMBER FRIEDMAN: Actually, I was hoping  
18 I could bring this up before he left. But since he's  
19 gone, I'll be happy to do it later.

20 CHAIRPERSON FROINES: Okay. So let's take a  
21 ten-minute break.

22 I think, Melanie, this discussion, there was a  
23 lot of generalities and some specificity, so I don't  
24 know if the document needs to reflect any of that. But  
25 my current view is that as issues like this that are

1 methodologic in nature get raised, it's -- it is useful  
2 for you to add sections to the document, albeit brief,  
3 so that it shows the input of the panel in terms of the  
4 scientific questions. Does that make sense, what I'm  
5 saying?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
7 MARTY: Yes.

8 PANEL MEMBER LANDOLPH: We don't necessarily  
9 mean the credit, but just the fact that this issue came  
10 up and, you know, just put the question in and, you  
11 know, how you would deal with it. Or do you think we  
12 do need the credit?

13 CHAIRPERSON FROINES: No.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
15 MARTY: We try to do that normally.

16 CHAIRPERSON FROINES: And I don't think you  
17 need to put in the part about my saying that I don't  
18 trust EPA. So you can modulate some of that.

19 (Laughter)

20 CHAIRPERSON FROINES: Ten-minute break.

21 (Recess)

22 CHAIRPERSON FROINES: We're switching topics,  
23 and we are going to go directly to manganese, which is  
24 quite a new document.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Okay. Just to get everybody on the same page,  
2 you'll remember from the last couple of meetings we had  
3 a lot of discussion about primarily two of the  
4 Reference Exposure Level summaries, manganese and  
5 acetaldehyde; and then there are minor changes to a few  
6 more, and no changes to some.

7 So we're just going to really present the  
8 changes, not everything about it.

9 CHAIRPERSON FROINES: Melanie, I need to raise  
10 one administrative issue with the panel before you  
11 start.

12 We have gotten a set of comments in from  
13 various members of the public on manganese that went to  
14 the panel, actually. And it's my position, and I would  
15 hope to convince the panel, that any comments that come  
16 should go to OEHHA first -- should go to ARB, then  
17 OEHHA, you write responses, and then they came to the  
18 panel.

19 In other words, that no comments come directly  
20 to the panel. And we should set like a two-week time  
21 period in which that occurs so that we have an orderly  
22 process and, as Paul pointed out, we have the  
23 opportunity to have your input prior to our seeing the  
24 document.

25 So I guess what I'm saying is: Does the panel

1 generally agree with that view?

2 PANEL MEMBER FRIEDMAN: Well, I agreed with  
3 that. And I expressed it to Jim Behrmann, but he  
4 explained that there's some provision -- I don't know  
5 whether it's a law or what -- that allows people during  
6 the last two weeks before our meeting to send comments  
7 directly to us. So I don't know if we have control  
8 over that.

9 CHAIRPERSON FROINES: No, no. They can send  
10 them to us. There's nothing to prohibit that.

11 We, however, can set procedural guidelines for  
12 how we want this panel to operate. That's up to us.  
13 We don't need regulations or laws or -- and, you know,  
14 announcements from the mount.

15 We should have the option to set procedural  
16 guidelines for how this panel is going to run, and  
17 that's what the rules are going to be. If somebody  
18 wants to send us something yesterday for today, we just  
19 will ignore it.

20 PANEL MEMBER FRIEDMAN: Well, I -- I don't  
21 know --

22 CHAIRPERSON FROINES: We have the option to  
23 ignore it.

24 PANEL MEMBER FRIEDMAN: I would like that very  
25 much, just what you're proposing.

1           But is Jim here? Maybe he could --

2           MR. BEHRMANN: This is Jim Behrmann, liaison  
3 to the panel.

4           John, I would agree with you up until the very  
5 last sentence that you stated. The panel can, as the  
6 panel has discussed, the panel can establish procedures  
7 by which we ask people to provide comments.

8           The law provides that the public may provide  
9 written comments to the panel for its consideration.  
10 The panel has, and our notices reflect, we ask that the  
11 public submit comments in writing at least two weeks  
12 prior to the meeting.

13           And what that allows us to do is, it allows us  
14 to share those comments with OEHHA, ARB, and DPR staff,  
15 depending upon what the report is, and the panel then  
16 can have the benefit of their responses.

17           However, by law -- this is a public body very  
18 similar to the Air Resources Board; and by law, the  
19 public may submit comments in writing up to and at this  
20 very meeting. Someone could come in today, for  
21 example, and present a written comment.

22           Now, they do have to understand, however, as  
23 our board does, that any comments -- especially a  
24 lengthy comment, for example. If you come in and  
25 provide comments today, the day of the meeting, the

1 panel is simply, physically or whatever, unable to  
2 absorb and fully discuss and provide an adequate  
3 response.

4 So it's a balance.

5 CHAIRPERSON FROINES: But what I'm saying  
6 is -- I think I'm right about this: What I'm saying is  
7 that if a panel -- if somebody submits comments  
8 yesterday for today's meeting, the panel has the option  
9 to defer its evaluation of those comments until a  
10 subsequent meeting.

11 MR. BEHRMANN: That is correct, if you are  
12 delaying your final decision on the report to that  
13 subsequent meeting.

14 My point being, if you were to make a final  
15 decision today, for example, on say the manganese REL,  
16 you would not have the option then, if a comment were  
17 to come in today, of not considering that comment.

18 If you were going to take final action today,  
19 you would need to at least acknowledge the comment and  
20 briefly review it.

21 If you are not making a decision until the  
22 subsequent meeting, then you're fine deferring any  
23 consideration of it. Am I being clear?

24 PANEL MEMBER BLANC: Yes. I think that John  
25 didn't really literally mean the word ignore. What he

1 actually meant, as I heard it, was that we would take  
2 it into consideration but tempered with the limitations  
3 of input from OEHHA and our own weight of  
4 consideration.

5 And certainly I would take into account the  
6 comments just made. And part of my evaluation of such  
7 late comments would be whether my interpretation of  
8 them is as comments that lack substance but are  
9 intended to simply delay deliberation.

10 And I think what is important is, for the  
11 record, to indicate that all of the comments have been  
12 handled one way or the other; and in that, we would  
13 appreciate the help of OEHHA in their presentation to  
14 the panel summarizing briefly whatever has come in in  
15 the interval, even if it's material that's been  
16 delivered to us and not to them. Even though that  
17 presents another hurdle for you, but if that's  
18 acceptable.

19 MR. BEHRMANN: And if I might just add: OEHHA  
20 has been through, as they said earlier, earlier comment  
21 periods when they were developing the report.

22 So this is an additional provision in the law  
23 that the public may comment directly to the panel.

24 The panel does not often receive substantial  
25 or lengthy comments, in part because of the excellent

1 public process the departments themselves follow.

2 PANEL MEMBER BLANC: And that directly relates  
3 to the comment I just made which is that in fact if  
4 comments are repetitive, they simply indicate, you  
5 know, an attempt to go to us with the same material  
6 they have already gone in the public comment period,  
7 and really it's been commented and addressed previously  
8 and need not require extensive reevaluation by us.

9 CHAIRPERSON FROINES: I agree with what Paul  
10 said, and I did not mean to be quite so outspoken about  
11 it.

12 But I think Paul's point is very important.  
13 What we don't want -- we want two things, I think.

14 We want OEHHA to have the opportunity to  
15 look -- to review comments that come in since they are  
16 the people who prepare the documents that we review.  
17 So not having them have the opportunity is a major  
18 setback.

19 Second, we don't want this process of sending  
20 comments in at the last minute as a means to slow down  
21 a well-defined process.

22 So those are the two, I think, key issues.  
23 And so that I think we have to have -- and I don't  
24 remember what it says on our Notice of Meeting, but it  
25 needs to be made very clear that the panel requires

1 submission at least two weeks prior to the meeting.

2 And we have to make sure that that document  
3 goes out so that that can be timely.

4 MR. BEHRMANN: I would agree with your latter  
5 point and I would just clarify that we can ask that the  
6 comments come in at least two weeks prior to a meeting,  
7 so it is imperative that we issue our notices as soon  
8 as we can prior to a meeting.

9 CHAIRPERSON FROINES: But we can define those  
10 as committee guidelines for interaction with the  
11 public.

12 MR. BEHRMANN: Exactly.

13 CHAIRPERSON FROINES: It's our committee. We  
14 define the procedures.

15 MR. BEHRMANN: Committee guidelines. And I  
16 entirely respect your point that the ability of the  
17 panel to operate and do its job requires that you  
18 receive materials sufficiently far in advance that you  
19 can absorb them and consider them.

20 And I think for the most part -- I think all  
21 of the comments, in fact, that I'm aware of except for  
22 some relatively minor ones and short ones, most of the  
23 comments did come in far in advance of this meeting.

24 So I think it has allowed us to follow the  
25 guidelines that you have established.

1           PANEL MEMBER HAMMOND:  Maybe we could have, in  
2 the guidelines, the guidelines could have some preface:

3           To ensure the committee the opportunity  
4           to fully consider comments, we strongly  
5           encourage everyone to submit comments at  
6           least two weeks in advance.

7           MR. BEHRMANN:  We'll look at the wording in  
8 the notice.  I think that's an excellent point.

9           CHAIRPERSON FROINES:  The point of all this,  
10 of course, is that we're trying to do -- get the best  
11 possible review that we can.

12           This isn't a way to push back the public from  
13 having input.  We're not trying to harm the process;  
14 we're trying to improve the process.  And that's the  
15 key element that people need to understand.

16           Let's go Melanie.

17           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
18 MARTY:  So we're going to start out with manganese, to  
19 which there were a lot of additions after reviewing the  
20 panel comments and listening to you all.

21           So Bruce Winder is going to give the  
22 presentation.

23           OEHHA STAFF TOXICOLOGIST WINDER:  I'm going to  
24 take this presentation more or less in the order of the  
25 way it's presented in the document itself.

1           So in response to panel comments, we've added  
2 to the section two, physical and chemical properties,  
3 descriptions of manganese sulfate and permanganate.

4           Under section three, under occurrence and  
5 major uses, we've expanded the discussion here and  
6 described additional sources of manganese, including  
7 MMT, welding rods, crustal and metal erosion, and  
8 pesticides.

9           One of the other comments in this -- for this  
10 section, there was some question, what are the size  
11 particles to which people are being exposed? What are  
12 we talking about?

13           So we've included a description of some  
14 studies. The one shown on the screen right now is one  
15 conducted in Downey and Riverside looking at the  
16 manganese levels and in what size parcels they occur.

17           So in these two sites we show that Downey  
18 where the manganese is largely from vehicle exhaust,  
19 this kind of thing, 40 percent of the particles that  
20 occur in this .35 to 1 micron size range, less than  
21 20 percent in the 2.5 to 10 micron range.

22           Now in Riverside, some distance away from LA,  
23 we have a rather different situation. Here, the  
24 particulate matter derives from stuff blown in from LA.  
25 Some stuff comes off the desert as well as both

1 industrial and vehicular sources.

2 In this instance, 80 percent of the manganese  
3 was found in particle sizes 2.5 to 10 microns.

4 CHAIRPERSON FROINES: If you don't mind my  
5 interrupting, I want to disagree with you on this  
6 slide.

7 First, the reference in the back is  
8 misspelled. Costas Sioutas' name is misspelled. This  
9 is our work from our laboratories --

10 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

11 CHAIRPERSON FROINES: -- that you have  
12 referred to.

13 And there is this simplistic notion that I  
14 think we have to get past -- and I don't mean you make  
15 a simplistic, but a lot of people do. Which is that  
16 there is this concept that Boyle Heights and downtown  
17 LA are source sites, and Riverside is a receptor site.

18 Well, that went out with high buckle shoes, in  
19 fact. And the issue is --

20 PANEL MEMBER BYUS: Well, you're still  
21 responsible for a lot of our bad air.

22 (Laughter)

23 PANEL MEMBER BYUS: I'm not buying that you're  
24 not responsible for a lot of it, John.

25 CHAIRPERSON FROINES: No, but -- but --

1           PANEL MEMBER BYUS: I live in Riverside.

2           CHAIRPERSON FROINES: But there is -- we have  
3 loads of data on this. There are millions of freeways  
4 that are criss-crossing each other in the Riverside  
5 area. And those freeways are now a dominant element in  
6 terms of the particulate air pollution that exists.

7           And those mobile source related issues will  
8 produce particles that are in the ultrafine range. And  
9 so that it's one thing -- it depends on where your  
10 monitors are sited, what you're going to see.

11           And if you're close to a freeway, you're going  
12 to see air that's just like you see in Long Beach or  
13 Boyle Heights or South Central LA. If you have it away  
14 from roads, then you're going to see coarse particles  
15 coming off the desert, especially during Santa Ana  
16 conditions.

17           So that I think you need to acknowledge the  
18 fact that it's -- that it is not true that most of the  
19 particulate in the so-called receptor Riverside region  
20 derives from particles blowing east from downtown LA.

21           It's simply not -- because there's been so  
22 much development. If you look at the number of  
23 warehouses that have been built in the Riverside area,  
24 they go on for miles and miles and miles.

25           Those are all diesel trucks. Those are all

1 producing these products -- are producing in the  
2 ultrafine region. They're at 20 nanometers and 30  
3 nanometers.

4 So that all I'm simply saying without -- I  
5 don't want to beat you to death on this because I  
6 don't -- you know all this as well as I do. And that  
7 is I think you should acknowledge that there are  
8 receptor sites that reflect particles that are blown in  
9 from the western side of the basin; but you should also  
10 acknowledge that there's been enormous urban  
11 development including warehouses and freeways so that,  
12 depending on your monitoring sites, you're going to get  
13 some variation in results.

14 PANEL MEMBER HAMMOND: There are a couple of  
15 things. First, I think we can simply say that at two  
16 different sites in LA with different sets of sources  
17 and, you know, just leave it at that.

18 The other thing I'm concerned about is, I  
19 would like a fuller description of the manganese  
20 content by size. So for instance, you've got .35 to 1  
21 micron. Now, I don't know. Did you measure less  
22 than --

23 CHAIRPERSON FROINES: That was Costas'  
24 sampling.

25 PANEL MEMBER HAMMOND: Well, the question

1 is -- no, no. But my question is: What about under  
2 .35? What about between 1 and 2.5, and what about  
3 greater than 10?

4 I think you should put the full data there.  
5 That's not like that explains everything.

6 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I  
7 don't think that paper actually included anything other  
8 than these size ranges.

9 PANEL MEMBER HAMMOND: I'm sorry?

10 OEHHA STAFF TOXICOLOGIST WINDER: I don't  
11 believe that --

12 PANEL MEMBER HAMMOND: Only those two sizes?

13 OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

14 CHAIRPERSON FROINES: In that paper, yeah.

15 PANEL MEMBER HAMMOND: Oh, that data aren't  
16 available. Because -- that's quite unfortunate.

17 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I  
18 just --

19 CHAIRPERSON FROINES: We have other papers  
20 available, though. Not necessarily for manganese;  
21 that's what I don't remember.

22 PANEL MEMBER HAMMOND: This is about  
23 manganese.

24 It is useful to have then -- what -- how can  
25 that not be accounting for 100 percent? Or is this

1 compared to TSP?

2 OEHHA STAFF TOXICOLOGIST WINDER: This is  
3 showing that 80 percent of it was --

4 PANEL MEMBER HAMMOND: 80 percent of what?

5 OEHHA STAFF TOXICOLOGIST WINDER: Of the  
6 manganese.

7 PANEL MEMBER HAMMOND: Of what? What's the  
8 total? How do you know what the total manganese is?  
9 If you have accounted for everything, you know. But  
10 it's not what you record.

11 OEHHA STAFF TOXICOLOGIST WINDER: Sure. I --

12 PANEL MEMBER HAMMOND: That's not clear.

13 OEHHA STAFF TOXICOLOGIST WINDER: -- see your  
14 point.

15 PANEL MEMBER HAMMOND: And the same with the  
16 Downey site --

17 OEHHA STAFF TOXICOLOGIST WINDER: Right.

18 PANEL MEMBER HAMMOND: So, you know, is in the  
19 Downey site, is the remaining 50 percent at less than  
20 .35? Or is it between 1 and 2 1/2? Or is it greater  
21 than ten?

22 OEHHA STAFF TOXICOLOGIST WINDER: Whereas --

23 PANEL MEMBER HAMMOND: You know. If you're  
24 going to talk about particle size. Otherwise, I don't  
25 know what this means.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: We'll go back to the paper and pull whatever  
3 else we can out of the paper.

4 PANEL MEMBER FRIEDMAN: I had the same  
5 concern. And I'm just wondering, because I don't know  
6 that much about effects on the lungs and so on, why you  
7 picked these two ranges of sizes.

8 Do they have some particular toxicological or  
9 physiological significance compared to smaller ones,  
10 middle sized ones, or larger ones?

11 OEHHA STAFF TOXICOLOGIST WINDER: In fact,  
12 that's the case. And as I'll talk about a little later  
13 in the discussion, you'll see why.

14 The emphasis there, I'd like to point out, is  
15 at least in this study, they report that 80 percent of  
16 the magnesium was associated with this 2.5 to 10 micron  
17 range. That's a problem when we start talking about  
18 the effects in infants and children.

19 PANEL MEMBER FRIEDMAN: I'm sorry; could you  
20 speak into the microphone?

21 OEHHA STAFF TOXICOLOGIST WINDER: This size  
22 range, 2.5 to 10 micrometers, is important when we  
23 start talking about the inhalation in infants and  
24 children.

25 PANEL MEMBER HAMMOND: Well, I think

1 actually -- I mean, if we were designing an experiment  
2 and could have all our data, I think we would be very  
3 interested in how much is in the ultrafine because of  
4 the olfactory route that goes directly to the brain, so  
5 you've got a direct path without it being bypassed.

6 CHAIRPERSON FROINES: Not only that, but --

7 PANEL MEMBER HAMMOND: I think -- I'm not sure  
8 that we're only interested in 2.5 to 10 at all.

9 CHAIRPERSON FROINES: Yeah, I agree. I  
10 think -- I don't agree with the statement that it's 2.5  
11 to 10 is where we worry about children.

12 I mean ultrafines are going to deposit from  
13 the nasopharyngeal region down to the alveolar region,  
14 and there's going to be some translocation as well.

15 And that the reactive -- at one point in your  
16 document, you talk about reactive oxygen species, and  
17 you're going to get most of your reactive oxygen  
18 species in the ultrafine range. We find that very  
19 clearly.

20 PANEL MEMBER FRIEDMAN: Could you define  
21 ultrafine?

22 CHAIRPERSON FROINES: Less than .1 microns.  
23 But it depends on what sample you're using too.

24 PANEL MEMBER HAMMOND: It's not included here  
25 at all.

1           CHAIRPERSON FROINES: Yeah. So the fact of  
2 the matter is, if you look at -- if you postulate that  
3 one mechanism of toxicity is oxidative stress, then  
4 where you find the most oxidative stress is in the  
5 ultrafine region which is isn't addressed here.

6           I'm going to talk at some length about this  
7 issue of oxidative stress a little bit later, but -- so  
8 what Kathy's pointing out now, it's not your fault.

9           It's the fact that Costas Sioutas did a paper  
10 in which he got -- this is the data from his study. So  
11 you can't be asked to give us information that you  
12 don't have. So understand that I'm not saying that.

13           But I'm saying that the ultrafine issue is a  
14 major issue which is not addressed.

15           OEHHA STAFF TOXICOLOGIST WINDER: Okay.

16           CHAIRPERSON FROINES: Does that make sense?

17           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: At the last meeting, there was some discussion  
19 about what particle size fraction is manganese in. So  
20 we went out and looked for that, and this is the only  
21 thing we found.

22           And it's true. I found it rather odd that  
23 they jumped from 1 to 2.5 and didn't measure that. But  
24 that's what they did.

25           PANEL MEMBER HAMMOND: Or even less than .35

1 because usually your final sampler collects everything  
2 less than some cut-off point.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Right. So anyway, I apologize to Costas  
5 Sioutas for misspelling his last name.

6 PANEL MEMBER HAMMOND: But since John knows  
7 the data, he'll clarify.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Okay.

10 CHAIRPERSON FROINES: I'll ask Costas -- I'll  
11 ask Jamie Schauer if he's got some data below .2 or .1  
12 or .35. Because we've taken thousands of samples out  
13 there; I can't imagine we don't have data that would  
14 provide you some information.

15 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

16 Well, as we moved on into section four on  
17 Metabolism/Toxicokinetics, we have here a discussion of  
18 the developmental role of the blood-brain barrier, the  
19 idea that at various stages in development the  
20 blood-brain barrier is much more permeable to  
21 manganese, among other things, and so infants and  
22 neonates would be more readily exposed.

23 We also include discussion here of parenteral  
24 route of exposure, not only through total parenteral  
25 nutrition in children, but also it was pointed out that

1 IV drug use is another route by which people are  
2 exposed.

3 We extended the discussion on the roles of  
4 solubility, the oxidation state, and the valences of  
5 the manganese in terms of its toxicity, emphasizing  
6 here that the more soluble forms of manganese, such as  
7 the sulfates, tend to end up in the brain more easily  
8 and to higher levels.

9 The oxidation states and the valences are  
10 critical in terms of, for example, manganese 3 appears  
11 to be the more significant contributor to the toxicity  
12 of manganese.

13 All this tends to be manifest in these -- this  
14 next, the markers of oxidative stress. And here we're  
15 emphasizing what's happening primarily in the nervous  
16 system in which we see oxidative effects on  
17 neurotransmitters. We see oxidative stress in the form  
18 of raised biomarkers in up regulation. And so this is  
19 one of the major mechanisms by which toxicity is  
20 occurring.

21 Now in the context of nanoparticles, this  
22 question was also raised: What effect do nanoparticles  
23 have with respect to the exposure and uptake in  
24 manganese?

25 So we've included a study here which describes

1 the way in which nanoparticles facilitate the cellular  
2 uptake. And then we've included a study out of  
3 Dorman's lab which provides evidence of direct  
4 nose-to-brain transport in primates.

5 Now in section five, Acute Toxicity, there was  
6 some question as to, well, why didn't we develop an  
7 acute REL at this time?

8 And the reasons for this were that the studies  
9 we found were single dose studies making it very  
10 difficult to come up with any dose response.

11 The major endpoints from the studies were  
12 pretty much of uncertain toxicological significance.  
13 That is, they're talking about brain accumulation. A  
14 large number of studies focus on that. But we're not  
15 really sure how that information translates into  
16 manifestation of toxicity.

17 Then in these studies the routes of exposure  
18 were not particularly useful when we're trying to do an  
19 inhalation REL as they're based mostly on oral and  
20 subcutaneous injection.

21 Now in section six, these are -- this is a  
22 listing of the studies that we've added -- study  
23 descriptions that we've added to this document.

24 So we've added some follow-up studies, two out  
25 of Bouchard's lab which are a follow-up from the

1 Mergler study '94 of ferro metals production.

2 CHAIRPERSON FROINES: Can I go back a second?

3 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

4 CHAIRPERSON FROINES: I don't know. Paul may  
5 be helpful here. But under section four, there's  
6 considerable discussion about reactive oxygen species  
7 and oxidative stress as a potential mechanism of  
8 toxicity. And I think that's entirely reasonable.

9 However, it's clear that manganese binds to  
10 proteins. It binds to GSH. It binds to albumin. It  
11 binds to all sorts of things.

12 It seems to me that the binding of manganese  
13 to proteins could set in motion -- especially on a  
14 chronic basis, but even on an acute basis -- can set in  
15 motion changes in regulatory proteins, for example,  
16 that may activate various pathways that lead to acute  
17 effects and that the covalent bonding that occurs with  
18 manganese is also another mechanistic pathway that  
19 seems as reasonable as the ROS pathway.

20 So the binding of manganese with various  
21 proteins seems -- and would have to be defined -- but  
22 seems to me to be a pathway that can't be ignored when  
23 you're considering toxicity.

24 OEHHA STAFF TOXICOLOGIST WINDER: I think  
25 you're right about that. I've not seen much

1 information that bears on that, though, in terms of  
2 specific protein in a regulatory pathway that are bound  
3 by manganese and shown to be of toxic effect. But I  
4 think you have a point, that that's a reasonable --

5 CHAIRPERSON FROINES: Well, I mean, if you  
6 spend so much time talking about it's binding with  
7 things like albumin and also -- and there is a lot of  
8 discussion here about GSH levels. Well, if it binds  
9 with thiolates in GSH, it's going to bind with  
10 thiolates in proteins.

11 And therefore, that can set into motion a  
12 toxicity process that can have implications down the  
13 stream, especially in terms of inflammatory responses  
14 that might occur.

15 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. We  
16 can go back to that portion and add to that.

17 CHAIRPERSON FROINES: Are you okay with that,  
18 Paul?

19 PANEL MEMBER BLANC: Yeah. I mean I think  
20 that part of the reason why the oxidative stress  
21 discussion is disproportionately long is because that  
22 reflects what people have been discussing in the recent  
23 literature.

24 So I think part of their charge coming out of  
25 the last meeting was to be more meticulous in

1 addressing the most recent literature, and this has  
2 been the focus as they summarize the literature.

3           So I think it would be sufficient simply to  
4 have a sentence that says, you know: Although this has  
5 been an emphasis in the recent literature, it does not  
6 exclude the possibility of other mechanisms.

7           CHAIRPERSON FROINES: I think the --

8           PANEL MEMBER BLANC: I think it's asking a  
9 little bit too much from them to theorize de novo on  
10 mechanisms which in the peer-reviewed literature are  
11 not being --

12           CHAIRPERSON FROINES: Well, I'm sure there  
13 is -- but the point is that manganese binds with  
14 thiolate groups.

15           PANEL MEMBER BLANC: And I think also, by the  
16 way, part of this is a reaction to that the literature  
17 had previously been dominated by a presumption that it  
18 was manganese interference with enzymes that was  
19 accounting for dopamine imbalance and so forth. And I  
20 think that that theoretical --

21           OEHHA STAFF TOXICOLOGIST WINDER: It's being  
22 emphasized less now.

23           PANEL MEMBER BLANC: It's being emphasized  
24 less now. And so that accounts for -- you know, it's  
25 one of these sort of shifting things.

1           And so again, I think it's also good to say:  
2   Although this has been the emphasis of the recent  
3   literature, it by no means the excludes other  
4   possibilities.

5           And you can even say: Certainly in the past  
6   there was a lot of emphasis on enzyme inhibition, for  
7   example. Because that, you'll find ample reference if  
8   you want to include it. But beyond that, I wouldn't go  
9   into a lengthy --

10           CHAIRPERSON FROINES: Well, I would  
11   acknowledge the thiolate chemistry, and that's no  
12   problem.

13           PANEL MEMBER BLANC: If there is a reference  
14   to it.

15           CHAIRPERSON FROINES: I'm sure there is.  
16   Well, I mean the fact that it binds to GSH is by  
17   definition.

18           But the other thing I would mention is that --  
19   I don't think you need to get into it, but one has to  
20   have a little skepticism because the manganese ROS  
21   issue.

22           Manganese is going to be dominated by the  
23   Fenton reaction that produces hydroxyl radical. It's  
24   not going to produce -- I don't know how much  
25   superoxide it produces. We've never measured that.

1           But the -- so if there was any data where  
2 anybody looked at chelators to see if you could reduce  
3 the ROS formation, that would be -- in terms of the  
4 Fenton reaction, that would be interesting data.

5           PANEL MEMBER LANDOLPH: Can you explain what  
6 ROS means?

7           CHAIRPERSON FROINES: Well, ROS is three  
8 species. It's superoxide radical anion, it's hydrogen  
9 peroxide, and it's hydroxyl radical.

10           But metals tend to operate by the Fenton  
11 reaction which is a reaction in which the metal  
12 catalyzes the formation of hydroxyl radical.

13           So one can look at that pathway very nicely by  
14 looking at whether chelators can impact it.

15           And so it would -- if you could knock out some  
16 of your results with chelators, then you would -- that  
17 would add to your concern. I mean add to your sense of  
18 what's going on.

19           OEHHA STAFF TOXICOLOGIST WINDER: Okay.

20           CHAIRPERSON FROINES: And I'm assuming that --  
21 I'm sitting next to Charlie Plopper -- that when I make  
22 a mistake, he's going to pounce on me.

23           OEHHA STAFF TOXICOLOGIST WINDER: So we talked  
24 about these studies that we have added.

25           Now in context of animal studies we have added

1 more studies to early life exposures, including this  
2 one by Dorman, as well these two studies by  
3 Thiruchelvam and Barlow, looking at exposures to  
4 manganese in the form of maneb which is a fungicide  
5 contained in manganese.

6           These studies delineate how early life  
7 exposures to this fungicide followed by subsequent  
8 exposures as an adult to paraquat result in more severe  
9 neurotoxicity than seemed to be by the amount of  
10 exposure by itself or later exposure without the early  
11 life exposure. So this tends to support the argument  
12 that these early life exposures can be very serious  
13 concerns.

14           CHAIRPERSON FROINES: Can I -- I actually --  
15 can I just -- I'm sorry I'm doing this, but I want to  
16 disagree with you on one conclusion that you made.

17           You talked about the more recent Cory-Slechta  
18 paper in which they looked at adult exposure after the  
19 postnatal exposure. And then you talked about that  
20 there was recovery after one week of the challenge.

21           PANEL MEMBER BLANC: What page are you on,  
22 John? It would help.

23           CHAIRPERSON FROINES: I don't know. It's  
24 on --

25           PANEL MEMBER BLANC: 22, 21, 23?

1 CHAIRPERSON FROINES: It's on page 21.

2 So here was my take on this. If you -- you  
3 argue that you do see an effect, or she sees an effect,  
4 but that the effect in adulthood goes away a week after  
5 the challenges cease, right?

6 OEHHA STAFF TOXICOLOGIST WINDER: I think that  
7 was probably the way I worded this. I think the idea  
8 was that they saw an effect that disappeared when they  
9 have maneb exposure only without the prenatal.

10 CHAIRPERSON FROINES: Well, you say the  
11 results suggest that prenatal exposure to maneb causes  
12 damage to the nigrostriatal region of the male brain  
13 that is only revealed in adulthood following another  
14 neurotoxic insult in the form of paraquat. And that --  
15 okay. So that's the data.

16 You say here, you -- oh, shoot. I don't find  
17 it. But:

18 On the eighth day of challenge exposures  
19 locomotor activity was depressed in all  
20 animals exposed to maneb as adults but  
21 recovered to control levels within one  
22 week of the last alcohol exposure.

23 So you're assuming -- you're talking about the  
24 fact that you get locomotive changes from which there's  
25 recovery after a week of stopping the challenge, which

1 is all well and good.

2 But what if you're exposed to maneb on a  
3 continuing basis? You're not going to get,  
4 necessarily, recovery. You're going to have a chronic  
5 effect that occurs and that you may effect, over time,  
6 stopping having recovery and -- or would there at least  
7 be diminished recovery?

8 In other words, you can't do -- if you take an  
9 experiment, and you give it postnatally, and then you  
10 give it in adulthood, and if you're looking at the  
11 impact of the childhood exposure on the adulthood, then  
12 when you -- if you say, well, with maneb it, you know,  
13 we've got control, we've got -- we've got improvement  
14 after a week, that's true.

15 But then that's based on the design of your  
16 study, I think. Because you stop the challenge. But  
17 if you kept having the challenge, you might keep having  
18 the effect.

19 In other words, you could create a chronic  
20 effect.

21 PANEL MEMBER BLANC: But John, they were  
22 discussing this in the context of the neonatal  
23 susceptibility.

24 Again, I can't follow where you're reading  
25 from, from the second quote that you read. I can

1 follow the first quote, is in the middle of page 21.  
2 The second thing about the recovery to control levels,  
3 where is that from?

4 CHAIRPERSON FROINES: All I'm saying is that  
5 you should acknowledge the fact that if the design of  
6 the experiment had been different that you might have  
7 seen different results.

8 OEHHA STAFF TOXICOLOGIST WINDER: I think that  
9 would be an appropriate addition because what I'm  
10 trying to describe here is what -- the result of this  
11 particular experimental design.

12 CHAIRPERSON FROINES: I know this work  
13 backwards and forwards. My four students here just had  
14 it on a test yesterday at UCLA.

15 OEHHA STAFF TOXICOLOGIST WINDER: I hope I got  
16 it right for them.

17 (Laughter)

18 CHAIRPERSON FROINES: I hope so too.

19 But the point is that the -- this is a -- this  
20 issue of maneb is tremendously important in terms of  
21 the role of manganese. This Cory-Slechta's work is  
22 fundamentally important work on this topic area. And  
23 that -- so anyway. Point made.

24 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I  
25 think it would be worth adding some portion discussion

1 of that to this portion of it.

2 CHAIRPERSON FROINES: So the point I'm trying  
3 to make is basically that what you see -- it's not that  
4 you see only effects with paraquat. It's that you --  
5 your study design may prevent you from seeing effects  
6 with maneb.

7 OEHHA STAFF TOXICOLOGIST WINDER: In fact I  
8 would argue that what this is suggesting is that any  
9 number of subsequent insults to the system after  
10 exposure to maneb are likely to come up with very  
11 similar kinds of problems. It's just that this study  
12 did paraquat.

13 CHAIRPERSON FROINES: And you actually might  
14 raise the question also that -- paraquat produces  
15 reactive oxygen species, as we know. You might suggest  
16 that that might be a mechanistic pathway by which the  
17 effects you see later in life may be manifested. That  
18 wouldn't be inappropriate, I think.

19 PANEL MEMBER BYUS: Actually, just if you want  
20 me to confuse this even more: One of my colleagues in  
21 my department at Riverside has just shown that maneb  
22 man and paraquat trigger apoptosis in the brain,  
23 whether it involves reactive species or not.

24 Triggers apoptosis by a BCL mechanism. And  
25 they've -- he's actually defined the whole molecular

1 mechanism except for the initial reactive oxygen  
2 species, and it could have in fact irreversible  
3 effects.

4 CHAIRPERSON FROINES: Are you sure that's not  
5 a high dose experiment?

6 PANEL MEMBER BYUS: The original part was high  
7 dose, and then he's backed off on the doses.

8 But in any case, it just reiterates your --  
9 the potential possibilities for acute versus chronic  
10 effects and long-term versus short-term effects.

11 CHAIRPERSON FROINES: I think there is a  
12 fundamental issue that we all really in air pollution  
13 have to understand, which is that most people don't get  
14 sick from air pollution; some people do. And we don't  
15 know exactly why.

16 But the other thing that I think is worth  
17 mentioning is that one of the factors that occurs is  
18 that we are exposed to low doses of air pollutants on a  
19 chronic period of time.

20 So we have to realize that we are continuously  
21 exposed, and that we need to think about that as  
22 opposed to these kind of tox experiments where we do  
23 things one step at a time, and then we don't design  
24 experiments that deal with the continuous exposure in  
25 toxicology as effectively as we design these -- we

1 dose, and we dose, and we dose, and we see what we  
2 find.

3 But that's not what life is about. Life is  
4 about continuous exposure. And -- point made.

5 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

6 Now, this slide was an addition. The reason  
7 for this table is to show that we're seeing some  
8 support for our selection of our REL.

9 PANEL MEMBER BLANC: What page is this slide  
10 on?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
12 MARTY: 23. It's table 631.

13 PANEL MEMBER BLANC: Okay. Just so people can  
14 follow.

15 OEHHA STAFF TOXICOLOGIST WINDER: What this  
16 is -- what I'm doing here is comparing a couple of  
17 different studies. The study in the center by Dorman,  
18 et al. is looking at rhesus monkeys exposed to  
19 manganese sulfate by inhalation at the levels  
20 indicated. It was 60, 300, and 1500 micrograms per  
21 meter cubed. This is a subchronic study. They were  
22 six hours a day, five days a week, 13 weeks kind of  
23 thing.

24 Now over on the right side, the study by  
25 Schneider and Guilarte, also is looking at rhesus

1 monkeys. In this instance, these monkeys were exposed  
2 to IV to manganese sulfate. This is once a week over a  
3 course of first five weeks, 3.26 manganese per kilogram  
4 and that went up to 4.89 for the remaining nine or so  
5 weeks.

6 Now what the table shows are measured levels  
7 of manganese in these four different brain regions.

8 Now the Dorman study is exclusively looking at  
9 the manganese levels in these regions whereas the  
10 Schneider and Guilarte study also looked at neural  
11 behavioral effects.

12 What they find is among all these -- among the  
13 monkeys showing these levels of manganese in the brain,  
14 there is neurotoxicity.

15 Neurotoxicity in this case manifests as motor  
16 problems. They're trying to retrieve an item out of  
17 different-size wells. As well as repetitive behaviors  
18 seen among the treated animals.

19 Now what you see here is that the  
20 neurotoxicity observed by Guilarte is occurring at  
21 brain levels which were covered by the range seen in the  
22 Dorman study. That is to say the Guilarte numbers like  
23 this 1.18 is less than what Dorman found at 1500 but a  
24 little bit more than 300. So they're right in that  
25 range.

1           Now, across the bottom, what I've done is  
2   annualized the dose levels that Dorman used, the  
3   60 micrograms per meter cubed, for 13 weeks is the  
4   equivalent of 15 micrograms per meter cubed over the  
5   course of a year.

6           The reason I did this was for comparison with  
7   a human study, the Roels data that we used for the  
8   actual REL development. He calculated a lifetime  
9   integrated respiratory dose -- we show at the bottom --  
10   and what we found was that individuals expressing  
11   neurotoxicity had levels in this range.

12           So what we find is that from the Roels data,  
13   individuals with the manganese in the brain -- or,  
14   excuse me, exposed to manganese at this level of 60 to  
15   3700 micrograms per meter cubed per year, this range  
16   overlaps with what Dorman saw in terms of his  
17   inhalation at the same level that Guilarte saw  
18   neurotoxicity in the monkeys.

19           So what this does is suggesting that the  
20   nonhuman primates here are exhibiting neurotoxicity at  
21   the same level that humans are exhibiting toxicity in  
22   Roels study.

23           We have added to the developmental  
24   reproductive section the study by Chan et al. in which  
25   he was looking at perinatal exposure to manganese. And

1 what he is reporting is that the manganese distribution  
2 within the different brain regions is not homogeneous;  
3 it is quite heterogeneous. And he says this is both  
4 age and stage dependent. And he draws the -- he thinks  
5 this is related to both the blood-brain barrier  
6 development -- as the brain barrier becomes less  
7 permeate, we have less -- he sees less distribution,  
8 less deposit in these brain areas.

9           And he brings up a new line which is the idea  
10 that the degree of myelination in the brain doesn't  
11 proceed uniformly across all brain regions and seems to  
12 be associated with this level of manganese  
13 accumulation. The less myelinated nerves tend to  
14 accumulate manganese to higher levels faster.

15           Now, in response to the panel's comments last  
16 time, we went back to RELs data and did the analysis a  
17 second way. This time we were looking at the LIRD.  
18 That's lifetime integrated respirable dust.

19           And this is in comparison to what we did the  
20 first time which was to look at the current respirable  
21 dust and multiply it by the number of years of  
22 exposure.

23           By using the LIRD, we capture an individual's  
24 exposures for a given job; and if he changes a job  
25 position in which his exposure changes, this will

1 better capture that information.

2 Now as before, this -- the way the study was  
3 run was the individuals were scored on tests for  
4 eye-hand coordination, hand steadiness, and visual  
5 reaction time.

6 CHAIRPERSON FROINES: Can I ask you a  
7 question?

8 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

9 CHAIRPERSON FROINES: Can we -- I'm sorry; I'm  
10 playing catch-up because I'm on page 24 and 25.

11 OEHHA STAFF TOXICOLOGIST WINDER: All right.

12 PANEL MEMBER BLANC: He's much farther ahead  
13 than that.

14 CHAIRPERSON FROINES: Well, that means I'm  
15 slow.

16 PANEL MEMBER BLANC: Well, what I would  
17 suggest is that he finish his presentation, then we go  
18 back to the areas that we have questions on.

19 CHAIRPERSON FROINES: That's fine.

20 PANEL MEMBER BLANC: But it would be helpful  
21 if you kept us abreast of the corresponding page that  
22 you're on roughly.

23 OEHHA STAFF TOXICOLOGIST WINDER: All right.  
24 So in this BMC analysis --

25 PANEL MEMBER BLANC: It usually isn't such a

1 problem because frequently when you are presenting  
2 revised material it's not as extensively revised as  
3 this section is. But given the extent of the  
4 revisions, this is pretty tough to follow.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Page 32.

7 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, the  
8 new analysis appears on page 32. Let's see.

9 So what the new analysis shows for us is that  
10 the eight-hour REL appears to decrease by about a third  
11 from .26 to .17 micrograms per meter cubed.

12 Similarly, the chronic REL with the new  
13 analysis goes from .13 to .09.

14 This, as you may have seen or may recall from  
15 the previous presentation, this .09 is in the range  
16 that the US EPA published as being the likely range for  
17 their manganese, even though their current RFC is .05.

18 PANEL MEMBER BLANC: Can you go back to the  
19 previous slide? Because when I read the document, I  
20 had problems understanding what exactly it was that  
21 made you -- that allowed for the change or accounted  
22 for the change in the calculation.

23 You're still using the same REL study.

24 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

25 PANEL MEMBER BLANC: You're still using the

1 same data points? Or did you receive additional data?

2 OEHHA STAFF TOXICOLOGIST WINDER: We had these  
3 data. The data -- we had this rather large body of  
4 data. From that data, for the initial analysis we took  
5 this cross-section -- excuse me -- the current  
6 respirable dust levels. He reported both the LIRD did  
7 and the CRD.

8 We used the CRD in our first analysis. And  
9 what that gave us was for each individual the current  
10 level of exposure to respirable dust. We multiplied  
11 that by the number of years the individual was exposed.

12 PANEL MEMBER BLANC: All right.

13 OEHHA STAFF TOXICOLOGIST WINDER: But that  
14 didn't take into account that various individuals will  
15 change jobs from time to time and their exposure levels  
16 will fluctuate as a consequence.

17 The LIRD on the other hand takes that into  
18 account. It takes a look at each individual, how long  
19 they spent in a given position with whatever they  
20 estimated the exposure to be, and then that was added  
21 to whatever they were exposed to in their next job  
22 position, et cetera.

23 So it gives what's described as an integrated  
24 respirable dust exposure.

25 Now, the reason that that's important, as

1 Dr. Hammond pointed out, was this then is a better  
2 description of what the total exposure an individual  
3 might have gotten. So in principle, it more accurately  
4 displays what kind of exposure we have for each  
5 individual.

6 PANEL MEMBER BLANC: So it must have been  
7 therefore that what ultimately that showed was that  
8 there was more of a neurobehavior impact at a lower  
9 accumulative dose level --

10 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

11 PANEL MEMBER BLANC: -- than you had -- you  
12 had overestimated exposure previously, and that  
13 accounted for lower mathematical value; is that  
14 correct?

15 OEHHA STAFF TOXICOLOGIST WINDER: I believe  
16 that's correct.

17 So as I say, this is where these levels are  
18 now. So that's my presentation of the bulk of the  
19 changes.

20 Now we can go back . . .

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
22 MARTY: We did get a copy of the supplemental comments  
23 that were sent directly to the panel from the Manganese  
24 Interest Group. And so we have a few slides, if you  
25 want to hear what our response was, basically.

1           PANEL MEMBER BLANC: Yeah, why don't you start  
2 with that, and we can open it up.

3           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
4 MARTY: Okay.

5           OEHHA STAFF TOXICOLOGIST WINDER: The thrust  
6 of the concerns expressed by MIG as far as from my take  
7 on this is that our tenfold toxicokinetic uncertainty  
8 factor is really unjustified.

9           Now, my response to that, and this is already  
10 described in the document, is that according to the  
11 work done by Ginsberg in 2005 there's a three- to  
12 fourfold greater deposition of particles in this 1 to  
13 10 micrometer size in children's lungs versus adults.

14           This is where I was referring to the  
15 significance of the 80 percent of the manganese in the  
16 Riverside being in that range. This is a range where  
17 children would have a higher exposure according to  
18 Ginsberg's work. So that's part of our reason for  
19 having a higher toxicokinetic uncertainty factor.

20           PANEL MEMBER HAMMOND: Excuse me.

21           OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

22           PANEL MEMBER HAMMOND: I would just say: To  
23 say that the children have more deposition, a higher  
24 deposition than adults, does not say though that that's  
25 the size fraction that's most important for children.

1           Those are two different --

2           OEHHA STAFF TOXICOLOGIST WINDER: That's true.

3           But what we're saying here is in terms of a  
4 kinetic effect this is the problem that particular --  
5 so we would be talking about that in terms of  
6 toxicodynamics.

7           The other concern we have is that in these  
8 models that we've seen from the MIG group or from  
9 Dorman's group there's no addressing what happens in  
10 cases of iron deficiency.

11           In the document, there are reference to  
12 several studies in which it's been demonstrated that  
13 under case of iron deficiency there is much more  
14 efficient uptake of manganese from the nose to the  
15 blood and brain, from the lungs to the blood and brain,  
16 and also from the diet.

17           So to the extent that iron deficiency is more  
18 a problem among infants, this is another reason for  
19 being concerned about this exposure at this time, and  
20 that's another part of our toxicokinetic factor.

21           The other thing is that iron is critical to  
22 neural development as is manganese. Not only does  
23 manganese -- or iron interfere with manganese,  
24 manganese interferes with iron such that in cases where  
25 children are iron deficient and are exposed to

1 manganese, then we have more of a competition here  
2 between the residual iron and the manganese.

3           So it's this interaction isn't addressed in  
4 any of these models thus far.

5           PANEL MEMBER FRIEDMAN: What is the prevalence  
6 of iron deficiency in infants?

7           OEHHA STAFF TOXICOLOGIST WINDER: This I don't  
8 know. It's --

9           PANEL MEMBER FRIEDMAN: Is it a common  
10 problem?

11           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Mark Miller from OEHHA will address that  
13 question.

14           PUBLIC HEALTH MEDICAL OFFICER MILLER: I don't  
15 have an exact number. But it is quite common between  
16 nine months and two years of age as is evidenced by  
17 standard protocol that at regular well-child exams at  
18 that age hemoglobin is obtained because so many kids in  
19 fact are iron deficient.

20           So I don't have an exact number, but it's  
21 common.

22           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: That was Mark, our pediatrician.

24           OEHHA STAFF TOXICOLOGIST WINDER: So with  
25 these two concerns as well as we don't really know for

1 sure what manganese is doing in the brain at the levels  
2 that children might be exposed in these cases, do we  
3 still want to have this tenfold toxicokinetic factor?

4 Now, this is -- this goes to the point that  
5 Dr. Froines is making that in fact these early life  
6 exposures to various substances such as maneb may  
7 precondition animals, infants, to be more susceptible  
8 to neurotoxic assaults. So this is based on the study  
9 by Barlow.

10 This is a concern not just for paraquat but  
11 any number of things. As I pointed out here, the  
12 current PBPK modeling just does not address either of  
13 these concerns. Maybe with subsequent development,  
14 we'll have a better idea what's going on, but this is  
15 where things seem to be at this point.

16 So those are our responses thus far.

17 CHAIRPERSON FROINES: Wait. I'm back to my  
18 maneb again. What is this -- early life exposure, what  
19 are you saying there?

20 OEHHA STAFF TOXICOLOGIST WINDER: This is  
21 related -- this is based on the Barlow study.

22 CHAIRPERSON FROINES: Yeah, I know.

23 OEHHA STAFF TOXICOLOGIST WINDER: So that the  
24 early life exposures -- let's generalize this to  
25 children exposed to, say, in a farming environment,

1 they may be exposed to maneb just as a consequence of  
2 being in that environment.

3 When they are subsequently exposed, will they,  
4 like these mice, show this greater sensitivity to the  
5 neurotoxic insult?

6 We suspect that that might be the case, and  
7 that's part of the reason for wanting to maintain this  
8 toxicokinetic factor.

9 CHAIRPERSON FROINES: But we already dealt  
10 with that in our discussion, that this -- this issue of  
11 showing paraquat as being a key pesticide is a vast  
12 oversimplification of the issues.

13 I think you have to --

14 PANEL MEMBER BLANC: No, I think their point  
15 is they've shown a synergistic effect and that young  
16 animals are --

17 CHAIRPERSON FROINES: It's not synergistic.

18 PANEL MEMBER BLANC: It is because there was  
19 no effect by the paraquat alone.

20 CHAIRPERSON FROINES: That's potentiation.

21 Well, anyway, let's not quarrel with that.

22 PANEL MEMBER BLANC: In any event, I think  
23 that for the purposes of response -- I think we can  
24 come back to this. I think you haven't put the best  
25 foot forward in terms of the response.

1           Clearly you have a lot more factors in this  
2 that support the use of a tenfold uncertainty factor, I  
3 think the most salient of which is that the default  
4 public health protective approach to a toxin which  
5 primarily acts as a neurotoxin with cumulative lifetime  
6 effects is to presume that infants and children are at  
7 higher risk of effect until proven otherwise.

8           And one or two subpoints related to  
9 pharmacodynamics don't therefore establish that there  
10 isn't uncertainty. It may reduce areas of uncertainty,  
11 but not the uncertainty altogether.

12           OEHHA STAFF TOXICOLOGIST WINDER: Right. In  
13 fact, for the -- in the document itself where we talk  
14 about the various REL descriptions, we do say that  
15 there -- a toxicodynamic factor of ten is due to the  
16 greater susceptibility of children to neurotoxicity.

17           PANEL MEMBER BLANC: So I just want to, you  
18 know, put that into the record.

19           And perhaps this is a -- since this is so  
20 critical to the discussion, maybe I'll diverge here a  
21 little bit and just go back to page 20 of your document  
22 where, section 6.2.1, potential for differential  
23 effects in children.

24           There may be certain historical reasons why  
25 you developed a format where the discussion of the

1 potential for differential effects in children follows  
2 immediately upon the section of human effects. There  
3 is a certain logic to that.

4 But I would actually suggest that you move  
5 this section so that it follows your animal toxicity  
6 section. You're using data which you haven't yet  
7 presented to support your argument.

8 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

9 PANEL MEMBER BLANC: Appropriately so.

10 CHAIRPERSON FROINES: I wanted to --

11 PANEL MEMBER BLANC: Did everybody follow that  
12 point?

13 That may put you out of line with some of your  
14 other things, I don't know. But at least for this one,  
15 it seems critical enough.

16 And I think that you need -- because of the  
17 critical issue of backing up your tenfold adjustment,  
18 which I fully believe the data you present supports, I  
19 think that points 1 through 8 should be reviewed  
20 carefully; and where it is appropriate to be more  
21 explicit in the wording, you should be.

22 For example, point five, some infant formulas  
23 and foods are high in manganese -- therefore, when you  
24 combine dietary and airborne exposures, you are likely  
25 to have . . .

1 I mean, it may seem obvious to you because  
2 you've been knee-deep in this for so long, but I think  
3 that you need to say that.

4 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

5 PANEL MEMBER BLANC: And I -- I think that you  
6 should take Kathy Hammond's point in terms of point  
7 number seven which has to do with deposition of  
8 particles and just remember how that relates to point  
9 number eight which is where you talk about the nose but  
10 only insofar as iron deficiency affects absorption in  
11 the nose. But in fact, to the extent that children may  
12 have more deposition of larger particles in their nose  
13 or not, I think -- I don't know if there's data on  
14 that.

15 But that would to me be as relevant as whether  
16 they have more deposition of smaller particles in their  
17 lungs relative to adults. They may actually also have  
18 more.

19 OEHHA STAFF TOXICOLOGIST WINDER: Okay. We  
20 can we can add that.

21 CHAIRPERSON FROINES: Just to -- I don't want  
22 to beat a dead horse, but I really do object to that  
23 first point where you're -- I know the data shows that  
24 paraquat was the compound that caused the locomotive  
25 changes.

1           But we were -- we agreed that that was a  
2 reflection of the method by which the studies were  
3 done, and it may not be adequate.

4           And so I think you need to put something in  
5 that says paraquat was one finding; but if there had  
6 been chronic exposure, we might have had other  
7 chemicals that caused similar effects or even greater.

8           In other words, what I'm trying to get away  
9 from is you're pinpointing paraquat as an etiologic  
10 agent in this when in fact it may be a result of study  
11 design and not necessarily the toxicity.

12           OEHHA STAFF TOXICOLOGIST WINDER: Okay. We'll  
13 add that.

14           CHAIRPERSON FROINES: So you don't want to  
15 just -- paraquat may be the key chemical, but it may be  
16 that there may be other chemicals, and they may have  
17 under different design conditions that you would be  
18 seeing them.

19           So you just want to make it sound as though  
20 it's paraquat that was a key agent -- even though it  
21 is; you have to acknowledge it is a key agent, but go  
22 one step further.

23           OEHHA STAFF TOXICOLOGIST WINDER: Sure. Okay.  
24 Were there any other questions?

25           PANEL MEMBER BLANC: What about their other

1 points?

2 OEHHA STAFF TOXICOLOGIST WINDER: Those are  
3 the only slides that I prepared.

4 One of the other things that is predominant,  
5 and that is that they did a recalculation of one of the  
6 tables that I had in the original document, using what  
7 they -- what I used the proposed chronic REL for that  
8 calculation.

9 If children were exposed at that level versus  
10 the 250 -- .25 micrograms per mil they were showing in  
11 the Roels study, they felt this would be a much more  
12 reasonable example of what kinds of exposures an infant  
13 might be expected to see.

14 And they draw the conclusion from the table  
15 that in fact under these levels the inhalation -- the  
16 intake of manganese by inhalation is going to be  
17 infinitesimal or at most an infinitesimal or small  
18 portion, if that.

19 So trying to say, well, how can that be this  
20 is an issue? I interpret their table as just pointing  
21 out that at the level we're proposing in fact the  
22 manganese intake is appropriately low as opposed to,  
23 you know, being a source of real concern.

24 The reason for the table originally at that  
25 level was just to demonstrate that adults versus

1 children are going to have substantially different  
2 kinds of exposure at the same levels.

3 So beyond that, do you have a specific  
4 question regarding the comments?

5 PANEL MEMBER BLANC: Well, you know, they --  
6 again, we're reiterating their PBPK models --

7 OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

8 PANEL MEMBER BLANC: -- for manganese. Do you  
9 have any comment on that?

10 OEHHA STAFF TOXICOLOGIST WINDER: Well, we  
11 have reviewed all these models they've come up with  
12 including this most recent one Andy Nong.

13 We have been in touch with Andy and with  
14 Dorman's lab to try and get more of those data. We  
15 need to have more information regarding the parameters  
16 involved, the assumptions and this kind of stuff to  
17 evaluate them. We do not have that at this time.

18 PANEL MEMBER BLANC: So in terms of the papers  
19 that they mentioned, you're up to date in your reviews.

20 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

21 PANEL MEMBER BLANC: The revisions have  
22 included some papers that were not included before that  
23 relate to their --

24 OEHHA STAFF TOXICOLOGIST WINDER: Well, in  
25 terms of we reviewed the models, and the modeling was

1 not something we felt was appropriate because it was  
2 incomplete and we weren't able to verify --

3 CHAIRPERSON FROINES: Paul, they address it on  
4 page 33. Why don't you look at 33.

5 PANEL MEMBER BLANC: Yeah. My point is that  
6 your revision now includes a reference to and  
7 discussion of what was raised.

8 OEHHA STAFF TOXICOLOGIST WINDER: Right.

9 PANEL MEMBER BLANC: Yeah.

10 So John, what I would suggest now is we sort  
11 of go back and open it up.

12 CHAIRPERSON FROINES: Yeah. So I just want to  
13 ask you a quick question. And Melanie and I talked  
14 about this yesterday.

15 This issue of MMT, of course, is a major  
16 issue, especially if you live in Canada where it's  
17 used. And it's not used in the United States, and  
18 doesn't appear that it's going to be used in the United  
19 States, so I think that's fair. At this point --

20 PANEL MEMBER BLANC: You may want to wish you  
21 could comment on that next Thursday or Wednesday.

22 CHAIRPERSON FROINES: What?

23 PANEL MEMBER BLANC: Wednesday or Thursday if  
24 you wish.

25 PANEL MEMBER HAMMOND: Oh.

1 CHAIRPERSON FROINES: Yeah.

2 PANEL MEMBER HAMMOND: Oh, yes.

3 CHAIRPERSON FROINES: The one -- this is isn't  
4 really a question.

5 You talk about the Dorman study in here, and  
6 you talk about the mass median aerodynamic diameters  
7 with respect to the studies that were done. And I have  
8 a question.

9 Since one of the things that you raised in  
10 here is the combustion of MMT, the combustion of MMT is  
11 going to produce ultrafines by definition if you have  
12 combustion.

13 But there is no discussion about any particle  
14 size that are very small in that context. Does that  
15 basically mean that, as far as you know, nobody's  
16 looked, done experiments on ultrafines in terms of  
17 manganese MMT combustion products?

18 OEHHA STAFF TOXICOLOGIST WINDER: I don't  
19 recall seeing any studies on ultrafines with manganese,  
20 and specifically with MMT.

21 CHAIRPERSON FROINES: So that's a gap in  
22 basically in our knowledge.

23 OEHHA STAFF TOXICOLOGIST WINDER: As far as I  
24 know, that's correct.

25 PANEL MEMBER HAMMOND: Although, just given

1 what we know about combustion products in general, one  
2 would expect that the manganese would be in ultrafine  
3 particles from combustion.

4 CHAIRPERSON FROINES: Yeah. So you might put  
5 a sentence in there to say that this represents a  
6 research gap that would be valuable to address.

7 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

8 CHAIRPERSON FROINES: Other questions about  
9 manganese? Go around the room? Jim, why are you  
10 bopping up and down?

11 MR. BEHRMANN: Dr. Froines, before you leave  
12 manganese, I want to make sure we acknowledge on the  
13 record that there were four additional comments we  
14 received. Are you finishing up?

15 PANEL MEMBER BLANC: No, we have a ways to go.  
16 Don't worry about it.

17 MR. BEHRMANN: I'll come back.

18 PANEL MEMBER BLANC: Yeah, come back as  
19 needed, p.r.n.

20 CHAIRPERSON FROINES: Paul, do you have  
21 further comments?

22 PANEL MEMBER BLANC: Did you want me to start,  
23 as the Co-Lead?

24 First, I think the record should reflect that  
25 OEHHA was extremely responsive to the comments of the

1 last meeting, and this revision really reflects a very  
2 substantive amount of additional material and, I think,  
3 a thorough review of the literature through the spring  
4 of 2008, as you indicate at the outset.

5           So from that point of view, I think it's  
6 greatly strengthened.

7           And I think that some of the key issues of  
8 looking at the primate and the human data and reviewing  
9 it, whether or not it ultimately was that applicable,  
10 is much better. And you are to be commended.

11           I think one point that I had made to you when  
12 I first reviewed this was that you're still left with  
13 the most useful data set for your calculations being  
14 the Roels occupational exposure data set which, of  
15 course, has its limitations.

16           And one of the calculations that I suggested  
17 you do in parallel, not to replace it but to support  
18 the rationale, was an extrapolation from the primate  
19 data.

20           Now, it's partly related to the table you  
21 showed because one reason why you couldn't easily  
22 extrapolate from the primate data was because the  
23 endpoints of the best data were brain concentrations  
24 and not effects.

25           But now you have a table in which you show in

1 a parallel study in which there was parenteral  
2 administration and comparable brain levels that at  
3 those brain levels there were effects in primates;  
4 therefore, the reasonable presumption is that if  
5 neurobehavioral effects had been measured in the  
6 studies with inhalation, they would have also been  
7 present if biologically reasonable.

8           And I think the response I got was that that  
9 sounded like a good idea and you would sort of do that  
10 back-of-the-envelope calculation. But I think you'd  
11 already written this at that point.

12           OEHHA STAFF TOXICOLOGIST WINDER: Well, what  
13 happened is I was trying, going back to that, trying to  
14 get good conversion between the exposures that the  
15 monkeys got in these studies relative to what the  
16 anticipated human study.

17           The conversion numbers were not as readily  
18 available for that as they are, for example, for rats  
19 to do this kind of dosimetric adjustment. And then  
20 when you point out this other approach, that's when --  
21 went to that, you know, the --

22           PANEL MEMBER BLANC: But have you carried it  
23 to the last step? Is there something in here that's  
24 different than the text that I saw where you then said  
25 okay, now let's plug that in to our -- let's do a

1 benchmark calculation using those data, what would  
2 you --

3 OEHHA STAFF TOXICOLOGIST WINDER: From that  
4 table?

5 PANEL MEMBER BLANC: Right.

6 OEHHA STAFF TOXICOLOGIST WINDER: No, I have  
7 not done that.

8 PANEL MEMBER BLANC: I thought you said you  
9 were going to do that. Somebody said they were going  
10 to do that.

11 OEHHA STAFF TOXICOLOGIST WINDER: If I said  
12 that, I haven't, apparently.

13 PANEL MEMBER BLANC: Does the panel follow  
14 what I'm saying? We've done this before with other  
15 calculations, not to replace the Roels as the study for  
16 the benchmark but sort of as a thought experiment where  
17 you say, okay now, in order to see if this is falling  
18 into a reasonable range if we use the primate data with  
19 the following presumptions, this is what we would come  
20 up with as a benchmark.

21 OEHHA STAFF TOXICOLOGIST WINDER: I think I  
22 tried to get at that by showing the range over which  
23 Roels reported observing the neurotoxicity in that  
24 study.

25 There are issues with respect to how sensitive

1 are the monkeys with respect to these endpoints  
2 compared to humans, how comparable are the measures of  
3 neurotoxicity in the primates versus humans, that kind  
4 of stuff.

5           So I felt that this was, at least to the  
6 extent that I was able to from the data to address that  
7 particular question. But I haven't tried to come up  
8 with a specific number because, as I pointed out, the  
9 toxicity reported for the intravenous approach failed  
10 somewhere between the two upper dose levels that Dorman  
11 used. That seemed pretty fuzzy with respect to where  
12 exactly did it fall.

13           But I can go back and --

14           PANEL MEMBER BLANC: I think what one would be  
15 looking for is to see that you're within half an order  
16 of magnitude or somewhere that seems ballpark through a  
17 completely different method. It's always reaffirming  
18 to do it that way if you can.

19           You might -- you'd have a different -- I don't  
20 know what interspecies adjustments you use when you go  
21 from nonhuman primates to humans. Is it -- not one, is  
22 it?

23           OEHHA STAFF TOXICOLOGIST WINDER: Normally  
24 three.

25           PANEL MEMBER BLANC: So you'd have that.

1 OEHHA STAFF TOXICOLOGIST WINDER: Factor.

2 PANEL MEMBER BLANC: That factor in there.

3 And you'd still have the intraspecies child to  
4 adult because I think these were adult primates,  
5 weren't they?

6 OEHHA STAFF TOXICOLOGIST WINDER: Right.

7 PANEL MEMBER BLANC: The other thing on the  
8 same vein, by the way, is I think that the table that  
9 we discussed earlier which you then explained, you  
10 know, even on your slide you had an asterisk footnote  
11 that wasn't on actually where it appears in the text.

12 And I think this is a table that would really  
13 benefit from some footnote explication.

14 OEHHA STAFF TOXICOLOGIST WINDER: What page  
15 are you on?

16 PANEL MEMBER BLANC: Page 23, table 6.3.1.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
18 MARTY: The table you showed.

19 PANEL MEMBER BLANC: I think one footnote  
20 asterisk should make clear that no behavioral effects  
21 were seen at all of the levels in the column to the  
22 right.

23 OEHHA STAFF TOXICOLOGIST WINDER: Okay. Yeah.

24 PANEL MEMBER BLANC: And another asterisk  
25 should say that the annual dose in Roels for comparison

1 purpose was . . .

2 OEHHA STAFF TOXICOLOGIST WINDER: Right, okay.

3 PANEL MEMBER BLANC: So I think those are, to  
4 my mind, a couple of final things that would help.

5 And my earlier point about where the childhood  
6 should appear and that you should go over that very  
7 carefully and make sure there are no points that you  
8 missed.

9 Because it seems to me you actually have more  
10 supportive data than you usually do for increased  
11 childhood susceptibility; and in particular, you also  
12 have a full section in the animal toxicology on  
13 developmental and reproductive toxicity, and a piece of  
14 that developmental toxicity is developmental  
15 neurotoxicity, right?

16 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

17 PANEL MEMBER BLANC: So it's not -- now you  
18 didn't -- and there's a full paragraph of data that's  
19 new in there in terms of Chan. And you come back to  
20 Chan in those points, right? Point six --

21 OEHHA STAFF TOXICOLOGIST WINDER: Right.

22 PANEL MEMBER BLANC: -- is related to Chan in  
23 1992. But there is also the Tran 2002 study, Tran  
24 2002b which is not a new -- that you had cited  
25 previously because it's not new text.

1           So I guess the question is: Is there anything  
2 either in your expanded discussion of Chan or in Tran  
3 that you think needs to be in the potential  
4 differential effects?

5           I mean, you really go into Chan at great  
6 lengths, but the only thing you say about Chan is the  
7 newborn's brain is still developing. The blood-brain  
8 barrier is not completely formed. Is that the only  
9 take-home lesson from your lengthy analysis of Chan?  
10 Any regional areas that you think matter or any other  
11 nuance to that?

12           OEHHA STAFF TOXICOLOGIST WINDER: Well,  
13 based -- just based on Chan, I think that pretty much  
14 captures the essence there. We might be able to draw  
15 some conclusions from, you know, the description of  
16 Tran and Chan that ties it all together. So I think  
17 that's a point that could be elaborated a little  
18 further.

19           PANEL MEMBER BLANC: Yeah.

20           And in terms of human childhood data, other  
21 than the iron deficiency at one point would be if there  
22 is an easy review article that says, you know, that the  
23 prevalence of iron deficiency is ten percent or  
24 something, you might want to just say that.

25           But in this little mini epidemic of

1 intravenous-related neurotoxicity from potassium  
2 permanganate, were these of those adolescents? And was  
3 there anything to suggest that the adolescents did more  
4 poorly than the older adults in --

5 OEHHA STAFF TOXICOLOGIST WINDER: I didn't  
6 look at those data or those papers with that particular  
7 thing in mind. Most of them were young males. There  
8 may have been some that were adolescents.

9 PANEL MEMBER BLANC: So you might want to look  
10 at that quickly and --

11 OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

12 PANEL MEMBER BLANC: -- make sure that there's  
13 nothing there that we're missing.

14 OEHHA STAFF TOXICOLOGIST WINDER: Age of  
15 exposure.

16 PANEL MEMBER BLANC: Yeah.

17 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

18 PANEL MEMBER BLANC: So in terms of the  
19 comments, having looked at the material prepared by the  
20 Manganese Interest Group and Environ Corporation,  
21 having looked at it, I did not find it a convincing  
22 argument from a public health protective point of view  
23 that there was not sufficient questions in the existing  
24 data to warrant a tenfold safety factor for  
25 intraspecies variation that was childhood protective.

1           And I think that it's important to note that  
2   having some findings that might argue that you don't  
3   need to consider it are limited to certain areas alone  
4   and don't address the myriad of other issues. And you  
5   certainly have data which show potentiation, or  
6   synergism, depending on your use of terminology.

7           In terms of the other comments the panel  
8   received, these were basically brief comments,  
9   testimonials from people saying they are concerned  
10  about manganese. And I think that the deliberation of  
11  the panel indicates that we're concerned about  
12  manganese too, and so I'm glad for their echoing of  
13  that. But I don't believe it indicates any need for  
14  revision of your document in a substantive way.

15           CHAIRPERSON FROINES: Can I just interrupt you  
16  long enough to say does -- we're going to go around the  
17  room, clearly, but does anybody else on the panel have  
18  any disagreements with Paul with respect to those  
19  documents that came in late?

20           Because I'd like to go on the record to  
21  state -- Paul can just state it explicitly -- the fact  
22  that we don't find that there are reasons for  
23  alterations, given the comments.

24           PANEL MEMBER BLANC: I don't think there is a  
25  convincing argument to abandon a tenfold uncertainty

1 factor for childhood susceptibility.

2 CHAIRPERSON FROINES: Can you be a little  
3 closer to the mic?

4 PANEL MEMBER BLANC: I don't believe that  
5 there is a convincing argument against a tenfold  
6 adjustment for potential childhood susceptibility.

7 CHAIRPERSON FROINES: And there is no  
8 opposition on the panel to that statement?

9 (No response)

10 CHAIRPERSON FROINES: So we'll take that as a  
11 unanimous statement about the comments that came in  
12 late.

13 Joe? I think Paul's finished.

14 PANEL MEMBER BLANC: Yes.

15 PANEL MEMBER LANDOLPH: I just had a couple  
16 quick questions. One is for the manganese acute REL:  
17 Is there just no data or no good data to allow you to  
18 address that?

19 OEHHA STAFF TOXICOLOGIST WINDER: No good  
20 data. As I tried to address there, the studies we  
21 found were typically single-dose studies, most of them,  
22 and they were generally looking at either oral or IV  
23 administration, which doesn't really translate well in  
24 inhalation.

25 And they tend to measure just brain levels

1 without some sort of indication of toxicity. We don't  
2 know to what do those brain levels correspond.

3 PANEL MEMBER LANDOLPH: And was there any data  
4 in there on this nonspecific pulmonary edema that you  
5 could get a feel for where that occurred at and whether  
6 that was similar to levels at which you'd have the  
7 neurotoxicity symptoms?

8 OEHHA STAFF TOXICOLOGIST WINDER: My general  
9 impression from the papers I've read is that the  
10 pulmonary toxicity occurs at much higher level than the  
11 neurotox. So to try and come up with a REL, acute REL  
12 based on pulmonary toxicity might not be particularly  
13 protective of the neurotoxic effects. I don't have the  
14 data to make that clear.

15 PANEL MEMBER BLANC: Yeah, I would echo that.  
16 To see case reports of pulmonary toxicity, you have to  
17 go back to case reports from the 1940s. And I'm not  
18 even sure what those industrial processes were.

19 When you look at the levels you get in typical  
20 stick welding, they're quite high. And in fact, there  
21 are no convincing pulmonary effects from the manganese  
22 in stick welding.

23 So I think that even if OEHHA could go through  
24 the exercise of developing an acute REL, it would come  
25 out to be a number which wouldn't have relevance of --

1 public health relevance from any scenario in which it  
2 would be likely to occur for the purposes of even hot  
3 spot, you know, releases, you know, immediately down  
4 wind.

5 So I am comfortable with them just letting  
6 that go because I think it would just be -- you know.

7 PANEL MEMBER LANDOLPH: That's fine. And  
8 thank you for that response.

9 Then I had another question. The Manganese  
10 Interest Group's comments were dedicated toward talking  
11 about the homeostasis tending to damp down the  
12 manganese levels. And then I read other statements  
13 that you get an uptake through the nose which goes  
14 directly to the brain and subverts the blood-brain  
15 barrier.

16 I wonder if you felt you had adequately  
17 covered that discussion in your document?

18 OEHPA STAFF TOXICOLOGIST WINDER: I thought  
19 so. If you think it needs more elaboration, we can  
20 certainly add that.

21 PANEL MEMBER BLANC: I think we did. I did  
22 point out to you that I thought in your bullet summary  
23 of childhood susceptibility that the bullet on nasal  
24 deposition could be expanded, and I think that that  
25 would address your point.

1           PANEL MEMBER LANDOLPH: Yeah. And I think  
2 that would put you on better ground and directly  
3 address the Manganese Interest Group thing and state  
4 that although homeostasis does exist to a certain  
5 extent you subvert that mechanism when you have direct  
6 nasal uptake directly into the brain. I think that  
7 would put you on stronger scientific ground.

8           PANEL MEMBER BLANC: And also, by the way, to  
9 the extent that you might be dealing with organic  
10 manganese compounds you have absolutely no basis to  
11 assume that the homeostatic mechanisms would come into  
12 play. Nor do they come into play necessarily when  
13 exposure is through an inhalation route anyway. We  
14 know that from human data.

15           OEHHA STAFF TOXICOLOGIST WINDER: Okay.

16           CHAIRPERSON FROINES: It would be useful to  
17 find something on the ultrafines as well.

18           Craig?

19           PANEL MEMBER BYUS: I was able to read the  
20 comments, all of them, and the document. And I think  
21 it deals with it appropriately. I mean the whole topic  
22 of neurotoxicology/neuroinflammation is an extremely  
23 active area of research, and there's a lot we don't  
24 understand.

25           But a lot of it will become clearer probably

1 in the next five to 10 years, so it's going to be --  
2 we'll really come to a better understanding, I hope,  
3 and be able to extrapolate this to risk assessment and  
4 exposure.

5 CHAIRPERSON FROINES: Charlie?

6 PANEL MEMBER PLOPPER: Yes. I thought it was  
7 an excellent revision, and I agree with what Paul said.

8 I had one comment that I'll add to what  
9 everyone else has said. That is when I was looking  
10 through these and looking for your summaries of studies  
11 and rationales for setting these factors, the one thing  
12 that I had a difficult time -- maybe it's just from my  
13 biases -- that you don't -- it seems to me that there's  
14 problems with the concentration as well as the size in  
15 all these inhalation studies. And depending on which  
16 that is, the route will be different; that's what  
17 everybody is emphasizing.

18 But some of these studies are also done by  
19 gastric and -- by ingestion. And unfortunately, a  
20 large percentage of these -- some of these inhalation  
21 studies, actually exposures through the  
22 gastrointestinal tract.

23 And I had a problem trying to sort these out  
24 like the Dorman's table with Schneider. It would help  
25 if you had the size range for the Dorman particles

1 there. You have it, but it's five, eight pages ahead  
2 of time.

3 If there's some way to break that down for  
4 each one of these studies so that it's very clear, I  
5 think that would be of help with Manganese Interest  
6 Group as well, responding to their comments, is to  
7 explain exactly what the nature of this exposure is in  
8 terms of what the particle size is and how it gets  
9 there.

10 OEHHA STAFF TOXICOLOGIST WINDER: Okay. That  
11 information is available on some of these studies but  
12 not all.

13 PANEL MEMBER PLOPPER: Well, but then you need  
14 to say if it isn't because that's pretty important for  
15 making a judgment about the toxicity and the long-term  
16 effect, particularly in children because everything is  
17 going to change as you get smaller and smaller and  
18 younger.

19 OEHHA STAFF TOXICOLOGIST WINDER: Okay. We  
20 can handle that.

21 PANEL MEMBER PLOPPER: That was pretty much --  
22 I thought that that would probably address some of  
23 these graphs that they -- that the Manganese Interest  
24 Group had from the Dorman study as well.

25 Because it's not actually the same. If you

1 look at it from a biological perspective, the young  
2 adult versus the neonatal rats, that's not really the  
3 same exposure even though they put them in the same  
4 place. It's not the same exposure, but you have to  
5 address that because that's the issue here. I think,  
6 anyway.

7 OEHHA STAFF TOXICOLOGIST WINDER: All right.

8 PANEL MEMBER BYUS: Gary, do you have any  
9 comments?

10 PANEL MEMBER FRIEDMAN: I just want to thank  
11 the OEHHA group for their responsive revisions. I have  
12 nothing to add to what's been said.

13 PANEL MEMBER BYUS: Kathy?

14 PANEL MEMBER HAMMOND: Thank you also.  
15 Excellent.

16 PANEL MEMBER BYUS: Well, our chairman has  
17 stepped out of the room briefly. Perhaps we should  
18 wait for him to return.

19 PANEL MEMBER BLANC: We were going to hear  
20 about acetaldehyde? So why don't we do acetaldehyde.

21 CHAIRPERSON FROINES: Not yet. Not yet. No,  
22 we don't get to go on past manganese yet.

23 I want to raise a fundamental issue for this  
24 panel to make a decision on.

25 Manganese is a HAP. It's a Hazardous Air

1 Pollutant. Therefore, it was designated -- it was  
2 grandfathered in as a TAC. So manganese and compounds,  
3 unless I'm mistaken, is currently a Toxic Air  
4 Contaminant in the State of California.

5           And I think that -- but there has been no  
6 regulatory process that's been initiated as a result of  
7 its being a Toxic Air Contaminant. And my view is that  
8 the toxicity that's been demonstrated here today  
9 demonstrates that manganese is an extremely important  
10 compound in terms of atmospheric potential toxicity.

11           And I really think that this panel should go  
12 on record saying there needs to be follow-up at the Air  
13 Resources Board level with respect to manganese and  
14 that in particular it should be addressed as an SB 25,  
15 and we make that position clear from this panel, if  
16 people agree.

17           Paul? And you're the Lead, so what's your  
18 view on this?

19           PANEL MEMBER BLANC: Well, would it tell us  
20 what the implications of that are?

21           CHAIRPERSON FROINES: Well, the  
22 implications -- we are supposed to do risk assessment,  
23 and we're supposed to not do risk management.

24           PANEL MEMBER BLANC: Right.

25           CHAIRPERSON FROINES: But there seems to me to

1 be no reason that we can't recommend under SB 25 that  
2 manganese be taken up as an SB 25 compound, but we also  
3 would recommend that consideration be given to the  
4 beginning of some kind of policy process that would  
5 address the toxicity of manganese.

6 PANEL MEMBER BLANC: Well, you know, I would  
7 suggest just as a matter of sequence that you come back  
8 to that thought after we address the packet of these  
9 assessments because we haven't really approved it yet.

10 It makes more sense to me to first approve it  
11 in the context of approving the document and then  
12 saying that.

13 CHAIRPERSON FROINES: Well, the only reason I  
14 raise that now is we're about to go to acetaldehyde and  
15 formaldehyde, and that will take us back to when Stan  
16 gets here. But the important thing is that you leave  
17 at 1 o'clock.

18 PANEL MEMBER BLANC: Well, I would support --  
19 I mean, just to come back to it, you'll still have a  
20 quorum. And I certainly would support that.

21 CHAIRPERSON FROINES: But you're the Lead on  
22 manganese and played a crucial role, and I want you to  
23 give advice to the panel on whether you agree with what  
24 I'm suggesting.

25 PANEL MEMBER BLANC: I think it's --

1 CHAIRPERSON FROINES: Or disagree.

2 PANEL MEMBER BLANC: I think that even without  
3 the potential spectre of manganese gasoline additives  
4 the point would be well-taken.

5 I think with that added public health issue,  
6 it's all the more important because there could be a  
7 scenario under which, on a national level, such an  
8 additive was allowed. And I think it would be  
9 important for the Air Resources Board to be prepared at  
10 the state level for that.

11 CHAIRPERSON FROINES: So what I'm basically  
12 proposing is two things: One is that we do recommend  
13 that it be taken up as an SB 25 chemical and that --  
14 and basically reinforce the position that OEHHA took in  
15 this document. Because they say it explicitly.

16 The second thing I'm saying is that we  
17 recommend that ARB look at manganese from the  
18 standpoint of making policy decisions about subsequent  
19 activity that they may wish to pursue.

20 PANEL MEMBER BLANC: Oh, I would support that.  
21 I don't know the format in which you want to formally  
22 do that and the timing; but when it comes to it, if I'm  
23 not in the room I would have supported it had I been  
24 here.

25 PANEL MEMBER FRIEDMAN: Would that be a letter

1 from you to the head of the ARB?

2 CHAIRPERSON FROINES: Yeah.

3 PANEL MEMBER BYUS: Is it of importance or  
4 relevance to make an analogy to lead exposure in  
5 manganese at this time?

6 I mean it's -- there's a lot of similarities  
7 in the panel's long-term concern regarding lead in the  
8 atmosphere. I mean it's -- there's not exactly the  
9 same, but there is a similarity. It's worth making the  
10 analogy.

11 CHAIRPERSON FROINES: So unless I hear an  
12 objection, I'm going to assume there is general  
13 agreement. Kathy, you're okay?

14 PANEL MEMBER HAMMOND: Mm-hmm.

15 CHAIRPERSON FROINES: Charlie looks okay. And  
16 Stan, we take as a given. We'll talk with Stan when  
17 he's here.

18 So you're -- is what I said okay with you  
19 guys?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
21 MARTY: Yeah. I just wanted to point out that if you  
22 approve the report, in here it says that manganese will  
23 be listed as a toxic air contaminant that  
24 disproportionately impacts children. Under the Health  
25 and Safety Code, that allows us to do that.

1           And that actually triggers a needs assessment  
2 by the Air Resources Board for control. So I just want  
3 to get that out.

4           CHAIRPERSON FROINES: So we only need to make  
5 the first recommendation then rather than more.

6           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
7 MARTY: It wouldn't hurt to tweak it a little bit.

8           CHAIRPERSON FROINES: Okay. So that's very  
9 useful.

10           I did want to go on the record to have the  
11 panel actually approve what you recommended because I  
12 think that shows the seriousness of the situation  
13 because it's obvious. So thanks.

14           PANEL MEMBER FRIEDMAN: Do you mind just  
15 briefly saying what MMT is supposed to be -- how it  
16 helps to add it to gasoline? What is the rationale for  
17 even considering that?

18           CHAIRPERSON FROINES: Well, it's used -- it is  
19 used in Canada. So when you fill your gas tank up in  
20 Canada and drive back to the US, you've got -- anyway,  
21 joking aside, it increases octane. I think that's  
22 right. I think that's right.

23           And it's not approved in the United States.  
24 And of course, one would hope that given its toxicity  
25 that one would not see it being pursued as a gasoline

1 additive. We've got enough trouble with ethanol and  
2 biodiesel at this point to add another one.

3 PANEL MEMBER GLANTZ: I'm back.

4 CHAIRPERSON FROINES: Thank you, Melanie.

5 Shall we move on?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: The next compound we're going to describe the  
8 changes to the REL is acetaldehyde, and Karen Riveles  
9 will give the presentation.

10 CHAIRPERSON FROINES: I went into a sports bar  
11 down by the hotel last night, the Stanyon Hotel, and  
12 the sports bar was -- you could have heard people  
13 yelling on the Golden Gate Bridge because of the  
14 Philadelphia Phillies, and there was an awful lot of  
15 acetaldehyde that was in people's systemic circulation.

16 (Laughter)

17 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Thank  
18 you, Dr. Marty. My name is Dr. Karen Riveles, and I am  
19 here to discuss the changes made to the acetaldehyde  
20 noncancer REL document.

21 This is an overview of the changes we have  
22 made. The most major one was changing the key study  
23 that we used as the basis of the acute REL which I will  
24 go into more detail in subsequent slides.

25 OEHHA did use a study performed in human

1 volunteers investigating bronchoconstriction in  
2 asthmatics in response to inhaled aerosolized  
3 acetaldehyde by a group in Spain, Prieto.

4 Through personal communication with the  
5 author, I was able to receive the 95 percent confidence  
6 interval for the mean PC20 which was not mentioned in  
7 the paper itself.

8 These changes and additions are seen in  
9 revisions made in the document sent to the panel, and I  
10 will try to highlight some of the pages as we go on.

11 Again, this Prieto study was done in human  
12 volunteers. Of all of the human studies using  
13 aerosolized acetaldehyde solutions, this one had the  
14 largest sample size, using a sample size of 61 mildly  
15 asthmatic human volunteers and a control group of 20  
16 healthy subjects. And that is on page 20 of the  
17 report.

18 In addition, I just want to point out that the  
19 mean age of the subjects were between 29.3 and 32.1  
20 with an average of 30.7.

21 They were exposed to aerosolized acetaldehyde  
22 solutions ranging from 5 to 40 milligrams of  
23 acetaldehyde per mil for two minutes.

24 Bronchoconstriction was observed in asthmatics  
25 in response to the inhaled aerosolized acetaldehyde.

1           The paper determined a PC20 which is the mean  
2   acetaldehyde concentration causing a 20 percent  
3   decrease in forced expiratory volume.

4           The PC20 values for acetaldehyde ranged from  
5   1.96 to 40 mgs per mil, and the 95 percent confidence  
6   interval was therefore 4.72 to 38.3 mgs per mil which  
7   had a geometric mean value of 17.55 mgs per mil.

8           In the asthmatic group, 56 out of 61 of the  
9   subjects showed bronchoconstriction compared to zero  
10   out of 20 in the control group. So the lower 95  
11   percent confidence interval of 4.72 mgs per mil  
12   corresponds to approximately 142 mgs per meter cubed or  
13   79 ppm.

14           As we discussed at length at the last meeting,  
15   we used a -- we had to change -- we had to extrapolate  
16   the values from mgs per mil aerosolized solution to an  
17   approximate air concentration. And to do so, we needed  
18   the parameters of the nebulizer machine.

19           For this study, they used a Hudson 1720  
20   nebulizer which was operated by compressed air at six  
21   liters per minute with an acetaldehyde solution output  
22   0.18 mils per minute, so that is what was used for the  
23   conversion.

24           Now previously, as you recall, we were using  
25   the Silverman, et al. 1946 study as the proposed acute

1 REL. And this was based on eye irritation in human  
2 volunteers. And the REL we had calculated was 750  
3 micrograms per meter cubed or 420 parts per billion.

4 And after the panel's suggestions at previous  
5 meetings that this study was both antiquated and very  
6 subjective, we have a new proposed REL using a new key  
7 study of Prieto et al. 2000 of 470 micrograms per meter  
8 cubed or 260 parts per billion based on  
9 bronchoconstriction and asthmatic human volunteers.

10 If you are looking at the report, there is a  
11 detailed addition on page 9 of the -- including the 95  
12 percent confidence interval and the conversion to mgs  
13 per meter cubed. And then in the actual acute REL  
14 determination section, which is on page 20, first I  
15 detail using the Prieto, et al. study, I kept in the  
16 derivation of the Silverman study just by comparison  
17 and to show supporting evidence.

18 And finally, in the conclusion at the end on  
19 page 22, I suggest that the new REL based on the Prieto  
20 study is protective also of eye irrigation based on the  
21 Silverman study.

22 PANEL MEMBER BLANC: Just remind us, on the  
23 old Silverman calculations, there wasn't a necessity  
24 for an intraspecies adjustment, just as in this one, so  
25 it's one.

1 OEHHA ASSOCIATE TOXICOLOGIST RIVELES:

2 Correct.

3 PANEL MEMBER BLANC: In this one, there is an  
4 adjustment for the -- because you're going from a LOAEL  
5 to a NOAEL, in the Silverman, was that also the case?  
6 Or was it just the NOAEL?

7 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: In the  
8 Silverman, we only had a LOAEL.

9 PANEL MEMBER BLANC: So it was also similar  
10 that regard.

11 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: We did  
12 have a LOAEL uncertainty factor.

13 PANEL MEMBER BLANC: Right, for -- of ten? Or  
14 of three?

15 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: It was  
16 six.

17 PANEL MEMBER BLANC: Because it was eye --

18 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Because  
19 it was eye irritation versus bronchoconstriction which  
20 is considered more severe.

21 PANEL MEMBER BLANC: And then did you have any  
22 reason to have a childhood adjustment?

23 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: In  
24 the --

25 PANEL MEMBER BLANC: -- in the Silverman?

1           OEHHA ASSOCIATE TOXICOLOGIST RIVELES: In the  
2 Silverman, we had a value of ten for asthma  
3 exacerbation in children.

4           PANEL MEMBER BLANC: I see. Okay. I follow  
5 it.

6           PANEL MEMBER FRIEDMAN: I have a question.  
7           Could you go back to the second last slide?  
8 Was the 95 percent confidence interval around the  
9 geometric mean of 17.55? Is that what that refers to?

10          OEHHA ASSOCIATE TOXICOLOGIST RIVELES:  
11 Correct.

12          PANEL MEMBER FRIEDMAN: You know, maybe Stan  
13 could comment on this. But usually when I see 95  
14 percent confident intervals, the multiplying factor is  
15 the same.

16           In other words, the 4.72, the lower limit, is  
17 about a fourth of the mean whereas the upper limit is  
18 only twice that. I would have expected the upper limit  
19 to be four times as great.

20           But I'm used to looking at confidence  
21 intervals for relative risk, and maybe it's different  
22 for geometric means. Do you know, Stan? Does that  
23 look right to you?

24          PANEL MEMBER GLANTZ: I'm sorry. Just not --  
25 it's not symmetrical. You're doing it in logs, right?

1 PANEL MEMBER HAMMOND: Yes.

2 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The 95  
3 percent confidence interval that was provided was for  
4 the arithmetic mean, not the geometric mean. That was  
5 a policy suggestion of the panel at the last meeting.

6 PANEL MEMBER FRIEDMAN: What was it for?

7 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The 95  
8 confidence interval of the arithmetic mean, not the  
9 geometric mean.

10 PANEL MEMBER FRIEDMAN: So why aren't you  
11 using the arithmetic mean then -- you are using it.  
12 Why did you present the geometric mean? I guess I  
13 don't understand.

14 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Because  
15 at the last meeting I had reported that we were going  
16 to use 17.55, and so this is just to show you --  
17 because this was reported in the paper. The arithmetic  
18 mean was never reported in the paper.

19 PANEL MEMBER GLANTZ: I don't actually  
20 remember -- was I there when we talked about this?

21 If you're going to present the geometric mean,  
22 you should give the confidence interval for the  
23 geometric mean.

24 CHAIRPERSON FROINES: But she's using the  
25 arithmetic mean based on the data she was able to

1 gather.

2 OEHHA ASSOCIATE TOXICOLOGIST RIVELES:

3 Correct. We are not using either mean value.

4 Our point of departure now is the lower -- I'm  
5 sorry; I should have said this. Our point of departure  
6 now for the determination of our REL is the lower bound  
7 of the 95 percent confidence interval which is 4.72.

8 PANEL MEMBER FRIEDMAN: Of what?

9 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Of the  
10 arithmetic mean.

11 PANEL MEMBER FRIEDMAN: That's what you should  
12 state as part of the --

13 PANEL MEMBER GLANTZ: Okay. Well, if that's  
14 the case, I have to say I put my energy into the other  
15 document, so.

16 CHAIRPERSON FROINES: Stan, I can't hear you.

17 PANEL MEMBER GLANTZ: In getting ready for  
18 this meeting, I was concentrating mostly on the other  
19 document, and I missed this point.

20 But I think if you're going to use the 95 --  
21 the lower bound of the 95 percent confidence interval  
22 for the arithmetic mean, then the report should be  
23 about the arithmetic mean. You shouldn't be mixing the  
24 geometric and arithmetic means.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: We only did it on this slide. So that's --  
2 sorry.

3 CHAIRPERSON FROINES: We should have the  
4 geometric mean disappear.

5 PANEL MEMBER GLANTZ: Well, there are times  
6 that using geometric mean is dandy. But you should  
7 pick one or the other and justify it and being  
8 consistent in using that. You shouldn't mix --

9 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: We  
10 don't use it to derive our acute REL.

11 On page 11 of our report, we show a table of  
12 all of the aerosolized acetaldehyde provocation studies  
13 in adult human volunteers; and in each case, the PC20  
14 value was given in those papers a geometric mean.

15 And then for the Prieto 2000, through further  
16 communication with the author, we were able to obtain  
17 further data.

18 So the reason I presented it was simply as a  
19 point of comparison to the other adult human studies.

20 PANEL MEMBER BLANC: But, you know, one of the  
21 sources of confusion and one of the reasons why they  
22 probably presented the geometric mean has to do with  
23 the convention when you do methacholine challenge data  
24 where you're typically talking about doubling doses and  
25 so things are often presented as log-transformed data,

1 and geometric mean, I don't know but --

2 PANEL MEMBER GLANTZ: The geometric mean is --  
3 if the data is log normal, then a geometric mean makes  
4 sense.

5 PANEL MEMBER BLANC: Right, that's why it's  
6 done that way.

7 But I do have a question for you just since  
8 Gary brought it up about the confidence -- so what they  
9 did was, there were 62 subjects, right?

10 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: 61.

11 PANEL MEMBER BLANC: 61. So they gave you the  
12 data points for all 61, basically.

13 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: They're  
14 in the manuscript.

15 PANEL MEMBER BLANC: All 61?

16 OEHHA ASSOCIATE TOXICOLOGIST RIVELES:  
17 Correct.

18 PANEL MEMBER BLANC: Okay. So -- and the  
19 range of the levels at which they had their 20 percent  
20 fall went from 1.96 to 40?

21 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That's  
22 correct, but it was only in the paper in terms of a  
23 graph with points on it, not actual numerical values.

24 PANEL MEMBER BLANC: Did they give you the  
25 numerical values for all of them then?

1           OEHHA ASSOCIATE TOXICOLOGIST RIVELES: I did  
2 not ask for that raw data.

3           PANEL MEMBER BLANC: So what you asked for was  
4 the arithmetic mean, and the arithmetic 95 percent  
5 confidence interval?

6           OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That's  
7 correct.

8           PANEL MEMBER BLANC: Okay. So one thing  
9 that's a little bit surprising, unless the 1.96 was,  
10 you know, in -- if there were 60 observations, and 1.96  
11 was really an outlier, it's a little bit surprising  
12 that your 95 percent confidence interval is lower level  
13 of 4.72 and their absolute range went as far as it did.

14           So I guess you might want to just have a very  
15 brief communication with them or eyeball the data and  
16 make sure that that looks reasonable to you. When you  
17 look at the figure with the distribution, you see the  
18 very lower one, how many things are close to that very  
19 lower one?

20           You want to make sure that your 95 -- your  
21 lower 95 percent of 4.72 isn't too conservative.

22           PANEL MEMBER GLANTZ: Yeah. You know, just  
23 looking at this, I mean they're using a log scale here  
24 so the data are probably log-normal, just using the  
25 eyeball technique.

1           So if the data are log-normal, then you ought  
2 to be using the geometric mean and the confidence  
3 interval commuted off the geometric mean.

4           CHAIRPERSON FROINES: Talk into your  
5 microphone.

6           PANEL MEMBER GLANTZ: Okay. Just eyeballing  
7 this graph, you know, which has got a log scale for the  
8 dependent variables, and it looks sort of normal on a  
9 log scale which means it's probably log-normal.

10           When you have log-normal data, it makes a lot  
11 more sense to present the geometric mean and the  
12 confidence interval computed from the geometric mean,  
13 kind of like a confidence interval on a relative risk,  
14 which isn't symmetrical, rather than using the  
15 arithmetic mean in computing the confidence interval  
16 there.

17           So actually, I would use the geometric mean  
18 now that I see what the data looks like. And the  
19 geometric confidence interval.

20           PANEL MEMBER BLANC: But I want to say that  
21 what you've done in principle is the absolute right way  
22 to go. And although your number may change a little  
23 bit and perhaps may be slightly lower if in fact your  
24 value comes to be a little bit closer to -- it's going  
25 to fall probably somewhere between 4.72 and 1.96. It's

1 not going to go beyond 1.96.

2           So it may make your acute REL slightly lower;  
3 but in general, I think this is great that you have  
4 done this in terms of this is the right study to use  
5 and much better. You know, you're not an order of  
6 magnitude different than you were with the Silverman  
7 but it just makes a whole lot more sense.

8           CHAIRPERSON FROINES: So there may be a small  
9 change in the numbers when we have finalized it.

10           But I think we -- in terms of approving all  
11 these different chemicals today, we can say that  
12 we're -- we will accept this chemical with that  
13 proviso. Is that fair, Stan?

14           PANEL MEMBER GLANTZ: (Nodding head)

15           PANEL MEMBER BLANC: It's hard to believe  
16 that -- it's not going to change.

17           PANEL MEMBER GLANTZ: Yeah, it's not going to  
18 be wildly different.

19           PANEL MEMBER BLANC: And I think it's an  
20 important point because it might be slightly lower.

21           CHAIRPERSON FROINES: Might be a little bit  
22 more conservative.

23           PANEL MEMBER HAMMOND: I think it will go  
24 higher.

25           PANEL MEMBER GLANTZ: No, it will go higher

1 because when you -- when you -- because it's going  
2 to -- yeah, it will be higher because it will be a  
3 better fit to the log-normal.

4 But it's not going to be wildly different. In  
5 fact, it will be whatever it is.

6 PANEL MEMBER HAMMOND: I'm a little confused.  
7 I just apologize. Can we just back up on this?

8 What are we talking about the geometric or the  
9 arithmetic mean of? Is this multi -- they're multiple  
10 experiments, and they're trying to achieve a particular  
11 concentration?

12 PANEL MEMBER BLANC: No. What they did was  
13 they took 61 individuals.

14 PANEL MEMBER HAMMOND: Right.

15 PANEL MEMBER BLANC: And they each of them did  
16 a dose response curve as if it was methacholine, but it  
17 was this chemical to see at what point did they drop  
18 20 percent of their FEV1 and so for some people.

19 PANEL MEMBER HAMMOND: So geometric mean of  
20 the values where they dropped 20 percent.

21 PANEL MEMBER BLANC: Of the value for --

22 PANEL MEMBER HAMMOND: Of the 61 subjects.

23 PANEL MEMBER BLANC: Of the value for each of  
24 the 61 subjects at which they dropped 20 percent of  
25 their FEV1.

1           PANEL MEMBER GLANTZ: So they got a value for  
2 each subject which was the dose it took to get the  
3 effect; and then they have the distribution -- that  
4 graph that we were looking at is the value that got you  
5 down to 20 percent for the 61 people.

6           And so what we're talking about is if you're  
7 computing a confidence interval for the effect size,  
8 how should you do that?

9           PANEL MEMBER HAMMOND: You know, I'm not sure.  
10           To me, I have some concern about that, just  
11 the way of thinking about it. And that is that when  
12 we -- we're talking about human beings, which is great,  
13 you know.

14           But we have all that variability in human  
15 beings, which we know. And we actually have within  
16 that experiment a little bit of that information, of  
17 that variability. And at one level, it seems to me, we  
18 should be taking the lowest level, the lowest PC20  
19 should be the value we use, not the geometric mean of  
20 those.

21           PANEL MEMBER GLANTZ: Well, no, they're not.  
22           You're not basing the standard on the mean;  
23 you're basing it on the lower end of the confidence  
24 interval.

25           PANEL MEMBER HAMMOND: Of the mean, though.

1 Is that lower -- is that value lower than the -- and  
2 certainly the value should not be higher than the  
3 lowest PC20 that was observed.

4 PANEL MEMBER GLANTZ: Are you computing the  
5 lower confidence found for the population or for the  
6 mean?

7 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: For the  
8 population. Only one individual had 1.96 as their  
9 value.

10 PANEL MEMBER GLANTZ: Yeah. I think the  
11 problem here is that bringing the mean in just confused  
12 matters.

13 CHAIRPERSON FROINES: I think Kathy is right.

14 PANEL MEMBER GLANTZ: No, the confidence --  
15 they're saying the confidence intervals they were  
16 computing was for the population.

17 It's really that -- really, it seems to me  
18 what you're talking about is the fifth percentile of  
19 dose that creates the effect.

20 PANEL MEMBER HAMMOND: But aren't you saying  
21 that the value you're using of 4.72, that's the lower  
22 confidence interval, and yet we know that one  
23 individual actually had 1.96, is their PC20; is that  
24 correct?

25 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That is

1 correct.

2 PANEL MEMBER HAMMOND: So it strikes me that  
3 we know that at least one person out of 61 responded at  
4 half the level of the lower 95 percent confidence  
5 limit. Is that --

6 PANEL MEMBER GLANTZ: But that's what you  
7 would expect. Because if you've got 60 people, about  
8 three or four of them are going to be outside the 95  
9 percent range.

10 I think the problem here, it's a little bit  
11 like when we were talking about the shelf life this  
12 morning. I think the way you're using the language is  
13 very confusing.

14 But if you're setting -- my understanding is  
15 if you set this number, this is the -- if you look at  
16 the range -- if you look at the distribution of values  
17 that you've got, basically it's the fifth percentile --

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
19 MARTY: Right.

20 PANEL MEMBER GLANTZ: -- of all the values.  
21 So talking about the confidence interval --

22 CHAIRPERSON FROINES: Is it all the values?

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
24 MARTY: Right. 61.

25 CHAIRPERSON FROINES: You're keeping the 1.96

1 in?

2 PANEL MEMBER GLANTZ: Yes. But by definition,  
3 if you're in the fifth percentile, something's going  
4 to -- you're going to have one or two below that if you  
5 have 61 cases.

6 CHAIRPERSON FROINES: Sure.

7 PANEL MEMBER HAMMOND: Okay. Is there a  
8 factor -- now what factor is used to go from that value  
9 that you have, the 95 percent lower confidence limit  
10 number, to the REL then?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
12 MARTY: There's a cumulative uncertainty factor of 300.

13 PANEL MEMBER HAMMOND: Because one of the  
14 other issues I wanted to bring up -- and I'm not sure  
15 how to deal with this; it just concerns me -- is that,  
16 for good ethical reasons, the study was done with  
17 mildly asthmatic subjects.

18 And the reality, we know, is that there are  
19 severely asthmatic subjects out there that we're not  
20 about to do such experiments with, but we need to be  
21 protecting.

22 So how does one think about how we protect  
23 them without having the experimental data?

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
25 MARTY: We did a couple of things. The toxicodynamic

1 uncertainty factor for humans is 30.

2 PANEL MEMBER HAMMOND: That's to adjust for  
3 mildly to severe asthmatics.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
5 MARTY: In part.

6 PANEL MEMBER BLANC: So one --

7 PANEL MEMBER HAMMOND: I would defer to --

8 PANEL MEMBER BLANC: One thing that you might  
9 ask them for -- you're going to have to go back to  
10 them, right? So you're going to ask them for the, as  
11 we said, the 95 percent confidence interval, the  
12 geometric mean, so that's one thing.

13 But I would actually ask them for the numeric  
14 data points from the figure. And what I think you  
15 should do, if there were 61 individuals, the cutoff  
16 point at which three individuals responded would be  
17 roughly the lower 95. That would be the fifth  
18 percentile of the actual data.

19 PANEL MEMBER FRIEDMAN: Except it's two and a  
20 half each side, so it's really half of that.

21 PANEL MEMBER BLANC: That's correct. You're  
22 right.

23 So you know -- we know that one person  
24 responded at 1.96. If the next person responded at  
25 2.5, then you could make the argument that 2.5 is your

1 cutoff because that included the 2. -- that's your 95th  
2 percent of your observed thing, without making  
3 assumptions about the normal -- without normalizing the  
4 distribution.

5 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Just by  
6 eyeballing the data that are --

7 PANEL MEMBER GLANTZ: I think there actually.

8 CHAIRPERSON FROINES: Stan, let her finish.

9 PANEL MEMBER GLANTZ: Sorry.

10 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: There's  
11 two individuals that are in that bottom range, and then  
12 the next two are around, just eyeballing it, around  
13 between 4 and 5.

14 PANEL MEMBER GLANTZ: I think the -- and  
15 again, I missed the first part of discussion here, but  
16 I think the -- I mean they can test to how well the  
17 data fits the log-normal distribution. But just  
18 looking at it, it fits it, and that's the way, you  
19 know.

20 So I think that the idea of fitting it to a  
21 log-normal distribution and then using the geometric  
22 mean and geometric standard deviation to compute the  
23 lower 95th percentile -- the upper and lower bounds of  
24 the confidence interval, and then using that, I think  
25 that's better than just doing it from the raw data.

1           PANEL MEMBER BLANC: All right.

2           And again, the bottom line is that it is the  
3 right study, it is overall the right approach, you're  
4 probably not going to change it dramatically, and I  
5 support what you've done.

6           CHAIRPERSON FROINES: So I think we should  
7 move on.

8           PANEL MEMBER FRIEDMAN: Can I ask one more  
9 question?

10          CHAIRPERSON FROINES: Please.

11          PANEL MEMBER FRIEDMAN: Where is it written  
12 that the 20 percent decrement in volume is the thing  
13 you use. Isn't it a concern that people lose  
14 15 percent of their --

15          PANEL MEMBER BLANC: That's -- can I just  
16 comment that is standard, that is the standard  
17 definition of airway responsiveness.

18          And I think that your point is well-taken, and  
19 Kathy's as well that there are people who may be severe  
20 asthmatics who are a bit more responsive. But I think  
21 the tenfold safety factor going from the LOAEL to the  
22 NOAEL is a reasonable approach that would take that  
23 into account.

24          And then the threefold adjustment for children  
25 who have methacholine responsiveness that's maybe more

1 manifest, but probably that's because the caliber of  
2 their airways is smaller. So I think those --

3 CHAIRPERSON FROINES: So that gives you a  
4 value of 30, and which I think is a reasonable safety  
5 factor.

6 PANEL MEMBER HAMMOND: Actually, I'm not --  
7 I'm not the -- I am speaking -- I am uncomfortable a  
8 little bit, but I really defer to you because I know  
9 this is your area.

10 But do we have any data at all for any  
11 chemical for the difference in responsiveness? Because  
12 asthma is so different from other things. It's not  
13 necessarily a linear function.

14 So do we have for any chemical, X or Y, that  
15 severe asthmatics respond, that they are, you know,  
16 responsive. Their PC20s would be predicted to be  
17 one-fifth, one-tenth, one-twentieth of that for mild  
18 asthmatics?

19 PANEL MEMBER BLANC: Well, even when you test  
20 moderate asthmatics and there is a range of  
21 methacholine responsiveness, if you use methacholine as  
22 your test drug, then there is a range of responsiveness  
23 where, you know, people -- it's certainly more than  
24 tenfold within that range, but --

25 PANEL MEMBER HAMMOND: That's mild asthmatics.

1           PANEL MEMBER BLANC: No, not just mild  
2 asthmatics because you do --

3           PANEL MEMBER HAMMOND: I thought you said  
4 mild.

5           PANEL MEMBER BLANC: Even mild asthmatics, but  
6 you -- it becomes somewhat circular because people who,  
7 if you had a person with asthma who you did a  
8 methacholine test on and they were exquisitely  
9 responsive, you probably would no longer think of them  
10 as mild asthmatic, so it's a little bit complicated.

11           But since you have a range here, and you have  
12 a range in normal people, what's unusual about this  
13 chemical is in fact there are very few chemicals in  
14 which you can actually show differential responsiveness  
15 in asthmatics to nonasthmatics.

16           Sulfur dioxide. There is a little bit of data  
17 for chlorine, maybe, that we have done. And then there  
18 is this chemical which is why it's so interesting.

19           Whereas if you look at ozone, in fact  
20 asthmatics are not more responsive to ozone than  
21 nonasthmatics. There's a subset of people who are more  
22 responsive to ozone, but they're -- it doesn't --  
23 they're not asthmatics; and Charles, correct me if I'm  
24 wrong on that.

25           And the same thing is true for nitrogen

1 dioxide, and the same thing is true for -- I mean --

2 CHAIRPERSON FROINES: Can I interrupt you,  
3 Paul? Because I'm worried about time. We have 35  
4 minutes left to do formaldehyde, and then we have to  
5 leave.

6 And I think that they probably have their  
7 matching orders based on what you and Stan have said.  
8 And so that, based on those recommendations, unless  
9 Kathy has a specific recommendation, or Gary, that we  
10 should proceed so we can try and have you here for the  
11 formaldehyde discussion which is equally problem-laden.

12 CHAIRPERSON FROINES: Kathy, are you -- I  
13 don't mean to cut you off.

14 PANEL MEMBER HAMMOND: That's fine.

15 CHAIRPERSON FROINES: Because I thought that  
16 you were on a more general discussion rather than the  
17 specifics of this particular case.

18 PANEL MEMBER HAMMOND: Well, I was trying to  
19 work from the general back to the specific. But the  
20 problem was it is outside of my direct knowledge, and  
21 Paul knows that better than I. I was asking him about  
22 that.

23 But my concern was just -- I'll state my  
24 concern again, just to have it out there, and that is  
25 that maybe we don't have a linear kind of response as

1 much as in other things when looking at asthma and that  
2 therefore severe asthmatics might be much more  
3 sensitive.

4 And I think the problem is the -- and Paul  
5 said we really don't have a lot of these data, and part  
6 of that is because you don't want to go around  
7 experimenting with severe asthmatics.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: That's why we were okay with using an  
10 uncertainty factor of 300.

11 PANEL MEMBER HAMMOND: I actually --

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: You're right. There is no --

14 PANEL MEMBER HAMMOND: My only concern, is  
15 that sufficiently large? That's where my concern is.

16 CHAIRPERSON FROINES: Melanie, just to -- I  
17 think Kathy's point is really important -- and now I'm  
18 falling into the trap of commenting.

19 Melanie, what's your sense of the ambient  
20 concentrations of acetaldehyde, say in the Los Angeles  
21 basin, relative to your RELs that we're talking about  
22 here?

23 And I say that because we now all drive cars  
24 with ethanol in them, and that means we're producing  
25 large quantities of acetaldehyde. So this -- we have

1 to get this right because this is not a trivial issue  
2 by any stretch of the imagination.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: We have some data from south coast. In 2002,  
5 it was about 1.4 parts per billion, so a lot lower than  
6 this acute REL.

7 CHAIRPERSON FROINES: This REL is what?

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: This REL is 260 parts per billion, and the  
10 concentration from monitors in the south coast in 2002  
11 is 1.4 parts per billion. That's with ethanol in the  
12 fuel --

13 CHAIRPERSON FROINES: What about trailers with  
14 formaldehyde inside, like we've had with Katrina?

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: With acetaldehyde?

17 CHAIRPERSON FROINES: I'm sorry; my brain  
18 went -- my brain switched.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: That's okay. And concentrations tend to be  
21 higher indoors because there's a lot of sources  
22 indoors, so.

23 CHAIRPERSON FROINES: So what you're saying is  
24 that at this point, in terms of the REL, there is a  
25 significant difference between the existing levels of

1 exposure, existing airborne concentrations, and the  
2 REL.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Outside.

5 PANEL MEMBER HAMMOND: I'm sorry?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Outdoors. Indoors, it might be a different  
8 story depending on the sources.

9 PANEL MEMBER HAMMOND: On the outdoor data,  
10 though, your outdoor data was 2002 did you say,  
11 Melanie?

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Yeah, that was --

14 PANEL MEMBER HAMMOND: And is that before the  
15 ethanol got to be so prevalent? Going to go back to  
16 John's point.

17 If you're concerned about the ethanol, we need  
18 to have the data after the ethanol has been added.

19 CHAIRPERSON FROINES: The other thing Kathy,  
20 remember, is that we have a cancer risk assessment  
21 number too. And I don't know what that level is  
22 compared to the south coast air basin.

23 PANEL MEMBER HAMMOND: No, no.

24 I'm just trying to say if we're trying to  
25 compare -- if you -- because I think it's a valid one,

1 is about the ethanol in gasoline -- if we want to look  
2 at an outdoor level, it ought to be when we know that  
3 ethanol was being used widely in gasoline, and not  
4 before it. And I just don't know.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
6 MARTY: I don't know that we have that in California.  
7 But measurements have been made in Brazil, and we do  
8 have one citation in here; and in that case, it's 100  
9 percent ethanol.

10 PANEL MEMBER HAMMOND: Is what?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
12 MARTY: It's 100 percent ethanol.

13 CHAIRPERSON FROINES: Yeah, but the quality of  
14 the studies in Brazil are really problematic.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
16 MARTY: 35 parts per billion.

17 PANEL MEMBER HAMMOND: Actually, that's  
18 interesting because then that makes it about 20 times  
19 higher than what you measured in the south coast. But  
20 it's still about an order of magnitude less than the  
21 acute REL.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
23 MARTY: And you can get that high in a house.

24 PANEL MEMBER HAMMOND: And it isn't as if in  
25 Brazil all the gasoline --

1 CHAIRPERSON FROINES: You can?

2 PANEL MEMBER HAMMOND: -- all the gasoline  
3 isn't --

4 CHAIRPERSON FROINES: You can get --

5 PANEL MEMBER HAMMOND: Isn't 100 percent --

6 CHAIRPERSON FROINES: -- to this REL?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Not to the REL. No, no.

9 Well, we have another citation in here. US  
10 Homes ranged from 8.3 to 20 parts per billion. But  
11 some of those were higher, so that's comparable to  
12 outdoor air in Brazil.

13 CHAIRPERSON FROINES: So can we move ahead  
14 based on what I said about -- we've got suggestions  
15 from Paul and from Stan which I think everybody agreed.

16 And so we'll assume that we are going to  
17 approve the document based on what you come back with,  
18 and so that doesn't necessarily need to hold up any  
19 vote we might take today. Is that reasonable?

20 PANEL MEMBER BLANC: Oh, yeah.

21 And I want to reiterate that I think you were,  
22 again, extremely responsive; and I think it's a much  
23 better and more useful exercise now.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: I'd add that Karen responded with Dr. Prieto by

1 e-mail in Spanish.

2 CHAIRPERSON FROINES: Well, the other question  
3 that this raises, and it's outside of this meeting  
4 today, but given these numbers, what does the cancer  
5 risk assessment number suggest in terms of what we are  
6 currently breathing relative to?

7 I suspect that that's not so clean and simple  
8 an issue.

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
10 SALMON: There was a cancer risk value included in the  
11 report we did for the Governor's special order about  
12 ethanol back in -- was it in 2001? 2000.

13 And my recollection is that acetaldehyde  
14 certainly did contribute to the overall cancer risk  
15 that we were looking at from the various fuels.  
16 Although it was not, of course, the major contributor,  
17 it was certainly one that was in there. Contributions  
18 from things like formaldehyde and butadiene were  
19 higher, but the acetaldehyde --

20 CHAIRPERSON FROINES: I think.

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
22 SALMON: -- was not substantial.

23 CHAIRPERSON FROINES: I think this is really  
24 quite important because the question is we're using  
25 more and more ethyl alcohol, so that the numbers are

1 not going to be going down. And so if we have an  
2 issue, this is something that the ARB --

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: One of the --

5 CHAIRPERSON FROINES: I don't want to get into  
6 that.

7 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

8 SALMON: One of the other issues with the ethanol and  
9 gasoline study was that in fact much of the  
10 acetaldehyde, like the formaldehyde, is not in fact  
11 direct emission aldehyde anyway. It's generated by  
12 atmospheric chemistry.

13 So there isn't a one-to-one relationship  
14 between the amount of ethanol you put in the fuel and  
15 the amount of acetaldehyde in the air.

16 I'm not saying that there isn't an increase,  
17 particularly if you go to the high levels like  
18 60 percent ethanol or 100 percent ethanol, but  
19 nevertheless -- it's not a linear relationship.

20 CHAIRPERSON FROINES: I'll just stop  
21 because -- rather than comment.

22 Melanie, we're on formaldehyde.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Okay. There were far fewer changes in this  
25 Reference Exposure Level, and Bruce will go through

1 with you what changed.

2           OEHHA STAFF TOXICOLOGIST WINDER: One of the  
3 concerns expressed at the last meeting was our use of  
4 the word asthma-like to describe pulmonary symptoms, so  
5 we've gone through the document and removed that pretty  
6 much wherever it occurred, replaced that with  
7 respiratory symptoms.

8           In addition to another suggestion, we've added  
9 a supporting study for the acute REL, and we've  
10 introduced the role of aldehyde dehydrogenase 3 in the  
11 induction and exacerbation of respiratory symptoms.

12           And I'll discuss a little bit each of these as  
13 we go along.

14           The top bullet here where we're indicating how  
15 we're going to -- we're discussing how acute exposure  
16 to formaldehyde may reveal an underlying sensitivity,  
17 either of an immunological nature that an individual  
18 has, IGG or IGE, specific to formaldehyde, or a  
19 neurological nature in which they have a response  
20 mediated by the adrenals or pituitary or hypothalamic  
21 axis.

22           What's new with this one is the idea of  
23 genetic variability associated with ADH3.

24           Now, in terms of the support of the acute REL,  
25 we've added the description of Lang, et al. -- and this

1 is a study just recently published -- looking at  
2 chemosensory irritation, subjective symptoms in  
3 individuals exposed to formaldehyde.

4 The upshot of this study is that it came up  
5 with a NOAEL of .05 ppm which is the same as reported  
6 by Kulle, the study used for acute REL.

7 Now in response to some questions regarding  
8 whether or not wearers of contact lenses might be  
9 especially susceptible or sensitive to formaldehyde,  
10 we've included the study by Tanaka.

11 This examined a student exposed in an anatomy  
12 dissection class that were exposed to formaldehyde  
13 during the course of this class.

14 These individuals were wearing contact lenses  
15 here, reported significantly higher levels of  
16 irritation than did individuals who were not wearing  
17 contact lenses, who may have worn just glasses.

18 So what we're saying here is that this  
19 suggests that, yes, these individuals were likely to be  
20 more sensitive; however, we feel that contact lens  
21 wearers tend to be older individuals and that  
22 uncertainty factors we have for response of --  
23 pulmonary responses of the very young will tend to  
24 cover this as well. These two groups tend to be  
25 mutually exclusive.

1           Now with respect to ADH3, in the course of  
2 doing these revisions, we ran across some studies here  
3 that I think will provide some interesting explanation  
4 for variability we've seen in a number of studies as  
5 well as support for the mechanism for formaldehyde  
6 activity.

7           I'd like to go through this real quickly here.  
8 On the right-hand side of this schema you see how  
9 formaldehyde reacts with glutathione fairly rapidly  
10 when it gets into the system, forming this glutathione  
11 conjugate.

12           Now, this conjugate in the presence of ADH3  
13 is -- and NAD, is rapidly oxidized as formyl  
14 glutathione. The ADH3 also has as a substrate GSNO.  
15 This is the S-nitrosoglutathione, the glutathione  
16 conjugate of nitric oxide.

17           I show over here on the left side how nitric  
18 oxide syntheses generates nitric oxide from arginine  
19 which is conjugated with glutathione to form the GSNO.

20           Now, the significance of all this is that GSNO  
21 is a reservoir of nitric oxide in the system. It can  
22 directly nitrosylate a number of proteins which have  
23 direct bearing on bronchial dilation.

24           Now, the levels here of GSNO are what are  
25 critical. At low levels of GSNO, this tends to

1 stipulate the -- stimulate the activity of the  
2 5-lipoxygenase. This enzyme is responsible for the  
3 generation of cysteinyl leukotrienes. These are  
4 fairly -- the cysteinyl leukotrienes are significant  
5 bronchoconstrictors.

6 Now high levels of GSNO inhibit this activity.  
7 So we have kind of a double whammy here where high  
8 levels of GSNO inhibit the bronchoconstriction and at  
9 the same time enhance bronchodilation.

10 Now the significant part here is that GSNO is  
11 a substrate for ADH3. And as ADH3 is stimulated by  
12 formaldehyde exposure, NADH is generated, and this in  
13 turn in the presence of ADH3 removes GSNO from the  
14 system.

15 CHAIRPERSON FROINES: Could I say one thing  
16 about that?

17 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

18 CHAIRPERSON FROINES: I love what you did. I  
19 always love anybody who puts chemistry into the  
20 document.

21 But the lung lining fluid, before you get into  
22 an epithelial cell, the lung lining fluid has very,  
23 very, very high concentrations of GSH. And what I  
24 didn't understand -- now whether or not it has the  
25 dehydrogenase, that I'm not so clear on.

1           But it seems to me that there is a  
2 toxicokinetic issue about what goes on with lung lining  
3 fluid versus with respect to epithelial cell uptake.  
4 And I didn't know if there was any literature on -- and  
5 people who have looked at that issue.

6           OEHHA STAFF TOXICOLOGIST WINDER: This has  
7 been just fairly recently published, so I'm not sure  
8 that's clear. I'm not clear on that either, as to, you  
9 know the --

10          CHAIRPERSON FROINES: But you know what I'm  
11 getting at.

12          OEHHA STAFF TOXICOLOGIST WINDER: I see what  
13 you're getting at. I agree with you, but I don't  
14 know -- I haven't encountered any data that actually  
15 address that, that specific question. That's a good  
16 point.

17          CHAIRPERSON FROINES: And you've got a lot of  
18 ascorbate in there, so you've got electron sources.  
19 The ascorbate -- you have a huge amount of GSH, and you  
20 have a very large amount of ascorbate, so the ascorbate  
21 is a great provider of electrons for productive  
22 purposes.

23           And so it's -- the lung lining -- one cannot  
24 leave out the lung lining fluid and just think about  
25 epithelial cell uptake. Is that fair?

1 PANEL MEMBER PLOPPER: (Nodding head)

2 OEHHA STAFF TOXICOLOGIST WINDER: I agree.

3 What we're providing here is, you know,  
4 potential mechanism -- I'll show you some studies in  
5 which they've actually measured levels of GSNO in lungs  
6 of individuals that asthmatic versus nonasthmatic, and  
7 we'll see some differences there.

8 I'll return to that in a second.

9 Now the gist of this is that formaldehyde from  
10 a number of studies enhances the reduction of GSNO.

11 Now the study by Gaston, et al., this is a  
12 study of children, asthmatic children versus  
13 nonasthmatics. And what he reported here is that the  
14 GSNO levels were lower in the lungs of asthmatics  
15 versus the nonasthmatics. He's speculating that the  
16 ADH3 levels tend to be higher.

17 Now, building on this study is a study by Wu,  
18 et al. where they decided to examine the variations in  
19 the ADH3 genotype among asthmatic children comparing  
20 them with their parents who were nonasthmatic.

21 And in this case, based on his analysis, he  
22 found that the asthma risk associated with expression  
23 of this minor A allele was .77, less than one. Whereas  
24 individuals who were expressing this minor G allele,  
25 1.60, suggesting there was a substantially higher risk

1 among individuals with a particular genotype for ADH3.

2 This study provides some sort of basis to  
3 explain why there has been such variation among the  
4 different studies regarding asthmatic response to  
5 formaldehyde.

6 Now, these studies are backed up by a number  
7 of studies in animals in which again formaldehyde  
8 increased ADH3 activity and decreased GSNO levels.  
9 This has appeared both in mice and in -- some of these  
10 are in vitro.

11 Now, the Que study in the next bullet found  
12 that the elevated ADH3 levels depressed airway tone and  
13 enhanced responses to allergens and  
14 bronchoconstrictors, in this case methacholine, by  
15 increased GSNO metabolism.

16 So if we go back to, if you can imagine that  
17 schema for the reactivity here, in the presence of  
18 formaldehyde, the lungs are no longer quite as dilated,  
19 and we're suppressing the dilation while increasing the  
20 formation of the bronchoconstrictors.

21 So we're thinking that what's happening here  
22 is this suggests a mechanism for formaldehyde induction  
23 of respiratory symptoms is in part dysregulation of  
24 nitric oxide signalling.

25 That's what I have for that.

1           CHAIRPERSON FROINES: Charlie, I think you're  
2 the Lead. Who else is the Lead on this? I don't  
3 remember.

4           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
5 MARTY: Just Charlie.

6           PANEL MEMBER PLOPPER: Well, I think most of  
7 our concerns had to do with the use of asthma-like  
8 symptoms and the lack of a recognition for other  
9 sensory irritation things. I think that this document  
10 is -- you've done an excellent job of changing this and  
11 adding new things.

12           And like John, I really like the idea of  
13 putting the biochemical aspects in here, particularly  
14 with the glutathione.

15           But one thing that I had was just what John  
16 brought up, and that is that if you're going to discuss  
17 this, you need to discuss the pool regulation in the  
18 respiratory system. And there are a number of issues  
19 there.

20           First of all, the pool's not just the cells.  
21 It's the acellular lining layer, GSH pool, and then  
22 it's the extracellular pool that's on the abluminal  
23 side. And that's going to be regulated by the blood  
24 vessels, by vascular pools.

25           And ascorbic acid is going to vary by species.

1 It's out there at the same time. And -- but all the  
2 chemistry could be there on the surface to actually  
3 modify the glutathione pool and actually fit into parts  
4 of this scheme of biochemical transformation with  
5 formaldehyde.

6 In fact, I would suspect that most of the  
7 chemical that's produced by formaldehyde interaction  
8 with GSH, particularly in primates, is going to be on  
9 the extracellular surface to begin with.

10 So I think if you're going to put that in that  
11 you need to have something in there about the pool.  
12 And the reason for that is that what small data is  
13 available on children and immature animals, the GSH  
14 pool is regulated differently than it is in the adults,  
15 and it's more compromised and less -- there is less  
16 ability in developing animals certainly, in primates  
17 for sure, to regulate this pool.

18 So the compromise -- I guess by the time I got  
19 through thinking through these arguments, I was  
20 concerned that maybe this -- the factor wasn't enough  
21 because we don't really understand how compromised the  
22 pool is, but what -- everything that relates to oxidant  
23 stress where GSH is the -- one of the players in  
24 ameliorating it or balancing it, developing systems,  
25 particularly respiratory systems, is very compromised.

1           So the thing that's most difficult to  
2 understand is that actually in most species the steady  
3 state level of the total pool is about the same. But  
4 what is missing is the fact that once the pool is  
5 compromised it doesn't seem to come back.

6           OEHHA STAFF TOXICOLOGIST WINDER: I think a  
7 discussion of that would be appropriate.

8           PANEL MEMBER PLOPPER: Yeah. I think it --  
9 the literature is not great yet, but every time  
10 somebody attempts one of these studies where GSH is a  
11 critical mechanistic factor and they find that infants  
12 just don't respond.

13           So it's easier to deplete it, and nobody  
14 really understands why it's much more difficult for  
15 neonates or infants to reestablish it when it's  
16 dropped.

17           And all of those things would suggest that  
18 this is, I would say, a highly -- not as conservative  
19 as I might think would be necessary based on the  
20 biochemistry that we know about this now.

21           CHAIRPERSON FROINES: Are you suggesting that  
22 they should consider an additional safety factor?

23           PANEL MEMBER PLOPPER: Well, I think the  
24 problem is that I'm not sure how good the literature is  
25 that would support it. But what I'm suggesting is

1 that -- I know you probably don't want to redo this,  
2 but since you brought this in and it's becoming a very  
3 interesting and exciting new mechanism, particularly  
4 when you look at environmental compromise of airways  
5 disease, that it would be worth putting something in  
6 here on what's known about the pool.

7           And I think what you'll find when you do one  
8 of your thorough analyses is that there's enough to  
9 suggest there that you may have to relook at the  
10 factors because it may be more compromised than you  
11 think.

12           CHAIRPERSON FROINES: Maybe the solution would  
13 be to, one, describe what this discussion has been  
14 about, and then to say that therefore we may not be  
15 entirely conservative sufficiently, and that we will  
16 follow the developing literature in this area and go  
17 back and relook at it at a later time, like six months  
18 or a year; and if we think we need to change, we'll  
19 proceed -- something like that. In other words, have  
20 kind of a holding operation.

21           PANEL MEMBER PLOPPER: So put a framework  
22 together, conceptual framework, for taking in data as  
23 it becomes available on how -- whether this is  
24 compromised.

25           The fact of the matter is it is compromised,

1 so the problem is figuring out what it is and how  
2 formaldehyde may impact on it.

3 But I think you definitely need a section on  
4 extracellular fluid concentrations because the  
5 reactions there between formaldehyde and glutathione  
6 occur out in the extracellular space. So that's going  
7 to change the whole -- that's going to really  
8 compromise it.

9 CHAIRPERSON FROINES: And Melanie, there is a  
10 good literature on the extracellular space at this  
11 point. So there's a lot that you could draw from.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
13 MARTY: Okay.

14 CHAIRPERSON FROINES: You know, Frank Kelly in  
15 London and others have done a lot of nice work, and so  
16 I think that you'll find there is a sufficient  
17 literature that you can take another step.

18 OEHHA STAFF TOXICOLOGIST WINDER: All right.  
19 Were there any other comments or questions?

20 CHAIRPERSON FROINES: Gary?

21 PANEL MEMBER BLANC: I have some. Maybe I  
22 should do it before I go.

23 I want to try to focus on the things that are  
24 new, your revisions in response to previous discussion.

25 So you have two paragraphs or so on the Lang

1 study.

2 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

3 PANEL MEMBER BLANC: The Lang study, depending  
4 on how you look at it, had a NOAEL of .5, although you  
5 could argue that it had a LOAEL of .3.

6 OEHHA STAFF TOXICOLOGIST WINDER: Right.

7 PANEL MEMBER BLANC: The bench -- the study  
8 that you use that you obtained for your analysis with  
9 the same endpoint which was eye irritation had a NOAEL  
10 of .5, not a LOAEL of .5.

11 Can you say why it is that if you have a more  
12 recent study which suggests that what you took as a  
13 NOAEL is actually a LOAEL and that in fact the LOAEL  
14 could even be argued in their study was .3 you want to  
15 stick with a NOAEL of .5 from a different study, parts  
16 per million?

17 OEHHA STAFF TOXICOLOGIST WINDER: A couple  
18 things come into that consideration.

19 The Kulle study provided enough data that we  
20 were able to do a benchmark dose analysis, so this was  
21 in one part desirable.

22 The Lang study came up with a NOAEL, what  
23 they're considering a NOAEL, of .5. Because in this  
24 study they were also looking at the individual's  
25 personality, affect, this kind of stuff, which they

1 felt modified, you know, the response.

2 So while what you're saying is true, they saw  
3 an effect of .3 with spikes of formaldehyde higher. So  
4 this is part of the reason they were saying, okay,  
5 we'll consider this for the NOAEL.

6 But the other, probably the spikes, they  
7 weren't quite sure how to deal with that except to say  
8 that the personal affect, they felt once they  
9 considered that as a modifying factor --

10 PANEL MEMBER BLANC: It was in the .3 but not  
11 in the .5. .5 was still their LOAEL and was still  
12 significant.

13 So you could make the argument that, okay,  
14 we're going to use .5, not .3. But that's as a LOAEL  
15 not a NOAEL. Whereas in your study .5 was a NOAEL.  
16 Isn't that correct? Or did I miss something?

17 OEHHA STAFF TOXICOLOGIST WINDER: Let me see  
18 if I'm misstating it. Okay.

19 Yeah. They're suggesting that the -- I'm  
20 sorry. The .5 with peaks was the LOAEL. The .5  
21 without the peaks was the NOAEL. I'm sorry. I  
22 misstated that.

23 So the .5 that they report without peaks is  
24 still a NOAEL compared to --

25 PANEL MEMBER BLANC: It is. It's not really

1 that clear.

2 OEHHA STAFF TOXICOLOGIST WINDER: I guess I  
3 can go back and clarify that.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
5 MARTY: We smooshed those two concepts together in one  
6 sentence.

7 PANEL MEMBER BLANC: So then I think what you  
8 should do is go back, if you're still retaining the  
9 other one as your study for the purposes of your  
10 extrapolation, you should say it's supported by this  
11 other study which had a similar NOAEL even though it  
12 had, with peaks, they did get a response.

13 OEHHA STAFF TOXICOLOGIST WINDER: Yes. I  
14 agree.

15 PANEL MEMBER BLANC: And I think that you also  
16 should go back and think of your wording about the  
17 interaction with the affectivity and all of that --

18 OEHHA STAFF TOXICOLOGIST WINDER: Needs some  
19 clarification.

20 PANEL MEMBER BLANC: It needs a little bit of  
21 work.

22 OEHHA STAFF TOXICOLOGIST WINDER: All right.

23 PANEL MEMBER BLANC: Another thing that I want  
24 to ask: Have you actually gone and looked at the NIOSH  
25 health hazard evaluation data?

1           OEHHA STAFF TOXICOLOGIST WINDER: I've tried  
2 to find those data, looking both through the NIOSH as  
3 well as OSHA, US EPA, et cetera, trying to find some  
4 sort of data on irritation -- I'm sorry. I was doing  
5 that for acrylate. I was confusing those two.

6           No, I have not for formaldehyde.

7           PANEL MEMBER BLANC: Well, I think you should.  
8 Now, I can't tell you for sure whether one of the  
9 health hazard evaluations -- well, I know that one I  
10 was involved in, we actually went back and looked at  
11 other ones.

12           And the reason why, and the reason why I'm a  
13 little bit touchy about this .5 part per million, is  
14 because there were a series of health hazard  
15 evaluations, all of which said: We saw eye irritation,  
16 and our levels were .5 parts per million, but that's  
17 lower than you get eye irritation so it must not be  
18 true.

19           And there were, you know, a whole series of  
20 health hazard evaluations that had exactly the same  
21 findings. So I think that --

22           OEHHA STAFF TOXICOLOGIST WINDER: We should  
23 check the NIOSH.

24           PANEL MEMBER BLANC: You should check that.

25           Now, I know that you said in your presentation

1 that you avoided the term asthma-like, but I actually  
2 see it appearing here again.

3 OEHHA STAFF TOXICOLOGIST WINDER: There were  
4 places where it still -- in our reading, still seemed  
5 appropriate. Now perhaps that's subject to some  
6 discussion.

7 PANEL MEMBER BLANC: (Reading:)

8 Many of the studies described in this  
9 document have evaluated the relationship  
10 between formaldehyde inhalation and  
11 clinically diagnosed asthma or  
12 asthma-like symptoms.

13 OEHHA STAFF TOXICOLOGIST WINDER: Those are  
14 the phrases used in the studies.

15 PANEL MEMBER BLANC: Or what the authors  
16 describe as quote asthma-like symptoms.

17 OEHHA STAFF TOXICOLOGIST WINDER: Exactly.

18 PANEL MEMBER BLANC: If that's what you want  
19 to say.

20 OEHHA STAFF TOXICOLOGIST WINDER: All right.

21 PANEL MEMBER BLANC: And also I think you need  
22 to do a word find, and everywhere that you use the word  
23 sensitivity, unless you're not -- unless you're  
24 specifically talking about an IG mechanism or similar  
25 immunologic mechanism, I actually don't know what

1 sensitization, neurological sensitization, means.

2 OEHHA STAFF TOXICOLOGIST WINDER: This is the  
3 term that Sorg, et al. applied to their studies in  
4 which they suggested in their experiments exposure to  
5 formaldehyde resulted in release of corticosterone.

6 CHAIRPERSON FROINES: What? I didn't hear  
7 you.

8 OEHHA STAFF TOXICOLOGIST WINDER: Excuse me?

9 CHAIRPERSON FROINES: I didn't hear you.

10 OEHHA STAFF TOXICOLOGIST WINDER: That in the  
11 Sorg studies, what they're looking at is exposure to  
12 formaldehyde causing a release --

13 PANEL MEMBER BLANC: Of glucocorticosteroids.

14 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

15 PANEL MEMBER BLANC: And then --

16 OEHHA STAFF TOXICOLOGIST WINDER: And then the  
17 subsequent exposure after long-term relatively low  
18 level exposure, subsequent challenge to individuals who  
19 were exposed to formaldehyde at this low level had a  
20 higher response, corticoid release, than individuals  
21 who were not so challenged -- or not previously  
22 exposed.

23 PANEL MEMBER BLANC: I still wouldn't call  
24 that sensitization. And if they called it  
25 sensitization, I don't think you should use the term.

1 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

2 PANEL MEMBER BLANC: It could be a heightened  
3 response, an amnestic response, I don't care what you  
4 want to call it but just don't call it sensitization.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: We had this argument --

7 CHAIRPERSON FROINES: Yeah, it's not  
8 sensitivity. That's not right.

9 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: We had this argument already.

12 PANEL MEMBER BLANC: So just go through it.  
13 There was another place --

14 CHAIRPERSON FROINES: Well, the person who  
15 lost should become the person who won.

16 (Laughter)

17 PANEL MEMBER BLANC: Did I miss something?

18 CHAIRPERSON FROINES: Pardon me?

19 PANEL MEMBER BLANC: Was I not present for  
20 that argument?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Between us guys.

23 CHAIRPERSON FROINES: It's internal.

24 PANEL MEMBER BLANC: Okay.

25 There was another point where you used some

1 weird phraseology about externally evident asthma  
2 features, which is not what you mean.

3 OEHHA STAFF TOXICOLOGIST WINDER: I'll look  
4 for it. I'm not sure what you --

5 PANEL MEMBER BLANC: Yeah. I circled it. Let  
6 me see if I can find it -- oh. Outward -- it's in the  
7 same paragraph as the asthma-like symptoms:

8 Outwardly asthma manifests as a  
9 characteristic cough, wheeze, and  
10 shortness of breath due to spasmodic  
11 contractions of the bronchi.

12 First of all, I don't know what -- I would  
13 just get rid of the sentence altogether, but I don't  
14 know what outwardly means.

15 OEHHA STAFF TOXICOLOGIST WINDER: Symptoms  
16 that are observable versus, say, a biochemical response  
17 such as we've been describing with the ADH3 kind of  
18 thing.

19 But yeah, I see what you're saying. We can  
20 just delete that, yeah.

21 PANEL MEMBER BLANC: But anyway, I think the  
22 most confusing thing to me was this business about what  
23 you were using as the NOAEL and --

24 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

25 PANEL MEMBER BLANC: And in response to your

1 question about the uncertainties in the  
2 pharmacodynamics, is that really what -- basically what  
3 you're saying?

4 I mean don't you have a fall-back of using a  
5 value of three for the pharmacodynamic uncertainties?  
6 You use a ten for the toxicodynamic because of the  
7 childhood business.

8 OEHHA STAFF TOXICOLOGIST WINDER: Yes. We are  
9 currently using the one. We can easily go to a three.

10 PANEL MEMBER BLANC: I mean I -- I think if  
11 you don't you should say why not, or you could say we  
12 considered using a three but in the end ultimately.

13 CHAIRPERSON FROINES: Yeah, but I think -- my  
14 sense is that I raised it, Charlie raised it in more  
15 detail, and now you've raised it.

16 I think you need to go back and decide about  
17 this factor of three. Because it may be that, rather  
18 than waiting for the future, that you may conclude that  
19 the evidence is sufficient for an additional factor of  
20 three.

21 And so I would leave that as something as-yet  
22 unresolved pending your review of the discussion in the  
23 transcript of what's happened here today.

24 PANEL MEMBER BLANC: Well, let's come back  
25 then to the -- all right. Play both sides against the

1 middle.

2           Then you have a factor of ten for  
3 toxicodynamic uncertainty because children may have  
4 asthmatic responses but adults don't have asthmatic  
5 responses?

6           OEHHA STAFF TOXICOLOGIST WINDER: Well.

7           PANEL MEMBER BLANC: Because before when you  
8 used ten, it's been that you've shown that adults have  
9 asthmatic responses and then say, okay, if adults have  
10 asthmatic responses, children are even more likely to  
11 be having asthmatic responses and so forth.

12           But you haven't leapt from there's no evidence  
13 of asthmatic responses at this level to children would  
14 develop asthmatic responses at a level even though  
15 adults wouldn't. I mean because that's not the  
16 endpoint that --

17           OEHHA STAFF TOXICOLOGIST WINDER: What we're  
18 saying is that the children's responses would generally  
19 be more severe for a given exposure. Even if adults  
20 are responding with these respiratory symptoms we're  
21 calling asthma, the children's response would be much  
22 more severe and much more life threatening.

23           PANEL MEMBER BLANC: Well, could you make an  
24 argument that maybe it should still be roughly ten but  
25 it should be 3 in 3 rather than 1 and 10 because you

1 have two sets of uncertainties, but I'm not sure that  
2 the childhood one in this particular instance arises to  
3 the level of ten as opposed to some of the other  
4 examples we've dealt with.

5 CHAIRPERSON FROINES: Are there other comments  
6 on formaldehyde?

7 So Paul, before you leave, there have been  
8 sufficient number of comments about acetaldehyde and  
9 about formaldehyde, and to a lesser extent about  
10 manganese. I think I would feel more comfortable  
11 approving the document at the next meeting,  
12 December 5th, after you guys have had a chance to go  
13 through some of the things that have been raised today.

14 I think we're beginning to build up enough  
15 question marks that it's not just a question of going  
16 back and making some trivial changes. So I don't know  
17 how people feel about that though.

18 PANEL MEMBER BLANC: When is our next meeting?

19 CHAIRPERSON FROINES: December 5th.

20 PANEL MEMBER BLANC: Oh, that's very soon.

21 That would be fine. I think that because some  
22 of these things are rather contentious it might be  
23 safer for you guys, rather than, you know, making it  
24 crazy.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Also there's the issue of findings. So that  
2 would allow findings to be made and then discussed at  
3 the next meeting.

4 CHAIRPERSON FROINES: Well, it will mean that  
5 you all and I need to -- you need to resolve these  
6 issues that we've been discussing, and we need to work  
7 some on the findings.

8 And the good news is Eleanor is going to help  
9 on this, and so that we have a superstar. So we might  
10 be able to make it, but it's pretty tight timing.

11 So we'll just have to do the best we can.  
12 Stan's already written some findings on cancer, I  
13 think. No?

14 Jim, who wrote some findings?

15 MR. BEHRMANN: That was the noncancer team.

16 CHAIRPERSON FROINES: Who?

17 MR. BEHRMANN: That was the noncancer team.

18 PANEL MEMBER GLANTZ: That was the last guy.

19 CHAIRPERSON FROINES: Who wrote that?

20 PANEL MEMBER GLANTZ: I drafted it, but yeah.

21 I don't think the cancer document --

22 CHAIRPERSON FROINES: So we'll be okay, but it  
23 means that we just -- Melanie and I need to make sure  
24 we work on the timing of the -- that we can make it by  
25 then.

1           But it's going to need you to resolve these  
2 issues that Paul and Charlie and others have raised.  
3 Is that reasonable, Melanie?

4           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
5 MARTY: Sure.

6           CHAIRPERSON FROINES: I know you would like us  
7 to stamp it, but I think -- I have a feeling that  
8 there's enough questions raised that people wouldn't be  
9 necessarily completely comfortable with a blanket  
10 approval at this point. Because we're approving a  
11 whole series of chemicals.

12           Gary, are you guys -- am I talking -- are you  
13 in agreement with me?

14           PANEL MEMBER FRIEDMAN: I'm trying to  
15 remember. Wasn't there somewhere at least one where  
16 there was just a minor change?

17           CHAIRPERSON FROINES: Yeah. But here we've  
18 got acetaldehyde and formaldehyde, so we actually have  
19 some substantive issues that --

20           PANEL MEMBER GLANTZ: Well, I don't think -- I  
21 mean, I don't have any problem with putting it over,  
22 especially since we don't have findings written yet  
23 anyway.

24           I don't think there's a huge amount to be  
25 done, but this way there won't be any confusion.

1           CHAIRPERSON FROINES: But I think it's more of  
2 a safety factor for formaldehyde is really quite  
3 crucial because formaldehyde is such an important  
4 compound that -- in this -- in the air.

5           PANEL MEMBER GLANTZ: I think we should move  
6 on because nobody disagrees.

7           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
8 MARTY: I just want to remind the panel that we are  
9 assuming that you guys are done with the other  
10 compounds, so that would be --

11          CHAIRPERSON FROINES: Yes.

12          AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: -- arsenic --

14          CHAIRPERSON FROINES: Acrolein.

15          AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Mercury. We had a few minor changes with  
17 acrolein, but it was very minor so.

18          PANEL MEMBER HAMMOND: And are we just having  
19 one set of findings for all of these?

20          CHAIRPERSON FROINES: Yes.

21          AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: So the ones that you are still sort of  
23 outstanding are acetaldehyde.

24          CHAIRPERSON FROINES: Kathy, this is a first.  
25 You've never written findings on 2588 chemicals before.

1 I don't remember if we wrote an MTBE one.

2 But in general, on the 2588 chemicals, we've  
3 never written findings. We simply approved the  
4 document. This is the first that we will have written  
5 findings.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
7 MARTY: And part of it is because we are proposing that  
8 they be identified as toxic or contaminants that  
9 differentially impact kids under SB 25.

10 PANEL MEMBER HAMMOND: I thought we did do  
11 something like that.

12 PANEL MEMBER GLANTZ: No. We discussed it at  
13 the last meeting, but we put off -- we approved the REL  
14 document, the procedural part of the REL document. But  
15 that was the part I wrote, and then we put off -- I  
16 mean we discussed a bunch of the chemicals last time,  
17 but we decided that we were going to just have one vote  
18 and one set of findings for all the chemicals at once.

19 CHAIRPERSON FROINES: So we're going to take a  
20 half hour for -- sorry. What do you call it; the  
21 chairman's prerogative.

22 Chairman's prerogative is that we break now  
23 immediately for lunch, we have a half-hour lunch,  
24 because we have a whole bunch of people who have planes  
25 at 5 o'clock; and therefore, we can only run 90 minutes

1 which means about 3:30.

2 PANEL MEMBER FRIEDMAN: I'm going to have to  
3 leave at 2:15, so.

4 CHAIRPERSON FROINES: You're 2:15. So we can  
5 run until 3:30, but that's going to be cutting it a  
6 little tight. So it might be 3:15 we go.

7 So we should take a half-hour lunch and get  
8 back at 1:40, and then proceed.

9 (Lunch recess)

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1                                   AFTERNOON SESSION

2                                   --o0o--

3                   CHAIRPERSON FROINES:  So let's go.  I think  
4  our reporter is ready to go.

5                   DR. SANDY:  Okay.  So this presentation today  
6  is on this report, In Utero and Early Life  
7  Susceptibility to Carcinogens.  And the authors are  
8  myself and Dr. Claire Sherman, here to my right, our  
9  biostatistician; and Rajpal Tomar, our toxicologist;  
10 and Lauren Zeise who was unable to attend today.

11                   Here's an overview of what we are prepared to  
12 present for you.  We want to give some background and  
13 rationale for the analyses that were done and then  
14 discuss the different studies of age sensitivity or  
15 susceptibility that we looked at.

16                   And we looked at two different kinds of  
17 studies, studies we call multi-window exposure studies,  
18 and then studies we call chemical-specific case  
19 studies.  And I'll present that.

20                   And then we turn to Dr. Sherman to discuss the  
21 analytical approaches that were taken.  And we would  
22 talk about the cancer potency estimates and how we  
23 analyzed the multi-window exposure studies and the  
24 chemical-specific case studies.

25                   Then we'd present the results, and I would

1 present the multi-window exposure studies, and  
2 Dr. Tomar would present the chemical-specific case  
3 studies. And we'd have our conclusions.

4 We've got breaks in here for questions, and I  
5 know you won't hesitate to stop us at any point.

6 This is what we have planned. If you'd like  
7 to focus on one particular issue, the methods, or  
8 something else first, we are prepared to do that as  
9 well. But I'll continue on.

10 CHAIRPERSON FROINES: Martha, Dr. Friedman is  
11 going to leave at 3:30, I believe.

12 PANEL MEMBER FRIEDMAN: 2:15.

13 CHAIRPERSON FROINES: 2:15.

14 And Dr. Plopper is raising the question of the  
15 weather, if it gets worse and we have to worry about  
16 traffic getting to the airport. So we may stop around  
17 3:00 or at the latest 3:15, I think. So we'll be  
18 working within that kind of time window.

19 DR. SANDY: Okay.

20 CHAIRPERSON FROINES: So my sense is that  
21 maybe we give you the opportunity to do most of the  
22 talking today, and then we do a lot of the talking at  
23 the December 5th meeting.

24 DR. SANDY: Okay. That's fine.

25 PANEL MEMBER HAMMOND: How many days is that

1 December 5th meeting?

2 CHAIRPERSON FROINES: What?

3 PANEL MEMBER HAMMOND: How many days is that  
4 December 5th meeting? We've deferred a lot to that  
5 meeting.

6 PANEL MEMBER GLANTZ: That's okay. Let's go  
7 ahead.

8 DR. SANDY: So the basic rationale --

9 CHAIRPERSON FROINES: You'll be done by  
10 Christmas.

11 (Laughter)

12 PANEL MEMBER GLANTZ: 2012.

13 DR. SANDY: As John Budroe explained this  
14 morning, there is substantial public health concern  
15 over early life susceptibility to carcinogens, and the  
16 concern comes from both clinical findings and  
17 epidemiological studies as well as theoretical bases  
18 and from animal studies.

19 But the human data, we have evidence from  
20 exposure to DES in utero and increased cancer risk in  
21 the daughters and also some indication of some  
22 increased risk in the granddaughters. So that's a  
23 transgenerational effect. DES is presumed or generally  
24 considered to act probably primarily through  
25 nongenotoxic mechanisms such as alterations in DNA

1 revelation.

2 We also have evidence from X radiation during  
3 adolescence leading to an increased risk of mammary  
4 tumors in young girls that's expressed as they age.

5 There's evidence from radioactive iodine  
6 exposure early in life and increased risk of tumors.

7 And we have evidence from exposure to  
8 immunosuppressive agents during childhood and  
9 subsequent cancers. And again, many of the  
10 immunosuppressive agents are nongenotoxic.

11 We were asked to look at the cancer risk  
12 assessment approaches to see if they were protective of  
13 early-in-life lifestages. And back in the twentieth  
14 century, standard risk assessment approaches did not  
15 specifically take into account the fetus, infants, or  
16 children in estimating risk.

17 Now, we do recognize the need to address  
18 cancer risk from early-in-life exposures, and there's a  
19 need to develop methods and to analyze data sets, to  
20 come up with default approaches, which is what we've  
21 done here, and to develop these measures of early life  
22 susceptibility that can be used as defaults when you  
23 don't have chemical-specific data.

24 So typically, cancer risk assessments use  
25 cancer studies conducted in adult humans or adult

1 animals to estimate cancer potency, and we assume that  
2 cancer potency is the same across all life stages from  
3 birth through age 70. That's the standard assumption.  
4 And we also apply adult exposure parameters when we're  
5 estimating risk such as adult body weight, breathing  
6 rate, food and water consumption.

7           So there's a need to address early life  
8 susceptibility which in the past has not been  
9 addressed.

10           This slide is showing you the standard dosing  
11 periods in a rodent bioassay where most of our data for  
12 estimating cancer risk comes in the standard chronic  
13 long-term bioassay in a rat or mouse, starts about six  
14 to eight weeks of age, and goes until two years.

15           And the average life span of a rat or mouse is  
16 three years, so we're not even getting the whole life  
17 span but starting at six to eight weeks of age  
18 typically, and that's the end of the juvenile period or  
19 the beginning of the adult period, depending on the  
20 species and sex.

21           We are not measuring -- or studies are  
22 not done very often that include exposure during the  
23 postnatal or juvenile periods, and the in utero period  
24 is also not addressed in many studies.

25           So the question of how to account for the

1 potential differential cancer susceptibility of persons  
2 exposed early in life, EPA and OEHHA are suggesting  
3 that we apply age-specific adjustments to the standard  
4 adult-based cancer potency estimates to do this.

5           And this slide is pointing out that the  
6 age-specific adjustments to cancer potency take into  
7 account two things. The first is the inherent  
8 susceptibility of the young to the carcinogen, and  
9 that's what our analyses that I'll present here aim to  
10 characterize.

11           We're comparing activity when exposure occurs  
12 early in life to when exposure occurs during older ages  
13 for the same length of time between initial exposure  
14 and observation of effect.

15           You also need to account for the longer period  
16 of time that carcinogen exposure to the young has to  
17 manifest as cancer. And here you see that term you  
18 don't like, shelf life.

19           So we looked for studies of age  
20 susceptibility. By that, we mean where you have  
21 exposure to a carcinogen early in life and then assess  
22 cancer risk and can compare that to exposure only  
23 during adulthood.

24           And we wanted -- our approach was to compare  
25 the cancer potencies from those different exposures and

1 derive a measure of early life susceptibility.

2           And in thinking about -- go back -- what data  
3 are available, there are sparse data in humans on early  
4 life carcinogen exposures. Few chemicals have been  
5 studied. But there are -- there is a larger set of  
6 data in animal studies with multiple chemicals that  
7 have been studied. So we made a choice to focus on the  
8 animal data and try to mine that and do as much  
9 analysis as we could.

10           So we identified these animal cancer bioassays  
11 through extensive literature searches of online  
12 databases and review of Cancer Chem 2000 which is the  
13 public health service survey of pre-Internet, all the  
14 cancer bioassays that have been conducted that NIH has  
15 put together.

16           And we also looked at any references cited in  
17 papers that we have found of other studies. And we  
18 also worked with Ed Calabrese, and I got some papers  
19 from his single-dose database for carcinogens.

20           So we really scoured all the sources we could  
21 to come up with studies that had early life exposure  
22 and then reported cancer incidents in animals.

23           Then with all these studies, we had to have  
24 some criteria for what we thought were valid studies to  
25 look at. And our criteria for study inclusion are

1 listed here. We wanted treatment to be confined to one  
2 specific age window, either the prenatal window or  
3 postnatal or juvenile or adult, but not to cross across  
4 those life stages.

5 We also wanted treatment with a single  
6 chemical or chemical mixture. We didn't want to have  
7 co-carcinogen or initiation promotion studies in there.

8 We required that in the studies the animals  
9 not be compromised by severe treatment-related  
10 noncancer toxicity. And we wanted the study duration  
11 to be greater than 40 weeks unless death occurred  
12 earlier due to tumor.

13 Additional criteria were that the studies  
14 report the age at dosing and age at sacrifice and give  
15 site-specific tumor incidence.

16 We wanted studies to report what -- to have  
17 concurrent controls or in some cases appropriate  
18 historical control data, if it was a rare tumor that  
19 was seen.

20 We wanted the studies to be conducted on  
21 mammals and that there be at least ten animals per  
22 treatment group or control group.

23 And that the test compound be administered via  
24 diet, drinking water, gavage, or injection. So those  
25 were our criteria.

1           We identified 145 publications that met this  
2 criteria, then we looked within those publications and  
3 found some would report more than one study. And we  
4 noticed there were different types of studies.

5           So the optimal type of study would be what we  
6 call a multi-window exposure study where within the  
7 same study you had at least one early life exposure  
8 group and you had an older age of exposure reference  
9 group, and therefore we hope we've controlled for  
10 experimental variability and temporal variability and  
11 laboratory variability.

12           And in some cases, the older age of exposure  
13 reference groups may have been exposed as juveniles  
14 rather than adults. They didn't have adult. We would  
15 use those studies even if the referent group was a  
16 juvenile.

17           So this table just shows you the age-specific  
18 exposure windows as we defined them with the postnatal  
19 period being from birth to weaning and for the juvenile  
20 period being from weaning to sexual maturity. And that  
21 varied by -- sometimes by sex and the rat and by  
22 species, and then the adult period starting at the age  
23 of sexual maturity, or breeding age.

24           So of the multi-window exposure studies that  
25 we could identify, we had 22 studies or data sets with

1 prenatal exposure and a referent older exposure group;  
2 and the species were rat, mouse, and hamster. And they  
3 covered 14 carcinogens.

4 Our postnatal studies, we had 55 data sets,  
5 and we had rat, mouse, hamster, and gerbil, and we  
6 covered 18 different carcinogens. The juvenile data  
7 sets, we only had studies conducted in the rat, and --

8 CHAIRPERSON FROINES: I'm confused. You keep  
9 using the word carcinogen. Were these chemicals that  
10 you knew to be carcinogens?

11 DR. SANDY: Yes. That was another criterion  
12 that we don't have spelled out, but we require that the  
13 chemical be recognized as a known carcinogen.

14 CHAIRPERSON FROINES: What does that mean?

15 DR. SANDY: IARC, Prop 65, US EPA.

16 CHAIRPERSON FROINES: Okay.

17 DR. SANDY: Now we found in looking at these  
18 multi-exposure window studies that target tumor sites  
19 can vary by age of exposure. And I've given some  
20 examples here for urethane, dibutyl-nitrosamine and  
21 vinyl chloride where you can see, depending on when the  
22 chemical exposure occurs and what lifestage you may get  
23 a different mix of tumors --

24 PANEL MEMBER GLANTZ: Could I ask a question?  
25 Because I thought when I was reading it when you talk

1 about a multi-window study you were -- say if you were  
2 looking at urethane, you were comparing prenatal with  
3 adult exposure?

4 DR. SANDY: That's correct.

5 PANEL MEMBER GLANTZ: Okay. But then how  
6 come -- how come you don't have adult -- but I thought  
7 it was using the same cancer outcome. No?

8 DR. SANDY: It's looking at cancer outcome,  
9 what was the treatment-related cancer? So in urethane,  
10 we had a prenatal and an adult exposure group. And we  
11 see that the adults, they got thyroid tumors. The  
12 prenataally exposed animals got heart sarcomas.

13 So we analyzed the tumor incidents and  
14 calculated a potency for the heart sarcoma in the  
15 prenatal group. In the adult group, we saw thyroid  
16 tumors and treatment-related increases in the thyroid  
17 tumors and developed a cancer potency based on that.

18 PANEL MEMBER GLANTZ: Okay. Well, let me -- I  
19 just want to -- because I found this very confusing  
20 when I read it, and I'm beginning to understand why.

21 So what you did -- see, I thought what you  
22 were looking at when you were doing these multi-window  
23 studies is you were insisting on the same outcome in  
24 the adults as the -- no?

25 DR. SANDY: No.

1           PANEL MEMBER GLANTZ:  So what you're  
2 basically -- now things are making a little more sense  
3 to me.  So what you're doing is you're just saying how  
4 many tumors of any kind the rats exposed to urethane  
5 get in the prenatal period.  And then compare that to  
6 the number of tumors of any kind that the rats got when  
7 they were exposed as adults.

8           Is that what you were doing?

9           DR. SANDY:  Well, I'll qualify that to  
10 treatment-related tumors.  So we didn't just count  
11 total tumors in each animal, but if there was a  
12 treatment-related increase in a particular tumor type  
13 or site, then we thought that was a tumor response.  
14 And we used that data.

15           So for the -- we have another multi-window  
16 study here, postnatal and adult.  It's all from the  
17 same paper.  But in the postnatally exposed animals,  
18 they had multiple sites where the treatment-related  
19 tumors were increased.  So we would calculate a  
20 potency -- and we'll go through this in detail --

21           PANEL MEMBER GLANTZ:  Okay.

22           DR. SANDY:  Liver sarcoma, another potency for  
23 heart sarcoma, another for total nerve, and another for  
24 kidney.  And then we did a multi-site potency analysis  
25 to sum across statistically and get one potency value

1 for that.

2 PANEL MEMBER GLANTZ: Okay. But then in terms  
3 of the way these studies were done, so for the  
4 prenatal -- or say the postnatal one. Were those  
5 animals exposed to urethane beginning postnatally and  
6 then for the rest of their life? Or is it just the  
7 postnatal period?

8 DR. SANDY: Just the postnatal period.

9 PANEL MEMBER GLANTZ: Okay. Well, it wasn't  
10 clear to me if it was beginning then and continuing --

11 DR. SANDY: No.

12 PANEL MEMBER GLANTZ: -- through their whole  
13 shelf life, or if we were going to take them off the  
14 shelf. Okay. Thank you.

15 DR. SANDY: No. It was just in that lifestage  
16 window. So --

17 PANEL MEMBER GLANTZ: Okay.

18 DR. SANDY: -- if it went across from  
19 postnatal into adult, we wouldn't include that study.

20 PANEL MEMBER GLANTZ: Okay.

21 CHAIRPERSON FROINES: I think everybody's  
22 confused.

23 PANEL MEMBER GLANTZ: I'm less confused than I  
24 was a few minutes ago.

25 PANEL MEMBER HAMMOND: I understood it.

1           PANEL MEMBER LANDOLPH: I am less confused  
2 too, but I would echo Stan's comments. I think just in  
3 some footnotes you could explain maybe that the tumor  
4 types might differ between the periods, so if you look  
5 at that.

6           CHAIRPERSON FROINES: Charlie?

7           PANEL MEMBER PLOPPER: The other thing that  
8 confused me is that a lot of your studies that are  
9 actually adult are actually juveniles in the results,  
10 so you don't have a juvenile column.

11           In this group, wasn't there animals exposed  
12 prenatally, postnatally, during the juvenile period,  
13 or -- and then the adult is actually exposed for the  
14 last half of the juvenile period right before sexual  
15 maturity?

16           I was confused by that all the way through  
17 here because it looks like the data, the studies that  
18 I'm familiar with, that they didn't actually do an  
19 adult exposure. And then you're using that, the  
20 juvenile, what is it, weaning to sexual maturity, and  
21 using that as an adult study if they didn't do adults  
22 starting with sexual maturity, correct?

23           DR. SANDY: That's correct. If we didn't have  
24 an adult exposure group but we had a group exposed as  
25 juveniles, we would -- in some cases, we would consider

1 that as the referent group.

2 PANEL MEMBER PLOPPER: Okay.

3 DR. SANDY: And we say in the document that  
4 that may underestimate the age of susceptibility  
5 differences because we're using juveniles in those  
6 cases.

7 PANEL MEMBER FRIEDMAN: I'd like to -- may I?

8 CHAIRPERSON FROINES: Please.

9 PANEL MEMBER FRIEDMAN: I'd like to have a  
10 better understanding of why you'd excluded studies  
11 where there was toxicity before cancer formation.

12 Because in humans, you know, one can think of  
13 arsenic, could produce acute toxicity and then later  
14 cancer. Or things like smoking which can produce  
15 severe pulmonary disease and then later lung cancer.

16 So I'm not sure that exclusion would  
17 necessarily not be of -- the studies you're excluding  
18 might not necessarily be of interest.

19 DR. SANDY: We were excluding studies that had  
20 poor survival due to noncancer toxicities.

21 PANEL MEMBER FRIEDMAN: So you mean they won't  
22 live long enough to see that --

23 DR. SANDY: That was the thought.

24 PANEL MEMBER FRIEDMAN: It might be good to  
25 specify that a little more clearly.

1           PANEL MEMBER BYUS: I have a question related  
2 to the treatment-related tumors. What about the  
3 spontaneous tumors which no treatment group would get  
4 at age two to three years? You know, all animals get a  
5 whole series of tumors if you let them live long  
6 enough. In a sense, do you subtract them out? Because  
7 they're going to be there regardless of any treatment.

8           DR. SANDY: So if we take the example of  
9 urethane in the prenatally exposed animals, we have  
10 animals exposed at different doses prenatally and a  
11 control group, and they are followed for the same  
12 period of time.

13           PANEL MEMBER BYUS: But the control group's  
14 going to have the older -- they're the older ones.  
15 They're going to have a higher number of these  
16 spontaneous tumors which are not going to be related to  
17 the treatment. You see what I'm saying?

18           And so you're not going to see them at all,  
19 necessarily, in the juveniles. You see what I'm  
20 getting at? I'm not sure since I haven't actually seen  
21 how you did all the calculations, when you said  
22 treatment-related, I think that's great. But in a  
23 sense, you ought to subtract out the spontaneous  
24 tumor -- normally you do it -- with a carcinogen, you  
25 do no carcinogen and carcinogen.

1 DR. SANDY: Yeah.

2 PANEL MEMBER BYUS: So all of them, you know,  
3 because depending on what animal strain you're using  
4 and what its susceptibility is, there is usually two or  
5 three kinds of tumors that show up in reasonably high  
6 percent -- number of animals if you let them live long  
7 enough. It's not due to the treatment at all.

8 DR. SANDY: I think I understand what you're  
9 saying.

10 PANEL MEMBER BYUS: You see what I'm saying?

11 DR. SANDY: This will be more clear.

12 PANEL MEMBER BYUS: Okay.

13 DR. SANDY: For the prenatally exposed  
14 animals, we have the treated and the controls and just  
15 performing a normal cancer potency estimate with that  
16 data so -- and then we're taking that potency estimate  
17 and taking a ratio of the prenatal potency to the  
18 juvenile -- so I think we've taken into account the  
19 spontaneous background rate of tumors in older animals.

20 PANEL MEMBER BYUS: So are they all then  
21 living the same amount of time? So everybody lives the  
22 same amount of time; it's just the exposure that's  
23 different. Correct? Is that true?

24 DR. SANDY: Not --

25 PANEL MEMBER BYUS: Because if they don't,

1 then you're going to have to --

2 DR. TOMAR: In majority of the cases, that's  
3 true. What happens in some of the cases, some group  
4 are sacrificed earlier. But what we have done is we  
5 have account for the time had they lived for that long  
6 a time. Tumor is increased, depends on a certain  
7 affect factor.

8 PANEL MEMBER BYUS: Yeah, but if they're  
9 not -- if they're not all sacrificed at the same time,  
10 you're going to have this problem with the spontaneous  
11 tumor incidence complicating your calculations.

12 DR. SHERMAN: But there are only two studies  
13 where that was actually the case. The rest of them  
14 were -- I think the only reason why we adjusted was the  
15 difference in the number of days was approximately 90.  
16 It wasn't the majority of the study length.

17 PANEL MEMBER BYUS: Let me ask one more  
18 question, then. So are they all sacrificed at one time  
19 and then autopsied, or are they dying throughout and  
20 then you take what -- because in most tumor  
21 experiments, they go at different times over a period  
22 of six months.

23 DR. SANDY: So let's make sure we're talking  
24 about just the prenatally exposed and their controls as  
25 one experiment. Are they all sacrificed at one time?

1           PANEL MEMBER BYUS: My -- I mean you can come  
2 back and discuss this; I don't want to belabor it. But  
3 my root concern is: If you just take any animal  
4 strain, there is a spontaneous rate of tumors that's  
5 going to show. The longer they live, the more there  
6 are going to be; the more you're going to have  
7 depending on how long they live. And that's a curve,  
8 you know, you can plot, numbers of tumors of certain  
9 kinds depending on the animal strain.

10           PANEL MEMBER HAMMOND: Can you do an age  
11 adjusted --

12           PANEL MEMBER BYUS: Yeah, well, that's what to  
13 do. You're going to have to subtract that curve out of  
14 the numbers and kinds of tumors depending on when in  
15 fact they're sacrificed or die in order to do this kind  
16 of comparison.

17           CHAIRPERSON FROINES: Martha, I -- before you  
18 go on, I'm in a bad place because I don't have what  
19 appears to be the study you're talking about.

20           PANEL MEMBER GLANTZ: It's appendix J. It's  
21 in the binder they sent under the -- and it's the back,  
22 latter part. It's the big thick part.

23           CHAIRPERSON FROINES: Appendix J?

24           PANEL MEMBER GLANTZ: Yes.

25           CHAIRPERSON FROINES: He kept telling me D,

1 and I kept trying to find D.

2 PANEL MEMBER GLANTZ: It's J.

3 PANEL MEMBER BYUS: So tell me, am I making  
4 myself clear here? I mean again, there is a  
5 spontaneous tumor rate.

6 Now obviously, the numbers of tumors that show  
7 up, it's age dependent, obviously. Spontaneously, the  
8 longer and older they are, the more they are. And if  
9 you autopsy and do a complete autopsy and look for  
10 everything with every animal, you'll obviously find  
11 more than if you don't.

12 So there's a spontaneous rate and that you're  
13 going to have to sort of adjust for that depending on  
14 where they were sacrificed and where they showed up.  
15 Depending on when the carcinogen was given.

16 DR. SANDY: Only if the tumor of interest, the  
17 tumor that's identified as a treatment-related tumor --

18 PANEL MEMBER BYUS: Correct. Now sometimes  
19 they're -- sometimes the number of spontaneous tumors  
20 go up due to your exposure. Sometimes it's some other  
21 tumor. I mean -- okay?

22 PANEL MEMBER GLANTZ: Well, I guess the  
23 question is, how does -- how do you --

24 PANEL MEMBER BYUS: Sarcomas, for example, are  
25 ones that you usually see later on, that are

1 spontaneous. That's what made me think of this.

2 PANEL MEMBER GLANTZ: So I guess the question  
3 is, as you can tell, there was a lot of confusion. We  
4 love you, but we're still confused.

5 CHAIRPERSON FROINES: Stan, can you talk into  
6 your microphone?

7 PANEL MEMBER GLANTZ: How do you define that  
8 it's a treatment-related tumor then, given that you're  
9 identifying different treatment-related tumors?

10 PANEL MEMBER BYUS: You have a no-carcinogen  
11 group --

12 PANEL MEMBER GLANTZ: Right.

13 PANEL MEMBER BYUS: -- that you follow for the  
14 same time in terms of whenever they -- if you have your  
15 carcinogen group dies at age one and a half years, you  
16 have a --

17 PANEL MEMBER GLANTZ: But then if you have a  
18 control group --

19 PANEL MEMBER BYUS: There is no exposure  
20 group, that -- you subtract that out.

21 PANEL MEMBER GLANTZ: But isn't that going to  
22 solve the problem you're talking about?

23 CHAIRPERSON FROINES: That doesn't work  
24 because it's one thing to have historical controls that  
25 you haven't seen that cancer, like naphthalene, but

1 there are --

2 PANEL MEMBER GLANTZ: Well, no, but --

3 CHAIRPERSON FROINES: But there are -- you're  
4 confusing --

5 PANEL MEMBER GLANTZ: No. My understanding is  
6 they're only picking studies where they had a control  
7 group in that study. They weren't using historical  
8 controls, right?

9 DR. SANDY: Only in a very rare occasion where  
10 there's a rare tumor and --

11 PANEL MEMBER GLANTZ: So that, the problem  
12 you're raising isn't a problem, John. But I guess if  
13 you're taking the control group -- so I guess is what  
14 you're saying, Craig, is that even in the control group  
15 you're going to get a certain number of thyroid tumors?

16 PANEL MEMBER BYUS: Not necessarily thyroid  
17 but sometimes sarcomas -- you know, there are  
18 various --

19 PANEL MEMBER GLANTZ: Right, but aren't they  
20 taking that into account?

21 PANEL MEMBER BYUS: It's very strain-specific,  
22 at least dependent on the strain of animals, and  
23 obviously the older they are. The incidence goes up  
24 significantly as you go longer.

25 CHAIRPERSON FROINES: Wait. Let me interrupt

1 because this has been going on for quite a while.

2 If you look in the toxicology textbook, Doull  
3 and Clayson, Casarett, whatever it is; there is a whole  
4 table that shows spontaneous tumors by strain and so on  
5 and so forth. Okay. It's well-documented. So  
6 having -- since we all know in this room that that  
7 occurs, what is the relevance of that to this?

8 And she should answer the question about what  
9 is the relevance, if any, to that.

10 DR. SANDY: I think we've taken it into  
11 account by the way the studies are done and the way  
12 we've analyzed them.

13 So the control group and the treatment group  
14 for the period of -- the exposure window we're  
15 interested in, they in most occasions, most cases, are  
16 sac'd at the same time. You don't have the control  
17 living longer.

18 The postnatally exposed animals may live  
19 longer than the prenatal, and the adult exposed may be  
20 living longer.

21 PANEL MEMBER BYUS: Then it doesn't work. If  
22 they're all sacrificed at the same time, I think you've  
23 taken care of it. But if they're not, you have an  
24 anomaly.

25 If they're all sacrificed at the same time,

1 you're comparing everything at the same age of  
2 sacrifice, then you've taken care of that spontaneous  
3 tumor incidence.

4 PANEL MEMBER LANDOLPH: But she's comparing  
5 slope, so it's okay. They're potencies, so I don't  
6 think there's anything wrong with that.

7 PANEL MEMBER BYUS: Well, she's calculating  
8 total tumor number.

9 DR. SANDY: No, I'm not. No, I'm not.

10 That's why I'm puzzled because if there is a  
11 spontaneous increase in some other tumor type that we  
12 haven't identified as being treatment-related --

13 PANEL MEMBER BYUS: All right.

14 DR. SANDY: -- it doesn't -- it's not analyzed  
15 in that potency estimate.

16 PANEL MEMBER BYUS: All right. All right.  
17 Perhaps.

18 DR. SHERMAN: I would also like to point out  
19 that we don't actually have the individual animal data.  
20 What we have are tabulations from manuscripts. So for  
21 a particular dose, these are the number of animals that  
22 had a specific tumor, and then the number of animals  
23 that were in that group.

24 So in effect, we wouldn't be able to, if they  
25 weren't sac'd at the same time, to account for the

1 spontaneous tumor effect simply because we don't have  
2 the individual animal data.

3 PANEL MEMBER BYUS: Okay.

4 CHAIRPERSON FROINES: I would appreciate if  
5 you would send us electronically the primary documents  
6 so that we're not reading a secondary document.

7 PANEL MEMBER BYUS: There's 140 papers,  
8 though. I don't want to look at all of them.

9 PANEL MEMBER GLANTZ: Let's let them go on.

10 CHAIRPERSON FROINES: No. I'm not going to  
11 let them -- no. I'm sorry.

12 I would like to see the primary literature on  
13 this topic. Now if it's 140 papers, then you can make  
14 judgments and send a smaller percentage and I'll get  
15 back with you if I want more. But I want to see some  
16 of these primary -- I want to see some of these papers,  
17 not -- not in this. I want to see them -- I want to  
18 read them.

19 Because we already earlier today had a  
20 discussion about the nature of the methodology of the  
21 design of the study made a difference in the conclusion  
22 that was drawn, and the conclusion that was drawn was  
23 not entirely adequate.

24 So I want to make sure that the study design  
25 is something I feel comfortable with.

1 DR. SANDY: Okay.

2 The point of the slide was that depending on  
3 the age and exposure you can get tumors at different  
4 sites. And I wanted to mention that the analysis by  
5 Barton et al., they took a ratio of potencies at the  
6 same sites. So they would have compared thyroid tumors  
7 in the adult exposed, thyroid tumors in the postnatally  
8 exposed if they had that.

9 So we've taken a different approach because of  
10 this and because of the fact that we also see that many  
11 carcinogens cause tumors at multiple sites, and I've  
12 listed a few examples here.

13 Instead of going site to site, we have done  
14 this multi-site potency analysis within a window. So  
15 within one prenatal exposure period, if there's  
16 multiple sites, treatment-related tumors, we have a  
17 single multi-site potency that represents the total  
18 cancer risk.

19 CHAIRPERSON FROINES: Martha, have you done a  
20 subsequent analysis of metabolic pathways in terms of  
21 what kinds of pathways exist at what ages so that you  
22 could make some estimate about whether or not the  
23 toxicokinetics change depending on the age under study?

24 DR. SANDY: We know that that does happen, and  
25 it involves different enzymes for different carcinogens

1 for --

2 CHAIRPERSON FROINES: Sure.

3 DR. SANDY: -- both detoxification and  
4 activation, and it can be very complicated.

5 And we have an example which we'll hear about  
6 on the case studies with ENU, which is a direct-acting  
7 agent, and DEN, which requires metabolism where you  
8 see -- I'm stealing Raj's thunder here -- that the  
9 prenatally exposed animals when they're exposed to DEN,  
10 they're not -- there's no increased sensitivity  
11 compared to adults because you don't have the capacity  
12 to activate.

13 We presume that's the answer, but we don't see  
14 that with other carcinogens that we know need to be  
15 metabolized.

16 So it's very complicated. And for each  
17 specific carcinogen, we could spend a lot of time and  
18 write a whole paper to try to explain the results we  
19 see. So we haven't done an across-the-board analysis.

20 CHAIRPERSON FROINES: Well, I'll give you an  
21 example that -- I mean with benzo(a)pyrene every  
22 toxicology textbook has the diol epoxide as the primary  
23 pathway which is total bull. Because that's not the  
24 primary pathway.

25 The formation of three quinones really

1 represents the primary pathway. Then you have radical  
2 cations. So that you have perhaps five different  
3 pathways with benzo(a)pyrene. The one we learn about  
4 in school is the one that doesn't appear in the  
5 cancers. So that this is really quite a crucial issue  
6 in terms of sorting out what may be causing it.

7           Not to mention the actual distributional  
8 issues that may be occurring. Because obviously if  
9 you're going to get cancers at different sites there  
10 are obviously distributional questions that need to be  
11 considered.

12           So what you're saying is you're looking at the  
13 picture more broadly at this stage and the details of  
14 these kinds of factors you're not really involved in at  
15 this point.

16           DR. SANDY: The point of this analysis was to  
17 come up with some sort of measure or default age  
18 adjustment factor for each exposure window based on all  
19 the data. We searched the animal -- the literature for  
20 animal cancer data, and we're saying in the absence of  
21 chemical-specific data with age sensitivity  
22 information, perhaps we can analyze these data and come  
23 up with some general default approaches.

24           CHAIRPERSON FROINES: Yeah. But you realize  
25 the problem we're having right here -- and I think the

1 problem will continue -- the problem is that you have  
2 one goal in mind with respect to this process, but  
3 you're getting all these toxicologists who are  
4 interested in toxicology, and the risk assessment  
5 adjustment factors is so far down the field from where  
6 we are that you're getting stuck from us with these  
7 questions that have to do with what's the basic  
8 mechanisms that we're talking about.

9           So we've got a trap that we have to get -- in  
10 a sense get past so we can proceed. And I think we'll  
11 have to defer maybe some of our tox questions and  
12 figure out how to get them answered, which is why I  
13 would like to see some of the primary documents as a  
14 way of doing some of the work ourselves rather than  
15 having you -- because you actually have a different  
16 objective that I think -- than I do.

17           DR. SANDY: Right. I think the questions  
18 you're asking right now would be more appropriate for  
19 if we were developing a special age factor for a  
20 particular carcinogen. Then you want to understand the  
21 mechanism --

22           CHAIRPERSON FROINES: Right.

23           DR. SANDY: -- very clearly and what's the  
24 best adjustment factor.

25           Here, we're saying we've collected all the

1 carcinogens and their data, and we're going to show you  
2 sort of a meta analysis of that for the prenatal window  
3 and for the postnatal and for the juvenile to try to  
4 come up with some age adjustment factors that might  
5 make sense in general for a carcinogen that you know  
6 nothing about except that it causes cancer but you  
7 don't understand the mechanism.

8           So. Shall we move on?

9           CHAIRPERSON FROINES: Yeah. I'll tell you,  
10 that -- as a strategic issue, the -- what this -- I  
11 agree a thousand percent with what you're doing. So  
12 don't misunderstand. And I think it's extremely  
13 laudable and difficult.

14           I'm worried about what happens when we go into  
15 a courtroom, and industry says by the way, you haven't  
16 looked at the mechanistic features of what you've done.

17           And so I think that there are bumps down the  
18 road as this proceeds, is what I'm saying.

19           DR. SANDY: In addition to doing this  
20 multi-window exposure analysis, we've also tried to get  
21 at what you're asking us now.

22           If we have data, maybe from single-window  
23 exposure studies, on the same carcinogen, so ten  
24 different laboratories around the world have studied a  
25 certain carcinogen and exposed a set of animals during

1 one exposure window but not an adult exposure window,  
2 can we use that data in some way to come up with  
3 another measure of age sensitivity? So we call this a  
4 chemical-specific case study approach.

5 And we'd like to think of it as a meta  
6 analysis of single-window exposure studies conducted  
7 with exposures in the prenatal period or the postnatal  
8 or the juvenile or the adult.

9 We put that all together and try to come up  
10 with these factors. And Raj will be talking about  
11 that. So that's it.

12 CHAIRPERSON FROINES: Martha, you don't mean  
13 prenatal twice?

14 DR. SANDY: No. That's a typo; I apologize.

15 So this is a stopping point before we move on  
16 to the statistical approaches. Do you have any further  
17 questions?

18 PANEL MEMBER BYUS: I do have quite a bit of  
19 questions, but I will defer them if you want.

20 CHAIRPERSON FROINES: I don't -- I honestly  
21 don't know the best approach.

22 PANEL MEMBER BYUS: What is your dose  
23 parameter? I mean how are you comparing the dose  
24 administered to a juvenile, little tiny rat or mouse,  
25 to the adult?

1           Are you administering it -- is it going to be  
2 the same on a per body weight basis? What's the  
3 comparison dosage?

4           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
5 MARTY: I think if they finish the presentation, a lot  
6 of that will get answered. So we actually have  
7 additional slides available to you.

8           PANEL MEMBER BYUS: Okay.

9           CHAIRPERSON FROINES: Melanie, because we're  
10 short of time and because everybody wants to ask  
11 questions, we've got a dilemma.

12           What do you -- tell me what you think would be  
13 the best procedure? I think you just told me, which is  
14 to be quiet for a while and let us get on with it.

15           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
16 MARTY: Yeah, just let them finish. And then, you  
17 know, we have the next meeting also, and they have many  
18 more detailed slides to address your specific  
19 questions.

20           CHAIRPERSON FROINES: I'm actually, just  
21 between you and me, getting worried about the next  
22 meeting. The next meeting -- seems like Kathy's  
23 question was right -- it's going to take about a week  
24 long. Of course we'll make \$700, so it will -- we'll  
25 be rich beyond our wildest dreams.

1 DR. TOMAR: Just to answer the question of  
2 dose, all the doses were converted into milligram per  
3 kg body weight basis.

4 PANEL MEMBER BYUS: Okay.

5 DR. TOMAR: If the doses were given to a  
6 one-day-old animal, the weight was given by the paper  
7 or it was calculated on the basis of the available  
8 data.

9 And on the basis of that weight, whatever dose  
10 was given, it was converted into milligram per kg body  
11 weight throughout the whole history of our analysis.  
12 Every dose has been treated the same way.

13 DR. SHERMAN: Okay. I'm going to present the  
14 mathematical and statistical approaches.

15 PANEL MEMBER GLANTZ: You should tell them  
16 your name.

17 DR. SHERMAN: Oh. I'm Claire Sherman.

18 This presentation is a little bit different  
19 than probably what you've seen in the past. We are not  
20 focused on looking at low dose extrapolation.

21 Everything that we're looking at is based on  
22 model fit and deriving distributions. So I want to  
23 just give you a broad overview of exactly how we're  
24 going to go about doing this.

25 We first fit a dose response model to bioassay

1 data, and we're strictly focused on the observable  
2 range of the data, nothing outside the range of the  
3 data.

4           We have our dose response model, and our slope  
5 parameter represents potency. And our main focus  
6 throughout this work is the comparison of the slopes.  
7 Either essentially across these different age  
8 windows -- I -- okay.

9           So here's an example of what a dose response  
10 line would be for prenatal exposure, and then for the  
11 adult. So effectively what we're looking at is the  
12 difference between the dose responses for those two  
13 particular age windows.

14           Okay. So the dose response model that we used  
15 was a linearized multi-stage model. The basic reason  
16 for using this model is it has a lot of mileage. We've  
17 used it for years. But it's also incredibly flexible.  
18 There are very, very few dose response data sets out  
19 there that do not fit this model. We wanted to find a  
20 single model that would fit all of the data that we  
21 were throwing at it.

22           So the linearized multi-stage model  
23 effectively can fit both linear and nonlinear dose  
24 response patterns, and that was the basic reason for  
25 using it as well as people's familiarity with it.

1           So this is what the model looks like  
2 mathematically, and I'm sure you've all seen this.  
3 Okay. And then some of the things I'm just pointing  
4 out is that at low doses the linearized multi-stage  
5 model reduces to a two parameter model, and it's very  
6 simple.

7           But then when the intercept is small, the  
8 linearized multi-stage model turns out to be a linear  
9 model which is shown at the bottom where  $q_0$  is  
10 the intercept and  $q_1$  is the slope. And that is the  $q_1$ ,  
11 the slope, the potency estimate, that we'll be focusing  
12 on.

13           So here we go back to our original dose  
14 response curve for the prenatal dose group. You see  
15 that  $q_1$  -- yeah?

16           PANEL MEMBER BYUS: Tumor multiplicity, tumor  
17 number, that's what tumor response means?

18           DR. SHERMAN: Tumor response is --

19           PANEL MEMBER BYUS: Multiplicity?

20           DR. SHERMAN: No. It's not tumor  
21 multiplicity. It's presence or absence of tumor.

22           PANEL MEMBER BYUS: Incidence?

23           DR. SHERMAN: Yes, it is incidence.

24           PANEL MEMBER BYUS: Okay. So -- okay.

25           So it's not total tumor numbers?

1 DR. SHERMAN: No. Incidence.

2 PANEL MEMBER BYUS: Okay. So it's appearance  
3 of a single tumor.

4 DR. SHERMAN: Tumor of a particular type.

5 PANEL MEMBER BYUS: Of a particular type.

6 DR. SHERMAN: And then we'll get into --

7 PANEL MEMBER BYUS: Okay.

8 DR. SHERMAN: -- multi-site --

9 DR. SANDY: And it's number of animals with  
10 tumors over the --

11 PANEL MEMBER BYUS: Got it.

12 DR. SANDY: -- effective number of animals.

13 DR. SHERMAN: It's the typical bioassay data  
14 that you would see.

15 PANEL MEMBER BYUS: For incidence.

16 DR. SHERMAN: Exactly.

17 PANEL MEMBER BYUS: All right. That's all.

18 DR. SHERMAN: Okay.

19 So here we see the cancer potency estimate or  
20 the slope for the prenatal dose group, and then we can  
21 compare that to the slope that you would see for the  
22 adult dose group.

23 So again, we're just making comparisons  
24 amongst these slopes. And that is effectively the  
25 comparisons that we're making. Okay. And if you keep

1 that in mind, everything else will hopefully fall into  
2 place.

3 Okay. So cancer potency estimation, this is  
4 very similar to what you've seen before. Potency, as I  
5 said, is characterized by the slope parameter  $q_1$ , and  
6 it's estimated via maximum likelihood methods.

7 CHAIRPERSON FROINES: Why did you choose  
8 maximum likelihood?

9 DR. SHERMAN: That seems to be the standard.

10 CHAIRPERSON FROINES: No, it's actually not.

11 DR. SHERMAN: Then what is?

12 CHAIRPERSON FROINES: Well, let's go ahead.  
13 Let's go ahead.

14 DR. SHERMAN: Okay. Profile likelihood  
15 methods are used to determine the empirical  
16 distribution of  $q_1$ .

17 The reason why I'm sort of looking at you in a  
18 questioning way is normally in risk assessment  
19 guidelines by US EPA and others they use maximum  
20 likelihood estimation to get the potency, and then they  
21 use profile likelihood methods to get at the upper  
22 bound. So.

23 Okay. So in order to get --

24 CHAIRPERSON FROINES: That was my point.

25 DR. SHERMAN: Okay.

1           So we fit the linearized multi-stage model to  
2 experimental data in a stepwise manner. Now this is a  
3 little bit different than what's normally done.

4           We start out with a two-parameter linearized  
5 multi-stage model. If it adequately fits the data,  
6 using a goodness-of-fit test, then we have a two  
7 parameter model and we move forward.

8           Then we trace the profile likelihood of the  
9 slope parameter in increments of one half percent. And  
10 then via Monte Carlo method we sample from those half  
11 percent increments 100,000 times to arrive at the  
12 potency distribution.

13           Now if for some reason a two parameter model  
14 does not adequately fit the data, we then fit a  
15 three-parameter model. And then if that adequately  
16 fits, then we again trace the profile likelihood and  
17 use Monte Carlo.

18           What I do want to point out is with the  
19 linearized multi-stage model all the models fit to the  
20 data that we had with either two or three-parameter  
21 models. There were none above a three-parameter model.

22           So this is an example of what a cancer potency  
23 distribution would look like. Okay.

24           So for some chemicals, there might be multiple  
25 target tumor sites. So a potency distribution is

1 computed for each treatment-related tumor site in an  
2 experiment.

3 Now I think somebody had pointed out in a case  
4 of where they might not be treatment-related or  
5 essentially the potency would be flat. What we could  
6 have done, and what we looked at very early on in this  
7 process, is the case of taking the entire pathology  
8 that was run for a particular study and basically  
9 computing all of the potency distributions for each  
10 tumor site that was available.

11 One of the problems with doing that is for  
12 some studies they might have done ten different tumor  
13 sites, and some of those tumor sites would be fairly  
14 insignificant, but if you have a bunch of them, when  
15 you sum them, all of a sudden they can become  
16 significant.

17 So a decision was made early on to only go  
18 after the treatment-related tumor sites because we  
19 didn't want to exaggerate any sort of effect.

20 DR. SANDY: And I'll just add that our  
21 standard risk assessment process is to only analyze  
22 treatment-related tumors.

23 DR. SHERMAN: Okay. So we sum across the  
24 site-specific potency distributions, and then we get a  
25 total cancer potency. And this is kind of what it

1 looks like. So in the first box above we might have a  
2 lung potency distribution.

3 We add that to the liver potency distribution,  
4 and then at the bottom we have a multi-site potency  
5 distribution. Now in the case of the bottom  
6 distribution, it doesn't look that much different than  
7 the liver potency distribution. It's because it's  
8 actually fatter, the multi-site potency distribution,  
9 and it's because of the symmetric distribution of the  
10 lung potency.

11 So that's how we go about finding these  
12 multi-site potency distributions. We essentially sum  
13 all of the treatment-related tumor site potency  
14 distributions and get a final multi-site potency  
15 distribution.

16 PANEL MEMBER GLANTZ: But I don't see how you  
17 can do that. I mean I'm not criticizing, but if you're  
18 doing that in the adults and you have a different set  
19 of tumors than you do in the juveniles, say, how can  
20 you then go and compare them?

21 Because if you go back to what you said a  
22 couple minutes ago about not just wanting to add  
23 everything up and looking at, say, total tumors -- I  
24 mean this is the part that I got completely lost in  
25 when I was trying to read it.

1 DR. SANDY: What we're trying to do is  
2 characterize the cancer risk from exposure in the early  
3 life window.

4 PANEL MEMBER GLANTZ: Right.

5 DR. SANDY: And is it greater, less than, or  
6 equal to the cancer risk when exposure occurs as an  
7 adult.

8 And you want the total cancer risk. If you  
9 think of tobacco smoke, that causes tumors at multiple  
10 sites. You don't want to just focus on one. You want  
11 to take what's the total risk from smoking.

12 So we're taking the total risk from exposure  
13 to a particular carcinogen, and then we're comparing  
14 total cancer risk when exposure occurs early to when  
15 exposure occurs later in life.

16 PANEL MEMBER GLANTZ: Right. But if you're --  
17 let's just say for the sake of argument that you have  
18 one kind of tumor that's produced from the early  
19 exposure and three other tumors that are produced late  
20 or for adult exposures.

21 I still don't see quite how -- it just seems  
22 like an apples and oranges comparison. I'm not saying  
23 it's wrong, but I just --

24 PANEL MEMBER BYUS: It is. You're right. But  
25 they don't have a choice. There is no other way to do

1 it.

2 PANEL MEMBER GLANTZ: Okay. Then the other  
3 thing that -- I mean again, and maybe this is just me  
4 being thick when I was reading this, and maybe I missed  
5 something in one of the earlier slides. But the adding  
6 together -- the potencies are the slopes, right?

7 DR. SHERMAN: Are the --

8 DR. SANDY: Well, we tend to think of -- yes,  
9 q1 is the slope. But there is a distribution.

10 PANEL MEMBER GLANTZ: Right.

11 DR. SANDY: Confidence interval. And what  
12 we're actually doing is we're not picking a single  
13 point.

14 PANEL MEMBER GLANTZ: Oh, no. I understand.  
15 That was the one thing I did understand.

16 But does it make sense to add the slopes?  
17 Because isn't that the slope of the dose response, and  
18 the thing that's on the X axis of the dose response is  
19 the concentration or the level of exposure, right?

20 So why, if you have -- although I guess you're  
21 saying that you're just counting tumors.

22 PANEL MEMBER LANDOLPH: Yeah, add the slopes,  
23 it's like adding the treatment-related tumors --

24 DR. SANDY: Exactly.

25 PANEL MEMBER LANDOLPH: -- basically. And

1 you're just asking are they more or are they less in  
2 the adult window, in the early window than in the adult  
3 window.

4 PANEL MEMBER GLANTZ: Okay.

5 PANEL MEMBER LANDOLPH: It's reasonable.

6 PANEL MEMBER GLANTZ: I'm just trying to  
7 understand this. And reading it, I felt very  
8 inadequate.

9 DR. SHERMAN: Me too, when I wrote it. Okay.

10 Are there any questions so far about potency  
11 distributions or multi-site potency or anything else  
12 that's come up so far?

13 So I'm first going to talk about the  
14 multi-exposure window studies, and Martha referred to  
15 those already as containing multiple experiments in the  
16 same study where one experiment occurs in an earlier  
17 exposure window and another experiment occurs in an  
18 older exposure window, preferably in adults.

19 And again, Martha showed the slide so we can  
20 effectively push on.

21 CHAIRPERSON FROINES: Can I just be sure I  
22 understand what you mean by -- go back -- by multiple  
23 exposure window studies contain multiple experiments in  
24 the same study?

25 DR. SHERMAN: Effectively, what you have is a

1 prenatal -- an animal exposed, and -- well, okay.  
2 Let's just say postnatal. Animal exposed during a  
3 postnatal window, and then they're followed through for  
4 a particular period of time; and then coincident, you  
5 have mature animals that are exposed and followed for  
6 the same period of time. And that's occurring in the  
7 same study.

8 DR. SANDY: So one experiment where you have a  
9 control group and some treated groups. And those  
10 treated groups are exposed only in a certain window.  
11 Call that --

12 CHAIRPERSON FROINES: But the treated groups  
13 are what -- the defining feature is the time.

14 DR. SANDY: The time of exposure.

15 CHAIRPERSON FROINES: And not multiple  
16 experiments. Right?

17 DR. SANDY: Right. The multiple experiments  
18 means --

19 CHAIRPERSON FROINES: It's not a meta  
20 analysis.

21 DR. SANDY: No.

22 CHAIRPERSON FROINES: It's a time-defined.

23 DR. SANDY: Yeah.

24 CHAIRPERSON FROINES: Okay.

25 DR. SANDY: Okay.

1           Just maybe on this slide, so what we're saying  
2 is that you've got a postnatally exposed group,  
3 treatment and controls; and you have an adult group,  
4 treatment and controls. In the same study. We call  
5 that a multi-window exposure study.

6           So we're comparing the potency from the  
7 postnatally exposed to the potency from the adult  
8 exposed. That is same investigator, same laboratory,  
9 same time.

10           PANEL MEMBER LANDOLPH: And Martha, if you  
11 could put that nice figure in the document, it would  
12 make it much easier to demonstrate. That's a very nice  
13 figure. Please.

14           DR. SANDY: Okay.

15           CHAIRPERSON FROINES: I'm amazed somebody says  
16 there were 140 papers? I'm amazed there are that many  
17 studies that were done.

18           DR. SANDY: We found about 145 papers with  
19 early life exposures, but we only found -- I don't  
20 recall if it's 55 -- I don't recall how many  
21 publications had multi-window exposure studies reported  
22 in them.

23           I was reporting the larger group of studies  
24 where there might be just a postnatally exposed group,  
25 and that's all they reported.

1           But when we looked -- it narrows down into a  
2 smaller group of studies when we look for multi --

3           CHAIRPERSON FROINES: Those are the ones that  
4 are worth looking at.

5           PANEL MEMBER PLOPPER: Most of the ones you  
6 listed don't include all of those groups. They may  
7 have two of those groups plus the adults.

8           DR. SANDY: Or one group.

9           DR. SHERMAN: Or one group.

10          DR. SANDY: And that's enough to call it a  
11 multi-window exposure.

12          PANEL MEMBER PLOPPER: Okay. And that's what  
13 I think needs to be clear in here is that it has to  
14 have two different age group exposures.

15          DR. SANDY: Yes.

16          PANEL MEMBER PLOPPER: That makes a big  
17 difference. Yeah. Okay.

18          DR. SHERMAN: Okay. So we're first going to  
19 talk about these multi-window studies and the  
20 distribution or the age sensitivity factor distribution  
21 that results from the -- so what we're doing is  
22 comparing the cancer potency from early life exposure,  
23 compared to the later life exposure.

24                 And the way that we do this is by taking the  
25 quotient of the cancer potency distributions for the

1 early life versus the later life.

2           And the idea behind this is that it represents  
3 essentially the spectrum of cancer induction  
4 sensitivity in an early life exposure window relative  
5 to adults. And here's a sort of picture of how you can  
6 look at this.

7           If we have an early life potency -- and that  
8 can also be a multi-site potency for, say, a prenatal  
9 or postnatal window -- and then we divide that potency  
10 distribution by the reference group distribution,  
11 either an adult potency or a juvenile potency, then the  
12 resulting age sensitivity factor distribution is what  
13 you see to the right.

14           And generally speaking, the age sensitivity  
15 factor distribution, because it is a ratio  
16 distribution, tends to be right skewed.

17           PANEL MEMBER LANDOLPH: And then when you're  
18 reporting age sensitivity distribution factors or age  
19 dependent factors in here, are you reporting the mean  
20 of the distribution for that ratio?

21           DR. SHERMAN: We generally report percentile  
22 simply because they're right skewed so that would mean  
23 that the mean would be shifted more towards the right.

24           If it were a symmetric distribution, then it  
25 would be reasonable to report the mean.

1           PANEL MEMBER LANDOLPH: So you just report one  
2 number for the ratio.

3           DR. SHERMAN: No, no, no. We actually report  
4 multiple percentiles.

5           DR. SANDY: This ASF distribution pictured  
6 here is presented in the next slide in a different  
7 form, but it's still presented as a distribution, not a  
8 point estimate. Right.

9           DR. SHERMAN: So. Let me go through this.  
10 This is what -- these are all the studies, multi-window  
11 studies, that had postnatally exposed animals as well  
12 as adult animals.

13           And these are the age sensitivity factors that  
14 were computed. And then the whiskers of these box  
15 plots, the ends of them represent a 90 percent  
16 confidence interval.

17           DR. SANDY: If I can just tell you, it's on  
18 page 27 of appendix J.

19           CHAIRPERSON FROINES: I know what this is.  
20 This is my iPhone turned sideways.

21           (Laughter)

22           PANEL MEMBER BYUS: So it's the symbol itself,  
23 the peak in the distribution plus the ninety percent to  
24 the sides?

25           DR. SHERMAN: No, no, no. Well, these are

1 effectively box and whisker plots so that the colors  
2 represent whether the study -- pink is female, blue is  
3 male, and I think if it's purple it's a mixed  
4 male/female study. And then if it's a rectangle or a  
5 triangle or another shape, that represents the  
6 species -- is it strain or species?

7 DR. SANDY: Species.

8 DR. SHERMAN: Species.

9 PANEL MEMBER LANDOLPH: That's fine. I still  
10 didn't get my question answered.

11 So any one rectangle, there's one rectangle  
12 there.

13 DR. SHERMAN: Okay.

14 PANEL MEMBER LANDOLPH: So -- and it has  
15 outline, it has error bars, if you will, to the width  
16 of distribution, and that's fine. So what is the  
17 rectangle itself?

18 DR. SHERMAN: The rectangle is the 25th  
19 percentile to the 75th percentile.

20 PANEL MEMBER LANDOLPH: Okay. That's what I  
21 wasn't --

22 DR. SHERMAN: It's the typical box plot,  
23 except the whiskers actually represent the bottom fifth  
24 percentile and the top ninety-fifth percentile.

25 PANEL MEMBER LANDOLPH: Okay. That's fine.

1 Thank you for answering that question. But I had to  
2 pull it out of you.

3 DR. SHERMAN: Sorry, I didn't --

4 PANEL MEMBER LANDOLPH: And you need to please  
5 put that in the document, big letters. Capital  
6 letters. Make it real clear. Because that was totally  
7 lost on me.

8 DR. SANDY: It's in there.

9 PANEL MEMBER LANDOLPH: Okay. It's hidden.  
10 Make it blocked. Because that didn't come across to me  
11 at all.

12 PANEL MEMBER GLANTZ: So -- I mean, yeah.  
13 Because this is another place I got -- I was feeling  
14 like massively confused by this whole thing.

15 So if you look at this graph on page 27 or  
16 that you have up there, when you say postnatal age  
17 sensitivity factor, so this is -- every one of these  
18 studies, it's a different chemical, and you're looking  
19 at the total cancer -- the ratio of the total cancer  
20 potencies, comparing postnatal exposure to adult  
21 exposure.

22 DR. SANDY: Correct. And if these box plots  
23 have an asterisk, then that indicates that instead of  
24 an adult referent group it was a juvenile referent  
25 group, so there's a number of asterisks.

1           And there are 18 chemicals, but there's 55  
2 studies. So for some chemicals, we have multiple  
3 studies.

4           PANEL MEMBER HAMMOND: It's nice that you're  
5 helping step us through this. Okay. Taking DEN, the  
6 chemical, then we actually have -- I can see two  
7 different sexes going across there.

8           But what are the different -- for any one sex,  
9 what -- what do we have? What are the potencies as we  
10 go across? Different cancer sites or --

11          DR. SANDY: No. Different experiments.

12          PANEL MEMBER HAMMOND: Oh. Different studies.

13          PANEL MEMBER GLANTZ: So each one of these  
14 things is a study.

15          DR. SANDY: So --

16          PANEL MEMBER HAMMOND: So four different  
17 groups of people did both postnatal and juvenile?  
18 Males and females.

19          DR. SHERMAN: There are small numbers that you  
20 probably can't see on the slide, but certainly on the  
21 document. And they reference the manuscripts from  
22 where the data came from.

23          PANEL MEMBER HAMMOND: Where are those  
24 numbers?

25          DR. SANDY: The numbers aren't on there.

1           PANEL MEMBER GLANTZ: They're secret numbers.

2           DR. SANDY: They're reported in the order in  
3 which they are presented in an appendix to this, table  
4 B2 has all the -- many of the percentiles, and it tells  
5 you the strain of the animal, the investigator. So  
6 around A16, you'll find table B1. That's prenatal. So  
7 postnatal starts I guess on A18.

8           PANEL MEMBER BYUS: It's really hard to read.

9           CHAIRPERSON FROINES: I think we're going to  
10 have to work on this table. This table is just not  
11 transparent.

12           PANEL MEMBER HAMMOND: I think that's true,  
13 but I think sometimes it helps -- if you don't mind.  
14 If you don't want me to do this --

15           CHAIRPERSON FROINES: I'm not concerned about  
16 whether -- I'm thinking about whether we understand it  
17 or not, but I'm more concerned about how it gets  
18 projected to the public on the outside of this room.

19           PANEL MEMBER HAMMOND: I understand that too,  
20 but we need to understand it first.

21           For DEN, I see -- might be four sets of bars  
22 with male and female. I'm just picking one thing  
23 because there are a bunch of them. But I only see two  
24 studies, Mohr et al. in '75 and then '95. 20 years  
25 later he repeated the experiments?

1 DR. SANDY: I think you're looking at prenatal  
2 rather than postnatal.

3 PANEL MEMBER HAMMOND: Oh, yeah.

4 DR. SANDY: Table B2.

5 PANEL MEMBER HAMMOND: Gotcha. So which  
6 table?

7 DR. SANDY: Page A19 at the top, DEN.

8 PANEL MEMBER HAMMOND: Got it. Okay.

9 So now we have -- oh. So now we have one  
10 study that's a mouse with one strain and another study  
11 that had two different strains of mice.

12 DR. SANDY: A19.

13 PANEL MEMBER HAMMOND: So now we have one  
14 study that's the mouse, one strain, the Rao. And the  
15 other one is the Vesselinovitch who used two strains of  
16 mice and used different days, that's why they're  
17 different bars. Okay. Okay. Beginning to get it.

18 Probably what you do want to do is have the  
19 numbers that you apparently had at one point, you know,  
20 to identify the studies. There's plenty of room. You  
21 could just throw it across the bottom.

22 DR. SANDY: Mm-hmm.

23 PANEL MEMBER HAMMOND: So if we look at that,  
24 then we also see that there really is a gender  
25 difference. That's one of the -- I think that was in

1 one of the earlier slides.

2 CHAIRPERSON FROINES: I'm sorry Kathy. I  
3 can't hear you.

4 PANEL MEMBER HAMMOND: I think earlier in one  
5 of the slides that came up before, that there's a  
6 gender difference in the age -- the window sensitivity.  
7 I think one of the very early slides in this discussion  
8 had that and you can see it right in that example, that  
9 males show more difference in sensitivity by the window  
10 whereas the females to some degree aren't showing  
11 nearly as much.

12 DR. SANDY: And it depends on the chemical.

13 PANEL MEMBER HAMMOND: On the what?

14 DR. SANDY: On the chemical.

15 PANEL MEMBER HAMMOND: Yeah. I'm just staying  
16 in one little world. One little world.

17 PANEL MEMBER LANDOLPH: These figure legends  
18 too, if you could enlarge those for us that would help.  
19 It's really tough to read.

20 DR. SHERMAN: Another thing I'd like to point  
21 out on this graphic is the horizontal line that appears  
22 at one. What that indicates is that there's no  
23 difference with regard to postnatal versus adult  
24 exposure in terms of cancer risk.

25 So, you know, you can just look at it and you

1 see patterns and whatnot. And that's why it's  
2 presented as broadly as it is. And you can also see a  
3 lot of variability, but we'll get to that.

4 PANEL MEMBER HAMMOND: Do you have -- this is  
5 postnatal.

6 DR. SHERMAN: Yes.

7 PANEL MEMBER HAMMOND: And it might be  
8 postnatal to juvenile or to adult, and that's indicated  
9 with an asterisk. Is there a similar prenatal chart?

10 DR. SANDY: Yes. And we'll get to the results  
11 section, actually go through what this means. But we  
12 were trying to go through the methods.

13 PANEL MEMBER HAMMOND: I'm sorry.

14 DR. SANDY: We want you to be, you know, to  
15 understand this. So please ask the questions so we can  
16 answer them.

17 PANEL MEMBER LANDOLPH: And I'd recommend that  
18 nice figure you put in about distribution in early life  
19 and distribution in later life and dividing one by the  
20 other to get distribution. Maybe use that as an  
21 illustrative figure to help guide the reader to  
22 understand exactly what you did, please. Thank you.

23 DR. SHERMAN: Okay. So now we have a whole  
24 bunch of postnatal age sensitivity factor  
25 distributions, but what we'd like to do is combine them

1 in a way to get one all-encompassing age sensitivity  
2 factor distribution across all the chemicals for the  
3 postnatal window.

4 And the way that we do that is combine these  
5 ASF distributions across all the chemicals for a given  
6 exposure window. In this case, the postnatal window.  
7 And then, again, we use Monte Carlo sampling methods.

8 Now, the methods that we used to create this  
9 ASF mixture distribution for the postnatal window --  
10 and this will be the case for also juvenile and  
11 prenatal -- is first we make sure that each chemical is  
12 equally likely to be sampled. The reason being is that  
13 we didn't want to essentially have one chemical  
14 dominate versus the other.

15 And for each chemical, we have a single ASF  
16 distribution that represents it. So effectively what  
17 we're doing when we create this mixture distribution is  
18 if a chemical has a single ASF distribution for it,  
19 that's the distribution that is representative for that  
20 chemical.

21 However, for chemicals that have multiple  
22 studies representing it, what we do is we effectively  
23 take a mixture of those, create a mixture distribution  
24 for that chemical, and then we basically sample across  
25 all the chemicals.

1           So effectively, what we do for chemicals that  
2 have multiple studies is we first create mixture  
3 distribution within that chemical, and then once we  
4 have a distribution for each chemical, then we sample  
5 equally across all the chemicals to end up with a  
6 single mixture distribution.

7           PANEL MEMBER GLANTZ: So if you have, say,  
8 three studies of a given chemical, is there a  
9 probability of one-third of getting your sample -- or  
10 your Monte Carlo thing drawn from each one.

11          DR. SHERMAN: That's correct.

12          PANEL MEMBER GLANTZ: Okay.

13          DR. SANDY: And that was for the method that  
14 we called method one where each of the studies within a  
15 chemical were equally weighted. And as we indicate  
16 here, we did some sensitivity analyses, trying  
17 different weighting methods which we can go into.

18          DR. SHERMAN: So, as Martha said, method one,  
19 we equally sampled from each of the ASF distributions  
20 within each chemical.

21                 So this is what one of these mixture  
22 distributions looks like, particularly for postnatal.  
23 And the reason why this was chosen as the illustrative  
24 example is because it had so many studies.

25                 And I actually like showing the density

1 function for this mixture distribution because most of  
2 the time people think of distributions as looking bell  
3 shaped or, you know, fairly normal.

4 For all these different chemicals for the  
5 postnatal distribution, you note that it's effectively  
6 a multi-modal distribution. And this comes about  
7 because you have some chemicals, their ASF  
8 distributions tend to be much less than one. You have  
9 some distributions that are right around one, and you  
10 have some distributions that are much greater than one.  
11 And that's where those multiple modes come from.

12 PANEL MEMBER GLANTZ: But isn't the shape of  
13 this going to really be heavily dependent on which  
14 chemicals you happen to have in the data?

15 DR. SHERMAN: Absolutely, and that's why all  
16 the chemicals are equally likely to be sampled. We  
17 batted that back and forth because we didn't have any  
18 way of sort of deciding on those chemicals. We said  
19 we're going to equally put them in the mix.

20 PANEL MEMBER HAMMOND: This is a question for  
21 the toxicologist, just another way to think about this.  
22 If one knows about mode of action, which maybe one  
23 doesn't, maybe one would classify them into groupings.

24 I don't know if when you look at this if one  
25 can say oh, well, you know, aromatic compounds tend to

1 have -- they're the ones that have the 100 to 1 ratio.  
2 I mean I notice that the benzidines would be too  
3 extreme for the male and the female, but whatever.

4 But if there were any kind of like mode of  
5 action or any sense of, well, when they operate in this  
6 mechanism, then we see huge differences by age  
7 windows -- or is that a totally crazy idea?

8 DR. SHERMAN: This --

9 PANEL MEMBER HAMMOND: Because if that were  
10 true and if you could do that, then you should actually  
11 sample based on those --

12 DR. SHERMAN: Absolutely, but in this case we  
13 basically made the assumption that we don't have mode  
14 of action and whatnot, that we're just taking this as  
15 the body of information we have for multi-window  
16 studies in the absence of mode of action, and here's  
17 what we effectively find out.

18 PANEL MEMBER HAMMOND: Is it true we don't  
19 have that information?

20 DR. SANDY: For these 18 chemicals in the  
21 postnatal window sets, we know that two are thought to  
22 be acting primarily through nongenotoxic mechanisms,  
23 and that's TCDD and PBBs.

24 The rest are considered to be genotoxic in  
25 mode of action. Many of them, almost all of them,

1 require metabolic activation. There's probably four in  
2 here that don't. But we didn't feel we had enough,  
3 even though we've looked extensively at the literature  
4 to pull out these experiments, we didn't feel we had  
5 enough data to bin them by mechanism.

6 So what we've really done is sort of a meta  
7 analysis of what we had. And you're right, Dr. Glantz  
8 said, it is dependent on the chemicals for which --

9 PANEL MEMBER HAMMOND: That was --

10 DR. SANDY: -- people did the studies.

11 PANEL MEMBER HAMMOND: Right. And you know, I  
12 understand -- I mean I'm not criticizing you because  
13 this is what you have to deal with. You have to deal  
14 with a lot.

15 But if it turned out that because there was a  
16 lot of interest in dioxins and they did ten different  
17 dioxins, you know, and they only did five other  
18 chemicals, you wouldn't really want to be sampling.

19 You know. If you were to say these really are  
20 kind of subsets of one class or something? You don't  
21 really want to sample all the chemicals equally at that  
22 point or -- I'm just trying to think of why you might  
23 want to think about that. I don't know. It's a  
24 challenge.

25 PANEL MEMBER GLANTZ: Yeah. It's like when I

1 look at this, what it says to me is there's probably  
2 three different kind of sets of responses that you have  
3 here.

4           There's one that probably -- you know, there  
5 is the low one, you sort of see a hump, and then it  
6 kind of goes down, it's a little right skewed. And  
7 then there is the big kind of normally distributed peak  
8 in the middle, and then there's another one there.

9           So when I look at a picture like this, I think  
10 there's really three different populations.

11           DR. SHERMAN: Absolutely. And in fact, in the  
12 document, it basically says those that tended to be in  
13 the case for adults had a greater risk of cancer  
14 compared to postnatal, those below one, those about  
15 one -- that would be the middle, very peaked one -- and  
16 then those with the postnatally exposed animals had a  
17 much greater cancer risk than adults, and there the  
18 peak is, you know, much greater than, you know, close  
19 to about 80.

20           So in fact you do have effectively three  
21 distributions. And that's actually borne out if you go  
22 back to the box plots. You can see what chemicals  
23 actually contribute to those three different humps.

24           PANEL MEMBER GLANTZ: Just picking up on that  
25 then, kind of taking Kathy's question and turning it

1 around, if you look at which chemicals contribute to  
2 the three different humps, and you say you have three  
3 different subgroups of chemicals, do the chemicals that  
4 fall into these different subgroups have anything in  
5 common that would help you understand what's going on  
6 here.

7 DR. SANDY: Well, another complication is the  
8 gender differences, the strain differences, the species  
9 differences.

10 PANEL MEMBER HAMMOND: And the benzidine's an  
11 incredible example. That's amazing. It is two  
12 extremes depending on gender.

13 DR. TOMAR: There are very few chemicals we  
14 really know what the real mechanism of action is. We  
15 can speculate, but we really don't know the exact  
16 mechanism, what causes the tumor. We can correlate  
17 with something or another.

18 DR. SANDY: And I guess the point of all this  
19 is to try to come up with some information you can  
20 apply to carcinogens for which you know nothing about  
21 mechanism or you know nothing about sensitivity.

22 PANEL MEMBER HAMMOND: As an example from what  
23 you said earlier, if you could find that genotoxic  
24 things were different from those that were not  
25 genotoxic, we might be able to know if it was

1 genotoxic. We might know that much.

2           And then you might -- but of course, you mean,  
3 you know, you all have gone down this road trying to do  
4 something that no one also has tried to do. And you've  
5 done wonderful things. It's always easy to say oh but  
6 you should have done it this way and you should have  
7 done it that way. I understand.

8           CHAIRPERSON FROINES: Kathy, what you just  
9 said, you know, there may be multiple factors, may be a  
10 metabolic pathway.

11           PANEL MEMBER HAMMOND: Right. Right. Those  
12 are only examples. I don't want that -- I mean we're  
13 all just scientists who are interested in pursuing it.  
14 It's not really a criticism because it's just like so  
15 hard to do, and it's impressive.

16           DR. SHERMAN: And I just want to point out  
17 that this is the density function. The next slide --  
18 sorry. That's not the next slide.

19           CHAIRPERSON FROINES: We have ten minutes  
20 left. So can you plan what -- how you want to spend  
21 that ten minutes? And then we're going to walk out the  
22 door.

23           DR. SANDY: Would you like us to complete the  
24 methods section?

25           CHAIRPERSON FROINES: Yes.

1 DR. SANDY: All right. We'll try to do that.

2 CHAIRPERSON FROINES: And can I make a  
3 request? It's very frustrating to not have the slides  
4 and have to be reading them off the screen and then no  
5 way to -- when I leave here, there's no way I can think  
6 about it because I don't have the slides.

7 DR. SANDY: I'll try to get you a copy.

8 CHAIRPERSON FROINES: Everybody should have  
9 the slides.

10 PANEL MEMBER BYUS: Again, the more I listen  
11 to this, the better I like it. Seriously. But I do  
12 need -- to me, I find myself looking for trivial  
13 explanations for this data rather than real  
14 explanations. And the farther -- I mean that's just  
15 naturally because I -- that's the way I think.

16 And the farther out I get in this data, the  
17 more away it gets from the possible trivial  
18 explanations, so it's hard for me to look at it because  
19 I keep thinking about were there strain differences?  
20 Was the carcinogen administered in different ways and  
21 that's why there's different groups? You know.

22 Or the different tumor sites, is that where it  
23 lies? I still -- I understand a little more about the  
24 spontaneous where -- were they all sacrificed at the  
25 same time? So these are the kinds of things I'm trying

1 to deal with at the front end. I --

2 CHAIRPERSON FROINES: Figure out how to use  
3 your ten minutes.

4 PANEL MEMBER BYUS: You did a nice --

5 CHAIRPERSON FROINES: Seven minutes.

6 PANEL MEMBER BYUS: -- not being particularly  
7 strong in statistics, you did a wonderful job  
8 explaining all the rest of it. I think at the other  
9 end I see exactly now what you're doing and your  
10 methods and it sounds very interesting to me.

11 But I'm still looking at the front end, you  
12 know, in my own mind. And I would expect -- I mean  
13 just off the top of my head I would also expect you  
14 to -- I mean it's interesting and provocative enough it  
15 should be published and peer-reviewed before any real  
16 policy -- you know what I'm trying to say. This needs  
17 to be really peer-reviewed in a major way. Am I wrong  
18 on that?

19 CHAIRPERSON FROINES: Another peer review.

20 PANEL MEMBER BYUS: No, no, no. I don't mean  
21 us.

22 CHAIRPERSON FROINES: Wait a second folks,  
23 wait a second, dammit. This is not -- this is  
24 irrelevant. Discussing whether it should be  
25 peer-reviewed or not is not a good use of the five

1 minutes that they now have.

2           What is it you want to accomplish in five  
3 minutes? I think that there's a problem. The problem  
4 is Stan has carefully read this document because he's  
5 the Lead on it. It's clear that the rest of us have  
6 not digested it at the same level that Stan has, and I  
7 don't know about Joe.

8           But the point is that we -- there's a lot of  
9 work left to be done so that the key question is what  
10 would be most useful for you to tell us right now, and  
11 then we'll continue this --

12           PANEL MEMBER GLANTZ: And I'll be happy to  
13 answer that as somebody who --

14           CHAIRPERSON FROINES: I'm asking --

15           PANEL MEMBER GLANTZ: Well -- but let me --  
16 what I would suggest is that you don't go through the  
17 sensitivity analysis, that you keep -- because I'm  
18 understanding this a lot better than I did when I  
19 walked in here, and I think the sensitivity analysis is  
20 a relatively small detail.

21           So why don't you go on to the next big --  
22 yeah. This I was like totally confused by this.

23           DR. SANDY: Okay.

24           DR. SHERMAN: So the density function that you  
25 saw earlier we now rewrite --

1 DR. SANDY: That one.

2 DR. SHERMAN: Which is that one -- is now  
3 written as or displayed as a cumulative distribution  
4 function. And what this effectively represents is, you  
5 know, what -- what percentage of, say, animals -- I'm  
6 sorry. Let me get this together.

7 We have a vertical line at one. Actually, go  
8 to the next slide because that will make it easy for  
9 them.

10 DR. SANDY: Yeah.

11 DR. SHERMAN: Okay. So we take a vertical  
12 line at one, and then dash a horizontal line across, we  
13 see that approximately 20 percent of the studies or a  
14 little less than 20 percent of the studies had an age  
15 sensitivity -- I don't want to say 20 percent of the  
16 studies because that's not correct either.

17 20 percent of the postnatal cumulative ASF  
18 mixture distribution had values that were one or less.  
19 Okay. And effectively what that means is that you have  
20 80 percent of the remaining part of the distribution  
21 being greater than one.

22 What this figure shows is essentially method  
23 one. Method two and method three are different  
24 weighting factors. And what we found out is that  
25 effectively method one and method two weren't that

1 different and that method three, which was essentially  
2 taking the study with the largest median age  
3 sensitivity factor and using that as the representative  
4 distribution for that chemical.

5           So effectively you're taking the distribution,  
6 effectively taking the most severe distribution, and  
7 using that in the mixing formula, and effectively what  
8 that does is it pushes the cumulative distribution  
9 over. So now instead of 20 percent of the distribution  
10 having ASF values less than one, now it's ten percent.

11           But essentially with this mixing distribution  
12 and with these sensitivity analyses, there isn't that  
13 much difference. And then we can look at other  
14 effective percentiles. So we have one which is of  
15 basic interest.

16           But for ASF values of ten or less, we have  
17 approximately 70 percent of the ASF distribution  
18 being -- having an ASF ten or less which means that  
19 30 percent of the distribution was greater than ten.

20           And then we even have a study -- not  
21 studies -- the postnatal mixture distribution having  
22 values greater than -- ASF values greater than 100, and  
23 that is essentially the top five percent of the  
24 studies.

25           So you see there's effectively for the

1 postnatal studies, there is a wide range. However, a  
2 majority of those studies have -- essentially majority  
3 of the studies when we mix them up have ASF values  
4 greater than one. Which indicates that animals exposed  
5 postnatally have a greater cancer risk for the  
6 chemicals that were studied.

7 DR. SANDY: So that's the methods for the  
8 multi-window studies. We can go on and talk about the  
9 methods we used for the case -- chemical-specific case  
10 studies if you like.

11 CHAIRPERSON FROINES: You're done.

12 DR. SANDY: We're done. Okay.

13 PANEL MEMBER GLANTZ: Well, just before  
14 everyone runs out, as one of the leads, I found this  
15 very helpful, and I've already talked to Melanie.

16 I'm going to get together with these guys  
17 between now and the next meeting and try to work with  
18 them to further translate this into English.

19 (Laughter)

20 PANEL MEMBER HAMMOND: I actually wonder what  
21 it would look like if you were to do something terribly  
22 simplistic, okay?

23 Where you would take each study, and within  
24 each study you could have a ratio. When the study  
25 itself looked at juveniles and postnatal, you've got

1 the ratio that that study reported, and then you could  
2 just do your cumulative distribution that way.

3 How different would that be rather than do all  
4 this Monte Carlo distributions?

5 DR. SANDY: Well, so this slide here, these  
6 are the ratios.

7 PANEL MEMBER HAMMOND: That's right.

8 DR. SANDY: The distributions for each --

9 PANEL MEMBER HAMMOND: So if you did a  
10 cumulative probability with those ratios you could plot  
11 that. How different would it be? Because it's a lot  
12 more transparent. That's all. Very simplistic, but at  
13 the same time it's very transparent.

14 PANEL MEMBER LANDOLPH: Yeah. I agree with  
15 that completely.

16 CHAIRPERSON FROINES: Melanie, I have a  
17 question for you. I spent a lot of time looking at  
18 this technical support document for cancer potency  
19 factors, and then we spent a lot of time doing --  
20 working on this particular approach.

21 And the question is, I think we need to have  
22 some clarity on the questions that this panel needs to  
23 address. Because there's an awful lot that we did not  
24 talk about today.

25 So in terms of preparation, it was unclear how

1 one prepares when you have this plus what we just went  
2 through. So there needs to be, it seems to me, at  
3 least for me anyway, some definition as to the process  
4 on this particular exercise that we're going through.

5 We're going to have to sort that out. It's  
6 not just a question of Stan spending time with you and  
7 learning how to simplify it for other people. It's a  
8 question of how do we have a coherent process.

9 PANEL MEMBER GLANTZ: Well, I think, and if  
10 Melanie and the others can correct me -- I think the  
11 main document, at least for me, it was pretty  
12 straightforward.

13 And I mean I have some things that I'm going  
14 to give them that are not worth the panel's time. But  
15 the big thing -- and I think they responded pretty well  
16 to the public comments.

17 The big thing that's different here, I think,  
18 is this stuff, is the effort to try to take into  
19 account early life exposures and adjust the risk  
20 estimates accordingly.

21 So even though this is an appendix, this is  
22 the main part of the document from my -- you know, in  
23 terms of what I think is in here that really needs to  
24 be -- you know, really carefully understood and  
25 evaluated and we have to make a recommendation on how

1 reasonable we think it is. The rest of the document, I  
2 thought was -- maybe I missed something -- but I  
3 thought it was pretty straightforward.

4 CHAIRPERSON FROINES: Well, I'm a  
5 toxicologist, and I have a whole -- I have lists of  
6 issues to raise that have to do with the science, and  
7 the science in relation to policy.

8 And so that because we are involved in -- we  
9 are involved in a very changing time with respect to  
10 toxics policy in general and carcinogenesis more  
11 specifically.

12 And so I think we need to figure out -- we  
13 need to have some clarity about how we're going to  
14 approach it.

15 I don't think -- it is not true that this was  
16 just something that you -- it's not useful to say that  
17 you found it to be something you understood. It's much  
18 more complicated than that.

19 PANEL MEMBER GLANTZ: I agree.

20 But what I'm just saying is -- and if other  
21 people don't agree, that's why we have the committee --  
22 but in terms of from the perspective of the things I  
23 know about, I think this stuff is the really major  
24 thing that's different from what we've -- from the  
25 earlier versions, and I do think this needs a lot of

1 work, this appendix J.

2 CHAIRPERSON FROINES: Let me say one thing,  
3 one thing, and I'll turn to you.

4 PANEL MEMBER GLANTZ: Maybe --

5 CHAIRPERSON FROINES: This clearly without any  
6 doubt whatsoever is the most important contribution in  
7 this whole cancer potency issue.

8 What they've done here is fundamentally new,  
9 it's going to be very controversial, and it's very,  
10 very, very important. I don't think there's any  
11 question. One of the questions we had, and I had, was  
12 trying to understand all the subtleties and details,  
13 and that we can work out over time.

14 But there's a whole other -- we're dealing  
15 with a much larger document and that has a lot of  
16 issues associated with it we also need to talk about.

17 So Melanie it's -- what I'm trying to get is  
18 over the next -- with Jim's help, I think, we can work  
19 out a process so that we get some clarity about how  
20 we're going to do this.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
22 MARTY: Okay. I just want to say that in support of  
23 what Stan just said the biggest change in our view with  
24 the cancer risk assessment methodology is this  
25 application of age dependent adjustment factors and

1 that this appendix is meant to provide some of the  
2 science behind why you would make a policy decision to  
3 weight age at exposure.

4 CHAIRPERSON FROINES: It is given.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: And this is the answer to your question, this  
7 slide.

8 PANEL MEMBER HAMMOND: I notice that, yeah.

9 And to Craig's question about the underlying quality of  
10 the data in the study, it dawns on me that this is  
11 actually comparable to doing a meta analysis on  
12 epidemiology studies.

13 And so one could say, you know, when you do a  
14 meta analysis the first thing you do is you have  
15 criteria for what's going to be an acceptable study.  
16 You can't do a study that has, you know, fewer than,  
17 you know, 200 people.

18 PANEL MEMBER GLANTZ: Well they have --

19 PANEL MEMBER HAMMOND: Let me -- I'm just  
20 trying to say.

21 PANEL MEMBER GLANTZ: Oh.

22 PANEL MEMBER HAMMOND: So I think just as you  
23 do in an epidemiology study, you have these criteria  
24 for meta analysis, I think we could take Craig's  
25 concerns, you know, there must be concern criteria,

1 maybe you have them, for what would be an acceptable  
2 for this toxicology study to enter into this meta  
3 analysis you're doing, and so you can be very clear  
4 about that, and then you could deal with some of those  
5 issues that he has.

6 So certainly you wouldn't have taken any  
7 study. You probably looked at the quality of the  
8 study. And you can be clear about that.

9 PANEL MEMBER GLANTZ: That was one of the  
10 earlier slides, actually.

11 PANEL MEMBER BYUS: Well, the data you showed,  
12 the inclusion data, I thought was very nice.

13 I just want to go through, as John said  
14 originally, a couple of the papers, you know, which  
15 ever, one of the ones that have a high -- hundredfold  
16 difference or tenfold, whichever, a couple of them,  
17 maybe one at a hundred, one at tenfold, and just show  
18 where you started from the raw data and how you got  
19 basically into the initial analysis.

20 Which tumors were you comparing, what were the  
21 groups, you know, how many, what was the incidence  
22 values, what's -- you know, and how you compiled it.  
23 That's all.

24 That's what I want to see from the front end.  
25 The rear-end analysis I think sounds pretty good to me.

1 I just don't have a good sense of the -- it's not in  
2 here. I mean you mention it but you don't really --  
3 just again, there's so many potential trivial  
4 explanations.

5           And I'm sure you did it right. I just can't  
6 see it. The methods aren't there, so that's all I want  
7 to see.

8           DR. SHERMAN: Would it help with the  
9 accompanying manuscripts that I basically send you the  
10 Excel spreadsheets that have the data, and the data  
11 that we used are highlighted? And then in addition to  
12 that a PDF file that actually shows -- I won't include  
13 the programming, but that has essentially what those  
14 distributions look like and the fits to the model.

15           PANEL MEMBER BYUS: Right. And I don't want  
16 to see all 50. I just want to see one or two --

17           DR. SHERMAN: Okay.

18           PANEL MEMBER BYUS: -- key significant ones.  
19 You tell me where there's a big difference, a tenfold  
20 difference, say, and a hundredfold difference.

21           CHAIRPERSON FROINES: I think that I've said  
22 it, Melanie said it, Stan said it, whoever else may  
23 have said it. But everybody agrees that this is the  
24 centerpiece of this activity. However, it is not the  
25 only piece. And the other pieces are substantial.

1           But there's a third element that we're going  
2 to have to take very seriously. It's one thing to  
3 produce a document that scientists on this panel can  
4 understand and make suggestions and so on and so forth,  
5 and that will proceed and there will be greater clarity  
6 over time.

7           But this is a document that is going to need  
8 to be understandable by a very large body politic  
9 besides the people in this room. And the clarity for  
10 people who are involved in toxics policy issues is very  
11 important.

12           And we're not at a place now where we have a  
13 document which we can demonstrate and justify the  
14 science that's within it, and we're going to have to  
15 work on that I think.

16           Do you understand what I'm saying? No.

17           AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF  
18 MARTY: Well, yes and no. I mean I think you're being  
19 a little hard. I do. Because I think there's a lot  
20 more in the document than you're remembering.

21           But I think it's also good that we can do an  
22 executive summary in lay language which we do for lots  
23 of documents to get at this overall, you know, to get  
24 to more of the policy wonks.

25           PANEL MEMBER HAMMOND: The people who

1 commented on the lead document, not counting the MIG  
2 group, are not going to ever be able to understand  
3 this. You can't write it for that population.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Yeah. And I'd also like to remind you that EPA  
6 is already doing weighting by age and exposure. They  
7 just stuck their foot in a trap by trying to limit it  
8 as they've tried to limit it to chemicals that they  
9 haven't really even decided what the mode of action is  
10 but it's mutagenic. So.

11 CHAIRPERSON FROINES: But Melanie, not to beat  
12 a dead horse, but do you realize when this emerges  
13 publicly this is going to be on the front page of the  
14 LA Times with an article by Marla Cohn, and she's going  
15 to go through the implications of actually making  
16 adjustments for carcinogenesis in prenatal and  
17 postnatal.

18 This is going to be a front page story. And  
19 so we really need to figure out how do we both have a  
20 good statement of the science so it's accepted by the  
21 scientific community -- it's not just an executive  
22 summary -- but how are we going to make sure that we  
23 have understanding of it because the implications are  
24 so significant.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Yeah. I mean --

2 PANEL MEMBER GLANTZ: Don't miss your plane.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: It may be a new story in California, but EPA's  
5 been doing -- you know, their document came out in  
6 2005.

7 CHAIRPERSON FROINES: Let's just --

8 PANEL MEMBER GLANTZ: You're going to miss  
9 your plane.

10 CHAIRPERSON FROINES: They may have been doing  
11 this since 2005, but it's not --

12 PANEL MEMBER GLANTZ: I mean the first step --  
13 I don't disagree with anything you're saying, John.

14 But I think the first step is having this  
15 presented in a way that we can understand it, which I  
16 understand it more than I did a few hours ago.

17 And then after we can figure it out, if we can  
18 understand it and think it's reasonable, then we can go  
19 to the next step of making it so like only very smart  
20 people can understand it, and then they can iterate  
21 again for like regular people.

22 But I think that -- so that's my -- and I'll  
23 take the time to work with these guys to try -- this  
24 was a much better presentation than the written  
25 document. Okay.

1           And in fact, some of these slides are in the  
2 written document, and some of them aren't. And it was  
3 much clearer. But let me work with them.

4           CHAIRPERSON FROINES: Stan, you're a little  
5 bit missing my point. I'm not trying to say write the  
6 classic comic book version of this. I'm not  
7 simplifying this so that this is a Batman comic.

8           What I'm saying is that the written document  
9 has to -- it has to evolve in a way so that there is  
10 clarity to it for this panel, and then that will set  
11 you in motion for the other things. But that's the key  
12 issue.

13          PANEL MEMBER GLANTZ: Right. We're spending a  
14 lot of time agreeing. But you better get your plane.

15          CHAIRPERSON FROINES: I need a motion to  
16 adjourn.

17          PANEL MEMBER GLANTZ: I move that you adjourn  
18 and go to the airport.

19          PANEL MEMBER BYUS: Second.

20                                 \*   \*   \*

21                                 (Thereupon the AIR RESOURCES BOARD

                               SCIENTIFIC REVIEW PANEL meeting

22                                 adjourned at 3:29 p.m.)

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