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MEETING  
OF THE  
SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS  
CALIFORNIA AIR RESOURCES BOARD

SUNSET VILLAGE  
COVEL COMMONS BUILDING  
UNIVERSITY OF CALIFORNIA, LOS ANGELES  
THIRD FLOOR  
330 DE NEVE DRIVE  
LOS ANGELES, CALIFORNIA 90095-1492

FRIDAY, JANUARY 15, 1999

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REPORTED BY:

Caroline Jetter  
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APPEARANCES

MEMBERS PRESENT:

- Dr. John Froines, Chairman
- Dr. Paul Blanc
- Dr. Gary Friedman
- Dr. Anthony Fucaloro
- Dr. Craig Byus
- Dr. Roger Atkinson
- Dr. Stanton Glantz

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD:

- Mr. Bill Lockett, Deputy Ombudsman, Northern California
- Mr. Peter Mathews, Office of the Ombudsman

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

- Dr. George Alexeeff, Deputy Director for Scientific Affairs
- Dr. Melanie Marty, Senior Toxicologist

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

- Mr. Paul H. Gosselin, Assistant Director

ALSO PRESENT:

- Dr. James Collins

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- 2 Review of findings for  
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- 3 Update of draft report: The Evaluation  
of Methyl Parathion as a Toxic Air  
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- 4 Continuation of discussion of the  
proposed agenda for an SRP workshop  
entitled: 'Pesticides in the Air' -  
SRP and DPR staff

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1                   CHAIRMAN FROINES: I think it's Friday  
2     January 15. It's a little bit after 9:30, and let's call  
3     the meeting to order formally. Everyone has a copy of  
4     the agenda. I wanted to say at the beginning happy new  
5     year to everybody but more importantly to welcome Roger  
6     Atkinson to the panel.

7                   We have very major needs on this panel for  
8     exposure assessment issues, atmospheric chemistry  
9     questions and so Roger is a more than distinguished  
10    scientist in U.C. Riverside, and we're very, very pleased  
11    to have him with us. Thank you for accepting the  
12    position.

13                  And I'll just say on a substantive note  
14    that in doing risk assessments on pesticides, which is  
15    what's taking up a lot of our time lately, since the risk  
16    assessment is to a large degree also dependent upon the  
17    levels of exposure in the environment, that the exposure  
18    assessment question becomes absolutely paramount to our  
19    deliberations so that your being on the panel is going to  
20    be really important in that regard.

21                  And I think that one of the things we're  
22    going to want to talk about, as we move forward through  
23    some of the workshops, is how to develop protocols for  
24    characterizing atmospheric concentrations so we have  
25    confidence in the numbers when we actually do the

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1 calculations and determine what the levels of risk are so  
2 that they -- so your role is really important. And we've  
3 been blessed having Tony Fucaloro on the committee.

4 So that means we really have two people who  
5 have ongoing responsibility for some of the exposure  
6 questions.

7 Let's go directly to the agenda, and we'll  
8 go to the issue of the changes that have been made in the  
9 acute reference exposure document. And, I guess, is  
10 Melanie going to lead that?

11 DR. MARTY: Yes.

12 CHAIRMAN FROINES: Melanie, do you want me  
13 to discuss the results of our discussion last night and  
14 this morning, or do you want to -- how do you want to  
15 proceed on that?

16 DR. ALEXEEFF: My name is George Alexeeff  
17 with the Office of Environmental Health Hazard  
18 Assessment. I think you can discuss it now what you  
19 suggested to us this morning. That's fine. Or you can  
20 wait until we've made our presentation and then discuss  
21 where you want to go from there.

22 CHAIRMAN FROINES: Well, why don't you go  
23 ahead, and we'll come back to the issue of the specific  
24 chemicals.

25 DR. ALEXEEFF: What we thought we would do



1 today -- we met on the acute document -- was it in  
2 December 2, I believe. And we discussed it to a certain  
3 extent for several hours, and there were several  
4 suggested changes by the panel to the document.

5 At the same time we have received comments  
6 from the public up until a couple of days before the  
7 Scientific Review Panel meeting, and we hadn't had time  
8 to incorporate it in that document at that time.

9 So what we've done thus -- for today is  
10 we've reviewed the comments that it's been submitted up  
11 until December 2. We've provided some responses to the  
12 comments, and we'll -- I know we've provided it to the  
13 panel, and we'll also put it on our web site.

14 And we've also made proposed changes,  
15 proposed revisions both based upon comments made that  
16 were submitted and comments by the panel.

17 So what we're going to do today is discuss  
18 the changes that are being proposed from the last version  
19 to bring you up to date what the suggested changes were  
20 and also a couple of issues that came up at the last  
21 meeting. We'll be discussing those in a little more  
22 depth today.

23 CHAIRMAN FROINES: Roger, do you have the  
24 document?

25 DR. ATKINSON: I have the document.



1                   CHAIRMAN FROINES:  You got it this morning.

2    So if you can --

3                   DR. GLANTZ:  Can I just ask one --

4                   CHAIRMAN FROINES:  As you go through, try  
5    and give a little bit of background as you go so Roger  
6    gets up to speed.

7                   DR. ALEXEEFF:  Okay.  And I can --

8                   DR. GLANTZ:  Can I just ask one question.  
9    You gave us this Response to Comments document.  Have the  
10   changes that you talked about in here been incorporated  
11   into the text?

12                  DR. ALEXEEFF:  Yes.

13                  DR. GLANTZ:  So what are the changes?

14                  DR. ALEXEEFF:  We will be presenting those  
15   changes.  Now, since that time, there were some  
16   additional changes that have come up over time --

17                  DR. GLANTZ:  Okay.

18                  DR. ALEXEEFF:  -- that we'll mention here.  
19   Either typographical errors that we have subsequently  
20   found or someone has pointed out to us or some other  
21   changes that we felt we found better data on which to  
22   base the numbers.  There is a couple like that.

23                  DR. GLANTZ:  Okay.  But I just want to be  
24   clear because, when I read this and looked at the  
25   document, it looked like all these changes had already

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1     been incorporated.

2                   DR. ALEXEEFF:  That's correct.

3                   DR. GLANTZ:  You're talking about some  
4     other changes.  Okay.

5                   DR. FUCALORO:  What?

6                   DR. MARTY:  Okay.  I guess I'll launch into  
7     the presentation then.  Next slide.

8                   I'm Melanie Marty of the Office of  
9     Environmental Health Hazard Assessment.

10                   There were some suggestions that were made  
11     by SRP members at the December 2 meeting.  One of them  
12     was to change the uncertainty factor for extrapolating  
13     from a lowest observed adverse effect level to a no  
14     observed adverse effect level to 6 for mild adverse  
15     effects.

16                   We had been using 3 for mild irritation  
17     based on analysis by Alexeeff and coworkers, and at that  
18     meeting, the last meeting, we took another look at that.  
19     It was suggested to us to use a 95th percentile of that  
20     analysis, which was 6, and to apply it to not just a mild  
21     irritation but to all of our mild adverse endpoints.  So  
22     we have done that.

23                   Also the SRP suggested that at this meeting  
24     we discuss issues related to specific chemicals.  So I do  
25     have lots of slides pertaining to that.  These are the 15



1 chemicals which we received public comment. I do have  
2 slides that cover all of these issues. We don't -- if  
3 you want to go through them, we will.

4 CHAIRMAN FROINES: Let me just say since  
5 this issue of the chemicals -- specific chemicals came  
6 up, that I should tell the panel that, based on a  
7 discussion last night and this morning, that we think  
8 that we have to divide up the chemicals into groups and  
9 have the panel -- have members of the panel actually do a  
10 review for the next meeting so that we can actually say  
11 that the panel has read the document in its entirety as  
12 opposed to the panel having only read what is essentially  
13 10 percent of the document with the appendices, which  
14 represent 90 percent not having been read.

15 So in order to reduce the workload, we'll  
16 have to break it down, and Tony has asked that we break  
17 it down in teams of two, which isn't going to work out  
18 quite perfectly because there aren't -- it doesn't work  
19 out to do that.

20 But we'll come back to it. But just to  
21 alert the panel that I think we're -- in order to meet  
22 our obligation, we really do need to -- that is, to read  
23 the entire document, we're going to have to look at the  
24 individual chemical.

25 DR. BLANC: We have to give preferences on



1 the ones we'd like?

2 DR. FUCALORO: If no one has preferences  
3 except you, the answer is yes.

4 CHAIRMAN FROINES: If you want to sit there  
5 and develop a list of preferences that you would like,  
6 feel free to.

7 DR. BLANC: How many is it going to be per  
8 person?

9 CHAIRMAN FROINES: Well, there  
10 are -- essentially Tony and Roger, I think, are going to  
11 be the two exposure people who would not necessarily take  
12 chemicals, but they'd be working with the rest of the  
13 people. So it's one, two, three, four, five of us, and  
14 Peter would be --

15 DR. BLANC: For how many?

16 CHAIRMAN FROINES: 6 into 51.

17 DR. FUCALORO: 6 times 8.

18 DR. BLANC: So 7 or 8.

19 CHAIRMAN FROINES: Hopefully it can go very  
20 quickly because the methodology has been laid out. Let's  
21 come back to it.

22 DR. GLANTZ: Do I get any credit for  
23 working on the methodology?

24 DR. BLANC: No.

25 DR. MARTY: As I mentioned, there are a



1 number of revisions to the document which you have before  
2 you. Some are based on using the suggested LOAEL to  
3 NOAEL uncertainty factor of 6 for mild adverse effects.  
4 And I listed the chemicals in there which changed as a  
5 result of that decision.

6 Some were based on public comments that we  
7 received, and we changed the reference exposure levels  
8 accordingly. We also have additional suggestions today  
9 for chloropicrin and methyl bromide also based on public  
10 comments. Those last two changes are not in the document  
11 that you received in December.

12 CHAIRMAN FROINES: Usually when there's a  
13 part "A" and part "B" document, the part "A" deals with  
14 the "exposure." Are we -- do we have a sense that there  
15 is exposure to these chemicals -- to all 51 of these  
16 chemicals in California? In other words, is the part "A"  
17 requirements met?

18 DR. MARTY: We -- what we have is  
19 information from the ARB's air toxics emissions database,  
20 and we did look at that database before we developed  
21 reference exposure levels for these chemicals to see if  
22 they were emitted in California.

23 The emissions vary widely. Some of them  
24 are much more important than others. And also  
25 what -- the other thing that weighed in was whether or



1 not we had information to develop a reference exposure  
2 level.

3 CHAIRMAN FROINES: So you can  
4 say -- the ARB can tell the panel that every one of the  
5 51 chemicals that people are going to read has some  
6 measurable concentration in the environment.

7 DR. MARTY: You can say they're reported as  
8 emitted under the AB 2588 program. So you would assume  
9 that there is some exposure near a source at a minimum.

10 Again, though, it varies widely. We can  
11 look at the ATEDS database, and we can look at the most  
12 current update and see if there are some chemicals that  
13 are less important. If you want us to do that, we can do  
14 that.

15 CHAIRMAN FROINES: I think it would be good  
16 for the panel to know which chemicals people actually  
17 think are important in the state --

18 DR. MARTY: Okay.

19 CHAIRMAN FROINES: -- if it's not too  
20 inconvenient.

21 DR. MARTY: Yeah --

22 CHAIRMAN FROINES: Am I not loud enough? I  
23 feel like I'm screaming.

24 DR. MARTY: Let me talk with the ARB  
25 emissions inventory branch and get the latest



1 information, and then what I can do is send it to you.  
2 Now, the information is in pounds per year. It's not in  
3 concentrations at any specific receptor. So --

4 CHAIRMAN FROINES: I should say to the  
5 panel that this is an issue which is coming up now  
6 frequently with the Carcinogen Identification Committee  
7 under Prop 65, and that is the question of whether or not  
8 we are identifying carcinogens on that committee that are  
9 actually used or have any potential exposure in  
10 California and in many cases their laboratory  
11 curiosities -- there's just no use.

12 And I think on this panel we should only be  
13 dealing with chemicals for which there is an issue and  
14 not simply -- we don't want to get trapped in the kind of  
15 tyranny of lists where people are doing work that isn't  
16 essential and so that's why it's an important issue

17 DR. ALEXEEFF: Genevieve just mentioned to  
18 me that the information on the exposure should be in the  
19 compound summary volumes that ARB has prepared. So we  
20 should probably give Dr. Atkinson a copy. The other  
21 panel members have received it.

22 Remember the large volumes of the TAC  
23 summary information? So that exposure information should  
24 be in there as well.

25 The other thing -- the difference between



1 these compounds and those that we have been discussing  
2 under the Toxic Contaminant Program is these are already  
3 listed. So these are already required to take some sort  
4 of action on as opposed to the TAC process, which has to  
5 develop the basis for listing.

6 CHAIRMAN FROINES: Just for the panel to  
7 note, the reason they're already listed is because  
8 they're hazardous air pollutants under the Clean Air Act  
9 amendments.

10 DR. ALEXEEFF: That is one of the reasons.  
11 Either they are hazardous air pollutants, or they could  
12 be Proposition 65 chemicals, or there could be other  
13 reasons that they're on this list, the hot spots list.  
14 But most of them are on there because they are hazardous  
15 air pollutants or most of them are hazardous air  
16 pollutants.

17 CHAIRMAN FROINES: One of the things we  
18 don't need to take up today but we'd like to begin to  
19 think about reconciling the chemicals on Prop 65 with the  
20 chemicals here so that, if it's here, it should be on  
21 Prop 65. If it's on Prop 65, it should be here. So  
22 that's something to talk about at some future date

23 DR. ALEXEEFF: Well, Proposition 65 is  
24 limited to two types of health effects -- reproductive  
25 developmental and carcinogenicity. So this arena that



1 we're talking about now includes other health  
2 effects -- neurotoxicity and immunotoxicity. So this  
3 list is bound to be larger than the other list.

4                   What has been done here is that the  
5 original hot spots list has been divided into two lists.  
6 One is chemicals that are on the big list which is over  
7 750 chemicals, and the other one is those chemicals for  
8 which the emission information is required to be  
9 obtained.

10                   So this -- the chemicals we're talking  
11 about are those that the emission inventory has required.  
12 So this is already a sublist of the big list. So there's  
13 substances that are on the Proposition 65 list for which  
14 we do not believe there's emissions in California. So  
15 they're not taken care of in this program.

16                   We've already cut those out. Most of those  
17 would be -- for our program most of those would probably  
18 be pharmaceuticals that -- for which we don't expect air  
19 emissions.

20                   DR. MARTY: Okay. I thought I'd just  
21 briefly go over this LOAEL to NOAEL extrapolation  
22 uncertainty factor. Previously we had for mild  
23 irritation an uncertainty factor of 6, and now we have  
24 for all mild adverse effects an uncertainty factor of 6.

25                   Previously it was 3. I'm sorry. Now it is



1 6. This is based on an analysis of 112 acute inhalation  
2 studies which identified LOAELs and NOAELs so we could  
3 get the ratio of the LOAEL to the NOAEL for mild adverse  
4 effects.

5 For the lowest LOAEL reported to the NOAEL  
6 in the same study, for that ratio, a SAS analysis  
7 indicated that the 50th percentile is 2.2. The 90th is  
8 5, and the 95th is 6.2. And that's where we get the 6.  
9 We added an appendix, Appendix F, to the document which  
10 has the analysis in it.

11 DR. FUCALORO: And a 10 is, I guess, the  
12 99th percentile?

13 DR. MARTY: Yes, 10 is the 99th percentile.  
14 The time extrapolation defaults were also of concern to  
15 the SRP. We had a question last time regarding why, for  
16 the Haber's Law equation, we use a default value for the  
17 exponent "N" of 1 when we are extrapolating from less  
18 than one hour to one hour.

19 At the same time we're using a default  
20 value of 2 for that same exponent when extrapolating from  
21 greater than one hour to one hour, and basically, the  
22 answer is that it's a more health-protective approach to  
23 use in the absence of data indicating otherwise.

24 And just a very simple example, Haber's Law  
25 is right there.  $CNT$  equals  $K$ . If the concentration of



1 the NOAEL is 2 at ten minutes, if you use an exponent of  
2 2, then your extrapolated concentration at 60 minutes  
3 would be 0.8.

4 If you use an exponent of 1, your  
5 concentration allowable -- or however you want to term  
6 that -- at 60 minutes is equal to 0.3. The difference  
7 does get larger with shorter and shorter durations of  
8 exposure.

9 So if you do that extrapolation from a very  
10 short exposure, you get a rather large difference between  
11 the one hour extrapolated values for different values of  
12 "N."

13 Overall, for a greater than one-hour to  
14 one-hour extrapolations, we decided to use 2, which was  
15 the midpoint of the range of empirically derived values  
16 for the exponent "N" provided in table 12 of the  
17 document.

18 DR. ALEXEEFF: So I'm wondering -- you  
19 know, we're happy to discuss this point some more right  
20 now, if it makes sense to do so. So our -- what we've  
21 derived in the document are one-hour values, but the  
22 information that we often have in the literature may be  
23 either greater than one hour or less than one hour.

24 If there is data to show exactly how to  
25 extrapolate, we will use that empirical information in



1 the calculation. But when there is no data, we have a  
2 default procedure. And the procedure depends on if we're  
3 going from a short time to one hour or a long time to one  
4 hour.

5                   And the calculation that we've provided  
6 there shows that -- you know, how much difference there  
7 can be in this calculation. And that's why we chose  
8 that. And we've done an analysis of -- in the document  
9 there is a table which discusses all the empirical "N"  
10 values we've been able to find in the literature and  
11 derive.

12                   And we did a brief sort of distributional  
13 sort of analysis on that, and the values of 1 and 2 are  
14 kind of, you know, surrounding the two sides of the 50th  
15 percentile there. So depending upon which way one wants  
16 to extrapolate, it's important to look at  
17 the -- you know, to choose one of those two.

18                   And both of those two can fit to a certain  
19 extent. Maybe I didn't exactly describe the distribution  
20 aspect of it, but in any case, there is a table on table  
21 12 which shows all the different values, and you can see  
22 that in many empirical cases it could be 1, and in many  
23 empirical cases it could be 2 or slightly greater.

24                   And we haven't been able to derive on the  
25 empirical evidence any sort of clear rule, you know, or



1 decision-making process as to -- on an effect basis as to  
2 when to use 1 or when to use 2.

3           Like, the thought originally was that maybe  
4 with irritants it would be closer to 2. But if you look  
5 at the table, that's not the case. So we have -- we're  
6 hoping over time maybe to come up with some sort of  
7 better empirical basis on maybe certain types of  
8 mechanisms might have a different extrapolation  
9 procedure. But at this point we haven't been able to  
10 resolve that.

11           DR. MARTY: I think I need to add in one  
12 other issue and that is that the examples in table 12 for  
13 which "N" was derived are based on lethality. So they  
14 were not studies just looking at the irritation.

15           There aren't any available. So that's why  
16 we choose to use these. And there's a large number of  
17 irritants that were given at exposure concentrations that  
18 produced lethality, and I might add that some of them  
19 have an empirically derived value of "N" very close to 1.  
20 Okay. I --

21           DR. GLANTZ: Could I just ask one other  
22 question about that. This may reflect -- it's been a  
23 while since I read the comments, but as I recall,  
24 the -- some of the commenters are raising the issues of  
25 repeated dosages versus a single dose. Could you



1 just -- that's relevant in terms of this Haber's Law  
2 issue; right? Or am I getting something mixed up?

3 DR. MARTY: Yes, it is.

4 DR. GLANTZ: Could you just comment -- you  
5 know, kind of explain what the issue is and briefly, you  
6 know, kind of summarize what the commenter said in your  
7 response to it? Because I think that's an important  
8 point.

9 DR. MARTY: Okay. I'll cover this a little  
10 bit --

11 DR. GLANTZ: When I read it, it seemed  
12 reasonable, but I forget.

13 DR. MARTY: I'll cover this a little bit in  
14 some of the later slides on specific chemicals.

15 DR. GLANTZ: Okay. Well, if you'd rather  
16 do that --

17 DR. MARTY: No. I can do it right now.

18 DR. GLANTZ: Okay.

19 DR. MARTY: Many commented that we should  
20 not use repeated dose studies to generate a one-hour  
21 reference exposure level. The idea is, of course, that a  
22 repeated dose study usually involves four to eight hours  
23 per day and maybe in some cases, you know, up to five to  
24 ten days.

25 And how do you rationally extrapolate that



1 back to an endpoint that you think might occur after one  
2 hour of exposure? So we did use repeated dose studies  
3 for reproductive and developmental toxicity endpoints,  
4 and part of the reason is we're trapped in that the  
5 standard protocol for repro tox study is to use repeated  
6 dose exposures because you don't know where in gestation  
7 the developmental or the reproductive effect may occur.

8 So we're pretty much stuck. If we're going  
9 to look at reproductive developmental toxicity as an  
10 endpoint, we're stuck with these types of studies that  
11 use repeated dose exposures.

12 There were a few other instances for  
13 different tox endpoints that we ended up using repeated  
14 dose studies. In one case that I can think of, the  
15 effective concern happened after the first day of  
16 exposure.

17 So we were fairly comfortable that it was  
18 okay to use that six-hour exposure and extrapolate that  
19 back to 1. In the other case that I can think of off the  
20 top of my head, benzene, which I'm going to get to right  
21 now -- Jim, can you put the slide up.

22 We were criticized for using repeated dose  
23 studies of immunotoxicity, and this was an infectivity  
24 model in the mouse. We ended up agreeing with the  
25 commentator that this probably was not the best thing to



1 do. So we changed the basis of the REL for benzene.

2 DR. GLANTZ: Well, now, when you do -- when  
3 you're going from the repeated dose studies to your one  
4 hour, let's say I gave -- I exposed a rat or something  
5 four hours a day for a week or for five days, would you  
6 consider that a four-hour exposure or a twenty-hour  
7 exposure?

8 DR. MARTY: We did -- we considered it a  
9 four-hour exposure. We took -- particularly justifiable  
10 in the case, I think, of reproductive and developmental  
11 endpoints.

12 We did receive comment that perhaps we  
13 should have gone for the cumulative 20 hour, and that  
14 example would have been. But the problem with that is  
15 you can assume for endpoints other than repro tox and  
16 developmental tox that there is a little bit of recovery  
17 in between those four-hour exposures.

18 So it's some justification for just using  
19 the one day's worth of exposure to extrapolate back to  
20 one hour.

21 DR. ALEXEEFF: I can clarify a little bit.  
22 You know, our desire is to pick the most appropriate  
23 study to a one-hour exposure. That's our ideal. The  
24 closer to one hour that has a sensitive endpoint in  
25 humans or sensitive humans, that's what we'd want.



1                   And the ideal in this document -- there's a  
2                   few substances like sulfur dioxide where you can do that.

3                   We're basically -- have to use the  
4                   information that is published in the literature. And in  
5                   cases where there are repeated dose studies, there's a  
6                   couple different types that occur.

7                   In some cases there is information -- let's  
8                   say, it's a ten-day study, and in the report it will say  
9                   "After the first day there was" -- "were signs of  
10                  irritation. After the fifth day the animals were having  
11                  convulsions."

12                  So under that circumstance, we had only  
13                  used the information under the first day, and we would  
14                  just take that out and make all the calculations assuming  
15                  that symptom.

16                  So in other cases, particularly in the  
17                  occupational environment studies, they would say "We  
18                  conducted a study, four exposures on four different days  
19                  within a two-week period on these controlled subjects,  
20                  and the subjects indicated" -- "expressed headache."

21                  But they wouldn't tell us in the article if  
22                  it was the first day or the -- you know, anytime during  
23                  the period or every time. So under those circumstances,  
24                  we may have had to just make the assumption that it could  
25                  have occurred on the first day.



1                   Now, the example that those are -- there's  
2 not that many of those types of studies. And then the  
3 example that Dr. Marty gave is the developmental study.  
4 In those cases, there's a very standard protocol for  
5 gestation days. Usually 6 to 15 animals are exposed, and  
6 that's the data that's provided. They don't provide  
7 information usually after one -- day one or day two or  
8 anything like that.

9                   And there are guidelines that have been  
10 developed for reproductive toxicity by the U.S.EPA, which  
11 we feel we are following, and there are also the  
12 guidelines that we operate under in our department, which  
13 is that a one-day exposure could have caused the  
14 developmental effect unless there's some information  
15 which says it didn't happen, and that's because of the  
16 critical period that occurs in the gestation period. So  
17 that's what we did here.

18                   So if it was a 6 to -- the most common  
19 comment we received were on developmental studies. So it  
20 stays 6 to 15, 6 or 7 hours per day exposure. So we used  
21 that 6 or 7 hours, converted it into one-hour exposure,  
22 and that's the dose that we used.

23                   DR. MARTY: Okay. We made some changes --

24                   CHAIRMAN FROINES: Just one quickie. When  
25 you have a study like four days of certain concentration,



1 you also, I assume, look at the toxicokinetics to look  
2 and see what you know about elimination clearance and the  
3 AUC overall.

4 DR. MARTY: If that data are available.

5 DR. BYUS: In that regard, if the drug has  
6 a long half-life, it clearly has accumulated over the  
7 time and so the concentration is going up if the  
8 exposure --

9 DR. ALEXEEFF: Right.

10 DR. BYUS: More frequent than the  
11 half-life --

12 REPORTER: I'm sorry?

13 DR. BYUS: Than the half-life.

14 DR. ALEXEEFF: Yes. If we had the  
15 information like that, then it would be considered  
16 inappropriate to do that calculation. I mean it would  
17 be -- if we knew that the chemical accumulated and that  
18 the effect was basically an accumulation because the  
19 half-life was so long, then we would not do that  
20 conversion using a one-day study.

21 CHAIRMAN FROINES: So the problem is you  
22 really don't have the data to -- go ahead.

23 DR. MARTY: We did make some changes to our  
24 proposed benzene reference exposure level. Again, this  
25 is -- the comment was not to use repeated dose studies of



1 immunotoxicity for the reference exposure level, and we  
2 agreed that for the infectivity model, repeated dose  
3 studies are problematic for extrapolating, for  
4 extrapolating to one-hour exposures.

5 We changed to the reproductive and  
6 developmental study that formed the basis of the level  
7 protective against severe adverse effects and this then  
8 becomes the reference exposure level.

9 In so doing, that change resulted in a  
10 change of the reference exposure level from 0.24 to  
11 1 ppm. So it was not a huge change anyhow. We provide  
12 that information in this revised document.

13 This just -- the next few slides just go  
14 over the study that was used. Coate, et al. (1984),  
15 where there was inhalation exposure to benzene of  
16 pregnant female rats, and the lowest effect measured was  
17 the decreased fetal body weight.

18 Next slide, Jim.

19 In this case the exposure duration was six  
20 hours per day for five days, and we just used one  
21 six-hour exposure to extrapolate to a one-hour  
22 concentration using Haber's Law and an exponent of 2.

23 Since there was an identified no observed  
24 adverse effect level, we did not need an uncertainty  
25 factor to extrapolate from the LOAEL. We did use



1 interspecies and intraspecies uncertainty factors of 10  
2 for a cumulative uncertainty factor of 100.

3 This resulted in our REL of 1 ppm. This is  
4 in the document, and it previously served as the level  
5 protective against severe adverse effects, and that has  
6 now become the reference exposure level.

7 We also are suggesting changes to the EGBE  
8 reference exposure level. We received a comment that  
9 EGBE is not a reproductive or developmental toxicant.  
10 And we agreed with the position of the commentator.

11 In essence, the study we had used was  
12 problematic because of lysis of the red blood cells that  
13 was seen in the rabbit -- the mother rabbits.

14 Instead we used two human studies on  
15 irritation of the eye and nose as the basis for the  
16 revised reference exposure level, and the REL changed  
17 from 2.5 to 2.8 ppm.

18 This next slide goes over a little bit of  
19 the data that we ended up using. There were essentially  
20 two studies that pointed to a no observed adverse effect  
21 level. One of them was Carpenter, et al. (1956), in  
22 which two subjects were exposed to 113 parts per million  
23 EGBE, and they experienced nasal and ocular irritation.

24 However, this study in and of itself we  
25 didn't think was sufficient since there were only two



1 subjects and only one exposure level. There is another  
2 study, however, Johanson, et al. (1986), in which seven  
3 healthy adults were exposed to 20 parts per million for  
4 two hours. There was no irritation observed in these  
5 seven healthy adults.

6 This level can, therefore, be identified as  
7 what we would call a freestanding NOAEL on which to base  
8 the REL. It's freestanding because there were not other  
9 concentrations used in the experiments, and we cannot  
10 figure out where the low observed adverse effect level  
11 might have been in that study.

12 After time extrapolation to one hour and  
13 the application of an intraspecies uncertainty factor of  
14 10, the REL is 2.8 ppm.

15 DR. BLANC: Can I just clarify something  
16 again with the lowest observed effect level and the no  
17 observed effect level. You're basing the RELs on the  
18 uncertainty factor -- you just lost me for a second.

19 Because I know sometimes we're using the  
20 lowest -- could you just repeat? I know you've gone over  
21 this before.

22 DR. MARTY: Okay. That's fine.

23 DR. BLANC: I just want to be crystal  
24 clear.

25 DR. MARTY: Sometimes the best available



1 studies do not identify a no observed adverse effect  
2 level.

3 DR. BLANC: They just have the lowest  
4 effect level.

5 DR. MARTY: All you have is the lowest  
6 level tested that had an effect.

7 DR. BLANC: Right. And then you use an  
8 uncertainty factor.

9 DR. MARTY: Correct.

10 DR. BLANC: When you actually have the no  
11 observed effect level, then what do you do?

12 DR. MARTY: Then we use that level --

13 DR. BLANC: Without an uncertainty factor?

14 DR. MARTY: Without an uncertainty factor.

15 DR. BLANC: Except for the intraspecies.

16 DR. MARTY: And inter. Inter- and  
17 intraspecies may be applicable. If it's people, there's  
18 no interspecies extrapolation, but if it's an animal  
19 study, we use --

20 DR. BLANC: A 10.

21 DR. MARTY: Right.

22 DR. BLANC: If it's human, there wouldn't  
23 be an uncertainty factor, or there would still be  
24 an -- within humans.

25 DR. MARTY: There is a within humans



1     uncertainty factor.

2                   DR. BLANC:  Okay.  So suppose I have -- if  
3     I have a no effect level of 1 in humans, 1 part per  
4     million, then your level would come up to be .1 because  
5     you'd always use 10.

6                   DR. MARTY:  Unless --

7                   DR. BLANC:  It was done in asthmatics.  And  
8     then you wouldn't use anything.

9                   DR. FUCALORO:  Excuse me.  That's a .1 for  
10    an REL.

11                  DR. BLANC:  For an REL.  For your RELs.

12                  DR. MARTY:  Correct.

13                  DR. BLANC:  If you had a lowest observed  
14    effect level in a mouse, can you just walk through what  
15    happens then?  A lowest --

16                  DR. MARTY:  A lowest observed effect level,  
17    we would use -- if it were a mild adverse effect level,  
18    we would use an uncertainty factor of 6 to try to define  
19    the no observed adverse effect level.

20                  DR. BLANC:  And then you'd do 10 and 10.

21                  DR. MARTY:  Yes.

22                  DR. ALEXEEFF:  So that the total  
23    uncertainty factor in that case would be 600.

24                  DR. BLANC:  The most it can be is a  
25    thousand if it was a serious effect because then you'd do



1 10, 10 and 10.

2 DR. MARTY: Correct.

3 DR. BLANC: So depending on the study  
4 number that you have, the difference between the REL and  
5 the number you're actually working with can be anywhere  
6 from 1,000 to 1.

7 DR. MARTY: Correct.

8 DR. BLANC: Is that --

9 DR. FUCALORO: It can't be 1, can it?

10 DR. BLANC: It can be 1 if it was a study  
11 in asthmatic humans.

12 DR. FUCALORO: That would give you a NOAEL,  
13 an N-O-A-E-L; correct? Say, of -- then you'd still put  
14 another factor on it to get the REL; correct?

15 DR. MARTY: If we had a no observed adverse  
16 effect level in asthmatic humans and we know that  
17 asthmatics are identified sensitive subpopulation for  
18 that chemical, then we would not apply an additional  
19 uncertainty factor.

20 If we were -- if the study was done in  
21 asthmatics but asthmatics are not particularly sensitive  
22 relative to general population, then we would have to  
23 apply another uncertainty factor.

24 DR. ALEXEEFF: If you turn in the document  
25 to page 43, there's a table of all the uncertainty



1 factors that we've used, on page 43, table 9, for each  
2 substance. And it tells you when we've had to apply  
3 uncertainty factors and then how large the uncertainty  
4 factors are.

5 DR. BLANC: Right.

6 DR. ALEXEEFF: In that table you can see  
7 that, for example, carbon monoxide, the total uncertainty  
8 factor is 1. For ammonia the total uncertainty factor is  
9 3 and then the next level is 60 for dioxane. The total  
10 uncertainty factor is 60. Then it goes to 100 and then  
11 600 and then 1,000.

12 CHAIRMAN FROINES: If I can make just one  
13 comment just for the panel, this means that, if the  
14 endpoint were reproductive or developmental, that the REL  
15 or the value that you calculate could differ than the  
16 value that would be calculated near Prop 65 since under  
17 Prop 65 it is required to use a safety factor of 1,000.  
18 So that the value that OEHHA has for developmental  
19 reproductive toxins in Prop 65 could differ considerably,  
20 in fact, from the value between the 1807 and Prop 65.

21 DR. ALEXEEFF: Generally the Proposition 65  
22 value would be more stringent by a factor of 10.

23 DR. MARTY: We also made changes to the  
24 hydrogen sulfide reference exposure level.

25 CHAIRMAN FROINES: One could argue -- I'm



1     sorry.  I'm sorry for prolonging this, but one could  
2     argue that we should modify that factor of a thousand  
3     because it's what was in the law.  It's not based on any  
4     science.  But that's --

5                     DR. BLANC:  Thank you for sharing that with  
6     us.

7                     DR. GLANTZ:  Let the record show that the  
8     chair was hoping to expedite the meeting.

9                     CHAIRMAN FROINES:  Let's go ahead.

10                    DR. GLANTZ:  And told me I wasn't allowed  
11    to talk.

12                    CHAIRMAN FROINES:  I never said that.

13                    DR. MARTY:  Okay.  We made some changes to  
14    the hydrogen sulfide REL.  This is, again, based on  
15    public comment.  We received comment that hydrogen  
16    sulfide odor detection can be accompanied by headache and  
17    nausea and that the Ambient Air Quality Standard is not  
18    solely based on odor detection.

19                    We were provided documentation of  
20    complaints of headache and nausea by the Air Districts,  
21    and we decided to return to the original proposal to use  
22    the Ambient Air Quality Standard, which is set for a  
23    one-hour exposure in the state.

24                    The acute reference exposure level then  
25    becomes 42 micrograms per cubic meter based on the



1 Ambient Air Quality Standard. The documentation for that  
2 Ambient Air Quality Standard indicates that the primary  
3 study that was the basis for the Ambient Air Quality  
4 Standard consisted of a panel of 16 people.

5 They exposed these individuals to hydrogen  
6 sulfide at increasing concentrations until the odor was  
7 detected. To some the odor was accompanied by adverse  
8 physiological responses. So we are terming the  
9 critical-effect physiological response to odor, namely  
10 headache and nausea.

11 And again, the Ambient Air Quality Standard  
12 used the geometric mean of the odor threshold, which is  
13 0.03 parts per million. I should probably add that we  
14 did receive comment after the public comment period that  
15 in actual fact the H<sub>2</sub>S Ambient Air Quality Standard is  
16 0.025, which would mean that it's 35 micrograms per cubic  
17 meter. Somewhere along the line it was rounded up. So I  
18 think we're going to stick with what we have here.

19 We did also in deliberating the hydrogen  
20 sulfide issue -- initially our proposed reference  
21 exposure level was for respiratory irritation. So the  
22 endpoint has actually changed. This number will not be  
23 used to evaluate impacts on respiratory irritation --  
24 impacts of respiratory irritation from hydrogen sulfide  
25 in a risk assessment.



1                   It's almost -- in fact, it is at this point  
2                   in a category all its own. That's physiological response  
3                   to odor.

4                   We also made changes to the xylene  
5                   reference exposure level based on the comment that more  
6                   data were available on irritation than was used in our  
7                   document and that these studies had more appropriate  
8                   exposure durations.

9                   We agreed with the commentator and ended up  
10                  using Hastings, et al. (1986), with support from two  
11                  other studies, Carpenter, et al. ('75), and Nelson, et  
12                  al. (1943). Initially, we had used Nelson, et al.  
13                  (1943), which had a three- to five-minute exposure  
14                  duration and had extrapolated to a 60-minute exposure  
15                  duration.

16                  And as I mentioned earlier, the shorter the  
17                  duration, the more important the choice of that exponent  
18                  "N" in Haber's Law becomes when you're extrapolating up  
19                  to 60 minutes.

20                  So this change using Hastings et al.  
21                  allowed a lesser time extrapolation. So we went from 30  
22                  minutes to 60 minutes, rather than from 3 minutes to 60  
23                  minutes. The result is it changed the reference exposure  
24                  level from .5 to 5 parts per million.

25                  Just a brief comment on the studies for



1 xylenes. Nelson, et al. (1943), exposed ten subjects for  
2 three to five minutes to 100 or 200 ppm. There was no  
3 irritation noted by the subjects at 100 ppm.

4 In Carpenter, et al. (1975), one of seven  
5 subjects reported nose discomfort at 106 ppm for a  
6 15-minute exposure. But this same individual did not  
7 report nose discomfort at higher concentrations to which  
8 he was exposed. So the authors considered 106 ppm to be  
9 a no observed adverse effect level for a 15-minute  
10 exposure.

11 CHAIRMAN FROINES: Do you agree with that?

12 DR. MARTY: We agree with that.

13 CHAIRMAN FROINES: Wow. Why  
14 isn't -- why -- perhaps you get some saturation  
15 phenomenon on a higher concentration and that the value  
16 of 106 was actually an occurrence that had -- that was  
17 meaningful.

18 DR. MARTY: I think taken in context of the  
19 rest of the available data, it points to 100 ppm as a  
20 NOAEL. In also reading the study, the individual who  
21 reported nose discomfort, the way he put it was that he  
22 thought maybe his -- he had some irritation in the nose,  
23 but it wasn't so striking as to be called irritation. So  
24 he called it discomfort.

25 CHAIRMAN FROINES: So how do you get to 5



1 parts per million? Because you're adding an interspecies  
2 variability term -- I mean an interindividual variability  
3 term of 10 and then a factor of -- you're not assuming a  
4 LOAEL. You're assuming it's a NOAEL. So you don't have  
5 6.

6 DR. MARTY: Right. The way it gets to 5 is  
7 because we extrapolate from 30 minutes in the Hastings  
8 study to 60 minutes using Haber's Law. Hastings had  
9 exposed 50 individuals to 100, 200 or 400 parts per  
10 million of mixed xylenes for 30 minutes to evaluate eye,  
11 nose and throat irritation.

12 The percent of subjects reporting eye  
13 irritation was not different from controls at 100 ppm.  
14 Thus these three studies together point to 100 ppm as a  
15 NOAEL for at least 30-minute exposure durations, and  
16 that's what we ended up choosing. It is -- it does point  
17 to the fact that we would like to have a stronger data  
18 set to develop a lot of these reference exposure levels.

19 CHAIRMAN FROINES: These issues become  
20 important depending upon the levels of aromatics and  
21 gasoline. So it's not a trivial issue.

22 DR. MARTY: I think that covers it for the  
23 changes that we made to a reference exposure level based  
24 on public comment except for two more that are coming  
25 down the line. Maybe I should do those first.



1 Jim, it's the chloropicrin slide.

2 DR. GLANTZ: While you're digging it out, I  
3 have -- I read through all of the comments and the  
4 responses, and I think OEHHA was very responsive. I  
5 think when the commenters brought forward reasonable  
6 evidence for a change. It was made in the cases where  
7 they didn't change something, and I thought they had  
8 pretty good reasons.

9 DR. MARTY: In the case of chloropicrin?

10 DR. GLANTZ: No. These are the new ones.  
11 We haven't seen --

12 DR. MARTY: Right. I'm going to go over  
13 the two new ones right now. It would be chloropicrin and  
14 methyl bromide that the panel has not seen.

15 We did receive comment on the chloropicrin  
16 reference exposure level. One of the comments was that  
17 we should not time extrapolate for trigeminal nerve  
18 mediated irritants. There is evidence for some irritants  
19 that irritation may be more concentration dependent than  
20 time dependent.

21 And so certain individuals in the  
22 scientific community think it's inappropriate to use  
23 Haber's Law to extrapolate.

24 However, we cannot find data to quantitate  
25 this phenomenon and particularly for chloropicrin here.



1 There is also a comment that we should have done or could  
2 have done a benchmark dose approach.

3 So we are now suggesting using a  
4 benchmark-concentration-type approach and applying  
5 appropriate uncertainty factors, but we are also  
6 continuing to use time extrapolation. The reference  
7 exposure level would change from 1 to 4.4 parts per  
8 billion.

9 DR. GLANTZ: That's if you do the  
10 benchmark --

11 DR. MARTY: Right.

12 DR. GLANTZ: So I'm unclear, though. What  
13 is it you're recommending?

14 DR. MARTY: Okay. The next couple slides  
15 will show that. We use the same study we used before.  
16 That is a study of the RD50 by Kane, et al. ('79). The  
17 study was conducted in mice, and the critical effect  
18 measured in the study is decrease in respiratory rate by  
19 50 percent or RD50, and this is the Alarie method.

20 So we took -- as a low observed adverse  
21 effect level, we took the RD50. In the study they  
22 provided a dose response curve and gave the equation that  
23 defines the line. So we use that equation to get the  
24 RD05, which is 0.79 parts per million.

25 This is analogous to the benchmark



1 concentration approach where you're looking for  
2 the -- you're extrapolating back to the 5 percent  
3 response rate.

4 The exposure duration was ten minutes. So  
5 we did use Haber's Law with an "N" value of 1 to  
6 extrapolate to a 60-minute exposure. The one-hour  
7 extrapolated RD05, then, is 132 parts per billion.

8 Since a NOAEL was identified, we didn't  
9 have a LOAEL uncertainty factor. We used an interspecies  
10 uncertainty factor of 3, which is what we have been doing  
11 with the benchmark concentration approach because we feel  
12 that we have pegged the 5 percent response rate much  
13 better than if you use the classical uncertainty factor  
14 approach where you're constrained by the investigator's  
15 choice of exposure level.

16 I probably should insert here that there  
17 have been some studies -- I think George did one -- that  
18 looked at where on a dose response curve the NOAEL comes  
19 out to be -- if you're just looking at the investigator's  
20 choice of doses, it usually ends up being at about what  
21 you would interpolate as the 5- to 10-percent response  
22 rate. So this goes back to why we chose benchmark  
23 concentration 05 initially in our benchmark concentration  
24 methodology.

25 We also applied an intraspecies uncertainty



1 factor of 10 to account for sensitive subpopulations for  
2 a cumulative uncertainty factor of 30. This gives a  
3 reference exposure level of 4.4 parts per billion.

4 DR. BLANC: So you've gone from 1 part per  
5 billion to 4 --

6 DR. MARTY: Right. Which rounds down to 4.  
7 1 to 4.

8 DR. BLANC: Although I think that the -- it  
9 was good that you were responsive in the way you were  
10 from a general point of view, I think, being responsive  
11 to the earlier comment from a different group wherein  
12 they called your attention to the fact that chloropicrin  
13 photooxidizes to phosgene, I believe you should stick  
14 with 1 part per billion so that you're consistent with  
15 your level for phosgene so that, even if all of it  
16 photooxidized to phosgene -- I think it would be an  
17 inconsistency in the document if, in fact, you were  
18 less -- you were more generous with the REL for  
19 chloropicrin than for phosgene.

20 I think you have to pick whichever's lowest  
21 and apply it to chloropicrin. Before it wasn't an issue  
22 because you were at 1 part per million anyway. But I  
23 think what you should do in your document is say, you  
24 know, we -- if we did this ultimate thing, we might come  
25 out to 4.9, but in this particular case because -- as



1 it's been pointed out to us, it photooxidizes to  
2 phosgene.

3 We have to use the lower level which we had  
4 achieved by different assumptions anyway. So actually, I  
5 wouldn't adopt this level. I would stick with the 1 part  
6 per billion since the kind of exposure scenarios we're  
7 talking about would likely be outdoors where there might  
8 very well be photooxidation, if one can assume. Is that  
9 a reasonable public health approach?

10 DR. ALEXEEFF: I think it's a reasonable  
11 approach. We'll look --

12 DR. BLANC: And also one of your  
13 commentators anyway -- you'd be responding to them  
14 anyway. Because they said, "Well, you have to take into  
15 account that it's broken down to phosgene."

16 DR. MARTY: It's the same commentator.

17 DR. BLANC: Oh, great. Then you're  
18 perfect. You're golden.

19 DR. MARTY: Okay. Then the other change  
20 which you folks haven't seen is the methyl bromide  
21 reference exposure level proposed revisions.

22 Our initial -- Jim, I got to use your  
23 slide. I can't find mine.

24 We did receive again comment that we should  
25 not use repeated dose studies for methyl bromide, but



1 this is the instance where the effects were seen after  
2 the first day of exposure.

3           Increasingly severe effects were seen  
4 following further exposure, but we're focusing on just  
5 the one day. There was also a comment that we should  
6 time extrapolate.

7           As you'll recall in the original proposal,  
8 we did not time extrapolate from the seven-hour exposure  
9 of a single day to one hour because there was some  
10 controversy over whether that was something that should  
11 be done based on outside review by Dr. Jerry Last at  
12 U.C. Davis.

13           This was review that was requested by the  
14 Department of Pesticide Regulation. So we had not time  
15 extrapolated it. We did, however, find in the literature  
16 a computed value for the exponent "N" in Haber's Law. So  
17 there obviously are some people out there who think that  
18 you can compute empirically a value for Haber's Law.

19           The commentator also suggested a different  
20 way of coming to a one-hour exposure level for humans,  
21 and the result of that methodology would be that a  
22 six-hour exposure at 100 ppm in rats is equivalent to a  
23 one-hour exposure at over 2,000 ppm in humans.

24           The methodologies counter to the human  
25 equivalent calculations done by U.S.EPA and others, and



1 we were not comfortable with the commentators'  
2 methodology. They also did not provide a sufficient  
3 justification for that particular method.

4 So we have some suggested changes to the  
5 methyl bromide reference exposure level. Zwart et al. in  
6 1992 reported empirically derived values of "N" for  
7 Haber's Law for methyl bromide. Based on the Irish, et  
8 al. (1940) data, the "N" is 1.33. Using that "N" and  
9 time extrapolating changes the reference exposure level  
10 from 1 to 4.45.

11 We used the same study, the Pharmaco LSR  
12 data in dogs where exposures varied from 103 to 394 parts  
13 per million. Various durations of exposure were used  
14 in this study. We show one seven-hour exposure. The  
15 critical effects seen were lacrimation, pulmonary  
16 toxicity and central nervous system toxicity.

17 There was a no observed adverse effect  
18 level then of 103 parts per million in this study. We  
19 extrapolated to the one-hour NOAEL using Haber's Law and  
20 an exponent of 1.33.

21 We applied a cumulative uncertainty factor  
22 of 100. 10 for interspecies and 10 for intraspecies  
23 variability. The resulting reference exposure level is  
24 4 ppm.

25 DR. FUCALORO: But, of course, the work in

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1 Zwart's study, as I pointed out I think before, had an  
2 endpoint of LC50; right? And you're applying that Haber  
3 Law exponent to a different type of endpoint, but you  
4 think that's valid.

5 DR. MARTY: Yes. We're doing that, and  
6 we've done it in other cases, and it's a function of the  
7 availability of data. And we do recognize that that is  
8 an uncertainty.

9 CHAIRMAN FROINES: How many do you have  
10 more?

11 DR. MARTY: We probably have 20 more  
12 slides, 15.

13 CHAIRMAN FROINES: 20 more slides.

14 DR. MARTY: Fifteen to twenty.

15 CHAIRMAN FROINES: How much time do you  
16 need on DEF and methyl parathion?

17 REPORTER: Wait. Could you state your  
18 name, please.

19 MR. GOSSELIN: Paul Gosselin.

20 DR. BLANC: Paul Gosselin in DEF.

21 MR. GOSSELIN: Based upon the discussions  
22 we've had and the comments and seeing some of the edits,  
23 that may take -- I don't know -- half hour.

24 CHAIRMAN FROINES: So you say methyl  
25 parathion stands comment about the panel's time



1 notwithstanding --

2 DR. GLANTZ: There has to be an uncertainty  
3 factor.

4 CHAIRMAN FROINES: No, no, no. I'll come  
5 to that. So you're saying, say, 15 minutes on methyl  
6 parathion and half an hour on DEF, and the panel could  
7 double that. So that's potentially an hour and a half.  
8 That's, say, an hour you need overall.

9 MR. GOSSELIN: Right.

10 CHAIRMAN FROINES: With some error margins  
11 there. So we're at -- so essentially we can use up to an  
12 hour, I guess, and my assumption is that I'm checking off  
13 each chemical we're going through.

14 So when we assign chemicals to the panel,  
15 I'm assuming that, as we go through each chemical, we can  
16 assume that we don't really need to assign those  
17 chemicals, if that's a fair assumption. Unless somebody  
18 wants to go back and revisit something we've discussed  
19 here.

20 DR. FUCALORO: That's very good, John.  
21 Because I was going to suggest that we forego doing this  
22 since we're going to review the chemicals individually,  
23 but you've actually turned it around saying that, since  
24 we're reviewing these right now, there's no need to  
25 assign them.



1                   CHAIRMAN FROINES:  If we can cover 20  
2  chemicals in the next hour, recognize that there may be  
3  problems --

4                   DR. COLLINS:  Twenty slides.

5                   CHAIRMAN FROINES:  How many chemicals?

6                   DR. MARTY:  It's a total of 15.

7                   CHAIRMAN FROINES:  Okay.  Well, that seems  
8  to me it would cut our out-of-meeting workload down  
9  considerably.  So I would argue that we go ahead and do  
10 it.  And I think we can be out of here about one o'clock  
11 if we do that still.

12                  DR. MARTY:  We do have a revised proposed  
13 acrolein REL.

14                  CHAIRMAN FROINES:  Is that okay with  
15 everybody?

16                  DR. MARTY:  Sorry.

17                  DR. FRIEDMAN:  I just want to clarify.  So  
18 that this quick review of changes in the RELs is supposed  
19 to substitute for our careful reading of each of these  
20 chemicals?

21                  CHAIRMAN FROINES:  Well, that's a question.  
22 That's why I was raising it.  If the panel is comfortable  
23 with the discussion that we have on the chemical, then we  
24 would not have to assign them.

25                  If the panel feels that they would like to

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1 go back and read it more in depth, clearly that would  
2 take precedent.

3 DR. FRIEDMAN: Are there people -- I am not  
4 knowledgeable in this area. Are there people on the  
5 panel who have studied these individual chemical reports  
6 and feel comfortable with them or -- because I feel a  
7 little bit uncomfortable, if that isn't the case, of our  
8 relying just on this half-minute presentation to make a  
9 judgment.

10 CHAIRMAN FROINES: I think there are  
11 varying -- if I had to guess, I'd say there are varying  
12 degrees of review going from 0 to 100 percent.

13 DR. GLANTZ: Well, I think -- I mean since  
14 I think I'm probably, except maybe for the chair, the  
15 only person who's read the whole report, I think that's a  
16 reasonable procedure, John, with the caveat that, since  
17 we're going to be considering the report again at the  
18 next meeting, that to the extent the members want to go  
19 back and read the rest of it and bring any additional  
20 issues to bear at the meeting on the compounds we talk  
21 about today, that's fine.

22 I think -- to me -- I mean the way I've  
23 dealt with this was to concentrate mostly on the  
24 methodology which is the first part, and the whole idea  
25 of this exercise, as we've developed it, was to come up



1 with a defensible methodology and then systematically  
2 apply it with making exceptions where there was a good  
3 reason to do it, which is, I think, what they've done.

4           And then I have to say that having done  
5 that, I've relied pretty heavily on the public comments  
6 and to see when criticisms are raised by the interested  
7 parties, because they know more than I do, and then to  
8 try to judge whether OEHHA had a reasonable response  
9 either in amending the report, as they've done in several  
10 cases, or defending the report.

11           So I think the important thing is to see  
12 that -- so effectively what's going on here is they're  
13 going through the compounds that there were comments on,  
14 and I think we could just go through the same exercise  
15 for the rest of them.

16           It's -- they're pretty much cookie-cutter  
17 analyses, if you look at them. I think everyone on the  
18 panel should look at the whole report and bring up any  
19 issues people have to bring up before we include.

20           DR. FRIEDMAN: If we do take that route of  
21 looking at the whole report, then I would appreciate the  
22 subdividing by assignments because that's an awful lot of  
23 work to review this carefully in the time we have, and I  
24 would appreciate to be given assignment of a few of them  
25 to look at carefully rather than having to be responsible



1 for the whole thing.

2 DR. GLANTZ: No. I think that's what  
3 John's saying. The question is should he -- for the ones  
4 which were discussed at the meeting, does he need to  
5 explicitly assign those out or not?

6 DR. BLANC: I would -- I'm sorry.

7 DR. GLANTZ: But I would --

8 DR. BLANC: I would just see that it's a  
9 little bit weighted so that somebody doesn't get all ones  
10 that weren't discussed or something, if that's the issue.

11 CHAIRMAN FROINES: I think that one way to  
12 approach it is to assume that we have gone through these  
13 to a certain degree, and if somebody from the outside  
14 wants to raise a question about a particular chemical,  
15 that can be taken up at some future time. I mean I think  
16 that with -- the process isn't a closed one.

17 I think as a matter of law I asked the  
18 question with -- to OEHHA and to ARB last time, "Does the  
19 panel have to go through every chemical and go through  
20 every number?"

21 And I think the legal answer so to speak  
22 was "no." But we felt that we still should go through  
23 the chemicals because the panel should have read the  
24 document, and we should have that within the context of  
25 our findings.



1                   So I think we're going one step better than  
2 we have to, but I think we also want to try to minimize  
3 the impact as well.

4                   So it seems to me that, if we subtract out  
5 the chemicals we're doing here and if there is major  
6 controversy surrounding any of those, we can take them up  
7 again, but that would give us a much lighter load.

8                   DR. FRIEDMAN: Perhaps we could -- you say  
9 the two of you have read the full report. We can regard  
10 you as lead persons as we have with previous reports and  
11 then I would feel more comfortable.

12                   CHAIRMAN FROINES: Well, I think the  
13 panel -- we should --

14                   DR. GLANTZ: Well, the lead --

15                   CHAIRMAN FROINES: -- divide --

16                   REPORTER: Wait. Wait. One at a time.

17                   DR. GLANTZ: The other lead person was  
18 Seiber, who's not here anymore. But yeah. I think we  
19 should just go on. Maybe the compromised position on  
20 this would be to assign out to, you know, divide -- was  
21 it 51 chemicals? The 51 chemicals up among the members  
22 of the panel but then indicate -- just remind people  
23 which ones we've already dealt with.

24                   And then the people can go take another  
25 look if they want but concentrate on the ones that



1 haven't been discussed.

2 CHAIRMAN FROINES: I would argue a little  
3 bit the opposite. I'd argue that we divide up the  
4 chemicals that haven't been discussed here today --

5 DR. GLANTZ: Okay.

6 CHAIRMAN FROINES: -- and that the two  
7 leads, which are now you and me, that we go back over the  
8 chemicals that have been discussed today to see --

9 DR. GLANTZ: Okay.

10 CHAIRMAN FROINES: -- if there's any  
11 particular problem.

12 DR. BLANC: All right. Fine.

13 DR. GLANTZ: Okay. That's fine.

14 DR. BLANC: Can I get back to methyl  
15 bromide for a minute?

16 DR. GLANTZ: Okay.

17 DR. BLANC: Can you comment on the acute  
18 human toxicity in your document where a workplace  
19 concentration of 35 parts per million for short,  
20 unspecified durations induced anorexia, nausea, vomiting  
21 and corrosion of the skin, although the methods of  
22 determination were crude --

23 CHAIRMAN FROINES: What page are you on,  
24 Paul?

25 DR. BLANC: That's on page --



1 DR. MARTY: C-197.

2 DR. BLANC: C-197.

3 DR. ALEXEEFF: Yeah. What that study  
4 refers to, it was a study of workers involved in dried  
5 fruit fumigation, and the level here is -- of 35 reflects  
6 exceedences over time, over the background.

7 So there was some general background  
8 concentration of undetermined measure. And on occasion  
9 there were spikes up to 35. So it's not -- it's even a  
10 little more complex than the repeated concentrations we  
11 were referring to before, where you have exposures each  
12 day of a certain concentration.

13 In this case, we have some sort of chronic  
14 background exposure and then repeated spikes, and what  
15 was happening, as I recall in this case, the 35 was  
16 occurring when they were opening up the chambers.

17 DR. BLANC: Would they have acute symptoms  
18 at the time of 35 --

19 DR. ALEXEEFF: Right. They would have  
20 acute symptoms until they instituted new controls.

21 DR. BLANC: And when they instituted the  
22 new controls --

23 DR. ALEXEEFF: The symptoms went away.

24 DR. BLANC: Because if the level is 35 and  
25 you assume that was a one-hour exposure and you used an



1 inter -- intraspecies of 10, that would be 3.5. You'd  
2 also -- you'd have to go to a no effect level which would  
3 be a .35, which would be considerably lower than the new  
4 proposal you have of 4.8 parts per million.

5 DR. ALEXEEFF: Yeah. I think --

6 DR. BLANC: Makes me a little  
7 uncomfortable, I must say.

8 DR. ALEXEEFF: You have a good point.  
9 We'll go back and look at that study again.

10 DR. BLANC: And I just have to say that the  
11 4 parts per million range of methyl bromide makes me  
12 uncomfortable. It seems to me that, given how potent  
13 that is, I'm surprised the calculations yielded a value  
14 that high. It just strikes me as being on the high side.

15 So and also given the amount of human  
16 exposure experience, it might be worth a recheck of the  
17 literature just to make sure there aren't any human case  
18 reports that you've missed that would be relevant.

19 Because if you combined even a couple of  
20 case reports with this old industrial report and if it  
21 seems like you're in a range where 30 parts per million  
22 is causing problems -- in fact, anything that was causing  
23 problems at 100 parts per million, in fact, would get you  
24 back to 1 part per million, wouldn't it? Because you  
25 have an intraspecies factor of 10, and you need 10 to get



1 to a no effect level; is that right?

2 DR. ALEXEEFF: Yeah. For the most part,  
3 you're right. And we will go back. We'll look at this  
4 study. We'll look at the other case reports. And this  
5 particular study, it's in the document because it's  
6 clearly not strictly a chronic exposure level. So we're  
7 not talking chronic here.

8 DR. BLANC: Right.

9 DR. ALEXEEFF: But it's not really acute  
10 either. So we can go back to look to see where it sort  
11 of fits on that continuum and look at that information  
12 again.

13 And the interesting thing about methyl  
14 bromide -- I don't really -- it's not really that potent  
15 of a compound. It's really more insidious that creates  
16 the concern about it in that the type of health effects  
17 that occurs and the fact that these effects can be  
18 delayed and the type of neurological symptoms that occur.

19 I think there's sort of some issues like  
20 that and that there's not a clear -- there's not -- it's  
21 what I would refer to as kind of a -- an all or none kind  
22 of effect.

23 You're dosing either the animals or the  
24 humans are being exposed, and there's no reported health  
25 impact. And all of a sudden at a slightly higher dose,







1 the exposure? Is that when you say "crude"?

2 DR. MARTY: No. I think we don't  
3 know -- it's not a very accurate measure of exposure --

4 DR. BLANC: Well, it only matters if it's  
5 accurate in that it was actually 350 parts per million  
6 and they thought it was 35.

7 DR. MARTY: Right.

8 DR. BLANC: If it was 3.5 and they thought  
9 it was 35, it's not a problem.

10 DR. MARTY: Right.

11 DR. BLANC: Except in the other direction  
12 for you.

13 DR. MARTY: Right.

14 DR. BLANC: In using it. So is it that you  
15 think that it's -- that they underestimated exposure?

16 DR. MARTY: I think we can say we don't  
17 know.

18 CHAIRMAN FROINES: But I think that Paul's  
19 point about 100 gets you down to 1, not 4.4, is also very  
20 relevant. I mean I don't know anybody in this room who  
21 wants to -- who would say that there aren't effects of  
22 methyl bromide 100 parts per million.

23 DR. BLANC: Yeah. I mean even if you put  
24 an uncertainty factor upwards that they underestimated  
25 the dose in that study by a factor of 3, it would still



1 be lower --

2 CHAIRMAN FROINES: Than the value you're  
3 proposing.

4 DR. ALEXEEFF: Yeah.

5 CHAIRMAN FROINES: Blanc gets assigned the  
6 methyl bromide.

7 DR. BLANC: Well, no. We've discussed it  
8 here. So actually, no.

9 Can I ask another question about methyl  
10 bromide too while we're on the subject in terms of what's  
11 driving the REL or the irritant effects, not the  
12 neurological effects; is that right? Or --

13 DR. MARTY: Yes.

14 DR. BLANC: And in terms of the mechanism;  
15 is that right?

16 DR. ALEXEEFF: No. Did you ask if  
17 irritation was driving? No. It's the neurological  
18 effects.

19 DR. BLANC: In this model. In the human  
20 one it would be -- it would be anorexia, nausea and  
21 vomiting. So it would be a nonneurologic endpoint, for  
22 example, if you use that.

23 DR. ALEXEEFF: I don't know if it would be  
24 or not. I don't know what the mechanism of those effects  
25 are in this case. I don't think it's an odor mechanism



1 that we're referring to.

2 DR. BLANC: No. I didn't mean -- I meant  
3 odor irritant perhaps.

4 DR. MARTY: I don't know if the nausea and  
5 vomiting would be mediated by the CNS. I think that's  
6 what we're saying.

7 DR. BLANC: Right. The reason I ask that  
8 question is because, if part of -- you know, it may very  
9 well be that at the acute lethal effects clearly in  
10 humans are from CNS toxicity and uncontrollable seizures.  
11 In fact, it's a very interesting toxin from that point of  
12 view.

13 CHAIRMAN FROINES: What happens to the  
14 respiratory rate at these concentrations in the animals?

15 DR. MARTY: I don't know. George may know.

16 CHAIRMAN FROINES: Are they closing down?

17 DR. ALEXEEFF: It's labored breathing, and  
18 I believe it's a reduced rate.

19 CHAIRMAN FROINES: Reduced rate so that the  
20 internal dose may be lower than the measured dose. When  
21 you think about that --

22 DR. BLANC: Well, the only reason I'm going  
23 down this road is because, if there's two separate  
24 pathways of effects, one is the CNS  
25 lethality -- seizures, et cetera -- but the other is that



1 it's an irritant.

2 It may be an irritant because of the  
3 bromine moiety. I don't know the chemistry of the  
4 breakdown of methyl bromide. And so you may have a  
5 wealth of data just on bromine if it does break down to a  
6 certain extent to methyl bromide breaks down to bromine.

7 You might want to find that out too because  
8 I think that there's more data in terms of irritant dose  
9 response with bromine.

10 DR. ALEXEEFF: Well, yeah. Methyl bromide  
11 is metabolized to bromine, but I don't know that that  
12 irritant effect is really operating here. I'll have to  
13 go back and look at that Watrous study.

14 I was just rereading our summary here, and  
15 I notice that there is also skin corrosion.

16 And now I'm wondering if I'm confusing it  
17 with a slightly different study where the operators were  
18 collecting methyl bromide in ampules and spilling it on  
19 their hands. So we'll go back and look at that study  
20 just to be sure that we have it clearly characterized and  
21 see if there's a way -- if this study sheds actually some  
22 light that we need to take into account and look at the  
23 other studies.

24 DR. FUCALORO: When you say the breakdown  
25 metabolically is to bromine or bromide or --



1 DR. ALEXEEFF: Bromide ion.

2 DR. FUCALORO: Well, yeah. Because I'd be  
3 very surprised if it went to bromine, I think.

4 DR. ALEXEEFF: Yes, we're talking about an  
5 alkylating agent, and once it methylates, the  
6 bromine -- the bromide, excuse me. Is released.

7 DR. FUCALORO: There's different levels of  
8 irritation between bromine and bromide.

9 CHAIRMAN FROINES: Let's move on. We'll  
10 certainly revisit this again.

11 DR. MARTY: Okay. We -- the revised  
12 proposed acrolein REL is up on the board. Essentially we  
13 revised it because the SRP -- pursuant to the SRP  
14 suggestion of using an uncertainty factor of 6 for that  
15 LOAEL to NOAEL extrapolation for this mild adverse  
16 effect.

17 We had previously used an uncertainty  
18 factor of 3. So what it did was reduce the REL by half.  
19 There's a few issues with the study in that there was not  
20 an identified NOAEL, and the duration of exposure was  
21 short, five minutes.

22 And I think that we've already discussed  
23 that that leads to uncertainty in using the  
24 extrapolation.

25 We also got comment on acrolein. One of



1 the comments was to use the NRC eye irritancy threshold  
2 in an NRC document, 1981.

3           However, in looking at the document,  
4 there's no clear basis for the threshold. And the study  
5 we used, Darley, et al. (1960), showed irritancy below  
6 the threshold cited in the NRC document. So we were not  
7 comfortable with changing that.

8           There also was comment on inability to  
9 measure concentrations that low. This has no direct  
10 impact on developing the reference exposure level, the  
11 commentator was concerned that it would not be  
12 particularly useful if you couldn't measure it anyway.

13           We did get comment on ammonia. As you'll  
14 recall, we used a benchmark concentration approach,  
15 pooled data from four human studies. Because we were  
16 using a benchmark concentration approach, an uncertainty  
17 factor of 3 was used to account for intraspecies  
18 variability.

19           The commentator discouraged combining data  
20 sets into a benchmark analysis and wanted us to select  
21 one. However, we believe that one of the positive  
22 attributes of the benchmark concentration approach is the  
23 ability to combine data sets because it allows fuller use  
24 of the data.

25           We did receive comment on arsenic. Our



1 reference exposure level for arsenic, just to review the  
2 study population, it's a repro developmental tox study in  
3 mice. Inhalation exposures were -- the exposures were by  
4 inhalation.

5 The critical effect was decreased fetal  
6 body weight. There was no observed adverse effect level  
7 determined in the studies. So we relied on the lowest  
8 observed adverse effect level.

9 The exposure duration was four hours per  
10 day for three days of gestation and only chose the  
11 four-hour exposure to back extrapolate to 1 using Haber's  
12 Law with an "N" value of 2.

13 The issue really lies in the fact that  
14 there's a cumulative uncertainty factor of a thousand to  
15 give you a reference exposure level of 0.38 micrograms  
16 arsenic per cubic meter.

17 The comment that we received included  
18 comments that we should not use repeated dose studies. I  
19 think we discussed this earlier. That it's unavoidable  
20 if you're going to consider repro developmental toxicity.

21 We received comment that the uncertainty  
22 factor of a thousand is too large. However, we don't  
23 have data demonstrating a NOAEL in the study, and that's  
24 the methodology that we're using.

25 We also received comment that we should



1 have separate pentavalent and trivalent arsenic reference  
2 exposure levels. While there's some merit to that  
3 comment, in the hot spots program, the facilities do not  
4 speciate their metals emissions. They just report total  
5 arsenic or total nickel or total chromium and so forth  
6 such that we felt compelled to use a reference exposure  
7 level that's based on a more toxic arsenic compound in  
8 order to account for the possibility that it is all  
9 trivalent.

10 We also received comment that the arsenic  
11 REL should not be lower than the arsine REL. Arsine, I  
12 think, people recognize as a potent toxicant. In this  
13 case it's really a function in the available data and the  
14 methods used.

15 There's a large uncertainty factor applied  
16 to the arsenic REL because of the lack of available data.  
17 Of course, the arsine REL has a lower uncertainty factor.  
18 There also -- arsine has a peculiar toxicity in that  
19 lysis of red blood cells occurs following exposure to  
20 arsine gas but not following exposure to arsenic  
21 compounds.

22 DR. FUCALORO: Your argument has been  
23 essentially to take the most prudent course and consider  
24 everything to be trivalent as opposed to pentavalent  
25 because trivalent is, in general, more toxic and then to



1 use soluble arsenic. Am I --

2 DR. MARTY: I think the soluble is more of  
3 a nickel issue.

4 DR. FUCALORO: Okay.

5 DR. BLANC: Can I ask a question also about  
6 RELs when it's a reproductive outcome not touching on the  
7 multi-data exposure? The intraspecies uncertainty factor  
8 is used to account for at-risk populations.

9 It's always been my assumption that, when  
10 we talk about at-risk populations, we're talking about  
11 asthmatics or the very young or the very old or  
12 reproductive age. When your endpoint is reproductive  
13 outcome anyway, what's the rationale for the human  
14 intraspecies variations of 10? Because you're already  
15 talking -- are you assuming that there are some pregnant  
16 humans that are 10 times more at risk than other -- that  
17 there's an equal variation in risk within the pregnant  
18 population? Because that seems a bit of a stretch.

19 DR. MARTY: That is the implied assumption,  
20 yes. I don't think we have data one way or the other.

21 CHAIRMAN FROINES: It's not just a question  
22 of sensitive population, though, in the sense of the  
23 asthma versus nonasthma. It's also a question of  
24 heterogeneity in general.

25 DR. BLANC: I always thought it was



1 a -- not an issue of, in fact, a bell-shaped curve but of  
2 a non-Gaussian distribution where there were -- here you  
3 had one peak for normal people and then the asthmatics  
4 were way down here -- yeah. You couldn't even  
5 assume -- this was not just the 95th percentile issue,  
6 but have I been wrong on that --

7 DR. ALEXEEFF: I think that -- I haven't  
8 seen a good explanation for the justification of the  
9 ten-fold uncertainty factor for intraspecies for  
10 reproductive. So nothing comes to mind as to what the  
11 implicit assumptions are, and we will -- I'll ask our  
12 reproductive experts to see what is being thought there.  
13 But what does come to mind is --

14 DR. BLANC: Because you don't -- excuse me.  
15 Because you don't use it if it was -- coming back to our  
16 earlier conversation, if this was a study of asthma -- of  
17 asthmatics in humans, you wouldn't be using the factor.

18 You wouldn't have an intraspecies because  
19 you'd assume that's our target part of the population.  
20 If you had, in fact, not a study of rats exposed to  
21 arsenic but you had a human reproductive study of arsenic  
22 and showed a reproductive adverse outcome, you wouldn't  
23 use a factor of 10 either, or would you in intraspecies?

24 DR. MARTY: Would use a factor of 10. That  
25 whole concept is actually very complicated



1 in -- is people mix up different definitions of sensitive  
2 subpopulation within it.

3 I think for a chemical that we know a  
4 sensitive subpopulation is asthmatics and you study it in  
5 asthmatics, then we're fairly comfortable not introducing  
6 another uncertainty factor.

7 We actually have a comment that we should  
8 be because the asthmatics studied generally in these  
9 types of chamber studies are not people who are severely  
10 sick. They're mild to moderate asthmatics. So --

11 CHAIRMAN FROINES: Paul, I would even  
12 argue -- I'd argue that that in fact to assume no  
13 uncertainty factor within an asthmatic is to oversimplify  
14 the science of --

15 DR. BLANC: Well, I was just trying to get  
16 a concept of what the rationale was, the stated  
17 rationale, whether or not it's -- I'm not suggesting that  
18 you reverse course if this is your standard procedure.  
19 I'm just really trying to get a sense as to what the  
20 underlying rationale was.

21 DR. MARTY: And I think the heterogeneity  
22 concept is really the underlying thread to using  
23 intraspecies variability uncertainty factors.

24 CHAIRMAN FROINES: Yeah. That's what I  
25 would argue. Now, one of the interesting things about



1 this is Dale Haddis has just written a major document  
2 looking at the underlying precepts of this ten-fold  
3 safety factor.

4           What I'll do is get a copy from Dale and  
5 make it available to everybody, and we can talk about it  
6 in the meeting, say, in the April workshop and talk about  
7 the -- this particular issue because it is a really  
8 important issue, I think.

9           But since Haddis has done a major document  
10 looking precisely at the questions we're talking about  
11 here, it's probably worth having that work to review  
12 before we have a full discussion about it.

13           DR. ALEXEEFF: So in getting back to your  
14 comment, though, the little evidence that I have seen  
15 looking at the comparison of the human response to animal  
16 response, and the example that comes to mind is  
17 thalidomide and the sensitivity of the dose of  
18 thalidomide from animals to humans, it's about two orders  
19 of magnitude in terms of what dose was -- the women were  
20 taking when they were pregnant versus some of the animal  
21 studies. I think it's the rat.

22           It's about 50-fold in that case. So I  
23 think that in the past what the -- and I will  
24 double-check. The particular folks have simply looked  
25 that for reproductive effects it appears about two orders



1 of magnitude from the animals.

2 But I don't think they actually thought  
3 through the kind of question you're asking, but I'll see  
4 if they have.

5 DR. BYUS: A comment about thalidomide,  
6 that's a metabolic -- what's the development toxic agent  
7 is the metabolic conversion of thalidomide into something  
8 that causes the developmental toxicity. It's probably at  
9 the level of metabolism differences between the rat and  
10 the human, both in level of metabolism and then sort of  
11 selectivity of metabolism as well. I'm sure that's what  
12 the difference is there.

13 CHAIRMAN FROINES: Since we don't know the  
14 mechanism, we're still stuck on that one.

15 DR. FRIEDMAN: May I ask which direction  
16 it -- the 50-fold difference is it? If you extrapolate  
17 from the rats, is it 50-fold safer or 50-fold more  
18 dangerous?

19 DR. ALEXEEFF: Humans are more sensitive to  
20 the effects. It requires a much smaller dose.

21 DR. MARTY: We also received comment on  
22 formaldehyde. In our reference exposure level, a key  
23 study used was Kulle, et al. (1987), and we estimated our  
24 reference exposure level by a benchmark concentration  
25 approach.



1                   The resulting benchmark concentration from  
2 this analysis was .44 parts per million formaldehyde,  
3 which was time adjusted using an "N" of 2 to a resulting  
4 value of .74 parts per million.

5                   We applied an uncertainty factor of 3 to  
6 account for individual variation to derive our acute  
7 reference exposure level of .25 parts per million. We  
8 received comment that we should have used categorical  
9 regression analysis, which was published by Paustenbach,  
10 et al. (1997), and which is the basis of the revised  
11 threshold limit value.

12                   We did review Paustenbach's paper, and we  
13 continued to recommend our benchmark analysis. The  
14 threshold limit value does not consider sensitive  
15 subpopulations. We don't think it was appropriate to  
16 just adopt the results of their analysis.

17                   DR. BLANC: What is the TLV? What is the  
18 value --

19                   DR. MARTY: What's the number?

20                   DR. BLANC: Yeah.

21                   DR. MARTY: I don't remember.

22                   DR. BLANC: Is it less than or more than  
23 ten times your ultimate REL?

24                   DR. MARTY: It's more than our REL, but I  
25 don't believe it's tenfold.



1 DR. ALEXEEFF: It's in the comments.

2 CHAIRMAN FROINES: There are Swedish  
3 studies that have --

4 DR. MARTY: I think it's 1.

5 CHAIRMAN FROINES: -- acute effects down as  
6 low as a tenth of a point.

7 DR. BLANC: That's a different issue. I  
8 was just -- I would just suggest that in your response to  
9 the comments, if you didn't say it, I might have missed  
10 that. That you say, if we actually took your approach  
11 and then added the intraspecies uncertainty factor, you  
12 would actually end up with a lower level than what we  
13 did.

14 DR. MARTY: Okay. I'm remembering that  
15 it's 1 ppm, but I don't know for positive.

16 CHAIRMAN FROINES: What's the --

17 DR. BLANC: That's an eight-hour TLV?

18 DR. MARTY: Uh-huh. That's an  
19 eight-hour --

20 DR. BLANC: So you would also have to not  
21 only do that but -- so you'd actually get quite a bit  
22 lower.

23 DR. MARTY: Well, that would counter it.  
24 That would go in the other direction.

25 DR. BLANC: Oh, that's right.

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1                   CHAIRMAN FROINES: This is distressing. I  
2 think -- what's your REL?

3                   DR. BLANC: .25. Well --

4                   CHAIRMAN FROINES: I'll go over that.

5                   DR. BLANC: Yeah. I mean you had left me a  
6 message too about that. My point with the NIOSH health  
7 hazard evaluations was not that there was a  
8 well-delineated dose response, but in fact, if you look  
9 at those as a group, the lowest effect level is less than  
10 1 part per million in that they go -- there are a variety  
11 of health hazard evaluations that they have done where  
12 there have been reports of irritation.

13                   But they are eight-hour-a-day exposures.  
14 So by and large. Because even if you don't assume that  
15 it's a cumulative effect, do you just say what do people  
16 have by the end of the day?

17                   So I don't know what kind of number that  
18 would give you, but one of the things I was struck by,  
19 when I was involved in one of those, was that NIOSH kept  
20 going back to different work sites and finding that there  
21 was irritation at less than 1 part per million,  
22 either .25 or .5.

23                   And then the conclusion would be, well, we  
24 saw these effects, but reviewing the literature, the  
25 threshold for an effect is 1 part per million. And



1 rather than saying, well, maybe the literature threshold  
2 is actually incorrect, and they never really synthesized  
3 all those health hazard evaluations.

4 So that was my point in looking at those  
5 because I think you'll see a pattern of exposure effects,  
6 and I would agree that John should take a close look at  
7 this because there's quite a bit of --

8 CHAIRMAN FROINES: The Scandinavian studies  
9 are not cited in here.

10 DR. BLANC: It may be that because many of  
11 those studies are shift-long that, when you extrapolate  
12 back --

13 DR. MARTY: You'd end up with a higher  
14 number.

15 DR. BLANC: Can you do algebraically just a  
16 quick back of the envelope calculation what -- if there  
17 was, in fact, an eight hour effected .3 parts per  
18 million, what that would come out to be?

19 DR. GLANTZ: What do you want to do? You  
20 want to say if there's an effect of how many .3 parts --

21 DR. BLANC: .3 parts per million with eight  
22 hours of exposure using a Haber's consonant of 2.

23 DR. ATKINSON: It would increase by a  
24 factor of about 3.

25 DR. BLANC: It would be less. The level --



1 DR. ATKINSON: One hour level would go up.  
2 Yes, that's right.  
3 CHAIRMAN FROINES: So it goes to what?  
4 DR. BLANC: I don't know. He's doing that.  
5 DR. COLLINS: .3 squared would be .09?  
6 DR. BLANC: No. It should go the other  
7 way.  
8 DR. GLANTZ: No. It's the other way.  
9 It's -- hold on.  
10 DR. COLLINS: Time 8 is 72; square root  
11 between 72 would be .2 something.  
12 DR. GLANTZ: 8. Take the square root of 8.  
13 DR. FUCALORO: Number --  
14 DR. GLANTZ: That's about .85.  
15 DR. BLANC: Okay. And .85 parts per  
16 million, divided by 10?  
17 DR. GLANTZ: Would be .085 parts per  
18 million.  
19 DR. BLANC: And divided by -- instead of 10  
20 by 3, if we assume this was a bunch of human studies?  
21 DR. GLANTZ: Divide that by 3 -- divide by  
22 3, you get .28.  
23 DR. BLANC: What did you have? You have  
24 .25? So you make them out to a very similar number,  
25 depending, but I think it warrants.

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1                   CHAIRMAN FROINES: Okay. So we're going  
2 to -- formaldehyde's clearly a major, major, major  
3 chemical in this regard. So let's get it right. Let's  
4 take a break.

5                   DR. GLANTZ: We'll have formaldehyde and  
6 methyl bromide; right?

7                   CHAIRMAN FROINES: Pardon me? Methyl  
8 bromide and formaldehyde are not finished as far as we're  
9 concerned.

10                  DR. GLANTZ: Yeah. Paul will take care of  
11 those.

12                  DR. BLANC: No, no. That's -- you're the  
13 lead people.

14                  CHAIRMAN FROINES: Let's take a break.  
15 Let's take a quick ten-minute break.

16                               (A ten-minute break was taken.)

17                  DR. MARTY: For isopropanol we had several  
18 comments. The study used was Nelson, et al. (1943), to  
19 expose subjects for three to five minutes to 400 parts  
20 per million. These individuals reported mild irritation  
21 of the eyes, nose and throat and indicated that 200 ppm  
22 "would be tolerable."

23                               We used the 200 parts per million as an  
24 implied no observed adverse effect level, time adjusted  
25 that to one hour and applied an intraspecies uncertainty



1 factor of 10.

2 We did get comment to wait for a new CMA  
3 study of the irritation threshold --

4 DR. GLANTZ: Who is the CMA --

5 DR. MARTY: It's the Chemical Manufacturers  
6 Association. Isopropanol panel. And our response  
7 essentially is we can revisit the reference exposure  
8 level when new data become available.

9 We got comment that the REL is considerably  
10 lower than both the TLV and the PEL. However, such  
11 comparisons are generally not too informative since the  
12 occupational standards are not applicable directly to the  
13 general population.

14 We got comment that time extrapolation is  
15 inappropriate. However, there is a lack of data to  
16 substantiate it one way or the other for this particular  
17 compound.

18 We also got comment that it is incorrect to  
19 add in the hazard index approach chemicals that impact  
20 the upper and lower airway. However, we do have this  
21 relatively simple assumption of additivity in that the  
22 whole organism -- in the whole organism effect may be  
23 additive.

24 And while a chemical may impact the upper  
25 more than the lower airway and the second chemical might



1 impact the lower more than the upper airway, we do  
2 believe that the effects are likely to be additive.  
3 There is some information in literature that supports  
4 that.

5 We also got comment on nickel primarily  
6 from NIPERA and INCO, Incorporated. In the nickel  
7 reference exposure level we use human studies of  
8 individuals with occupational asthma.

9 These people were exposed to 67 micrograms  
10 of nickel per cubic meter. And the critical effects were  
11 measured decreases in FEV1. There was not a NOAEL  
12 observed in this study. The issues essentially  
13 were -- is the effect of a 15 percent decrement in FEV1  
14 mild or severe?

15 And in fact, the study reports those  
16 individuals who had greater than or equal to a 15 percent  
17 decrement. So we're continuing to call that mild  
18 although, in fact, it may be mild to moderate and  
19 possibly even to severe.

20 There is also a comment that the reference  
21 exposure level should not be applied to metallic nickel  
22 or insoluble nickel compounds since the exposure was to  
23 nickel's sulfate hexahydrate, which is a soluble form.

24 And, again, this brings us back to the  
25 issue that in the hot spots program, the facilities are

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1 not speciating their emissions. They're reporting total  
2 nickel. So we feel it is a health-protective assumption  
3 to use the more -- to use the soluble nickel compounds as  
4 the basis for the reference exposure level.

5 We did apply the changed uncertainty  
6 factor from LOAEL to NOAEL extrapolation of 6. So the  
7 resulting reference exposure level is now 6 micrograms  
8 per cubic meter, and prior to that, it was 11.

9 DR. BLANC: Do you make a comment in  
10 your -- in the body of your summary, if it is available,  
11 of the estimate of the percent of the general population  
12 which is -- has skin sensitivity to nickel?

13 DR. MARTY: I don't think we have that in  
14 here. I certainly don't remember that.

15 DR. BLANC: I mean it's actually a common  
16 sensitization, but what I don't remember is if people who  
17 are sensitive to nickel in terms of contact dermatitis  
18 are more or less likely also to react with bronchospasm  
19 if they inhale it.

20 DR. MARTY: We do have a statement that  
21 positive -- out of the seven individuals with  
22 occupational asthma, nickel platers, that positive  
23 reactions to skin testing were found in three of those  
24 individuals, and they also experienced dermatitis in the  
25 workplace. I'm not sure that answers the question --



1 DR. BLANC: I only bring it up because I  
2 think it is reasonable, in fact, in this particular case  
3 to be thinking about, you know, what would a sensitized  
4 person do when they inhale this stuff.

5 Whereas if you were talking about  
6 isocyanates, the probability of there being a significant  
7 number of people in the general population who  
8 were -- are presensitized to isocyanates and, therefore,  
9 if there was a release of isocyanate in Westwood, you  
10 know, would you be worried about the people who would be  
11 having an amnestic allergic response, or do you have to  
12 just worry about the acute irritant response? It's a  
13 different question.

14 So I think it is reasonable to be using the  
15 endpoint that you're using. I don't know -- if you don't  
16 feel that you need to make that statement more explicitly  
17 in your supporting information, that's fine. But --

18 DR. MARTY: I think that's an interesting  
19 point. I would like to add that.

20 CHAIRMAN FROINES: I'm going to take the  
21 chair's prerogative and say that this -- we won't close  
22 nickel off, and we'll ask Paul to review what you've done  
23 on nickel because nickel is a particularly difficult  
24 compound, I think.

25 And it's difficult with respect to its



1 chronic toxicity particularly its carcinogenicity, and  
2 it's difficult in terms of its pulmonary issues. And for  
3 example, FEV1 changes deserves a look at, I think.

4 So let's keep the door open on nickel, I  
5 think, for the time being until the next meeting.

6 DR. MARTY: We have comments on our REL for  
7 phenol, and essentially, to be succinct -- essentially,  
8 we were -- the comment was that we should not rely on a  
9 freestanding NOAEL, which is what we had done from  
10 Piotrowski, (1971).

11 Unfortunately that's the best available  
12 human acute inhalation exposure data. And also the  
13 commenter suggested using a threshold cited in a review  
14 article, but we could not find a clear basis for the  
15 threshold cited. So it's one of those problems.

16 And finally, we got comments on toluene.  
17 In that reference exposure level we used a study by  
18 Anderson, et al. (1983), who exposed 16 men to  
19 concentrations ranging from 10 to 100 ppm for six hours.

20 No symptoms were reported at 10 and 40 ppm.  
21 However, at 100 ppm, people had headaches, dizziness, a  
22 feeling of intoxication and slight eye and upper  
23 respiratory irritation.

24 We chose the highest NOAEL. And that was  
25 40 parts per million. We received comment that the NOAEL



1 should actually be 100 parts per million according to the  
2 way the commentator read the Anderson study. We reviewed  
3 the study, and it is clearly -- 100 ppm is clearly not a  
4 NOAEL.

5 The commentator also suggested looking at  
6 another study which they believed had a NOAEL of 75 ppm,  
7 which would have been higher than the 40 that we chose.  
8 We had already looked at that study, and the author's  
9 report reflects that 75 ppm. So that also is clearly not  
10 a NOAEL.

11 Finally, we got another comment, not on the  
12 reference exposure level but on the level protective  
13 against severe adverse effects, and it's the same  
14 comment. Not to use repeated dose repro tox study. So  
15 we've actually been through that. That's it.

16 CHAIRMAN FROINES: I missed something.  
17 What's the REL for toluene?

18 DR. FUCALORO: 9.8 parts per million.

19 CHAIRMAN FROINES: How many?

20 DR. FUCALORO: Am I right? 9.8 parts  
21 per --

22 DR. MARTY: Parts per million. We had --

23 CHAIRMAN FROINES: Gary?

24 DR. FRIEDMAN: May I ask a general question  
25 about these exposure studies for volunteers? Are the



1 volunteers kept blind, or is there, like, a placebo  
2 period? You know, in studies of drugs, one always likes  
3 to compare the effects of a drug whether beneficial or  
4 adverse with what -- with a placebo because there is  
5 placebo effects.

6 And I'm wondering, you know, are -- the  
7 volunteers said, you know, "Let us" -- you know, "We're  
8 going to put something in the environment. Let us know  
9 when it bothers you"? Are there controlled periods where  
10 they -- the volunteers are kept blind and they don't know  
11 whether they're being exposed or not? How are these  
12 studies done?

13 DR. MARTY: In general, that is how they  
14 are conducted. So there will be exposures to air only,  
15 say, for example, in an inhalation chamber and then  
16 exposures to whatever chemical at varying levels and for  
17 varying durations.

18 DR. FRIEDMAN: And the volunteers are kept  
19 blind to whether they're being exposed or not to the  
20 chemical?

21 DR. MARTY: Correct. In some cases, not in  
22 all cases. But in -- for example, in the toluene  
23 exposure -- they may even jump between -- first they do  
24 air. Then they'll do a higher concentration in some  
25 group, a lower concentration in some group. So they'll



1 bounce around, not even just do it in increasing  
2 concentrations unless they're specifically looking for a  
3 threshold for odor.

4 For example, most of the odor threshold  
5 studies to keep on incrementally increasing the  
6 concentration. I'm sure you can find examples where the  
7 studies were not done with the subjects blinded.

8 CHAIRMAN FROINES: It's interesting, isn't  
9 it, how many studies you cite are at least 50 years old.  
10 It shows you how limited a data we operate with, you  
11 know, and we -- it really is scary that we have such  
12 limited data.

13 And we also look at all these things as  
14 though they're -- people aren't exposed to anything else  
15 but the chemicals by themselves, and clearly people are  
16 exposed to mixtures of all these things.

17 And so we tend to underestimate or at least  
18 we don't really have a handle on how we assess mixtures  
19 in any kind of context. It's a sorry state of affairs in  
20 some respects.

21 DR. BLANC: Can I just ask in terms of  
22 toluene vis-a-vis the xylene that we discussed earlier?  
23 It's interesting that the -- the -- in the toluene -- I  
24 mean they're within an order of magnitude, but there is a  
25 difference of almost fivefold between the two levels now,



1 the two RELs.

2 DR. FUCALORO: Are you talking about  
3 between xylene and toluene?

4 DR. BLANC: Yeah.

5 DR. FUCALORO: You know, also in  
6 carcinogenicity, from what I understand, the difference  
7 between toluene and benzene is great; is that correct?

8 DR. BLANC: Well, that's -- there's a clear  
9 mechanistic reason for that. Do you -- just from  
10 a -- from a scientific point of view, do you feel  
11 comfortable with that gap between the two?

12 Would you have thought they would have  
13 come -- I know it's driven by the data that you have  
14 available to you, but in most respects we tend to think  
15 of xylene and toluene as being quite similar.

16 And in fact, there are 5 -- you know, if it  
17 was -- if it was a factor of, you know, 2, I would be  
18 perhaps not even pressing the point.

19 DR. MARTY: It's actually a factor of 2.

20 DR. BLANC: Oh, I'm sorry. It is a factor  
21 of 2. I'm sorry. Well, then nevermind. Maybe they're  
22 close enough that it doesn't matter.

23 DR. FUCALORO: And then there are three  
24 xylenes.

25 CHAIRMAN FROINES: One of the interesting

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1 things from a standpoint of the SB521, where we did the  
2 reports for the -- on MTBE. You know, one of the  
3 proposed alternatives to the use of MTBE is to use  
4 reformulated gasoline with significantly higher  
5 concentrations of toluene as the octane enhancer so that  
6 we may find ourselves looking at toluene again if MTBE  
7 becomes not the oxygenated choice so that we ought to  
8 make sure we're happy with the toluene numbers because I  
9 suspect they're going to come back on us, and we're going  
10 to have to think about them again sometime.

11 So thank you very much. These are  
12 really -- it takes a long time to go through all those,  
13 but I think these are really quite good discussions.  
14 They're a much better science -- level of science, I  
15 think, than some times. And so the pace is slower than  
16 we might like, but I think it's good -- I thought he was  
17 going to make a comment.

18 DR. GLANTZ: No. Actually, I was going to  
19 agree with you for a change. I mean I have to say --

20 DR. FUCALORO: Make sure the recorder gets  
21 that.

22 DR. GLANTZ: Right. Yeah. Maybe we should  
23 go off the record. No. I mean I have to just say, as  
24 the one lead person who's been with us from the beginning  
25 since Seiber isn't on the panel, I mean I feel very good



1 to have the whole group going through things like this  
2 because, you know, I've done the best that I can with  
3 this. But there's obviously a lot of expertise here that  
4 I don't have. So I think that -- I mean it's going to  
5 take two meetings, I guess, but it's worth it.

6 Because I think the report -- I mean each  
7 interation of this report, I think, is getting better,  
8 and I think it's going to be a very solid document by the  
9 time we're done.

10 CHAIRMAN FROINES: Well, it will also help  
11 us hopefully procedurally and intellectually to deal with  
12 the chronic document which is really going to be a tough  
13 one because there's so many chemicals and so many  
14 different issues to address.

15 Paul, sorry we've taken so long to get to  
16 you.

17 DR. GLANTZ: We should go get the whips and  
18 chains now, huh?

19 CHAIRMAN FROINES: Paul, last I -- one of  
20 the issues that came up in our discussions, when Tony and  
21 I and Bill were talking, is we wanted at some point to go  
22 over the whole concept of the MOE because the MOE is  
23 clearly a distinct procedure compared to this REL process  
24 we've just been going through.

25 I think for the sake of time to get into



1 that issue today is probably not timely. But can we take  
2 it up and have -- at some point have staff come and have  
3 a discussion about the underlying scientific basis for  
4 the MOEs and go from there?

5 DR. ATKINSON: What's an MOE?

6 MR. GOSSELIN: Margin of exposure. And  
7 actually, we went back and talked to staff, and I think  
8 it would be a good discussion to have, and we actually in  
9 our own internal guidance have similar procedures that  
10 OEHHA's presented on the RELs and the methodology on  
11 calculating out MOEs.

12 I think what you'll see in future documents  
13 is the presentation of the toxicity of the material and  
14 the uncertainty factors and the exposure estimates in a  
15 similar fashion as to what you've been seeing in other  
16 documents. That will help consistency.

17 It will have us go back and change sort of  
18 our standard procedure of doing the MOE calculation, but  
19 essentially, it's all the same data endpoints. It's a  
20 matter of how -- at what point you do the calculation,  
21 but we can bring that up at -- whenever you want to  
22 schedule that.

23 CHAIRMAN FROINES: Yeah. I think -- you  
24 know, Roger asked the question. I'm tempted to explain  
25 it, but I think we'll just get off the track, and I think



1 maybe, if we actually devote time to it, we can have an  
2 in-depth discussion because it really is quite crucial to  
3 the designation of compounds of toxic air contaminants  
4 based on their noncarcinogenic endpoints.

5 And that's what the real issue is, Roger.  
6 It has to do with not some of the carcinogenicity risk  
7 assessments are substantially different.

8 DR. GLANTZ: I actually think it would be  
9 helpful to -- if you could in the new reports to put in  
10 an REL and an MOE because they're basically just  
11 different ways of expressing the same information. And I  
12 think that would lead to more unity between the different  
13 kinds of reports.

14 CHAIRMAN FROINES: Well, I think the  
15 panel -- I think it's useful to go over the  
16 question -- the assumption that you just made, which is  
17 that they are essentially the same information.

18 I don't think that's necessarily true. It  
19 may be true, but I think it's something -- that's exactly  
20 what we want --

21 DR. GLANTZ: I think having a discussion is  
22 a good idea, but I think in terms of the reports, if DPR  
23 likes the MOE presentation, I don't think there's  
24 anything intrinsically wrong with it, but I think if we  
25 also included in the reports an REL, that would just



1 allow for greater comparability of the two sets of  
2 documents.

3 MR. GOSSELIN: Yeah. Our intent is to do  
4 that.

5 DR. GLANTZ: Okay.

6 CHAIRMAN FROINES: It's also precisely the  
7 reason why, when I first introduced Roger in the  
8 beginning, said that how we calculate -- how we determine  
9 exposure becomes so central because it defines in a sense  
10 whether or not a chemical becomes designated as a toxic  
11 air contaminant.

12 And this panel -- Roger has disagreed with  
13 DPR on that issue in the past, and let's not, you know,  
14 bring up old wounds. Let's just go ahead.

15 So I think that the panel -- everyone on  
16 the panel has the current proposed DEF findings. And let  
17 me say that there is still one place where there -- one  
18 of the things the panel doesn't know is that in December,  
19 I guess it was, I went over the OEHHA document, OEHHA  
20 findings, and I went over the panel's findings, the draft  
21 of the panel's findings, and in the draft of the panel's  
22 findings, the numbers between that draft and the OEHHA  
23 draft were quite different. There was not consistency.

24 So we went back and tried to make the  
25 numbers consistent, and we found one place this morning



1 where the numbers are still not consistent, and George  
2 said that he would go back and make sure that in this  
3 case the problem was -- is with the OEHHA findings. And  
4 so George said that he would bring the OEHHA findings to  
5 be consistent with our findings.

6 Right now our findings have one difference  
7 in -- numerically with OEHHA and so we're going to  
8 end -- we're going to try and end up that the OEHHA  
9 findings on pesticides and our findings are consistent  
10 with one another or unless we have a major disagreement,  
11 which I would assume that we would resolve this.

12 So that's the one place where there was a  
13 comment. Now, it was my understanding that Paul Blanc  
14 had a comment or two.

15 DR. BLANC: Yeah. At what point do you  
16 want to --

17 CHAIRMAN FROINES: Let's start. We can go  
18 around the room --

19 DR. BLANC: Okay. Well, there were a few  
20 places where I think the wording should be clarified, and  
21 I want you to correct me if I'm wrong in my  
22 misunderstanding.

23 So just to go through the points as I see  
24 where word changes would help the clarification, on point  
25 number two, "Environmental Fate and Exposure," I assume



1     implication when the statement is made "Fresno County  
2     receives the largest usage of DEF of California  
3     counties."

4                     That's the largest usage in pounds? In  
5     total pounds? I think it would be helpful to say which  
6     county has the largest per capita usage as well. Unless  
7     it's a different county. Unless it's the same county.

8                     And then I would say it has the largest  
9     usage in pounds and per capita because we've had other  
10    exposures where the pound usage may be less than a  
11    particular county, but it's a very low -- you know,  
12    there's not very many people in the county, and  
13    geographically it's not that big.

14                    MR. GOSSELIN: You're talking pounds per  
15    capita population?

16                    DR. BLANC: Yeah. I mean to suggest that  
17    really Fresno is -- you know, is the big issue. But I  
18    don't know, for example, whether or not, you know,  
19    Imperial County -- it may be actually per capita more  
20    exposure there, if you did it that way.

21                    DR. FRIEDMAN: What would that mean,  
22    though? In other words, if the county was sparsely  
23    populated, the compound may be safer because it's being  
24    put far away from the people. Yet you'll get a higher  
25    per capita exposure because there's fewer people that



1 you're dividing the pounds by. So I'm not sure that  
2 that's a meaningful addition.

3 DR. BLANC: Well, it's probably as  
4 meaningful as saying that most of it is used in Fresno  
5 County. I don't know what that means either. Maybe just  
6 deleting the sentence then, if we don't want to go down  
7 that pathway.

8 The implication singling out Fresno says  
9 that that's where the public health issue is biggest, and  
10 I'm not sure that's the truth -- I mean the implication  
11 we want to make.

12 DR. GLANTZ: Paul is shaking his head.  
13 What did you want to say?

14 MR. GOSSELIN: I think the only thing we  
15 wanted to point out in that was where the predominant  
16 amount of use occurs, and in the report we listed all the  
17 counties that had usage.

18 The one thing -- the way we handle this is,  
19 if we do have an unacceptable exposure based upon, in  
20 this case, data that would have come from the high-use  
21 counties, Kern and Fresno -- I think it was Kern and  
22 Fresno -- those exposures would be used in any of the  
23 counties that DEF is used.

24 So it's not -- we don't base this upon  
25 numbers of people being exposed. It would apply



1       irrespective to that across the state.

2                   DR. BLANC: Well, maybe a better way of  
3 saying it would be "pounds per square mile of county."  
4 Maybe that's the way --

5                   DR. FRIEDMAN: Yeah. I think that would  
6 make much more sense.

7                   MR. GOSSELIN: I would still say Fresno  
8 would probably --

9                   DR. BLANC: My second point --

10                   CHAIRMAN FROINES: Wait. Wait.  
11 One -- these are our findings. So we have in or out  
12 whatever we want. These are not DPR findings.

13                   DR. BLANC: Well, if you could get the  
14 information, what I would prefer is a sentence that says  
15 "Fresno County receives the largest usage of DEF in  
16 pounds of California counties; County "X" receives the  
17 largest pounds per square mile of area."

18                   DR. BUYS: Even that is semimeaningless  
19 because it's really sprayed on crop lands, and wherever  
20 its use is, is really --

21                   DR. BLANC: Well, then I would just --

22                   DR. BUYS: I could be confined to  
23 even -- it's undoubtedly fine in much more specific  
24 areas.

25                   DR. BLANC: Well, then I would just delete



1 the sentence about Fresno County then.

2 DR. BYUS: So would I.

3 CHAIRMAN FROINES: My time estimates are  
4 really going to go to hell if we --

5 DR. BLANC: Let's just delete the sentence  
6 on Fresno.

7 DR. BYUS: You're absolutely right, what  
8 you're saying.

9 DR. BLANC: My second point is that --

10 DR. GLANTZ: Who agreed to that?

11 CHAIRMAN FROINES: I don't know.

12 DR. BLANC: Is there any dissent? Hearing  
13 no dissent, the sentence is deleted. The second is point  
14 three, which currently states "DEF breaks down (e.g.,  
15 photooxidizes) to n-butyl mercaptan," et cetera, et  
16 cetera.

17 Now, my understanding is that DEF is first  
18 activated -- although the exact chemical nature of the  
19 activated moiety is not clear -- and then breaks down to  
20 the n-butyl mercaptan, and this becomes confusing  
21 elsewhere in the document.

22 So I would suggest the following wording,  
23 if it's consistent with the science, which would be "DEF  
24 oxidizes to an active moiety which then breaks down"  
25 deleting the parenthetic "e.g., photooxidizes"



1 to -- because I don't think that's how you get to the  
2 n-butyl mercaptan.

3 DR. ATKINSON: Is that known? I haven't  
4 seen any data on the atmospheric loss processes of DEF.  
5 Are there any?

6 MR. GOSSELIN: I don't believe so. Because  
7 that gets back to -- in the human studies that there  
8 wasn't any data nailing down the sulfoxide active moiety.

9 DR. ATKINSON: Okay.

10 MR. GOSSELIN: But it's -- because of the  
11 other studies, they know that there is that intermediate  
12 one that is the cholinesterase inhibiting moiety. It  
13 just hasn't been analyzed and characterized.

14 DR. ATKINSON: In the atmosphere does it  
15 exist as a gas, or is it particle-associated? DEF?

16 MR. GOSSELIN: I believe it's a particle.

17 CHAIRMAN FROINES: Isn't it an aerosol?

18 DR. FUCALORO: Its boiling point is 150  
19 degrees at three-tenths of a millimeter mercury.

20 DR. ATKINSON: Yes. It's what?  
21 Three-tenths at 150 degrees?

22 DR. FUCALORO: Millimeter mercury. 150  
23 degrees, yes.

24 DR. ATKINSON: Yeah. And I would -- my  
25 guess is that that means it's going to be at least



1 partially in the gas phase. In the gas phase it will  
2 react with a lifetime of about an hour with OH. Nobody's  
3 ever looked at it. You might expect the oxon to be one  
4 of the products.

5 So I think you need a whole new section on  
6 what happens to this stuff in the atmosphere. There are  
7 data on other organophosphorus compounds, somewhat  
8 simpler ones, both kinetics and products, and some of  
9 that should be in.

10 CHAIRMAN FROINES: What do we do with  
11 paragraph 3?

12 DR. ATKINSON: Paragraph 3 means rewrite  
13 it.

14 DR. GLANTZ: We were kind of hoping to  
15 rewrite it right now. This has been going on for a long  
16 time.

17 MR. GOSSELIN: Actually, in the  
18 environmental phase section on -- I don't know if people  
19 brought their volume. But on page 13 --

20 DR. ATKINSON: 13 of what? Okay. The  
21 document.

22 CHAIRMAN FROINES: I think we should delete  
23 paragraph 3. Because in the first place, we are -- we  
24 have in here essentially a -- the implication of  
25 paragraph 3 is associated with its atmospheric chemistry.



1                   Then later we're going to get into  
2 metabolism, and the question is, if we want to put  
3 something about -- in about the fate of DEF, we better  
4 know what that is we want to say.

5                   DR. GLANTZ: Yeah. But as I recall, wasn't  
6 the issue of the n-butyl mercaptan important because  
7 that's potentially very toxic? Don't we want to point  
8 out that, you know, the DEF turns into that somewhere in  
9 here?

10                  DR. FRIEDMAN: Can we do it in sort of a  
11 general way that doesn't conflict with other knowledge?  
12 Just so that it becomes converted to without talking  
13 about what its --

14                  DR. ATKINSON: But does anybody know  
15 whether it's converted to that in atmosphere, or this is  
16 just the environment in general?

17                  CHAIRMAN FROINES: I think that's what it  
18 means.

19                  DR. GLANTZ: What were you going to say,  
20 Paul?

21                  MR. GOSSELIN: I'm just trying to read  
22 through the environmental fate section in the studies.  
23 They did from a couple studies monitoring DEF -- did pick  
24 up DEF and the n-butyl mercaptan and n-butyl disulfide.

25                  And so I think there was some body of



1 evidence that, yeah, DEF did convert down and break down  
2 to those --

3 DR. ATKINSON: So these are field studies.

4 MR. GOSSELIN: Uh-huh.

5 DR. ATKINSON: Nobody has done any lab  
6 studies on it.

7 DR. GLANTZ: Do we have any more copies --

8 MR. GOSSELIN: There was some laboratory  
9 experiments in 1980. Photooxidation to --

10 CHAIRMAN FROINES: Well --

11 MR. GOSSELIN: Yes. Within 11 hours  
12 n-butyl mercaptan and n-butyl disulfide.

13 CHAIRMAN FROINES: What I would suggest is  
14 that the issue of the atmospheric chemistry and breakdown  
15 products of DEF we leave -- hold over and Roger take a  
16 look at it and suggest some language --

17 DR. ATKINSON: I will.

18 CHAIRMAN FROINES: Because right now we're  
19 trying to do something that we're not prepared to do, and  
20 we don't even have documents in front of us. I hate to  
21 put it off because it would be nice to bring this to  
22 closure. But I think Roger is raising important points  
23 and unless somebody can easily --

24 DR. ATKINSON: I'll look at that.

25 CHAIRMAN FROINES: See, the problem we have



1 here is we have three people, myself and Paul and Roger,  
2 who were not at the October meeting when this issue came  
3 up and so there are gaps that I think will continue to  
4 emerge.

5 DR. BLANC: Well, I'm not sure that we need  
6 to hold it over because, you know, Roger is focusing on  
7 the -- as if this just referred to the atmosphere, what  
8 goes on in the atmosphere. This is a more general issue  
9 of the total environment.

10 I think we could have wording that would  
11 subsume the important issues.

12 DR. GLANTZ: Yeah. What about just  
13 deleting "e.g. photooxidizes"?

14 DR. BLANC: Well, I think the two  
15 things -- that, one, taking rid of that parenthetic  
16 statement and the other is making clear in the same  
17 paragraph that -- because, when I read this, I was  
18 confused by it.

19 The DEF is oxidized to an active moiety.  
20 Just so that that's clear and up front and then say  
21 either DEF directly or through that oxidated moiety can  
22 be broken down to these other two chemicals which are  
23 also important in terms of their effects.

24 Because what was confusing about -- I don't  
25 care whether it does other things too, but all the things



1 that are discussed in the findings either refer to DEF  
2 using that as shorthand for actually what is its active  
3 moiety, which is not clear what it is, or we're talking  
4 about these two other breakdown products.

5 But the way that number three is currently  
6 worded, it confused me later on when we started about it  
7 being oxidized to an active moiety.

8 CHAIRMAN FROINES: But we're talking about  
9 two different issues. We're talking about metabolic  
10 activation in vivo, and we're talking about environmental  
11 chemistry, and those are different issues.

12 You see, the active moiety is not produced  
13 in -- an active moiety may be produced in the atmosphere,  
14 but the point is that the compound -- DEF is bioactivated  
15 in the liver presumably or wherever, and that's the other  
16 side of this coin.

17 DR. BLANC: I see.

18 MR. GOSSELIN: I think the main point in 3  
19 is that still may -- what's still important is that there  
20 is data to show, field and laboratory, that DEF does  
21 break down by, you know --

22 DR. BLANC: By whatever means.

23 MR. GOSSELIN: -- by whatever means to  
24 n-butyl mercaptan and n-butyl disulfide. Those two  
25 components besides DEF may pose some health --

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1 DR. BLANC: Okay. Then I have another  
2 suggestion that I think will solve all these problems.  
3 It's pretty simple. One is take out the parenthetic  
4 comment "e.g., photooxidizes" because some of it breaks  
5 down through hydrolysis in the environment so that we  
6 shouldn't say that.

7 And simply inserting the phrase on the  
8 second sentence where it says "Therefore, the health  
9 effects associated with the use of DEF include the direct  
10 effects of DEF (through its active metabolite) and may  
11 also include the effects of NBM and NBD."

12 Because that would highlight to the reader  
13 of that issue. Because otherwise it was quite confusing  
14 later on when suddenly we were talking about the active  
15 moiety of DEF.

16 DR. ATKINSON: I think it would be best to  
17 put 3 as DEF is transformed in the environment, at least  
18 in part, to the mercaptan and on dimethyl sulfide.

19 DR. BLANC: Okay. That's fine with me.  
20 Did you get that wording, John?

21 CHAIRMAN FROINES: Yeah. But I'm relying  
22 on Bill to get the wording.

23 DR. BLANC: Bill, it would read "DEF is  
24 transformed in the environment, at least in part,"  
25 delete parenthetic phrase, "to" -- blah, blah, blah,

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1    blah. "Therefore, the health effects associated with the  
2    use of DEF include the direct effects of DEF (through its  
3    active metabolite) and may also include the effects of  
4    NBM and NBD."

5                   CHAIRMAN FROINES: I think that takes care  
6    of it, but the question still begging is, is there an  
7    atmospheric transformation product of DEF that may itself  
8    have toxicity in it?

9                   So I would still ask Roger to look at that,  
10   and we can add that if that's the case. So that  
11   the -- there are still really the two issues.

12                  DR. BLANC: Yeah. I agree with that.  
13   My -- should I keep going on my --

14                  CHAIRMAN FROINES: Yeah, please.

15                  DR. BLANC: Point number -- skipping to  
16   point number 15. "Symptoms reported by people  
17   potentially exposed to DEF through occupational exposure  
18   or through ambient air near DEF-sprayed fields included  
19   ocular and respiratory irritation (e.g." -- blah, blah,  
20   blah.

21                  And the current phraseology is "and  
22   apparent cholinergic effects," parenthesis -- blah, blah,  
23   blah, blah. And I would say -- I would delete the word  
24   "apparent" because I don't know what that means there,  
25   and I would clarify by saying "and cholinergic effects

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1 consistent with acetylcholinesterase inhibition." And  
2 then the rest of it.

3 DR. GLANTZ: Then leave the list of the  
4 symptoms.

5 DR. BLANC: Yes. That's fine. And on  
6 number 16, the next one, I would delete the word  
7 "symptoms resembling" and replace it with "findings  
8 consistent with" so that it would say "One case report  
9 describes the development of findings consistent with  
10 OPIDN."

11 DR. FRIEDMAN: Is OPIDN ever defined before  
12 that? Is that abbreviation --

13 MR. GOSSELIN: Number 9.

14 DR. BLANC: Again, and the next one, number  
15 17, I know that you've already changed the wording  
16 but -- based on the bold -- but actually would suggest a  
17 different wording so the last sentence would say "The  
18 inhibition of neural" -- it should be -- it should be  
19 actually just either "NTE" or "neuro-target esterase."  
20 So I don't know why the word "neural" is there. But  
21 the --

22 CHAIRMAN FROINES: "Neural" should go out?

23 DR. BLANC: Yeah. Because you never  
24 measure in the nerve. You measure, I think, usually in  
25 the lymphocytes or some other marker, but "inhibition of

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1 NTE in sensitive species is a biomarker that correlates  
2 with the induction of OPIDN" would be a better wording, I  
3 think, rather than "may be one of the factors."

4 Because I don't think there's evidence that  
5 it's the factor. It's just a good mark for it would be a  
6 more --

7 CHAIRMAN FROINES: We talked about that  
8 this morning, and that language is better. Say it again.

9 DR. BLANC: So it would say "The inhibition  
10 of NTE in sensitive species is a biomarker that  
11 correlates with the induction of OPIDN." So those were  
12 the word changes that I caught at least so far.

13 CHAIRMAN FROINES: Gary? Tony?

14 DR. FUCALORO: Just -- environmental fate.  
15 I just have a question.

16 REPORTER: Move up to your microphone.

17 DR. FUCALORO: Sorry. Looking at the  
18 document "Environmental Fate," dated November, '98, I  
19 just don't understand this entry at the bottom  
20 the -- "an ultimate property ultraviolet  
21 absorbance" -- which I think is spelled wrong -- "less  
22 than 50 at 300 nanometers." I mean I don't understand  
23 what that means.

24 DR. ATKINSON: It means "units," for one  
25 thing.

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1 DR. FUCALORO: I mean 50 -- if it's -- I  
2 mean if it's absorbance units, I mean, how can  
3 you think it's -- I mean 50 is a number -- you can't  
4 measure 50 absorbance units by no machine I know. I mean  
5 it's not even -- I don't quite understand that, and I  
6 think absorbance is spelled with an "A," isn't it?  
7 B-e -- b-a-n-c-e?

8 DR. ATKINSON: Absorbance?

9 DR. FUCALORO: Absorbance. But  
10 that's --

11 CHAIRMAN FROINES: No. It's "E," isn't it?

12 DR. ATKINSON: I don't --

13 DR. FUCALORO: Could be.

14 MR. GOSSELIN: We can go back and --

15 DR. FUCALORO: I don't understand 50. I  
16 mean, you know, absorbance is a -- if you have an  
17 absorbance of 2, it means that that 1 part in 100 gets  
18 through. If you have an absorbance of light, if you have  
19 an absorbance of 3, it's 1 part in 1,000. There's no  
20 machine that can measure an absorbance of 50 or 20 or 10,  
21 as a matter of fact.

22 DR. ATKINSON: So what you need is the  
23 absorption cross-section and the correct units.

24 DR. FUCALORO: Right. Which would have to  
25 have been units. Absorbance is unit less because it's in

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1 a log as an exponent.

2 CHAIRMAN FROINES: I just think we're going  
3 to have a lot of fun with Roger on this committee. I'm  
4 looking forward to it. Craig?

5 DR. BYUS: Yeah. I just think it's nicely  
6 done. I'm just reading over to make sure that this whole  
7 issue of the serum cholinesterase inhibition and the  
8 calculation of NOELs is adequately illuminated here  
9 relative to the actual appearance of symptoms.

10 It appears to me that it is. I mean are  
11 the lead people happy with this? I mean this is  
12 the -- you know -- 19. It's this whole issue of the  
13 subchronic identified NOEL of 2.4 milligrams per meter  
14 squared for DEF based on blood cholinesterase inhibition  
15 is the lowest number, and I -- so what -- the last  
16 sentence in this is that -- so what did you do then?

17 The adjusted NOAEL as noted for  
18 the -- could you explain to me the last sentence? What  
19 that means?

20 MR. GOSSELIN: The adjusted NOAEL?

21 DR. BYUS: Yeah.

22 MR. GOSSELIN: That's taking --

23 DR. BYUS: In other words, how did you  
24 go -- you got the NOEL of 2.4 and the NOAEL of 12.2 and  
25 then you now have the adjusted NOAEL of 4.3. Just

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1 explain to me --

2 MR. GOSSELIN: It's using the respiration  
3 differences. We have standards for the rats and then we  
4 have standards for adults and standards for children, and  
5 we calculate both scenarios.

6 So this is adjusting -- and I think what  
7 this reference is just the adjusted NOAEL that was based  
8 upon the six-year-old child, which is -- comes out to be  
9 the lowest adjusted NOAEL compared to adults which has  
10 been what we would derive the assessment for general  
11 population.

12 DR. BLANC: And at the October meeting  
13 somebody maybe can clue me in as to -- and I apologize  
14 for not being more familiar with the transcript of that  
15 meeting -- the level of comfort on this committee for  
16 accepting serum cholinesterase as being a marker of an  
17 effect which was not an adverse effect.

18 DR. BYUS: I brought this up with -- this  
19 was at this meeting. This was one of the big points of  
20 discussions, and it's still perhaps. It doesn't affect  
21 the methyl parathion as much because the number they come  
22 up with on other studies is actually lower than the serum  
23 cholinesterase value.

24 So in a sense it really doesn't matter, at  
25 least so far. Now, they're still calculating and still

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1 getting more information, but so far the number they  
2 chose is lower than the one where the serum  
3 cholinesterase -- so it's not an issue.

4 But it still is an issue here. My personal  
5 feeling is that, if you're inhibiting your serum  
6 cholinesterase, this is indicative of your brain  
7 cholinesterase must be inhibited also. I mean it's  
8 simply a matter of affinities in the chemical.

9 There's no way you could only inhibit serum  
10 cholinesterase without inhibiting some cholinesterase in  
11 your central nervous system. Now, whether you see some  
12 adverse effect of that -- in other words, whether that  
13 shows up as lacrimation or these other cholinesterase  
14 symptoms is another question.

15 But in my opinion, you don't want to walk  
16 around with your serum cholinesterase inhibited by 20 to  
17 30 percent. That's indicative to me of some significant  
18 level of exposure. Your brain cholinesterase has to be  
19 inhibited.

20 Now, whether you see symptoms or not is  
21 another question. There appears to be some threshold  
22 effect -- threshold by which you see these symptoms. And  
23 we're going to hopefully deal with this question, I hope,  
24 in this workshop. Because it's a very -- apparently the  
25 EPA -- now, correct me if I'm wrong, Paul. The EPA

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1 has -- in the past has decided to not to use serum  
2 cholinesterase as an --

3 MR. GOSSELIN: No. They do.

4 DR. BYUS: But now they've changed it. I  
5 said in the past. But now they've changed their mind and  
6 are calculating the risk factors based on the inhibition  
7 of serum cholinesterase.

8 CHAIRMAN FROINES: Paul's asking the  
9 question is plasma cholinesterase inhibition an NOAEL or  
10 an NOEL? I think that's his question.

11 DR. BYUS: I'm not sure --

12 CHAIRMAN FROINES: The U.S. Supreme Court  
13 is very clear that clinical symptoms are not the criteria  
14 for defining adverse effects. The inhibition of enzymes  
15 in the -- with -- lead in the association with hemoglobin  
16 levels is an adverse effect.

17 The reduction of motor nerve conduction  
18 velocity is an adverse effect. Enzyme inhibition is an  
19 adverse effect so that one cannot simply say that you  
20 need to -- according to the U. S. Supreme Court, you do  
21 not have to have clinical symptoms to define adversity.

22 DR. BLANC: Well, Paul --

23 DR. BYUS: My point as a biochemist here is  
24 that inhibition of brain cholinesterase would be  
25 considered an adverse effect, but you can't measure that

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1 in individuals without -- certainly in humans without  
2 taking biopsies of their brain or what you can't do. You  
3 can do it in animals, but you can't do it in humans.

4 But you can take serum levels, and you can  
5 measure the serum cholinesterase, which is a different  
6 enzyme, but it has many of the same characteristics  
7 as -- of the brain enzyme, and it has a certain relative  
8 affinity for this chemical as relative and very near what  
9 the brain enzyme is.

10 So if you -- my contention is that, if your  
11 serum cholinesterase is inhibited, your brain  
12 cholinesterase must be inhibited by some factor. Maybe  
13 not by quite as much but by some factor. It's just that  
14 you can't measure it.

15 So what they're saying is you can't measure  
16 it. You may not see symptoms either. But you have been  
17 affected.

18 DR. FUCALORO: But you're saying the serum  
19 cholinesterase is a surrogate for measuring enzyme -- the  
20 brain. But also the issue, as I recall, was that serum  
21 cholinesterase inhibition was also a bad effect in and of  
22 itself; right? An adverse effect in and of itself, and I  
23 guess once Peter brought up some case --

24 DR. BYUS: The further statement that was  
25 made -- I don't mean to bring up my stuff again, but

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1 since you weren't there, the DPR said -- somebody  
2 on -- the staff person said that there's no known  
3 function of serum cholinesterase, and that's not true.  
4 It does have known functions.

5 It does function, for example, in some drug  
6 clearing reactions and so, if you inhibit that enzyme,  
7 you're taking certain drugs, you may have had an adverse  
8 effect on top of that. It does have known functions.  
9 That is clear.

10 It may not have known functions in sort of  
11 the normal etiology of an individual, but certainly, if  
12 you're exposed to other drugs under certain situations,  
13 yes, and if this enzyme were inhibited by  
14 organophosphates, you could have additional adverse  
15 effects. That's the point there.

16 DR. FUCALORO: Yeah. I just wanted to  
17 mention that. Because it was mentioned the last time.

18 DR. BYUS: Exactly. And so I mean this is  
19 what we went over and discussed, and this is one topic  
20 that we would hope to explore in some detail in this  
21 workshop to really -- and my understanding of -- I had to  
22 come up to a lot of speed on this topic. But that's kind  
23 of my feeling, what I just said to you. The last --

24 CHAIRMAN FROINES: Comments on that?

25 DR. BLANC: Well, I have a suggestion

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1 unless there's a statutory requirement to a different  
2 effect and so let me ask my question first. In our  
3 findings, are we required to comment on both the no  
4 effect level and a no adverse effect level?

5 CHAIRMAN FROINES: We don't have -- there  
6 are no criteria for our findings.

7 DR. BLANC: Then I suggest that our findings  
8 address the no effect level based on 2.4 milligrams per  
9 meter and that we make the calculation for the adjusted  
10 no effect level rather than the no adverse effect level  
11 for the 24-hour respiratory rate in the six-year-old  
12 child, and I assume that the ratio would be the same so  
13 that the ratio 4.3 to 12.2 times 2.4 would give us the no  
14 effect level for the six-year-old child.

15 And let us not -- I think it's -- as a  
16 procedural matter it's not fair for me to come in at this  
17 late date and reargue the issue about whether we should  
18 also be calling that a no effect level. Let's just in  
19 our findings focus on the no effect level rather than the  
20 no adverse effect level.

21 CHAIRMAN FROINES: So are you suggesting  
22 that we use the 2.4 milligram per cubic meter in  
23 calculating the 24-hour --

24 DR. BLANC: Yes.

25 CHAIRMAN FROINES: -- calculating the

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1 adjusted NOEL?

2 DR. BLANC: Yes. And let's just not  
3 address a NOAEL. Let's just not --

4 DR. BYUS: This is what Stan  
5 originally -- I don't --

6 DR. BLANC: Because I'll tell you --

7 DR. BYUS: -- suggested.

8 DR. BLANC: -- I could not support  
9 this -- I can't support suggesting that the implication  
10 here is that -- the explicit implication is that  
11 acetylcholinesterase inhibition is not an adverse effect.

12 DR. BYUS: Serum.

13 DR. BLANC: Serum. And I don't accept that  
14 argument because I think it is as clearly a marker of an  
15 adverse effect as the neuro-target esterase is a  
16 correlate of risk of delayed peripheral neuropathy for  
17 exactly the same reasons.

18 DR. FRIEDMAN: Which adverse effect would  
19 you -- what does -- which adverse effect does it  
20 represent?

21 DR. BLANC: It represents all the  
22 cholinergic adverse effects of having your cholinesterase  
23 inhibited at your nerve endings even though you're  
24 measuring it in the blood and in your CNS as well.

25 Both of which we can't measure. We never

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1 measure nerve ending acetylcholinesterase. We always use  
2 either RBC or serum cholinesterase. RBC or serum  
3 cholinesterase -- and as our marker of the presumed  
4 effect at the nerve endings.

5 DR. BYUS: You can measure it with animals.  
6 It's measured in some of the animal studies --

7 DR. BLANC: The brain.

8 DR. BYUS: Right. Not at the nerve endings  
9 but at the brain.

10 DR. BLANC: Right.

11 DR. FRIEDMAN: Does this get across the  
12 blood brain barrier?

13 DR. FUCALORO: That would be the key;  
14 right?

15 DR. BLANC: Almost all of these do. That's  
16 why -- one of the reasons why they --

17 DR. BYUS: Peripheral as well.

18 DR. BLANC: Most of the clinical things  
19 that we follow are effects that -- at the peripheral  
20 nerves but --

21 CHAIRMAN FROINES: Autonomic?

22 DR. BLANC: Autonomic and the neuromuscular  
23 junction, but there clearly are CNS effects as well.

24 DR. FUCALORO: Paul, can I ask you a  
25 question. I think I'm understanding what you're

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1 suggesting. Your concern with the NOEL -- because you  
2 would actually like to see that as an NOAEL; correct?

3 DR. BLANC: Right.

4 DR. FUCALORO: But as a compromise you're  
5 willing to -- you're just getting rid of some of the  
6 vocabulary but having the same quantitative conclusions?

7 DR. BLANC: No. The quantitative  
8 conclusion, we would be making the quantitative  
9 calculation for the NOEL that's been made for the  
10 NOAEL --

11 DR. FUCALORO: So we would have a ratio of  
12 6 to 1 or something like that.

13 DR. BLANC: Yeah. I don't know what -- if  
14 somebody would divide -- no. It would be -- well, it  
15 would be something like a factor of 3 less than 2.4  
16 because the ratio 4.3 to 12.2 times 2.4 must come out to  
17 be .8 or something. I don't know.

18 CHAIRMAN FROINES: What we would be  
19 essentially saying, Tony, is, if you look at that, you  
20 see the sentence that starts out "The report identified  
21 an acute air." We would say "The panel has identified an  
22 acute air NOAEL of 2.4 milligrams per" --

23 DR. FUCALORO: I do understand, yeah.

24 DR. BLANC: Well, I was just going to say  
25 NOEL, and I wouldn't -- I would be willing to go even

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1 further, but as a compromise, I'm willing just to refer  
2 to the NOEL.

3 CHAIRMAN FROINES: But Paul, you can't have  
4 it both ways. You either call it an NOAEL or otherwise  
5 you can't use it for this calculation.

6 DR. BLANC: Why?

7 DR. BYUS: The crux of the question is do  
8 you believe inhibition of serum cholinesterase is an  
9 adverse effect or not?

10 DR. BLANC: Yes, I do. But --

11 DR. BYUS: You either do or you don't. And  
12 I certainly -- I mean I do.

13 DR. BLANC: And I do.

14 DR. BYUS: And you do.

15 DR. BLANC: But I wasn't at the October  
16 meeting.

17 CHAIRMAN FROINES: But the point is that  
18 your compromise -- you can't -- your compromise is trying  
19 to -- it doesn't really work. You have to say the  
20 adjusted NOAEL is this value of 2.4 adjusted for the  
21 respiratory rate of .68.

22 DR. BLANC: Why can't you just say the  
23 adjusted NOEL is this?

24 CHAIRMAN FROINES: Well, I think you  
25 should -- if we're going to use 2.4, because it's an

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1 adverse effect level, we should call it an adverse effect  
2 level. We shouldn't try and call it a no effect level  
3 but treat it as an adverse effect level.

4 DR. BLANC: I see.

5 DR. GLANTZ: I think then, what you should  
6 do -- because you do want to have this document or the  
7 findings make some sense in the context of the report.  
8 And we don't want to reopen the report. I don't think.  
9 Unless Paul wants to.

10 MR. GOSSELIN: No.

11 DR. GLANTZ: So what I would suggest is to  
12 rewrite this slightly, and somewhere -- I mean you talk  
13 about the report identified this -- da, da, da. And then  
14 somewhere I think we should insert a sentence that says  
15 "The panel believes inhibition of blood alcohol  
16 cholinesterase is an adverse effect."

17 DR. BYUS: I agree.

18 DR. FUCALORO: I think that's good.

19 DR. GLANTZ: And then say, "Based on that,  
20 we" -- "the panel differs with the report and says that  
21 the NOAEL should be" -- whatever. The 2.4.

22 DR. BLANC: That's fine. I would be  
23 comfortable with that.

24 DR. GLANTZ: And then continue on --

25 DR. BLANC: I would be comfortable with

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1 that.

2 CHAIRMAN FROINES: Is everybody comfortable  
3 with that?

4 DR. GLANTZ: That way someone who looks at  
5 this and looks at the report, they will at least  
6 make -- they'll understand where these different  
7 numbers --

8 CHAIRMAN FROINES: Can we do this -- Bill?  
9 If we write the language -- and you and I can do this  
10 after the meeting -- we can then circulate it -- can we  
11 circulate it to the panel, and if everybody buys off, we  
12 can just go ahead and send it to Paul and say "Here we  
13 are"?

14 MR. LOCKETT: Yeah.

15 CHAIRMAN FROINES: So we don't have to take  
16 the -- I'd rather not carry this over to another meeting.

17 MR. LOCKETT: What the panel is agreeing  
18 on, they are agreeing on. And then we're just  
19 memorializing it, and they're confirming what we  
20 memorialized.

21 DR. BLANC: Then I would recommend the same  
22 thing with Section 19, which is parallel.

23 MR. GOSSELIN: And if I was going to -- I  
24 was going to add too I was going through the findings.  
25 They do calculate out both values that, if you were going

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1 to insert that finding on this, that it could be sort of  
2 at the end and generalized all the way through.

3 And that's just sort of a procedural  
4 suggestion. Because at the end, both values are  
5 calculated out, and if you want to put your perspective  
6 on it, you can carry it all the way back.

7 CHAIRMAN FROINES: I'll do it.

8 DR. BLANC: You'll have to go through.  
9 You'll have to modify point 20 in a similar way because  
10 it also derives from the same numbers.

11 DR. FUCALORO: Using just a completely  
12 parallel modification; right?

13 DR. BLANC: Right. And --

14 DR. FUCALORO: Then we can rely upon you  
15 and Bill to do that.

16 CHAIRMAN FROINES: Well, you'll --

17 DR. FUCALORO: I'll take a look at it and  
18 convince myself that's true, but I think --

19 CHAIRMAN FROINES: Everybody will see it.  
20 So --

21 DR. GLANTZ: And when you show it to us,  
22 could you do it like the changes highlighted for those of  
23 us with failing short-term memories?

24 DR. FUCALORO: Proving that it does make  
25 the blood brain barrier --

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1 DR. ALEXEEFF: George Alexeeff. If I could  
2 just make a comment. I just wanted to clarify something  
3 in my mind just so that -- and maybe to help clarify the  
4 panel, but it seemed to me, from what was being said, is  
5 that what we have is serum cholinesterase, which we  
6 believe is indicative that probably there's some other  
7 cholinesterase inhibition occurring even though we can't  
8 measure it at this time at important sites.

9 So -- but the serum cholinesterase itself  
10 is not in and of itself adverse. It's simply reflecting  
11 that we think there's other potentially adverse effects  
12 happening. That's what I wanted to clarify.

13 DR. BYUS: No. In fact, I started doing a  
14 literature search on this, started to work up this  
15 question, and we are going to hopefully deal with this as  
16 a topic in the workshop symposium. It's a very -- it's  
17 complex, but it's not that complex.

18 The point is serum cholinesterase, I think,  
19 from my reading in the literature looks like it could be  
20 adverse itself but that since -- and, again, the example  
21 I use is it's used in the metabolism of some drugs. And  
22 so it would be like cocaine.

23 I just pick that as an example, but it's  
24 used so that, if you were exposed -- I could be shown  
25 wrong this by an expert, but if you had been exposed

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1 to -- if your serum cholinesterase was altered, inhibited  
2 and you took cocaine, it would -- you know, the levels of  
3 cocaine would reach a higher value because you're  
4 inhibiting metabolism, and you could have toxic effects.  
5 You could even die.

6                   There's other examples of this too. Other  
7 drugs, other therapeutic drugs that are given are  
8 metabolized by this enzyme, and you calculate drug  
9 dosages based on metabolic rates, you know, half-life.

10                   So that if you inhibited that by 50  
11 percent, the half-life may go up by 50 percent. You wind  
12 up with doubling the therapeutic dose which puts you way  
13 up into the toxic range.

14                   So yes. In the normal etiology of things,  
15 people walking around, it may be not a problem. But it  
16 is in and of -- you know, because you take other drugs  
17 both illicitly and therapeutically.

18                   CHAIRMAN FROINES: I argue that it at least  
19 fulfills the criteria of an adverse effect as a surrogate  
20 in the same way that a DNA adduct is a surrogate for  
21 events that may occur subsequent downstream.

22                   DR. BYUS: And I cannot see how that cannot  
23 be a case until somebody who's an expert shows me --

24                   CHAIRMAN FROINES: Paul's right. The  
25 neurotoxic esterase is, in fact, a marker. It's not

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1 a -- well, we talked about that earlier anyway. So  
2 that -- you comfortable -- you folks comfortable with  
3 that? Nevermind. I didn't mean to open the barn door.  
4 Let's just go on. Let's get the cows back in the  
5 pasture.

6 DR. FUCALORO: Out of the pasture.

7 CHAIRMAN FROINES: Out of the pasture.

8 DR. BLANC: Can I ask about point 25? In  
9 the last sentence, which reads "This information could be  
10 used to calculate seasonal 'air concentration standards'  
11 to protect against these health effects."

12 What would be the implication -- this is a  
13 question for the chair -- of changing the word "could" to  
14 "should"?

15 CHAIRMAN FROINES: That's our prerogative.

16 DR. BLANC: Would then something happen if  
17 we did that? Would there be a response? An appendix?

18 A --

19 CHAIRMAN FROINES: No. It's advisory to  
20 the --

21 DR. BLANC: Well, then --

22 CHAIRMAN FROINES: -- chair.

23 DR. BLANC: I think we should -- it should  
24 be changed to "should," I think.

25 DR. BYUS: Does anybody know that study

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1 well enough? I mean this is -- now you're saying this  
2 based on this one study. I don't -- I remember reading  
3 about it, but I don't remember it enough to say we should  
4 use it.

5                   You know, that's -- if we're going to say  
6 that, we better know what we're talking about with that  
7 specific study.

8                   CHAIRMAN FROINES: Well, I think if  
9 we -- if we write findings based on those -- these  
10 conclusions, then in fact either we stand behind them or  
11 we have to find some other bases to come up with NOELs.

12                   I mean we're saying the NOEL is "X" value  
13 based on this literature and then you can't go back and  
14 say "Well, I'm not sure the study's any good."

15                   This is the academic approach where you  
16 don't want to, you know, make it too --

17                   DR. GLANTZ: I think we should say  
18 "should." The other thing I think you should do, when  
19 you're editing this to reflect this discussion --

20                   DR. FUCALORO: Actually, Stan, you said,  
21 "the other thing I think you could do."

22                   DR. GLANTZ: I think you should do is say  
23 "should." Okay. And the other thing that I think you  
24 should do, when you're editing this in light of this  
25 discussion, is the way the document is currently written,

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1 it keeps doing the old NOAEL and the NOEL.

2 And we're saying that what used to be  
3 called the NOEL should be called the NOAEL. So I think  
4 that, after we've made that statement, we should drop the  
5 references to the higher number.

6 DR. BLANC: In point 25.

7 DR. GLANTZ: Yeah.

8 DR. FUCALORO: That's fair.

9 DR. GLANTZ: For consistency.

10 DR. BLANC: Do you understand that point?

11 CHAIRMAN FROINES: Yes.

12 DR. GLANTZ: He should.

13 CHAIRMAN FROINES: When he makes it a  
14 "should," it becomes an order. So I --

15 DR. BLANC: The other thing that's  
16 inconsistent here in this sentence in that next to last  
17 sentence is that the milligram per kilogram dose for the  
18 rats studied and of .1 milligrams per kilogram per day,  
19 that was a reproductive study, but the endpoint was  
20 ataxia. Am I reading it --

21 MR. GOSSELIN: No, no, no. That was -- it  
22 is two studies. I think that was from the 90-day hen  
23 feeding study.

24 DR. BLANC: Oh, I see. So it's 1 for the  
25 hen --

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1 MR. GOSSELIN: .1. Right. For ataxia.

2 DR. BLANC: Okay. And .4; right?

3 MR. GOSSELIN: Right. For the rate --

4 DR. BLANC: And what was the actual level  
5 for the neuro-target esterase depression in the hen that  
6 was 30-fold lower?

7 CHAIRMAN FROINES: Oh, Paul, back to this  
8 could and should, before you get into this, because I  
9 think that we've now made the decision that we can't  
10 necessarily do until we deal with this issue. Because  
11 what this sentence now says is we're going to use the  
12 OPIDN work as the basis for regulatory decision making.  
13 But go ahead. Do you know what I mean?

14 DR. BLANC: Well, yeah. That's what I'm  
15 trying to get at. There is an ataxia outcome in the hen  
16 study. Let's see if I follow this correctly. At .1  
17 milligram; right?

18 MR. GOSSELIN: Uh-huh.

19 DR. BLANC: Now, that would be -- is ataxia  
20 not considered an adverse effect? That's just considered  
21 just an effect?

22 MR. GOSSELIN: No. Depending on the study,  
23 it would have been considered an adverse effect, but with  
24 both of these, there were probably some other  
25 circumstances in the studies as to -- maybe

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1 inconsistencies in the effect through different doses of  
2 some other variables as to why that wasn't used.

3 I think the important thing was -- is that  
4 there were some other effects and other studies but for a  
5 variety of reasons, and I don't have them with me right  
6 now. Those weren't highlighted. That was -- if that was  
7 a solid study and there weren't any other  
8 circumstances --

9 DR. BLANC: Okay. Well, let me take you  
10 where I'm going with this thought, which has to do with  
11 the point 26, which has to do with the neuro-target  
12 esterase in the chicken, and I assume it's the same  
13 chicken study.

14 My approach to neuro-target esterase with a  
15 known chemical which causes delayed peripheral  
16 neuropathy such as this, is that it is parallel to an  
17 acetylcholinesterase depression, a serum  
18 acetylcholinesterase depression so that I would not call  
19 neuro-target esterase inhibition an effect for which one  
20 calculates a no effect level, but it's a no adverse  
21 effect level.

22 The neuro-target esterase is so correlated  
23 with peripheral neuropathy, it's the only good marker we  
24 have in an animal species. It doesn't tell us that  
25 that's the mechanism, but it tells us that's the marker

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1 in the same way that plasma cholinesterase is not the  
2 mechanism by which the cholinergic effects are observed  
3 at a regular organophosphate.

4 CHAIRMAN FROINES: Can I -- let me -- this  
5 is the one point I wanted to make. Can I -- are you  
6 going to get into 26? Because if you're going to get  
7 into 26, I'll shut up.

8 DR. BLANC: No. That's where I'm going.

9 CHAIRMAN FROINES: Okay. Go ahead.

10 DR. BLANC: So therefore, I think that  
11 our -- again, consistent with what Stan said, I don't  
12 think we should ask you to rewrite the document, but I  
13 would strongly suggest that the Scientific Review Panel's  
14 comment be that we do not accept ignoring or -- not  
15 ignoring. Compartmentalizing the neuro-target esterase  
16 data as a no effect level.

17 And, in fact, it, parallel to the other, is  
18 an adverse effect if there are questions with the quality  
19 of study so that it can't be believed. That's a  
20 different issue which has to be dealt with, but if it was  
21 merely that this was discounted because it's a no -- it's  
22 treated here as a NOEL, and it's really an NOAEL issue.

23 DR. FRIEDMAN: Can I --

24 DR. BYUS: Not really. Now, as I  
25 understand this, the delayed neurotoxicity doesn't

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1 correlate as strongly with the inhibition of that enzyme.  
2 And the reason -- at least the data that they presented  
3 in support of that and certainly for methyl parathion,  
4 methyl parathion shows no delayed neurotoxicity at all.

5                   If you survey the various organophosphates  
6 based on compounds, specific delayed neurotoxicities  
7 versus not, some of them show the delayed effects, and  
8 some of them do not, and it doesn't appear to correlate  
9 extremely well with the inhibition of that enzyme.

10                   Now, I may be wrong about that, but I'm  
11 not -- it was -- the mechanisms there -- the correlation  
12 is less solid -- and at least as I remember reading all  
13 of it -- than it is between inhibition of serum  
14 cholinesterase and peripheral cholinergic effects.

15                   Is that -- I'm not an expert on this. We  
16 really need -- you know, that's the other correlation.  
17 It's a difficult --

18                   DR. BLANC: Well, the correlation is with  
19 the animal model. The animal model for delayed  
20 neuropathy is the chicken, and when you have a species  
21 which shows the delayed peripheral neuropathy clinically  
22 and then in that same species you have an effect level  
23 where you show decrease in neuro-target esterase, you  
24 have to assume, until proven otherwise, that that is a  
25 correlate of the adverse effect.

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1 DR. BYUS: But do -- say you take 15  
2 cholinesterase inhibitors, does the correlation hold up  
3 in that animal model?

4 DR. BLANC: For ones which there's no dose  
5 response ever for showing the --

6 DR. BYUS: No. For when there is. Do they  
7 call -- there's one thing with using one compound and  
8 showing it, but I'm saying cross-compounds.

9 DR. BLANC: My understanding is that the  
10 compounds which cause peripheral neuropathy also inhibit  
11 neuro-target esterase.

12 DR. BYUS: Okay.

13 CHAIRMAN FROINES: There is a  
14 high-structural dependence on delayed neuropathy, and  
15 there is a certain class of organophosphates that produce  
16 it, and those same compounds also inhibit neurotoxic  
17 esterase so that there's a strong structure activity  
18 relationship.

19 Gary?

20 DR. FRIEDMAN: I'm trying to -- as long as  
21 we're on point 25, I'm trying to understand that second  
22 to last sentence beginning with "however." I'm trying to  
23 figure out where the rat reproductive toxicity fits in.  
24 Is brain CH -- cholinesterase inhibition considered  
25 reproductive toxicity?

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1 MR. GOSSELIN: No. But sometimes in  
2 reproductive toxicity studies, early in those studies in  
3 the first day or two, they'll take -- either observe  
4 clinical signs or take various measurements and will  
5 actually in some cases derive some acute or subchronic  
6 values out of them.

7 So sometimes it's just sort of an effect  
8 that is seen early on before you get into developmental  
9 effects, and occasionally we use those.

10 DR. FRIEDMAN: I see. I wonder if that  
11 will be confusing to people. It seems to -- it isn't  
12 really a reproductive toxicity, but it's a reproductive  
13 toxicity study in which nonreproductive toxicity were  
14 observed. If everyone's comfortable with that --

15 DR. BLANC: I think you bring up a good  
16 point there. It would just make the sentence clearer to  
17 delete the word "reproductive." It's not relevant to  
18 this sentence that there was a reproductive study.

19 It could have been a study of inhalation  
20 irritancy and have found this too. That's not the point.  
21 They found this.

22 CHAIRMAN FROINES: Okay. So we'll delete  
23 it.

24 Paul, go ahead with 26. We're getting  
25 really tight on time.



1 DR. BLANC: Well, I just think that -- I  
2 don't think -- I actually don't think -- to reverse  
3 myself in earlier comments, I think that Stan's comment  
4 of the general approach where we shouldn't change the  
5 document, we should simply point out where we differ with  
6 it is still the right one.

7 The interrelationship between point 25 and  
8 26 is going to take major rewriting. I don't think we  
9 can do that here. I am comfortable with seeing a  
10 circulated version. I don't think you have clear  
11 instructions yet from the committee because I don't know  
12 if we've reached consensus on how to handle neuro-target  
13 esterase.

14 It would be my personal view to handle it  
15 in parallel with how we're handling the serum  
16 cholinesterase.

17 CHAIRMAN FROINES: Yeah. I've been waiting  
18 to get my turn here on this one. All -- I think that the  
19 point 26 is an extremely important point. They say and  
20 OEHHA also says these paragraphs are identical in the two  
21 sets of findings.

22 They say "First, a cross-route  
23 extrapolation needs to be performed. Second, this  
24 study" -- "this study" meaning the chicken study, the hen  
25 study -- "suggests an underestimation of risk using the

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1 90-day rat inhalation study."

2 In other words, we're not using the hen  
3 study. We're using the rat study. There is considerable  
4 uncertainty in quantifying applying the hen study for  
5 inhalation exposure. I have two points. One point is  
6 that the sensitive species for delayed neuropathy is the  
7 chicken. It's the hen. It's what we use to identify  
8 delayed neuropathy.

9 When one test compounds -- as I said,  
10 there's a strong structure activity relationship between  
11 organophosphates and delayed neuropathy. And so what  
12 people do is, when they have a particular organophosphate  
13 that has the structural characteristics that you think  
14 might lead to delayed neuropathy, they test them in the  
15 chicken because the chicken is the sensitive species.

16 So if we have -- if the sensitive species  
17 in the chicken -- is the chicken, then it seems that we  
18 have to be able to develop an ability to conduct a risk  
19 assessment in that species unless somebody can  
20 demonstrate mechanistically why the hen is an  
21 inappropriate model.

22 So it seems to me that what I want to do  
23 was to say that OEHHA and to -- the panel recommends to  
24 OEHHA and DPR that further investigation be carried  
25 out -- some language to that effect -- that looks at how

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1 one can make use of the hen data to develop appropriate  
2 risk assessment estimates for delayed neuropathy.

3 In other words, we don't say there is -- we  
4 say, you can say there is considerable uncertainty, but  
5 we don't want to leave it at that. We want to say "Go  
6 out, and figure out how to do it." Because that's the  
7 model we need to be able to make work because that's the  
8 endpoint that is most relevant for this particular  
9 neurotoxicity.

10 And the peripheral neuropathy associated  
11 with delayed neuropathy is much more serious in a chronic  
12 context than -- it's very serious in a chronic context  
13 whereas organophosphate toxicity is obviously more of an  
14 acute nature to some extent.

15 DR. FRIEDMAN: Is it possible that a  
16 substance could produce neuropathy in this very sensitive  
17 chicken and not produce it at all in the human?

18 CHAIRMAN FROINES: That seems to me that's  
19 a question of concern.

20 DR. FRIEDMAN: Because in that case you  
21 might not want to figure -- have some formula for  
22 extrapolating from chickens to people.

23 CHAIRMAN FROINES: But that's exactly what  
24 I'm saying. I think that the burden now is on OEHHA and  
25 DPR to go back and look at the evidence and say is there



1 evidence in humans based on the delayed neuropathies in  
2 chickens, and can we develop some risk assessment  
3 approach given the information we currently have  
4 available?

5 I'm not presuming that we have to use the  
6 chicken for risk assessment, but I think we have to try  
7 to look at the issues that underlie the most sensitive  
8 species, and somebody has to come back and say why  
9 mechanically we shouldn't assume the chicken may be  
10 relevant. In other words, you assume that it may be  
11 relevant and then go see if you can disprove its  
12 relevance.

13 DR. FRIEDMAN: Would that be a good topic  
14 for a workshop?

15 CHAIRMAN FROINES: Yes. Absolutely. I  
16 think this is a key question because, if every time a  
17 delayed neuropathy comes up, and we're dealing with  
18 pesticides, we simply say it's too hard to deal with.  
19 Then we haven't really met the burden -- our burden.

20 So I will rewrite this, and I think this is  
21 a particularly important issue for the panel and for the  
22 agencies because the chicken is in the end the sensitive  
23 species.

24 DR. BLANC: Well, I think, again, that part  
25 of these differences comes up -- you know, traces back to

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1 the regulatory background of your agency and that you've  
2 been used to dealing with FIFRA on EPA. These -- our  
3 kinds of deliberations are going to differ from that.

4 CHAIRMAN FROINES: Paul and we talked about  
5 this this morning before this meeting, and he's  
6 completely open. So it's been a very positive  
7 interaction in this. And so there's no tension between  
8 us and DPR.

9 I think that they've been very forthcoming  
10 in terms of their willingness to, you know, hear these  
11 kinds of concerns. So we appreciate that. So the good  
12 news is we got through DEF. The bad news is we're  
13 clearly not going to touch parathion unless you can do it  
14 in five minutes.

15 DR. ATKINSON: What --

16 DR. GLANTZ: What about me?

17 CHAIRMAN FROINES: I'm sorry. I apologize.

18 DR. GLANTZ: I have a tremendous amount of  
19 stuff.

20 DR. FUCALORO: I thought Paul covered it  
21 all.

22 DR. GLANTZ: No.

23 CHAIRMAN FROINES: Are you sure?

24 DR. GLANTZ: Yeah.

25 CHAIRMAN FROINES: I didn't mean to be

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1 rude.

2 DR. GLANTZ: Yes, you did.

3 CHAIRMAN FROINES: No, I didn't. On the  
4 contrary.

5 DR. GLANTZ: Okay. No. Everything I was  
6 concerned about is somebody else --

7 CHAIRMAN FROINES: Are you sure?

8 DR. GLANTZ: Yeah. But if you want, I'll  
9 make something up.

10 DR. FUCALORO: He'll have a go at it.

11 DR. GLANTZ: No. I'm quite happy. I think  
12 these changes are excellent.

13 CHAIRMAN FROINES: Okay.

14 DR. GLANTZ: I mean they were the kind of  
15 things that I was talking about last time.

16 CHAIRMAN FROINES: You promised that you're  
17 not going to bring this up again sometime. So you cut me  
18 off at that meeting.

19 DR. GLANTZ: No. I won't promise that, for  
20 the record.

21 CHAIRMAN FROINES: Please, bring up any  
22 comments right now.

23 DR. GLANTZ: No. I think the issues that I  
24 had had been aired already. I think with these changes  
25 it's fine.

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1 DR. ATKINSON: I would like to get a copy  
2 of the DPR report for my interest, if that's possible.

3 DR. FUCALORO: Pretty tough to discuss when  
4 your --

5 DR. GLANTZ: One other thing -- I guess one  
6 other thing that I -- I just think that we ought to make  
7 it important. A point we ought to make for the record,  
8 though, is that in the -- this is the first time we're  
9 going to be issuing findings where we say we're  
10 explicitly differing with a report we already approved.

11 And I think we should make it clear that  
12 that is not a reflection of some horrible political  
13 battle with DPR in this case. It's just simply a  
14 question of expediency and moving the process forward and  
15 to not reopen the report.

16 Because I don't think anybody wants to  
17 start reediting the report. So I think that's an  
18 important point because I wouldn't want somebody to read  
19 the findings and think that, you know, there was some  
20 great deal of bloodshed this time. That was all in the  
21 past. But the -- so I just think that's an important  
22 point for the record.

23 MR. GOSSELIN: I think the report's been  
24 crafted in a way that, you know, all the information is  
25 there for the panel and the agency to choose what's the

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1 most relevant endpoint either of concern or to regulate  
2 from and to try to make sure that all the information in  
3 there is presented and factual.

4 DR. GLANTZ: But I would hope, especially  
5 with our change to "should," that in terms we should move  
6 the regulatory process forward. I think the intent of  
7 the panel to use that sort of endpoint is clearly there.  
8 But I just think it's important that there not be any  
9 misunderstanding, but I think -- I'm quite happy with the  
10 findings as advised.

11 CHAIRMAN FROINES: I think there's another  
12 point which is that I think it's really terrific that we  
13 actually now have brought DEF pretty much to closure.  
14 And so we can all feel good about the fact that we've  
15 overcome that long history.

16 And so I think this has been a very  
17 cooperative exchange, and I think the record should  
18 really reflect that, and I think there's a consensus here  
19 that we're moving in the right direction.

20 DR. FUCALORO: You said, "consensus," not  
21 the majority. Not unanimity. I'm sorry.

22 MR. GOSSELIN: Do you want me to just --

23 DR. GLANTZ: I think at your next class the  
24 next time you meet here, you should just have your class  
25 come to this meeting.

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1 DR. FUCALORO: You did that.

2 DR. GLANTZ: I did that once, yeah.

3 CHAIRMAN FROINES: It was completely  
4 disruptive. If you'll remember --

5 DR. GLANTZ: But then your students can see  
6 how we regard --

7 CHAIRMAN FROINES: But your students  
8 actually tried to ask questions. We don't even let the  
9 affected industries ask questions.

10 DR. FUCALORO: One of your students thought  
11 this was Spanish II.

12 CHAIRMAN FROINES: Paul, go ahead. Do you  
13 want to make --

14 MR. GOSSELIN: Real quickly on methyl  
15 parathion. I didn't want you folks to forget about that.  
16 Since we made the presentation in November, staff have  
17 gone back, and at the workshop we held the registrar came  
18 in with a number of studies.

19 Some of them were voluminous, and staff  
20 have gone through those, reviewed those and are now  
21 incorporating those summaries into the document.

22 Dr. Byus had some literature references that we've  
23 tracked down and are summarizing, and we also identified  
24 some additional ones for ourselves.

25 The other significant issue is that EPA has

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1 issued their draft risk assessment on methyl parathion on  
2 December 18, which is actually a fairly significant  
3 document. Staffs have been checking all along the way on  
4 risk assessments, and we expect that they're dealing with  
5 the same studies.

6 But with that, we're going to need to  
7 review that, actually summarize that like we did with DEF  
8 into the document. We're hoping to have that done. Oh,  
9 and there was one other -- the commenter on how we deal  
10 with multiple exposures to OPs, and we need to add some  
11 language into the document on that.

12 We're hoping to have that drafted up,  
13 discussed with the leads and circulated probably in the  
14 next two to three weeks and then, hopefully, if all goes  
15 well, we can bring it back before the panel for wrap-up.

16 CHAIRMAN FROINES: Can we -- should we  
17 schedule it for the February meeting?

18 MR. GOSSELIN: I think -- I don't think  
19 we'll be ready for that. Because I think -- at earliest  
20 we would probably be getting the rewrites out probably  
21 the first week of February, and given everything else,  
22 just the timing, I'd like to make sure that everyone has  
23 a chance to get those rewrites discussed with the leads  
24 so we don't press things.

25 CHAIRMAN FROINES: So we'll schedule it for

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1 the March meeting then. Okay.

2 DR. GLANTZ: When is the February meeting?

3 CHAIRMAN FROINES: Pardon me?

4 DR. GLANTZ: When is the February meeting?

5 CHAIRMAN FROINES: Bill, I think it's  
6 February 10?

7 MR. LOCKETT: Yes.

8 CHAIRMAN FROINES: February 10. Now, we  
9 need -- DPR has requested that we designate two lead  
10 persons for MITC. And when will that -- when  
11 will -- when will documents or when will that  
12 process -- give us some sense of the process.

13 MR. GOSSELIN: The document is in its final  
14 stages. So probably a week or two. So as soon as we get  
15 the leads, staff are going to almost immediately start  
16 discussing some of the relevant issues and start to go  
17 over the issues with MITC.

18 CHAIRMAN FROINES: Bill Lockett, at this  
19 point, I think the logical thing would be to ask Roger to  
20 take on the exposure part of that document.

21 Who would be willing to take on the health  
22 effects part? Who had -- currently is a lead person on a  
23 document?

24 DR. GLANTZ: Who is or isn't?

25 CHAIRMAN FROINES: Who is. You're methyl

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1 parathion. You're --

2 DR. GLANTZ: Reference exposure level.

3 CHAIRMAN FROINES: Reference exposure.

4 DR. FRIEDMAN: I'm supposed to be on that  
5 chronic toxicity --

6 CHAIRMAN FROINES: Chronic toxicity. Paul,  
7 are you a lead on -- oh, you're molinate, aren't you?  
8 How could we forget.

9 DR. BLANC: Oh, yeah.

10 CHAIRMAN FROINES: So Peter Witschi. Is he  
11 a lead on chemical at this point?

12 MR. GOSSELIN: He was on DEF.

13 CHAIRMAN FROINES: Well, that's good. He's  
14 rotated off, and let's rotate him on to MITC.

15 DR. GLANTZ: Plus he's not here.

16 DR. BYUS: Plus he's not here.

17 CHAIRMAN FROINES: Plus he's not here.

18 Hearing no objections. The next meeting -- we also  
19 discussed that we want to find out -- we want to learn  
20 about how EPA is doing acute -- George, how EPA is doing  
21 acute RELs, and we'll talk with you later about -- look  
22 at the comparison between how you're doing it and the  
23 U.S.EPA.

24 And then the final issue is the April  
25 meeting. Bill gave me some dates.

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1 DR. GLANTZ: Do we have a March meeting? I  
2 didn't have a February one on my calendar.

3 CHAIRMAN FROINES: Bill, do we have a March  
4 meeting set up?

5 MR. LOCKETT: We have not scheduled one,  
6 no.

7 DR. FUCALORO: When's the workshop?

8 CHAIRMAN FROINES: April.

9 DR. GLANTZ: Oh, can I bring up one other  
10 issue?

11 CHAIRMAN FROINES: Sure.

12 DR. GLANTZ: Before we -- since it sounds  
13 like we're kind of wrapping it up here, this is the thing  
14 I mentioned to you the hall. I think now that we're rid  
15 of Pete Wilson, I'd like to suggest that we ask the staff  
16 to finish the job of listing ETS as a toxic air  
17 contaminant which -- in the most expeditious possible  
18 manner, I don't know who we -- how would we go about  
19 getting the ball rolling based on the existing report,  
20 which is my understanding, was written to AB 1807  
21 standards.

22 MR. LOCKETT: I think the next step would  
23 be for the panel to discuss it.

24 DR. GLANTZ: Okay. We're discussing it.

25 CHAIRMAN FROINES: To discuss Stan's

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1 request or discuss ETS?

2 MR. LOCKETT: No. To discuss Stan's  
3 request.

4 CHAIRMAN FROINES: Well, we'll put that on  
5 the agenda.

6 DR. GLANTZ: Okay. We can't just do it now  
7 and be done with it?

8 DR. BLANC: What's Stan's request?

9 CHAIRMAN FROINES: Stan would like -- the  
10 panel would like the ETS report, which is complete, to be  
11 taken to -- taken up by the ARB as a toxic air  
12 contaminant.

13 In other words, we would take it to the ARB  
14 and recommend that it be declared a toxic air  
15 contaminant.

16 DR. FRIEDMAN: Hadn't that been done  
17 already?

18 CHAIRMAN FROINES: No. All we did  
19 was -- the report was prepared. We reviewed it and said  
20 it was very positive and then --

21 DR. GLANTZ: No. We said it met  
22 the -- there was a bunch of maneuvering because of  
23 basically political pressure from the governor's office,  
24 but the report says the panel believes -- finds that the  
25 toxic air contaminant -- or says it meets the definition.

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1 I don't remember the exact words.

2 So there are findings, but when it was  
3 presented to the Air Resources Board, it was presented as  
4 an information item, not as an action item. So my  
5 understanding -- I mean I guess our lawyer people aren't  
6 here.

7 But what I would hope we could do is have  
8 no further action by the panel necessary other than  
9 making a recommendation that the Air Resources Board take  
10 the report and put out the necessary public notices, hold  
11 the necessary hearing and then vote the identification.

12 I think that's all that's left to do. Do  
13 you disagree -- would you say that's a correct statement,  
14 Bill?

15 MR. LOCKETT: I think that's a correct  
16 statement.

17 DR. GLANTZ: So it would simply mean -- it  
18 would simply mean that the panel requesting that the Air  
19 Board, based on the existing report, take the steps  
20 necessary to form --

21 DR. BLANC: Can we do that at the February  
22 meeting? Can that be an agenda item there at February?  
23 Stan, I would agree that -- let's just double-check what  
24 we need to do and what we don't need to do.

25 DR. GLANTZ: Okay. There's a small chance

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1 I won't be here. That's the only problem. But okay.  
2 I've waited seven years --

3 DR. FUCALORO: What the heck. Another  
4 month.

5 DR. GLANTZ: Huh?

6 DR. FUCALORO: Another month.

7 DR. GLANTZ: Another month. Okay.

8 CHAIRMAN FROINES: Bill, we don't have a  
9 date for the March meeting yet. So we'll poll the panel.

10 MR. LOCKETT: Well, because you met in  
11 January and February and April, we were trying to reflect  
12 the panel's view that they weren't necessarily wanting to  
13 meet every month.

14 CHAIRMAN FROINES: Hearing no opposition --

15 DR. GLANTZ: Why don't we have Witschi  
16 meet?

17 DR. BYUS: John, I've got one more  
18 comment -- one more statement just in relation to methyl  
19 parathion that's come up, which I think is something we  
20 might want to include in the workshop or discuss more, is  
21 the additive effects of these organophosphates.

22 There's hundreds of them used and sprayed,  
23 and they all work in a similar way, and this came up in  
24 Cal PIRG's comments on methyl parathion. And I think  
25 it's a very good one. What are the additive effects, the

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1 risk factors if you add all the organophosphates up in  
2 terms of exposure?

3 And it's not necessarily an easy question,  
4 certainly for DPR, but it's certainly a very good  
5 question, and it's a very valid question, and it's  
6 something we really should consider for each -- not just  
7 methyl parathion in-depth, but they all work by similar  
8 mechanisms here, and they're all basically sprayed in the  
9 same way.

10 So we should really deal with that question  
11 scientifically and really get a good answer to that  
12 question.

13 CHAIRMAN FROINES: Gary is beginning to put  
14 his papers together and so is Tony. We're really short  
15 on time. Gary has to leave for the airport. Let me just  
16 say one thing. I don't know if anybody's been keeping  
17 track, but the number of issues that have been said we  
18 can deal with this at the workshop means that the  
19 workshop will either have to be broken up into a few  
20 workshops, which I would propose, or we had better plan a  
21 week-long conference to deal with all these issues.

22 I think that all of those are very  
23 relevant. So I think that what we're talking about is a  
24 series of workshops over time. In each workshop we  
25 should deal with a couple of topics and then try and do

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1 it effectively.

2                   And what I think it means is that the panel  
3 is changing to some extent from a body where every six  
4 months or every three months -- I mean in the old days,  
5 what would happen is a chemical would come to the panel,  
6 and we would deal with it over a period of three or four  
7 months, and we would then make our findings, and it would  
8 go to the Board, and that would be it.

9                   Here what we're talking about, and I think  
10 it's not just with the DPR -- so that Paul doesn't need  
11 to feel like a pin cushion -- is that what we're talking  
12 about is the panel saying "We're going to hold workshops  
13 over time to address scientific issues that are relevant  
14 to our work as a panel around the issue of toxic air  
15 contaminants so that we may have two workshops a year or  
16 one a year."

17                   But what we're really saying is that we're  
18 going to take up some of the content -- scientific  
19 content of these issues and not simply be responsive to a  
20 particular document coming forward, and that's quite a  
21 change in the panel for those of you who haven't been on  
22 for a long period of time.

23                   And I think it's a good change, but it's  
24 something we need to be aware of that we are doing that.  
25 So this workshop may grow into one or two or three or

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1 The 13th is Tuesday. Yeah. I'll be here.

2 CHAIRMAN FROINES: Tuesday the 13th.

3 MR. LOCKETT: Dr. Atkinson is the only  
4 person we hadn't polled about those two dates.

5 DR. ATKINSON: I have no idea.

6 MR. LOCKETT: So I gather we will choose  
7 April 13 unless we hear otherwise.

8 CHAIRMAN FROINES: Unless Roger says he  
9 absolutely can't do it.

10 DR. FUCALORO: You checked my office;  
11 right?

12 MR. LOCKETT: Yes.

13 CHAIRMAN FROINES: I think it's absolutely  
14 crucial that Roger attend so that he'll be the --

15 MR. LOCKETT: So I guess my request is for  
16 the members present to put April 13 on their calendar  
17 now, and we'll call you if it's going to change.

18 DR. GLANTZ: Do you know where it's going  
19 to be?

20 MR. LOCKETT: That's a decision not made  
21 yet.

22 DR. BLANC: Palm Springs? It's not that  
23 time of year.

24 DR. GLANTZ: How about the Ahwahnee Hotel?

25 CHAIRMAN FROINES: Bob Spear just had a

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1 retreat of his Center to Occupational Environmental  
2 Health at the Sonoma Valley Mission Inn. That was really  
3 something. I'm sure everybody would agree to that.

4 DR. FUCALORO: Do we have to stay in the  
5 state?

6 MR. LOCKETT: We are trying to be  
7 thoughtful to the folks flying in from the various parts  
8 of the United States, and so it's thought to be either  
9 near SFO or LAX.

10 DR. BLANC: Well, but in fact, I was being  
11 somewhat -- whatever. In fact, if it's a nice place,  
12 that does actually in April still winter many places. It  
13 does effectively draw people to come --

14 DR. GLANTZ: I like the Ahwahnee.

15 DR. FUCALORO: It's not winter in the  
16 southern hemisphere --

17 DR. GLANTZ: It's easy to get there.

18 MR. LOCKETT: Are you going to fund that?

19 CHAIRMAN FROINES: Anyway, thank you  
20 everybody. I think this was a really very useful and  
21 good meeting. So we'll continue, and we've made it  
22 time-wise, I think.

23

24 (Whereupon the meeting was adjourned at  
25 1:15 P.M.)

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13 time and place set forth.

14 I further certify that I have no interest  
15 in the event of the action.

16 EXECUTED this day of ,  
17 1999.

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20 Caroline Jetter, CSR 11568

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