

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

SOUTH SAN FRANCISCO CONFERENCE CENTER  
255 SOUTH AIRPORT BOULEVARD  
SOUTH SAN FRANCISCO, CALIFORNIA

WEDNESDAY, NOVEMBER 28, 2001

10:00 A.M.

JAMES F. PETERS, CSR, RPR  
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APPEARANCES

MEMBERS PRESENT

Dr. John Froines, Chairperson

Dr. Roger Atkinson

Dr. Paul D. Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Anthony Fucaloro

Dr. Hanspeter Witschi

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Dr. Ellinor Fanning

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD

Mr. Jim Behrmann

Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD  
ASSESSMENT

Dr. George V. Alexeef, Deputy Director for Scientific  
Affairs

Mr. David Lewis, Staff Toxicologist

Mr. David Morry, Staff Toxicologist

Dr. David Rice, Staff Toxicologists

Dr. Andy Salmon, Chief, Air Toxicology and Risk Assessment  
Unit

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION

Dr. Keith Pfeifer, Pharm.D, Ph.D., DABT, Senior  
Toxicologist

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1 PROCEEDINGS

2 CHAIRPERSON FROINES: We need to start given the  
3 fact that two people have to leave at 2:00 o'clock.

4 PANEL MEMBER FUCALORO: Three.

5 CHAIRPERSON FROINES: Pardon me?

6 PANEL MEMBER FUCALORO: Three people have to  
7 leave.

8 CHAIRPERSON FROINES: Who are the three?

9 PANEL MEMBER FUCALORO: Craig, I and Roger have  
10 to leave.

11 CHAIRPERSON FROINES: And Peter. So at 2:00  
12 o'clock the meeting will end. We don't have really any  
13 choice. So I think we should begin. Now, we should have  
14 a brief discussion, at some point, about travel issues,  
15 but I think that given the fact that Gary and Paul aren't  
16 here, we probably shouldn't start with that because that  
17 would create a southern California bias.

18 PANEL MEMBER FUCALORO: B-i-a-s as opposed to  
19 B-y-u-s.

20 (Laughter.)

21 CHAIRPERSON FROINES: So anyway, we should  
22 officially open the meeting on November 28th, 2001 of the  
23 scientific review panel. And let's begin following the  
24 agenda and discuss at the outset the chronic REL issues  
25 that OEHA is going to be bringing forward.

1           Andy.

2           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Thank you. I thought I'd just start because we  
4 haven't been talking about the RELs for some little while  
5 now. I though I'd just remind you where we've got to with  
6 the noncancer chronic RELs.

7           (Thereupon an overhead presentation was  
8           presented as follows.)

9           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: We have been working on the review of the  
11 compound specific summaries and the proposed RELs. The  
12 methodology guidelines were reviewed by the panel and  
13 adopted in February of 2000.

14           We have had a first batch of RELs, which was  
15 included with the guidelines. Then two further addenda,  
16 which included additional RELs. And we're now in the  
17 process of dealing with an additional batch, which we're  
18 calling batch 2B.

19                               --o0o--

20           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: You saw this initially on March the 5th and we  
22 haven't had any opportunity to do anything with it until  
23 now. But basically what we're doing is we received some  
24 public comments which we have responded to and  
25 incorporated any additional information which came up

1 during that process. We have, of course, responded to any  
2 comments which the panel provided to us on March the 5th.

3 And there are one or two areas where we've been  
4 updating the methodology. One of the particular points  
5 which we discussed with the panel was the use of the  
6 benchmark concentration approach for several of the RELs.  
7 There are a couple of instances where there are new data  
8 as well. And so we now have the presentation of the  
9 revised versions which you have.

10 --o0o--

11 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

12 SALMON: The chemicals which you considered in March  
13 include the following. There are some which, in fact,  
14 were not considered at that meeting, but the first group  
15 is -- essentially, the review of the methodology is  
16 completed in March then some were deferred.

17 --o0o--

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: And there was another series where specific  
20 modifications and changes were required. So we are going  
21 to be looking at most of these.

22 --o0o--

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

24 SALMON: There's an additional compound which is carbon  
25 disulfide, which is actually held over from an earlier

1 group. And the reason for this was that we identified the  
2 need to go back to the original data. The study that's  
3 used as the basis of the REL is an epidemiological study  
4 which is, in fact, reviewed by federal EPA. It turns out  
5 that it was originally actually done by NIOSH and we  
6 needed to go back to the original data to reevaluate the  
7 benchmark dose calculation.

8 We have now finally received the original data  
9 and performed the updates, so we'll be presenting that as  
10 well.

11 --o0o--

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: So another thing which we are doing this time  
14 around, which is a first for us, is that responding to the  
15 requirements of SB 25 and given that we now have some  
16 initial guidance available in the form of our document,  
17 which you've been looking at for most of this year, we are  
18 attempting to provide a summary section for each of the  
19 RELs we're presenting today, which address the question of  
20 whether the proposed REL is adequate to protect the health  
21 of infants and children.

22 And we asked particularly for your guidance on  
23 this as to whether the approach we're taking is a sensible  
24 one, whether it's adequate. We are very much constrained  
25 in many cases by availability of data as you will see.



1 But anyway, so this is a particularly new item in this  
2 series.

3 --o0o--

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: So these are the ones that we're actually going  
6 to be presenting today, and there are some which we have  
7 decided we can't deal with today because we were unable to  
8 complete the update and review to our satisfaction and --  
9 mainly due to our -- well, when we went back and looked at  
10 the requirements of the panel and the requirements of the  
11 SB 25, we identified the fact that we did not have  
12 sufficient data available or methodology available to  
13 resolve the issue.

14 So in the case of ethylene glycol butyl ether or  
15 butoxy ethanol, one of the questions which the panel  
16 identified was that we should look at the dose response  
17 for irritancy. And this has clearly important for the  
18 suitability of the REL for protecting adult health, but  
19 it's particularly important for considerations of  
20 children's health as well.

21 And, at this point, we've not been able to  
22 identify satisfactory data or methodology for dealing with  
23 this, so we're going to have to work on this some more.

24 We've also not brought forward a revision of the  
25 fluoride REL, at this point, because we need to work out

1 with the Air Board, the exposure assessment people,  
2 whether this needs to be treated as a multi-media  
3 chemical. And if it does need to be, then as fluoride  
4 salts at least, may need to be -- then we need an oral REL  
5 as well as the inhalation REL.

6 Nitric acid --

7 CHAIRPERSON FROINES: Andy, would you say that  
8 again, about the fluoride issue?

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: The fluoride issue is the REL which we have  
11 proposed is basically a straightforward inhalation REL  
12 which has applicable vapor phase chemicals. But fluoride  
13 salts, in particular, of course, you know, it may  
14 initially be emitted as a particulate material or else  
15 become a particulate material in the course of atmospheric  
16 reactions.

17 And if it then is in particulate form, it may  
18 sediment out of the atmosphere, deposit on crops, deposit  
19 on soil and things like that. And for materials which  
20 behave like that, we need to provide an oral REL, which is  
21 used in the multi-media analysis defined by the hot spotss  
22 exposure assessment guidelines, and there are certain  
23 chemicals which are identified as potentially needing a  
24 multi-media analysis.

25 And so if it is concluded that emissions of

1 actually or potentially particulate fluoride is an issue  
2 in California, it certainly is some in other areas, things  
3 like brick works for instance are notorious for emitting  
4 particulate fluoride salts in some areas.

5 PANEL MEMBER FUCALORO: And this is way above  
6 what one would normally get in fluoridated water or  
7 toothpaste.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
9 SALMON: Depending on circumstances. There are examples  
10 in the world where there is at least locally a problem. I  
11 think the issue is whether that's important in California.

12 PANEL MEMBER ATKINSON: So how would you relate  
13 the, let's say, the atmospheric particle concentration of  
14 fluorides to what would be on soil or plants? I mean,  
15 there may be no relation whatsoever.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON: There's only an indirect relationship. There's a  
18 methodology for dealing -- which is a sort of default  
19 approach, for dealing with multi-media chemicals, which is  
20 in the Part 4 hot spots guidelines which you reviewed  
21 fairly recently.

22 It uses various sorts of atmospheric modeling to  
23 handle the way the emissions are distributed and  
24 potentially deposited. So I'm not saying that it answers  
25 all the questions that might be asked, but it's an

1 approach which is used to determine whether or not there  
2 might be a problem there at least.

3           Clearly, this can be a very complex issue, but  
4 the question we have, at this point, is whether we need to  
5 include fluorides in that approach. And if so, then we  
6 need to develop an oral, as well as, an inhalation REL.

7           CHAIRPERSON FROINES: Do you have a sense --

8           PANEL MEMBER ATKINSON: We do have almost done a  
9 couple of almost, a couple of inhalation from the oral.  
10 It's the oral where you depend upon the concentration of  
11 the fluoride and whatever you're getting it from.

12           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
13 SALMON: It might be we should develop separate RELs for  
14 hydrogen fluoride and other fluorides versus fluoride  
15 salts which would be particulates. Certainly, I mean we  
16 will look into that.

17           CHAIRPERSON FROINES: Do you have a sense that  
18 there is still a continuing use of hydrogen fluoride in  
19 the petroleum refinery?

20           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: It's my understanding that there is some  
22 continuing use. I don't know that -- it's my  
23 understanding that some refineries are moving away from  
24 that, but the last time we checked the emissions data  
25 there was, you know, there were real numbers there. May

1 be if we come out with this REL, it might accelerate that  
2 transition who knows.

3 CHAIRPERSON FROINES: Has ARB or the local air  
4 districts done monitoring so that there is a database?

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
6 SALMON: There are data on fluoride emissions in the hot  
7 spots database, yes.

8 The next one that we are not presenting today,  
9 which you have actually seen previously, it was nitric  
10 acid. And what we did here was we did a fairly standard  
11 analysis using, unfortunately, some rather old animal  
12 studies on nitric acid effects, and came up with a  
13 proposed REL which, you know, looks reasonable from the  
14 methodological point of view.

15 But when we examined this from the point of view  
16 of our SB 25 evaluation, we realized that there is a very  
17 significant problem with acid aerosols and the  
18 exacerbation of asthma, which is a big problem for  
19 children. I'm going to be discussing this a little bit  
20 more when I come to present sulfuric acid REL.

21 But the situation of the nitric acid was that it  
22 was fairly clear that the REL which we had using data  
23 available for nitric acid would not be protective of the  
24 children's health in relation to exacerbation of asthma by  
25 acid aerosols, if that is a problem with nitric acid, and

1 it seemed reasonable to us to suppose that it might be.

2 So we're going to have to go back and do some more work on  
3 this one and figure out how to include that consideration.

4           The phosphine REL, there is a question of how we  
5 defined the NOAEL and which endpoint we're using. And we  
6 have to review those questions, again, in light of the  
7 fact that there are several potential endpoints with  
8 slightly different NOAELs, different quality of data in  
9 the experimental record and some implications for some of  
10 those endpoints needing to be further considered under SB  
11 25 guidance. So we're, again, holding that one back so we  
12 can do more work on it.

13           And the final one, triethylamine, again, the end  
14 point is basically irritancy. And this will be apparent,  
15 I think, with the next group of chemicals. And when I do  
16 present the RELs, that irritancy appears to be quite an  
17 important and a fairly common endpoint. And there are  
18 implications which we need to consider in terms of the  
19 impact on children's health.

20           And in the particular case of triethylamine,  
21 there appears to be an inconsistency between animal and  
22 human data, which we're still trying to resolve. So this  
23 one we've proposed to defer.

24           I'll now start on the ones that we actually are  
25 going to present. And the first one of these is -- it's

1 been pointed out to me that the lead on this chemical was  
2 Dr. Blanc. And given that he is not here at the moment --  
3 but I assume maybe later -- the suggestion was, Mr.  
4 Chairman, whether you would want us to defer consideration  
5 of this particular one until he's here?

6 CHAIRPERSON FROINES: No, go ahead. I think that  
7 it will be fine.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
9 SALMON: Okay. This is the basis of the REL which you  
10 have seen fairly similarly presented before. We haven't  
11 changed the key study, but what we have done is that we  
12 have actually gone back to the original data from that  
13 study which we obtained after a rather torturous process  
14 of inquiry through the federal agencies.

15 And we've actually now calculated a benchmark  
16 concentration, BMC05, which is the benchmark which we are  
17 proposing to use regularly for this sort of analysis. So  
18 the modification here, firstly, is the calculation of the  
19 new benchmark from the raw data in the study.

20 We also looked at some other information. There  
21 was another study in the literature that looked as if it  
22 might be informative, but we were not able to actually get  
23 the original raw data, so we couldn't do the calculation,  
24 but that's available as a comparison.

25 And additionally, we have considered the

1 implications of carbon disulfide toxicity for children's  
2 health. And obviously this was reviewed in the SB 25  
3 document, which you've just finished working through.

4 --o0o--

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
6 SALMON: The situation that we identified there was that  
7 there was some specific concerns about carbon disulfide,  
8 but it didn't quite reach the level of concern where we  
9 could actually identify a differential impact. So we  
10 haven't proposed changing the REL to reflect any such  
11 differential impact on infants and children, but we do  
12 review some of our remaining concerns.

13 We've also incorporated in the summary some of  
14 the information relating to potential impacts on  
15 children's health, which was discussed also in the SB 25  
16 document. So I don't know whether you want to ask any  
17 further questions or make any points about this at this  
18 point, Paul?

19 --o0o--

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: Well, I'll proceed to the next one now. The  
22 revised summary on acrylonitrile.

23 CHAIRPERSON FROINES: Why did you pick -- why  
24 didn't you use 250 instead of 300?

25 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF



1 SALMON: I think because typically that -- well, that was  
2 the way the -- we normally round these things to one  
3 significant figure here. So the 300 is the number. The  
4 number didn't, in fact, change substantially from the  
5 previous version. Dr. Lewis was responsible for the  
6 analysis here, so I want him to respond.

7 STAFF TOXICOLOGIST LEWIS: We had done -- U.S.  
8 EPA had done the analysis. They used a BMC10, a ten  
9 percent benchmark dose. And their value by using their  
10 uncertainty factors was 700 micrograms per cubic meter,  
11 very similar to our 800 micrograms per cubic meter.

12 When we initially revised their approach before  
13 we had received the original data using a BMC10 and our  
14 preferred uncertainty factors, we had a value of 3,000  
15 micrograms per cubic meter, so this is slightly lower.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON: I think the issue which caused us to go back and  
18 reevaluate the benchmark was that our preference is to use  
19 the BMC05 with our defined range of uncertainty factors.  
20 Whereas, the U.S. EPA approach they tend to calculate a  
21 BMC10, and then, in fact, put in some additional  
22 uncertainty factors, which are not sanctioned by our  
23 guidelines, in order to allow for the perception that the  
24 BMC10 is, in fact, in effect level rather than being,  
25 broadly speaking, equivalent to a NOAEL.

1           So that's the reason for the slight differences  
2 in methodology between ourselves and the federal analysis.  
3 But, as you can see it comes out basically to  
4 approximately the same place in the end, and we feel that  
5 the approach we present here is more consistent with our  
6 guidelines and with the way we would like to use the BMC  
7 calculation methodology.

8           PANEL MEMBER FUCALORO: Just for the arithmetic,  
9 can I ask a question? In going from human equivalency  
10 concentration of 2.5 parts per million, rather going from  
11 6.9 parts per million would be the BMC right, so 2.5 is  
12 computationally one half times five-sevenths, essentially,  
13 right?

14           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
15 SALMON: Yes.

16           PANEL MEMBER FUCALORO: And then you bumped it by  
17 a factor of 100, and then rounded it off to the next  
18 highest? I just want to be clear on that.

19           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
20 SALMON: Yes.

21           PANEL MEMBER FUCALORO: And then you use a 3.1  
22 micrograms per cubic meter to get to the conversion factor  
23 in order to go from 300 to 800; is that correct?

24           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
25 SALMON: I think actually what we --

1 PANEL MEMBER FUCALORO: That's not quite right.

2 I mean, it should be 900.

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: What we actually do is we go back and we reround

5 the calculation in micrograms per meter cubed, and supply

6 the uncertainties and then do the rounding, so that we

7 don't generate rounding errors.

8 STAFF TOXICOLOGIST LEWIS: Yeah, that's correct.

9 There's no rounding till the end so we had -- it looked  
10 like we had 6.86.

11 PANEL MEMBER FUCALORO: Right, I understand.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: We always do the rounding at the last possible

14 step to avoid generating propagated rounding errors.

15 PANEL MEMBER BLANC: I mean I think it's

16 excellent that you modified the text to be consistent with

17 the evaluations that you did for the childhood project.

18 And on the same vein, do you think it would be useful to

19 insert under a source of exposure as a byproduct of the

20 breakdown of metam sodium in the first pair?

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: Yes, that would be a -- we will do that.

23 PANEL MEMBER BLANC: And do you feel that in the

24 process of the childhood literature review you've

25 basically caught up with all of the recent literature,

1 which this is one of the chemicals of which there tends to  
2 be a more evolving literature list there?

3 STAFF TOXICOLOGIST LEWIS: Yes, I think we feel  
4 very confident that. We did literature searches as  
5 recently as a week or two ago on that on several sources.

6 PANEL MEMBER BLANC: Right.

7 CHAIRPERSON FROINES: Andy, I don't want to get  
8 into this right now, but this notion of the BM05 versus  
9 BM10, it seems to me that in using a benchmark, one also  
10 needs to look at the nature of the data that you're doing  
11 the benchmark calculation from, in terms of the degree of  
12 extrapolation that you're pursuing.

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

15 CHAIRPERSON FROINES: And so it seems to me that  
16 one needs to have some flexibility within your guidelines  
17 in terms of the data set that's actually used for  
18 calculating the benchmark dose.

19 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
20 SALMON: Yes.

21 CHAIRPERSON FROINES: So I wouldn't tie myself so  
22 rigidly to a specific value, because you may want to --

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
24 SALMON: Well, I think that our philosophy in picking the  
25 BMC05, at least when we're reviewing, what I call,

1 "generaltox" animal studies, is that our experience to  
2 date has been that the BMC05 has generally been found to  
3 have properties fairly similar to the NOAEL, which we're  
4 used to dealing with, so that's why we're choosing that.

5           Now, I think it's a very valid point and one  
6 which we're struggling with that that may not be suitable.  
7 For instance, in some cases we're looking at epidemiology  
8 studies, we're particularly depending upon the nature of  
9 the endpoint. So, yes, I agree that we need to take  
10 everything somewhat on a case-by-case basis. But the BMC  
11 is our choice for a starting point at this stage.

12           And the other thing is, of course, that when we  
13 are calculating a benchmark, we are using the statistical  
14 tools which come in the software to evaluate the quality  
15 of it, and, you know, basically to ensure that we are  
16 looking at a reasonable data set and not extrapolating too  
17 far outside what's defined by the data, so that we do  
18 those things.

19           CHAIRPERSON FROINES: I think that's good. I  
20 mean, I think that's important, especially when you get  
21 into occupational studies at high exposure levels, where  
22 obviously you can be in a very different place if you  
23 weren't careful.

24           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
25 SALMON: Yes, I think our finding with the benchmark

1 calculation has been that, in general, it's proved a more  
2 satisfactory approach to do this calculation than to use  
3 the uncertainty factor NOAEL/LOAEL approach, when we don't  
4 have a NOAEL -- when we've basically got an unsupported  
5 LOAEL, we've often felt ourselves to be rather nervous  
6 about, you know, whether the LOAEL uncertainty factor of  
7 ten is, you know, appropriate.

8           In some cases it might be too large and in other  
9 cases too small. So particularly in that context I think  
10 we found the benchmark dose approach to be a more  
11 satisfactory way.

12           CHAIRPERSON FROINES: I'm a strong advocate of a  
13 benchmark dose approach. I think it's taken too long to  
14 be implemented for regulatory purposes. So you don't have  
15 an argument from me, but I still would argue that one has  
16 to look at the data carefully to make sure one isn't  
17 trying to use it when it wouldn't be appropriate.

18           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
19 SALMON: Yes, absolutely.

20           CHAIRPERSON FROINES: Go ahead.

21           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
22 SALMON: So the acrylonitrile, the modifications which  
23 were requested by the -- so acrylonitrile REL, we're  
24 basically responding to modifications requested by the  
25 panel at the last meeting when we considered this, and

1 also again including some consideration of impacts on  
2 children's health.

3           We were able to provide more information on the  
4 key studies adding actual tables of data into the summary.  
5 And, again, we switched over to using a benchmark dose  
6 calculation based on the key study here. And we also  
7 looked at an alternate study for a different endpoint,  
8 which we wanted to evaluate partly for comparison with the  
9 selected endpoint for adult effects, but also because the  
10 endpoint in question for neuro-toxicity is one which is of  
11 significance from the point of view of the children's  
12 health evaluation.

13                               --o0o--

14           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
15 SALMON: And this is what the derivation looks like. Now,  
16 the key study is still as it was when you last saw it.

17                               --o0o--

18           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
19 SALMON: But we're now using a benchmark dose calculation.  
20 And the new REL is, I think, reduced a little bit from the  
21 previous one, but basically it's replacing the previous  
22 methodology with the superior --

23           STAFF TOXICOLOGIST LEWIS: What's the previous,  
24 nine parts per billion?

25           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: Yes. Basically, we're using the benchmark dose  
2 calculation here, which we regard as preferable in this  
3 case.

4           And the other consideration which we've added  
5 here is the potential for impact on children's health.  
6 And there are two pieces of information that we were  
7 looking at here. One is that there is a developmental  
8 study, and that the chronic REL proposed for this endpoint  
9 was significantly lower than the developmental -- than a  
10 REL which you would propose on developmental effects.

11           So we feel that the processed REL is likely to be  
12 protective against developmental effects and  
13 neuro-toxicity again, as I was just saying now. We did  
14 look at that endpoint.

15           And although there is an neurotoxic effect from  
16 acrylonitrile in adults, this endpoint is less sensitive.  
17 And even allowing for the potential increased sensitivity  
18 of younger animals or humans to that endpoint, we feel  
19 that the proposed chronic REL, which is based on the  
20 histology changes in the upper respiratory tract, is  
21 likely to be protective of those endpoints for which we  
22 have concern as children having differential sensitivity.

23           So that's our proposed analysis on this one.  
24 Obviously, we're trying to work within the guidelines that  
25 we have put together on this issue, but this is an



1 exploratory exercise, so we very much welcome any input  
2 that you have on our approach here, if you think we're  
3 doing the right sorts of things and if this is adequate.

4 --o0o--

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: The next one up is beryllium. We updated the  
7 literature review for this analysis. There's been quite a  
8 number of things which have come out in the literature  
9 since the original version was put together. And in  
10 particular three references that Dr. Blanc suggested we  
11 should examine more closely have been included.

12 There was also discussion of the uncertainty. In  
13 fact, there's an issue here as to -- this is the  
14 intraspecies uncertainty factor, and there's a question of  
15 whether the responders are a sensitive subpopulation. And  
16 if so, whether -- you know, normally we're using a default  
17 of ten for this uncertainty factor, but in this case,  
18 we're using now an uncertainty of three. We had  
19 previously gone all the way down to one, but that was  
20 considered illadvised, so we've changed that.

21 Also, we did look for any evidence of  
22 differential effects on infants or children. We basically  
23 found no indication of any such effects, so we can't  
24 really add anything on that, other than to say there's no  
25 evidence that there was a problem here. The final thing

1 is that this is like the fluoride case, in that airborne  
2 beryllium is often going to be found in a particulate  
3 form, hence can settle out, and needs to be treated by the  
4 multi-media methodology in Part 4 of the guidelines.

5 So we need an oral chronic Reference Exposure  
6 Level. So we've included that, so that it can be included  
7 in the multi-media assessment on the Hot Spots Guidelines.

8 --o0o--

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: This is the actual derivation. Again, the study  
11 hasn't -- this is the derivation of the oral chronic REL.  
12 This is the inhalation REL, apart from the change in  
13 uncertainty factor hasn't altered. The chronic REL uses a  
14 dietary chronic oral REL was used in a dietary study in  
15 dogs. And the critical effect is intestinal lesions.

16 --o0o--

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: We're using a relatively standard benchmark dose  
19 methodology here, and come up with a chronic oral REL of  
20 0.002 milligrams or two micrograms per kilogram per day.

21 And this is, I think, in fact, fairly similar to  
22 what the U.S. EPA has.

23 STAFF TOXICOLOGIST LEWIS: It's actually  
24 identical to the U.S. EPA RFD.

25 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: We've been through the arithmetic and found  
2 ourselves to be in agreement with the federal axis.

3 PANEL MEMBER FUCALORO: I clearly misunderstood  
4 something though. Two slides ago, you talked about a UF  
5 sub H from 1 to 3. Now, what uncertainty factor was that?

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7 SALMON: This is for the inhalation.

8 PANEL MEMBER FUCALORO: Got you. This is all  
9 right.

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Apart from that change, the inhalation analysis  
12 has not -- you know, is not different than the version  
13 that you saw previously. The addition of the oral REL is  
14 the thing. And as you see in that case we're not looking  
15 at a sensitive subpopulation effect or anything like that,  
16 so we're using the standard default uncertainty factors.

17 PANEL MEMBER WITSCHI: I have a comment about  
18 your oral data. The effect in the study is they are  
19 probably close by the acidity of the beryllium sulfate.  
20 And if you go back to the literature on beryllium in the  
21 40s and 50s, there are several papers which very  
22 conclusively show that beryllium is not absorbed at all  
23 into the blood stream from the gastrointestinal tract,  
24 because it's precipitated presumably as phosphate. And so  
25 this would be mentioned somewhere.

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: Okay. I think that we took note, I think, of  
3 your comment previously that the intestinal absorption is  
4 low to negligible, but maybe we need to amplify our  
5 language a little bit to make it clear that we're aware of  
6 that, and so we will do that.

7 Yes, I mean, it's a slightly curious situation,  
8 but, you know, there's a pathological endpoint here by the  
9 oral root, so we feel obliged to respond to it at some  
10 level.

11 PANEL MEMBER BLANC: Yeah. I mean the issue here  
12 is that the significance of oral exposure, even without  
13 systemic absorption is the same issue as the effect of  
14 skin contamination through airborne sources, which would  
15 tend to potentially sensitize someone as well. So if you  
16 sensitize someone through oral primate, and then have them  
17 exposed by inhalation, they'd be, well, theoretically,  
18 particularly more likely to respond to the beryllium that  
19 they inhaled.

20 So for that reason, the oral exposure would be  
21 meaningful as nerve sensitization viewed without any  
22 absorption. The implication is not that you're absorbing  
23 beryllium systemically and then depositing it  
24 preferentially in the lung, but rather that you're  
25 becoming sensitized theoretically, I guess, through some

1 oral contamination. It's, I think, much more likely you  
2 become sensitized through skin contact and then because  
3 you're systemically sensitized, once you inhale it, you've  
4 developed chronic beryllium disease.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: It would be nice if we had experimental data that  
7 would enable us to analyze that kind of situation more  
8 fully, but unfortunately, you know, what you see is what  
9 we can find in the literature here. So we hope that we've  
10 addressed those issues in some way at least with the  
11 approach we're taking here.

12 PANEL MEMBER BLANC: Well, since you don't take  
13 into account the skin route, it doesn't bother me that you  
14 have the oral thing in there, because one probably  
15 counter-balances the other, even if it's, you know, overly  
16 conservative having the added oral burden that you can't  
17 really calculate the skin content burden.

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: Yeah, that's right, we don't have a good way of  
20 dealing with that, at this point, so this is hopefully  
21 providing sufficient protection.

22 Thank you.

23 --o0o--

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

25 SALMON: The next one I want to present is the

1 chloropicrin. This one has also been reworked with  
2 firstly responding to modifications requested by the  
3 panel, secondly, an inclusion of the benchmark dose  
4 calculation, and, thirdly again, consideration of the  
5 children's health impacts.

6           So this is the calculation as we have it, at this  
7 point, using BMC05 on the data from the Burleigh-Flayer  
8 and Benson study.

9           This compound obviously is a highly irritable  
10 material. In deed, that's its principle use, I believe.  
11 And the finding is irritation in the upper and lower  
12 respiratory tracts.

13                               --o0o--

14           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
15 SALMON: We have used, as I say, the benchmark  
16 concentration approach, coupled with a fairly standard  
17 uncertainty factor here, but, you know, we've got an  
18 uncertain intraspecies here of three because we're doing a  
19 human equivalent concentration using the RGDR methodology.

20           So this is basically similar to what we were  
21 doing before with the uncertainty with the NOAEL approach.

22                               --o0o--

23           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
24 SALMON: And the chronic REL proposed is 0.05 parts per  
25 billion or .4 micrograms per meter cubed, which is a

1 fairly low number reflective of the fact that there is a  
2 high irritant material.

3 --o0o--

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: When we looked at the children's health issue,  
6 we're conscious of the fact that this endpoint is  
7 potentially one which does have a differential impact on  
8 infants and children. The finding has generally been that  
9 irritants do exacerbate asthma at least in people already  
10 suffering from asthma.

11 There is some suggestion that actually induction  
12 of asthma or insensitive subjects including people who are  
13 atopic may also occur. But there, as you heard earlier,  
14 in the SB 25 discussions, there's a number of  
15 uncertainties about exactly what is going on here,  
16 particularly with agents like chloropicrin, which,  
17 frankly, there have simply not been studies with respect  
18 to this sort of consideration.

19 It's fairly easy to see why people have not done  
20 those response studies with chloropicrin on children. But  
21 nonetheless, from the point of view of undertaking this  
22 analysis, it represents a serious data gap. We are unable  
23 to point to any specific indications that the methodology  
24 is inadequate.

25 In particular, we do have the intraspecies

1 uncertainty factor of ten included in the calculation,  
2 which we believe, by default, allows for the existence of  
3 sensitive subpopulations within the general human  
4 population. And in particular we think that children, and  
5 especially asthmatic children, might be such a sensitive  
6 subpopulation.

7           So we're basically relying on the existing  
8 uncertainty factor of ten to accommodate that hypothesized  
9 sensitive subpopulation. We don't have any specific  
10 evidence or guidance, at this point, which would encourage  
11 us to do anything other than that, so this is what we're  
12 proposing.

13           CHAIRPERSON FROINES: One could argue that if one  
14 looks at the history dating back to the 1950s of risk  
15 assessment approaches, and the development of the  
16 uncertainty factor, safety factor approach, one would  
17 argue that the definition of the safety factor for  
18 intraspecies variability was never intended as a  
19 historical matter to address differences in adult versus  
20 children sensitivity.

21           And that there's no, sort of, underlying  
22 intellectual basis to make that assumption, so that it's  
23 something that I think needs to be reviewed as we move  
24 forward, because, in a sense, what you say is that we have  
25 a safety factor of ten and we assume that it includes



1 within the distribution children, but that's not  
2 necessarily an assumption that has an underlying basis to  
3 it. It's an add-on almost.

4           And I think that that's probably an inadequate  
5 way of looking at it. If you were writing it -- instead  
6 of putting up a set of numbers, if you were writing it in  
7 some sort of intellectual context, I don't think you would  
8 feel quite happy with that formulation, frankly.

9           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: I agree. And obviously, this is an area where we  
11 are going to have to put in additional work. We have a  
12 mandate under the SB 25 program to develop improved risk  
13 assessment guidelines for specifically taking into account  
14 effects on infants and children. And this is clearly one  
15 of the areas where such development is needed.

16           I think the situation we have at the moment is  
17 that we are lacking in either a default guidance, other  
18 than we're sort of vaguely trying to adapt to the purpose  
19 here. And we don't have any specific data on  
20 chloropicrin. I think what we hope is that in the long  
21 term, we may be able to identify cases where there are  
22 sufficient data that we can perhaps come up with something  
23 more satisfying as a general guideline and will then be  
24 able to extrapolate that to other chemicals like  
25 chloropicrins, which we don't have the data.

1           And, of course, if during that process we  
2 identify something which says that we're not right in  
3 making this default assumption here, then we would have  
4 to, by definition, that would immediately identify any  
5 chemicals where we had made the assumption as chemicals  
6 which should be added to the list of critical materials  
7 for reevaluation, bearing in mind that we have a program  
8 for checking into and prioritizing all the toxic air  
9 contaminants. And we actually have to have reevaluated  
10 another ten by 2004.

11           CHAIRPERSON FROINES: I just think as a general  
12 matter and we have to move on because we have a lot to  
13 cover that's important, but I don't think that population  
14 heterogeneity, which brings about the safety factor of  
15 ten, really includes variations in children's exposure  
16 physiology, so on and so forth.

17           And so that, in a sense, it's broadening the  
18 distribution, and therefore assuming a factor of ten is  
19 okay, and I suspect that it may not be.

20           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: If you can, you know, point us in a direction  
22 where we should go, at this point, with this REL, I think  
23 we'd be very happy.

24           CHAIRPERSON FROINES: Yeah, I agree. I think  
25 with this REL it's impossible, but even in terms of the

1 general premise, it's obviously a difficult one.

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Yes, we're at a preliminary stage.

4 --o0o--

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: The next one is --

7 PANEL MEMBER BLANC: One very small question just  
8 on the -- this is a methodologic issue in terms of how you  
9 handle these in general.

10 But on this particular chemical for the physical  
11 properties when you get to the vapor pressure, you site a  
12 reference for the vapor pressure, and it's a 1921  
13 reference, which is pretty long ago. You don't generally  
14 site, parenthetically, the reference source for vapor  
15 pressure in the introductions.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: I think --

18 PANEL MEMBER BLANC: And is that because you just  
19 couldn't confirm the vapor pressure from any other more  
20 recent source?

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: I think what happened here was that, I suspect,  
23 working from slightly different reference sources than  
24 this one, that we generally, use this, obviously is a  
25 slightly unusual chemical, and it has considerable

1   pesticidal uses and things of that sort.

2                   And also --

3                   PANEL MEMBER BLANC:  It gives the impression  
4   of -- anachronism isn't the right word, but you now one  
5   would --

6                   AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7   SALMON:  Yes.  In this particular case, the reference is  
8   from a treatise on chemical warfare.

9                   PANEL MEMBER BLANC:  I understand that.

10                  AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11   SALMON:  I suspect this is reflective of the unusual  
12   nature and terms and reference to the compound.

13                  PANEL MEMBER BLANC:  Yeah, but you should be able  
14   to find it in the MERCK Manual, too, I would think.

15                  AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

16   SALMON:  We have been enjoined to use primary references  
17   where they're available.  But maybe a more up-to-date  
18   reference, if we can find one, would be right.

19                  CHAIRPERSON FROINES:  Well, I think that the  
20   answer to the question would be to write the manufacturer  
21   of chloropicrin to the degree that anybody is making it.

22                  AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23   SALMON:  Well, we could probably obtain a more recent  
24   statement through the Department of Pesticide Regulation.

25                  PANEL MEMBER BLANC:  Yes.  And I assume that the

1 key papers that you have used that we're exposing animals  
2 through generating saturated vapors of this solution must  
3 have stated what the vapor pressure was?

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: Yes. Well, they probably cited this reference.

6 PANEL MEMBER BLANC: That's how you got to it in  
7 the first place?

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Yes, I think probably it is.

10 Diethanolamine, again, we are responding to early  
11 comments by the panel, and also including consideration of  
12 children's health impacts. And there's a change in the  
13 critical study and endpoint. This new study is one which  
14 was actually submitted to us. It's basically a regulatory  
15 type study that was done more recently than the one that  
16 we previously had access to.

17 But it's not especially remarkable in other  
18 respects, but it is a newer and more comprehensive study  
19 than the one that we were using previously.

20 And so it's a chronic inhalation study, and we're  
21 using a NOAEL/LOAEL approach here. My sense is that we  
22 were looking -- we looked at the data table in the  
23 analysis. In fact, we haven't got a data set here for  
24 which we can use the benchmark dose methodology, because  
25 we've got basically close to 100 percent response in some

1 of the -- well, in fact, in virtually all of the  
2 categories, so we were not able to get a statistically  
3 acceptable analysis using the benchmark dose approach. So  
4 this one we're staying with the NOAEL/LOAEL methodology.

5 --o0o--

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
7 SALMON: And so the LOAEL uncertainty factor we chose was  
8 an uncertainty factor of three based on the nature of the  
9 effect, which was the hyperplasia and metaplasia were in  
10 the larynx were in an extremely localized area. And the  
11 rest of the respiratory tract didn't show any changes  
12 until higher doses.

13 So we felt justified in arguing that this was a  
14 less severe effect than the more widespread irritation and  
15 pathological changes which we've chosen to regard as a  
16 critical effect in some other studies.

17 So we then applied the usual approach of  
18 uncertainty factors.

19 --o0o--

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: Subchronic uncertainty factor of three relates to  
22 the duration of the study which is a 90-day study. And,  
23 in fact, we come up eventually with a cumulative  
24 uncertainty factor of 1,000, which is, you know, the  
25 highest that we normally consider.

1           The proposed chronic REL based on the upper  
2   respiratory tract effects is considerably lower than the  
3   comparison REL, which was based on fetotoxicity. So from  
4   the point of view of any developmental effects, we see  
5   this proposed REL as protective of infants and children.

6           Again, we're seeing it is a respiratory irritant  
7   which might exacerbate asthma, and have, thereby, an  
8   adverse effect specifically on some children.

9           However, we felt that in this case the inclusion  
10   of the overall uncertainty factor of 1,000 would probably  
11   be sufficient to reassure us that we were okay with the  
12   proposed REL in the situation where there's no direct  
13   evidence that diethanolamine exacerbates asthma or would  
14   allow us to quantify any other means for differential  
15   impact on infants and children.

16           PANEL MEMBER BLANC: Although, there are case  
17   reports of allergic sensitization of asthma by  
18   diethanolamine, aren't there not? This is not an irritant  
19   just as this would, sort of, be presumably.

20           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21   SALMON: I don't know that we have any quantitative  
22   information about exposure that would allow us to use  
23   those.

24           PANEL MEMBER BLANC: You probably wouldn't.  
25   There would just be --

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: This is a recurrent problem with this sort of  
3 report, that, you know, it's something which may be out  
4 there but we don't know.

5 PANEL MEMBER BLANC: Well, you would have it to  
6 the extent that if it was one of the cases where someone  
7 did a specific inhalation challenge to document that  
8 causal relationship, then you would.

9 STAFF TOXICOLOGIST LEWIS: We did list one case  
10 report of a person occupationally exposed to  
11 diethanolamine with occupational asthma.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: I think the situation here --

14 PANEL MEMBER BLANC: Which reference is that?

15 CHAIRPERSON FROINES: Page A 28. It's under 4  
16 Roman Numeral 4 on A 28.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: Some of these in occupational studies are a  
19 little bit retro in terms of the methodology and  
20 conditions.

21 PANEL MEMBER BLANC: And when you pulled that  
22 case report, had they done an inhalation challenge, do you  
23 know?

24 STAFF TOXICOLOGIST LEWIS: I didn't see the  
25 report myself.



1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: I don't believe they did. No, I think it is  
3 literally just a case report.

4 PANEL MEMBER BLANC: You might just double check  
5 that, because that would give you at least that exposure  
6 level that would trigger a response in someone who's been  
7 sensitized. I'm not familiar with the case report, so I  
8 can't tell you.

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: I think, but we'll check into it anyway.

11 PANEL MEMBER BLANC: Now, sometimes it's so crude  
12 that it's only to have him go into the workplace and then  
13 they prove that he has dropped his FEV1, but sometimes  
14 it's a control exposure, and they would actually have a  
15 concentration level that you could cite.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: We'll make sure that there isn't -- when we can  
18 have another look for that, but at this point --

19 PANEL MEMBER BLANC: I don't think it would  
20 change anything else you've done. It would be just good  
21 for your documentation.

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: We would want to know. So we'll have another  
24 look and see if we can find anything.

25 PANEL MEMBER BLANC: In that particular paper,

1 yeah.

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Right.

4 CHAIRPERSON FROINES: The interesting thing about  
5 this compound is that given the toxicologic data that you  
6 site, it has interesting implications for occupational  
7 exposures.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Um-hmm.

10 The level that we came up with was quite a bit  
11 lower than I think the -- you know, we received this study  
12 as part of a public comment, basically. And I think they  
13 were expecting us to come up with an evaluation which was  
14 rather less stringent than the one that we actually  
15 produced. I'm not quite sure why they had that  
16 expectation, but it may have something to do with their  
17 perception of how the material was seen in terms of  
18 occupational health at the present time.

19 --o0o--

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: The next one I'd like to present is ethylene  
22 dibromide. And this is one which we came up with the  
23 analysis in March, but I think is a -- I think I'm correct  
24 in thinking that this is one of the ones that Dr. Friedman  
25 was in charge of, and he wasn't at that meeting, so we

1 deferred consideration to the present meeting. So this is  
2 basically the first time the panel, as a whole, has  
3 reviewed this one.

4 It's, basically, an occupational exposure study.  
5 And the subjects in question are, I believe, pile workers  
6 in Hawaii. The effect is reproductive toxicity, reduction  
7 in sperm count, abnormal and viable sperm, and various  
8 other related changes.

9 And in this case, we used the LOAEL/NOAEL  
10 methodology. We don't have a NOAEL. We don't also have,  
11 at this point, have the sufficient detail on the raw data  
12 of the study to be able to do a benchmark calculation, so  
13 we're staying with the NOAEL here, and the exposure  
14 continuity and duration allowed for in the usual way.

15 And this results eventually in using standard  
16 methodologies in proposal of a REL of 0.1 parts per  
17 billion or 0.8 micrograms per meter cubed. And this  
18 reflects the fact that this is a, you know, certainly an  
19 effect of concern, and that we don't have, in fact, a full  
20 chronic exposure duration with the study in a period that  
21 was about four to five years on average.

22 --o0o--

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
24 SALMON: As far as the impacts on children's health are  
25 concerned, there's an animal study which included

1 developmental toxicity endpoints in rodents. And we  
2 actually include an analysis of this in the summary for  
3 comparison, I think, which you -- anyway, basically the  
4 fetotoxicity in rodents was reported at significantly  
5 higher levels.

6           So we're thinking that the proposed REL should be  
7 adequately protected against those developmental effects.  
8 We have no direct evidence that the reproductive toxicity  
9 endpoints in humans would have a differential impact on  
10 infants and children, although it's possible,  
11 hypothesizing that adolescent boys might be more sensitive  
12 than adults then.

13           Given that metabolism is an important factor in  
14 the toxicity of this compound, there's a possibility that  
15 there might be metabolic differences between infants,  
16 children and adults. We don't have any evidence about  
17 this. So again, I think we're in a situation of wanting  
18 to put, if you like, put a thumb print on this as  
19 something that we should continue to look at carefully.  
20 But for the time being we are really stuck with, assuming  
21 that our regular methodology is sufficiently cautious, to  
22 protect the infants, children and adolescents as well as  
23 the adults.

24           PANEL MEMBER FRIEDMAN: Can I ask you about a  
25 different metabolic capability in children versus adults,

1 is there a certain direction that you would expect or  
2 could it go both ways, one they could metabolize it better  
3 or worse?

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: What we've seen so far, is that things can change  
6 in both directions. Typically the -- well, the  
7 differences from what you would call sort of childhood  
8 throughout adolescence and adulthood are typically not  
9 very large, but what you do see is quite significant  
10 changes between fetus, newborn and infant, you know,  
11 during that phase, there are changes.

12 And a lot of enzymes in the fetus are, you know,  
13 for instance, the cytochrome B450 enzymes are different.  
14 And the absolute level of their activity is often somewhat  
15 lower by the standard assays, but we often, in fact, see  
16 higher sensitivity in the fetus and the infant in spite of  
17 having lower activity of Phase 1 enzymes, because the  
18 activity of the Phase 2 enzymes is often lower, too, and  
19 obviously the toxicological outcome depends on the balance  
20 between the Phase 1 and the Phase 2 enzymes.

21 And in some cases the Phase 2 enzymes are more  
22 depressed in the infant or fetus than are the Phase 1  
23 enzymes. So the answer is it can go either way in terms  
24 of the outcome.

25 PANEL MEMBER FRIEDMAN: And what is Phase 1 and

1 Phase 2 mean?

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Phase 1 is the activating enzymes that typically  
4 the oxidative actions of cytochrome P450s is sort of the  
5 classical example, which is the thing which actually  
6 generates reactive intermediates, such as epoxies or  
7 things of that sort.

8 And the Phase 2 is the detoxifying enzymes,  
9 typically glutathione transferases, and ultransferases,  
10 things of that sort.

11 CHAIRPERSON FROINES: Andy, I'm very concerned  
12 about this 2:00 o'clock cutoff that we have, and so I'm  
13 going to have you go till 11:30. I'm very anxious to have  
14 the pesticide discussion today and the findings for SB 25.  
15 So I'm going to go till 11:30 with your presentation, then  
16 I'm going to cut it off and move on the agenda, and then  
17 we'll come back to anything we haven't finished as we get  
18 finished with the other two.

19 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

20 SALMON: Do you want me to try and --

21 CHAIRPERSON FROINES: So we should try and push  
22 ahead, you know, spending a lot of time on EDB is a  
23 exercise in futility, given how much, how little is used  
24 in the environment in California.

25 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: Well, if there are any comments or suggestions or  
2 additions that the panel wants to send us, obviously we'd  
3 be happy to deal with them.

4 --o0o--

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: The next one to look at is isophorone. The panel  
7 has reviewed the REL development for this compound in  
8 March. We're bringing it back to you here because we've  
9 added a section on differential impacts on children's  
10 health.

11 And in this particular case the REL is based on a  
12 developmental study. And we feel it's therefore  
13 reasonable to expect that it should be adequately  
14 protective of infants and children. However, there is no  
15 direct evidence in the literature that would quantify any  
16 differential effects of isophorone in children relative to  
17 adults.

18 So apart from this conclusion that since we're  
19 using developmental endpoints as the critical endpoint and  
20 that that's the basis of the REL, really we don't have  
21 anything else to add and we haven't otherwise changed the  
22 analysis significantly from when you last saw it.

23 So if this is seen as a reasonable response to  
24 the data from the point of view of considering the impacts  
25 on children's health, then this is it.

1           PANEL MEMBER BLANC: Given your allusion to  
2 children's health and given the aside that this chemical  
3 occurs naturally in cranberries, and given the fact that  
4 children's intake of juice per kilogram is rather high, do  
5 you need to include one of your orals or is it such a  
6 trace trivial?

7           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
8 SALMON: I think it's a relatively minor component. I  
9 don't, of course at this point, have an analysis for you  
10 on oral toxicity specifically. We don't have a mandate to  
11 consider food and constituents under the hot spots  
12 program. And I don't think that this qualifies as  
13 multi-media. So in this particular context, we don't have  
14 much of a handle on that issue, but it may well be that  
15 although this -- let me get to the right data here.

16           We don't have a particular reason for including  
17 oral isophorone at this point, and for the hot spots  
18 purpose, but it may well be relevant certainly in more  
19 general terms in consideration of children's health.

20           PANEL MEMBER BLANC: Okay.

21           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
22 SALMON: I think, I mean the question of oral exposures  
23 and sensitivity of children is clearly an important one  
24 with implications for our overall consideration of how we  
25 think about children's health impacts. And isophorone is



1 one of those things that we should probably look at,  
2 because as you point out there is a relationship to  
3 special exposure of children, so we should look at that.

4 And if we find anything which has any  
5 implications for this, then we can put it in, but I don't  
6 anticipate there being a direct implication at this point.

7 --o0o--

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: The next one that we are presenting, I'll try and  
10 get through this one as quickly as I can, we presented  
11 this previously to the panel, and we responded to the  
12 panel's comments including drawing our attention to some  
13 additional studies that we should review in the summary.

14 This is using a benchmark dose calculation on the  
15 rat data, which is an improvement on our earlier  
16 methodologies. Again, we're moving to the improved  
17 methodology here. It doesn't create a huge difference in  
18 the outcome of the analysis, but we feel that it's a  
19 methodological improvement.

20 The other thing, which we did, was we examined  
21 several papers where there was occupational exposure to  
22 maleic anhydride to see whether we could actually get a  
23 human basis for a derivation.

24 The problem with this is is that all the  
25 occupational exposures described, in fact, were mixed

1 exposures including, in particular, trimaleic anhydride  
2 which is a rather notoriously irritant and sensitizing  
3 material. So we don't really have a very good  
4 quantitative basis for a derivation from human data here.

5           However, what we did see is that even if you  
6 assume that all the anhydride is maleic in those studies,  
7 we still do have a somewhat reasonable protective basis  
8 using the REL, which we calculate from the rat data. So  
9 what we're doing is we're using the human data basically  
10 as a comparison to make sure we're not missing anything  
11 too crucial.

12           And apart from that, we're proposing to stay with  
13 the rat study, but to use the benchmark. We prefer the  
14 use of the benchmark dose calculation, because there  
15 isn't, in fact, an observed NOAEL. And as we were saying  
16 earlier, we feel, under the circumstances, that a  
17 benchmark approach is greatly preferable when you don't  
18 have a NOAEL.

19   --o0o--

20           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
21 SALMON: And the other interesting feature of this is that  
22 although the key study, which is statistically the one we  
23 chose to analyze by the benchmark approach, is the rat  
24 study, there were also studies in other species including  
25 monkeys. And the benchmark, which we calculate from the

1 rat study is consistent with the data observed in the  
2 monkeys.

3           So in this case we're proposing an intraspecies  
4 uncertainty factor of only three, which we generally  
5 propose when we have indications of the dose response in  
6 nonhuman primates, which we feel are more similar to  
7 humans and therefore justify a lower intraspecies  
8 uncertainty factor.

9           On that basis, we propose an inhalation REL of  
10 0.7 micrograms per meter cubed.

11                               --o0o--

12           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: Again, this gives us some concern in terms of  
14 children's health. And the endpoint is irritation and the  
15 maleic anhydride is a known respiratory irritant and  
16 inducer of asthma. And this would be an endpoint that  
17 does have a more severe impact on children and adults.

18           However, there is no evidence that we can use to  
19 quantify that effect. So until we have such evidence to  
20 quantify, we are, again, proposing to rely on the ten-fold  
21 intraspecies uncertainty factor to provide a margin of  
22 safety, but recognizing that asthmatic children will  
23 clearly be a sensitive subpopulation who might be  
24 marginally protected only, at this point, with this REL,  
25 but the aim of the REL being basically to protect the

1 majority of the population.

2 --o0o--

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: The next one -- I'm looking at the time here, I  
5 hope I'm not rushing you too much here.

6 The next one I want to present is methyl  
7 isocyanate, and the changes are quite limited. One of the  
8 things that the panel asked us to do, the earlier review,  
9 was to actually include some data on the amount or some  
10 indication of the amount that might be involved as a  
11 breakdown product from metam sodium use. It has been  
12 identified as a minor breakdown product in the environment  
13 after metam sodium use.

14 And this, in fact, looks as if it might be by a  
15 significant margin the largest single source of the  
16 material, at least in the Californian environment and  
17 possibly apart from a couple of specific industrial hot  
18 spots. So this is a value.

19 We don't have a number for the amount of methyl  
20 isocyanate that might be involved, but we do have a number  
21 of metam sodium used and it clearly is fairly  
22 considerable. This is an average over the years of '95 to  
23 '99.

24 The other issue is the differential impacts on  
25 children's health. We do have a reproductive study which

1 did not identify any increased sensitivity of the fetus  
2 relative to the parent. So we're thinking that, at least  
3 from that point of view, the chronic REL should be  
4 protective of infants and children.

5           Again, we have this concern that because it's a  
6 severe respiratory irritant, there may be a variety of  
7 different impacts on infants and children. And the fact  
8 of the matter is we don't have a direct quantitative  
9 indication of what that might be. So, again, we are  
10 having to rely on the defaults on intraspecies uncertainty  
11 factors at this point.

12           PANEL MEMBER FUCALORO: Can I ask you a quick  
13 question on the major uses and sources, maybe you  
14 mentioned this before. Based on the most recent  
15 inventory, the annual statewide industrial emissions from  
16 facilities reporting under the toxics air hot spots at  
17 California estuaries to be .29 pounds.

18           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
19 SALMON: Yeah.

20           PANEL MEMBER FUCALORO: That's it. .29 pounds.

21           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
22 SALMON: The major --

23           PANEL MEMBER FUCALORO: I know the major isn't  
24 the metam sodium, but --

25           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: I mean, obviously this material is used in  
2 various kinds of industrial processes, but it appears that  
3 those industrial processes are not ones which typically  
4 are carried out in California. So our concern --

5 PANEL MEMBER FUCALORO: .29 pounds, they'd even  
6 report that.

7 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

8 SALMON: Yes.

9 PANEL MEMBER FUCALORO: I mean, are you sure the  
10 number is right?

11 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

12 SALMON: Let's say I have as much confidence in that as in  
13 the other numbers we've pulled off the hot spots data.

14 PANEL MEMBER FUCALORO: No, no, seriously, is  
15 there not a typo or something?

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: I don't think so.

18 CHAIRPERSON FROINES: It's clearly wrong. We  
19 should check it. It's years old.

20 PANEL MEMBER FUCALORO: You may be wrong in terms  
21 of not --

22 CHAIRPERSON FROINES: A lot of the data that gets  
23 cited under the toxic hot spots is really one wouldn't  
24 want to bet one's life on by any means. So I think that I  
25 always just take it with a grain of salt and go on and

1 don't take it seriously for the most part.

2           Unfortunately, that's the state of that data and  
3 we probably should talk about it sometime in another  
4 meeting where we go back and look and see how dated that  
5 information is and really how much confidence one can put  
6 to it, because it ends up in all these documents as though  
7 those are realistic figures and they're not.

8           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Well, it's obvious that any reporting under that  
10 hot spots database is somewhat constrained by who chooses  
11 to report.

12           PANEL MEMBER FUCALORO: I guess I'm asking -- I  
13 mean, I don't want to belabor the point, but the hot spots  
14 reported as, estimated as -- I mean, you actually have a  
15 list of things that are saying that this toxic thing was  
16 under a pound a year in all of California.

17           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: That's the numbers we came up with.

19           PANEL MEMBER FUCALORO: That's the numbers you  
20 see.

21           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: Whether it's right, we need to check.

23           PANEL MEMBER FUCALORO: I can understand  
24 something like a dioxin, but I mean this is something --

25           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: We'll check into that and make sure there isn't

2 --

3 CHAIRPERSON FROINES: I think that the selection  
4 of values all have a certain ridicule value associated  
5 with them. And when you put something into a document  
6 that has a super high ridicule value, that's probably been  
7 a bad judgment.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: You feel we should simply delete that.

10 CHAIRPERSON FROINES: I would not -- yeah, I  
11 would.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: We can do that if you think that's appropriate.

14 CHAIRPERSON FROINES: .29 pounds?

15 PANEL MEMBER FUCALORO: First check it.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: Yes. Well, we'll check it and if we're not happy  
18 with what we find, we'll --

19 PANEL MEMBER BLANC: Well, the simple solution  
20 would simply be, the remainder of the sentence after it  
21 says "...in California were negligible."

22 PANEL MEMBER FUCALORO: And the metam sodium was  
23 not.

24 PANEL MEMBER BLANC: They're not reporting  
25 anything other than that.



1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: I think that's probably the most accurate way and  
3 diplomatic way of characterizing it, so we'll do that.

4 PANEL MEMBER BLANC: What you expect, because  
5 nobody uses those chemicals as a direct intermediate, it's  
6 an unanticipated byproduct by and large except in very,  
7 very limited -- I think it's Hopewell, West Virginia is  
8 the only place in the United State where it's used  
9 regularly as a chemical.

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Well, nobody is making a carburil in California.

12 PANEL MEMBER BLANC: So nobody should be  
13 reporting release of it.

14 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

15 SALMON: Yeah.

16 PANEL MEMBER BLANC: In fact, if anybody reported  
17 any release of it, it would make you wonder what they were  
18 doing.

19 (Laughter.)

20 CHAIRPERSON FROINES: But I think, at some point,  
21 at a meeting in the future, it would be worthwhile to have  
22 a discussion about the hot spots program, because we  
23 haven't had one in years and years and years, and it would  
24 be very useful to discuss the validity of the data that's  
25 currently in the hot spots program, because I won't go

1 into more detail, but my understanding of the program is  
2 that it's been on hard times. And so it's something that  
3 would be good for this panel to be aware since we have --  
4 since every chemical that we get has a value essentially  
5 from the hot spots program or very many.

6 And it would be useful to have a sense of how do  
7 we view that information. And I look back and Lynn's  
8 nodding his head and George is nodding his head, so I feel  
9 comfortable saying that.

10 But I think this is an area that's somewhat  
11 problematic, because our information on exposures tends to  
12 be a limiting factor in some respects.

13 Now, as a related question, and Lyn Baker may  
14 have an answer, which is it would be useful to know  
15 something about what kinds of exposures are occurring to  
16 MIC. And it's my understanding that whereas there has  
17 been some studies of MITC, I don't know if there has been  
18 any attempt to quantify MIC. Is there a comment, because  
19 I think that's a -- obviously, given the sensitivity of  
20 MIC because of Bhopal, it's not a trivial issue,  
21 potentially anyway.

22 MR. BAKER: Hi, Dr. Froines. Lynn Baker from the  
23 Air Resources Board. I can address that briefly. We did  
24 do some MITC monitoring a couple of years ago around a  
25 specific application, and we did do monitoring also for

1 MIC, but that was just a short-term study.

2           However, this year, we did do eight weeks of  
3 monitoring in Kern County for both MITC and MIC, so  
4 ambient monitoring, which we don't have the data yet, but  
5 early next year we will have that data available.

6           CHAIRPERSON FROINES: Well, that will be  
7 interesting to come back to, given the 15 million pounds  
8 currently in use, to see what it looks like.

9           Thanks Lynn.

10           And, Andy, one final question, at Bhopal do you  
11 have any sense, and I realize this is a very poor  
12 question, but was there any indication that children were  
13 differentially affected?

14           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
15 SALMON: Not --

16           CHAIRPERSON FROINES: I mean clearly there was  
17 such a horrendous event that it's hard to ask that  
18 question.

19           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
20 SALMON: Not that I'm aware of in terms of the acute  
21 effects. There were reports of some adverse reproductive  
22 and developmental outcomes, which would come within the  
23 purview of our consideration here, but those are hard to  
24 quantify, because of the -- among other things, because of  
25 the difficulty of collecting data in that population. In

1 fact, they have a fairly high level of disease related  
2 reproductive problems in the population already.

3 So that's a little bit of a gray area. But it's  
4 my belief that there are some reports of developmental  
5 issues following the Bhopal accident, but nothing  
6 specifically to say that the acute damage to the eye or  
7 the lung was particularly severe in children.

8 CHAIRPERSON FROINES: Thanks. I think we'll call  
9 a quit for a moment, hopefully getting back to it, if  
10 that's okay.

11 Does the panel want to take a five minute break  
12 so the court reporter can take a break?

13 Then we'll talk about the SB 25 findings.

14 (Thereupon a recess was taken.)

15 CHAIRPERSON FROINES: The next item on the Agenda  
16 is going to be the panel consideration of the findings of  
17 our deliberations based on SB 25.

18 You have an updated version of the document,  
19 which is most of the changes that have been put in are  
20 small and editorial in nature. There is one major change  
21 which I'll call your attention to that we thought was  
22 important under Section 15 on pesticides.

23 We've added a sentence, it's on page 615, and it  
24 states as follows, "In the toxic air contaminant program,  
25 there is" -- this is not, perhaps, written -- "there is a

1 parallel program where the Department of Pesticide  
2 Regulations identifies pesticides as Toxic Air  
3 Contaminants. The panel recommends that parallel or  
4 similar consideration of children be given in the  
5 evaluation of pesticides and their pesticidal use."

6           The intent of that sentence is to say that the  
7 decision to leave pesticides out of SB 25 needs to be  
8 reconsidered in the future, so that we can have inclusion  
9 of pesticides as well as other chemicals. And that's the  
10 purpose of that sentence, and that's consistent with the  
11 dialogue that occurred over the four meetings that we had  
12 on SB 25 where there was continually stated concern about  
13 the absence of pesticides. And so that's the one  
14 difference that you have over the draft that you've  
15 already seen.

16           So we need to decide whether this draft is  
17 satisfactory and whether we can send the findings forward.  
18 So I guess the best way to do that is to ask each  
19 individual for comments. We have comments from Stan  
20 Glantz who said that he thought that the document was  
21 fine, except we needed to make changes where we change  
22 PAHs to POMs to be consistent with the TAC listing, and so  
23 we've made those changes and you can see that in the text  
24 that you're currently looking at.

25           So why don't we proceed.

1           PANEL MEMBER BLANC: Can I just ask one  
2 clarification. The way you have the arrows drawn for that  
3 final -- for what would then become the next to last  
4 statement regarding methyl bromide, "one exception is  
5 methyl bromide noted in finding 13 above." And you have  
6 this little arrow suggesting that you're going to move  
7 that to proceed the sentence, "However SB 25 reiterated  
8 and confirmed by statutory," you were going to move that  
9 before that? That's the way I would interpret that arrow.

10           CHAIRPERSON FROINES: That was what we thought  
11 would work.

12           PANEL MEMBER BLANC: I would leave it where it  
13 is.

14           CHAIRPERSON FROINES: Where it is, okay, and put  
15 the other in between.

16           PANEL MEMBER BLANC: And you were proposing to  
17 put the other at the very end and I think that's fine  
18 where you have it. I just wouldn't -- it doesn't make  
19 logical sense to put the methyl bromide sentence, but I  
20 think ending with the sentence that you propose which is,  
21 "In the air contaminant program, there is a parallel  
22 program in which the Department of Pesticide Regulation  
23 identifies pesticides as Toxic Air Contaminants. The  
24 panel recommends that parallel or similar considerations  
25 of children be given in the evaluation of pesticides in

1 their pesticidal use" is fine as the final two sentences.

2 CHAIRPERSON FROINES: So do you have other  
3 comments, Paul?

4 Why don't we go to you first.

5 PANEL MEMBER BLANC: I don't have any problems.  
6 I think the version, as proposed, reflects the previous  
7 discussion.

8 CHAIRPERSON FROINES: Roger.

9 PANEL MEMBER ATKINSON: No, I don't have any  
10 comments.

11 CHAIRPERSON FROINES: Gary.

12 PANEL MEMBER FRIEDMAN: I thought it was fine. I  
13 just would like to ask for clarification of the  
14 handwritten item at the end of number six, I can't read  
15 the last part of it, "add sentence, health effects  
16 discussed." Is it --

17 DR. FANNING: Maybe I can address that.

18 Ellinor Fanning.

19 PANEL MEMBER BLANC: Can you just read it to  
20 start with?

21 DR. FANNING: The language isn't set yet, but it  
22 says here, "Health effects discussed are those pertinent  
23 to SB 25 and not necessarily all health effects associated  
24 with a specific substance."

25 So the idea being that your findings that a

1 particular compound should be listed as a high priority  
2 for children's health may not fully articulate all the  
3 important health effects that that compound has, but will  
4 really focus on the ones that you used in your  
5 deliberations to select that compound.

6 CHAIRPERSON FROINES: Let me give you an example  
7 of what's meant there. In the decision to list diesel,  
8 for example, emphasized asthma, the adjuvant effects of  
9 asthma, the enhancing effects of diesel on asthma. And so  
10 the basis for the listing of diesel was a noncarcinogen  
11 respiratory endpoint.

12 However, we also know that this panel has found  
13 diesel as a carcinogen in the past and so that -- but that  
14 was not the basis of identifying diesel within the SB 25  
15 context. But we wanted to call attention to the fact that  
16 there are other health endpoints that are not necessarily  
17 listed that may have consequences beyond their -- beyond  
18 the differential toxicity criteria.

19 PANEL MEMBER FRIEDMAN: I wonder if it wouldn't  
20 be worthwhile giving an example here like that because  
21 otherwise it's sort of unclear as to what you're talking  
22 about, whereas when you discussed that diesel example just  
23 now, it became very clear to me what you were talking  
24 about.

25 CHAIRPERSON FROINES: Okay.



1           PANEL MEMBER FRIEDMAN: I don't know if the  
2 others feel that this is clear what you mean and the other  
3 readers will know it's clear, then I don't feel strongly  
4 about that. To me, it would help to give an example like  
5 that.

6           CHAIRPERSON FROINES: Does everybody agree?

7           PANEL MEMBER BLANC: Do you mean -- when you say  
8 specific example, do you mean generically adult  
9 carcinogenicity or do you mean carcinogenesis due to  
10 diesel associated with diesel exposure?

11          PANEL MEMBER FRIEDMAN: Something like that.

12          PANEL MEMBER BLANC: So you mean specifically  
13 with a specific chemical citation?

14          PANEL MEMBER FRIEDMAN: Right, right.

15          PANEL MEMBER BLANC: I would actually recommend a  
16 middle ground where we simply said carcinogenesis in  
17 adults without going into -- because it would unduly  
18 weight it if we cite one chemical and we're not citing  
19 another one.

20          PANEL MEMBER FRIEDMAN: That would be fine. I  
21 would accept that.

22          PANEL MEMBER BLANC: Let me propose the precise  
23 language, since I think the record really needs to reflect  
24 what the precise sentence is we're adding. And therefore  
25 reading Ellinor's writing, I would say -- and putting in

1 the missing words, the sentence would be, "The health  
2 effects discussed are those pertinent to SB 25 and not  
3 necessarily all of the health effects associated with each  
4 specific chemical, for example, adult carcinogenesis."

5 PANEL MEMBER FRIEDMAN: That would be fine. I  
6 don't know if you need the word specific in there, just  
7 each chemical.

8 PANEL MEMBER BLANC: Fine, delete the word  
9 specific.

10 CHAIRPERSON FROINES: Gary, are you done?

11 PANEL MEMBER FRIEDMAN: Yes, sorry. No, I was  
12 happy with it except just clarifying that.

13 CHAIRPERSON FROINES: But you have no further  
14 comments.

15 PANEL MEMBER FRIEDMAN: Right.

16 CHAIRPERSON FROINES: Tony.

17 PANEL MEMBER FUCALORO: Under number 5, the  
18 second sentence says, "Available data on ambient air  
19 concentrations and health assessment values, including  
20 Reference Exposure Levels and Unit Risk Factors, were  
21 gathered for all TACs and used for a screening level risk  
22 ranking."

23 Now, that's a jumble of gerrands, participles and  
24 nouns used as adjectives, and I'm not sure I know what it  
25 means, so I think perhaps a clarification of that is

1 suggested.

2 Down several lines --

3 CHAIRPERSON FROINES: Wait, wait. Let's finish  
4 each thing before we go forward, because then we'll be  
5 finished with the document and we can go.

6 PANEL MEMBER BLANC: I would suggest the  
7 following change then to finish the sentence "...were  
8 gathered for all TACs and used for ranking risks at a  
9 screening level."

10 PANEL MEMBER FUCALORO: Yes. Then several lines  
11 down it says, "From the 37 compounds for which literature  
12 reviews were developed OEHHA and this panel identified 17  
13 TACs..." Is that accurate?

14 CHAIRPERSON FROINES: No.

15 PANEL MEMBER FUCALORO: Was it not just OEHHA who  
16 did it?

17 CHAIRPERSON FROINES: Yes. Well, no not  
18 entirely.

19 DR. FANNING: Well, actually that was intended to  
20 reflect the discussion where originally there were 11 on a  
21 list that OEHHA had brought to you. And the panel did act  
22 to add five or six more, I can't remember the numbers at  
23 this point, to that list. So perhaps it's not quite  
24 correct to say you both identified that.

25 PANEL MEMBER BLANC: I would say "...OEHHA,

1 responding to panel feedback..."

2 DR. FANNING: Okay.

3 CHAIRPERSON FROINES: Yeah, I think it's better  
4 for us not to -- we don't identify things.

5 PANEL MEMBER FUCALORO: I was concerned about  
6 that.

7 And this is my last one, this is a typo, it's  
8 very easy. The last sentence in that, it seems to be all  
9 in here, it's not the only one I read, but it's the only I  
10 have comments about. "Thus extensive exposure was a key  
11 criterion..." rather than "an key criterion." Just a  
12 typo.

13 That's all.

14 CHAIRPERSON FROINES: That shows that you were  
15 thorough, however, when you changed "ands" to "As", so we  
16 give you a gold star.

17 PANEL MEMBER BLANC: That means he has a good  
18 liberal arts education.

19 (Laughter.)

20 PANEL MEMBER FUCALORO: I didn't have one, I'm  
21 just teaching liberal.

22 CHAIRPERSON FROINES: Peter.

23 PANEL MEMBER WITSCHI: Yeah, I would say I'm very  
24 happy with the table on page five. I have a small  
25 suggestion since we identified benzene and vinyl chloride

1 as new carcinogens. We might as well also define arsenic  
2 as a human carcinogen.

3 What's the status of formaldehyde, by the way?

4 CHAIRPERSON FROINES: I don't think -- I think  
5 it's still probable.

6 PANEL MEMBER WITSCHI: It's still probable.

7 CHAIRPERSON FROINES: I believe it's still a 2A.

8 PANEL MEMBER WITSCHI: That's fine, but we  
9 definitely should identify arsenic as a known one. But I  
10 think this table is very well done. It reflects my  
11 concern I had with the longer descriptions quite well.

12 CHAIRPERSON FROINES: Yeah, I think the table  
13 really is a major improvement.

14 PANEL MEMBER FUCALORO: It was very helpful.

15 CHAIRPERSON FROINES: Craig.

16 PANEL MEMBER BYUS: Yeah, I was quite pleased. I  
17 think it was very nice findings considering the difficulty  
18 we had, a lot of the deliberations and the discussions,  
19 and I think it reflects it quite well. And I particularly  
20 like the pesticide addition to the report.

21 CHAIRPERSON FROINES: Ellinor, in between taking  
22 care of her newborn daughter, put in some very good work,  
23 obviously on these and so we appreciate her efforts.

24 So, at this point --

25 PANEL MEMBER BLANC: Can I just -- this is a very

1 technical point but the only wording therefore that has  
2 not gone on the record is actually the precise wording in  
3 the arsenic box. And so I would just suggest the  
4 following word change in the box, instead of  
5 "...epidemiologic data on lung cancer," it would be  
6 "...known human carcinogen based on epidemiologic data for  
7 lung cancer..." and then the rest of the sentence would be  
8 --

9 CHAIRPERSON FROINES: Well, I think that's okay  
10 but I think that we then need to change the vinyl chloride  
11 and benzene to be consistent with that.

12 PANEL MEMBER BLANC: Well, if you change the  
13 vinyl chloride to insert the word "known" before the word  
14 "human", then you would be consistent enough, I think,  
15 throughout.

16 DR. FANNING: Okay. Then also the language in  
17 finding 11 on PAHs to POM, you mentioned, John, that those  
18 changes have been made, but it's not actually on the  
19 record, so I don't know if we need to read through them  
20 briefly. But just that where the findings in the  
21 preceding version had been discussing polycyclic aromatic  
22 hydrocarbons, that language has now changed to the correct  
23 Toxic Air Contaminant Polycyclic Organic Matter. And I  
24 believe that has been changed throughout.

25 There's still reference to PAHs in the finding in

1 situations where we're talking about specific research  
2 studies looking at PAHs which are a subset of POM.

3 PANEL MEMBER BLANC: I think that's sufficient  
4 without reading the actual changes, but I do think that  
5 the -- I assume you were going to then have a formal vote.

6 CHAIRPERSON FROINES: We're about to.

7 Yes. Since we have comments on an individual  
8 level from each member of the panel, we now need a motion  
9 to adopt the findings.

10 PANEL MEMBER FUCALORO: So moved.

11 PANEL MEMBER FRIEDMAN: Second.

12 CHAIRPERSON FROINES: Any discussion?

13 All those in favor?

14 (Hands raised.)

15 CHAIRPERSON FROINES: The vote is unanimous.

16 Thank you very much.

17 This was a good effort, albeit difficult at  
18 times.

19 Okay. So moving on Paul Gosselin and DPR are  
20 going to update us on the organophosphate issues.

21 Is George here? Has George left?

22 I'm looking all around you. George, assume that  
23 this letter on our SB 25 findings goes to Joan Denton, and  
24 historically we would send our TACs to either Paul  
25 Helliker or Alan Lloyd, is I assume this goes to Joan

1 Denton. I assume that we can also copy Alan Lloyd and  
2 Paul Helliker as well.

3 DR. ALEXEEFF: I believe that's correct. It  
4 actually goes to the Director of OEHHA. And the director  
5 OEHHA has already sent a letter to Alan Lloyd as well, but  
6 it would make sense for you to CC the Air Board as well.

7 CHAIRPERSON FROINES: And I'm assuming that we  
8 will not CC Winston Hickox. We'll assume that Joan will  
9 communicate our findings to Winston Hickox.

10 DR. ALEXEEF: Right. I don't know what your  
11 normal process is for sending in comments.

12 CHAIRPERSON FROINES: We never have in the past.

13 DR. ALEXEEF: Right.

14 CHAIRPERSON FROINES: But SB 25 is a little  
15 different than anything we've done previously, so that  
16 we'll assume that you will send it forward.

17 Welcome.

18 Ready?

19 DR. PFEIFER: Sure. Good morning -- afternoon.  
20 I'm Keith Pfeifer with the Department of Pesticide  
21 Regulation. And I'm here today with Dr. David Rice from  
22 OEHHA and we are the joint coordinators for this  
23 cholinesterase work group project, and we will share the  
24 presentation today.

25 (Thereupon an overhead presentation was



1           presented as follows.)

2           DR. PFEIFER: And the first slide up there is an  
3 acknowledgement of the staff for both OEHHA and DPR that  
4 have worked quite diligently on this project.

5           Our last presentation to you was back in March,  
6 and I can say with very few exceptions, the work group has  
7 met every two weeks consisting of paper presentations,  
8 discussions, ideas of where we're going forward with this  
9 cholinesterase workgroup project.

10          So in saying that, I am here today as a  
11 representative for the people that you see up on the first  
12 slide. Can we go to the next slide, please.

13                               --o0o--

14          DR. PFEIFER: And basically today, what we'd like  
15 to do is give a brief overview of the process for  
16 developing the discussion papers; the format and general  
17 content of the discussion papers; an overview of the  
18 discussion paper topics, and one of your handouts was a  
19 more detailed paper on the topics with the exact titles  
20 and the authors; also a status of where we are with the  
21 various discussion papers; and then future workgroup  
22 activities.

23          So, as you can see, the first paper there, which  
24 I'll -- or first overhead, which I'll go through in the  
25 development of these discussion papers, we produced, what

1 we call, an initial draft. And this is reviewed and  
2 discussed by the cholinesterase work group, it's presented  
3 by the lead author.

4 Then based on the discussion, suggestions,  
5 comments, critique, we come up with what we call a revised  
6 draft. And, at this point, we would consider informal  
7 review, which can be done either by SRP members or also by  
8 a few, what we call, external experts. And we did this  
9 with two papers as far as the external experts.

10 On one paper on the functional observation  
11 battery, we solicited comments from Ginger Moser, who's  
12 one of the foremost experts in this area. On the paper on  
13 analytical variability, we got comments back from Barry  
14 Wilson at UC Davis and also Stephanie Padilla from U.S.  
15 EPA who, I think, are two of the foremost experts there.

16 And they were quite willing to look at these  
17 papers and give us good constructive comments.

18 CHAIRPERSON FROINES: What bullet are we are on  
19 here? Are we on the third bullet?

20 DR. PFEIFER: Bullet number two.

21 CHAIRPERSON FROINES: Bullet number two, okay.

22 DR. PFEIFER: And then based on those comments,  
23 we call the next draft a final draft based on the informal  
24 review.

25 Now, our idea and our plan for the final draft is

1 to have that draft reviewed by SRP members at their  
2 selection and also selected external experts. This is our  
3 plan.

4 We're currently developing a list of possible  
5 scientists that are considered experts in the field of  
6 cholinesterase inhibition and testing and research or  
7 neuro-toxicity. So this is one area that we're looking  
8 towards the future in.

9 And then when we complete these discussion  
10 papers, and, again, this is another area that is open for  
11 suggestion or discussion, we'd like to present these two,  
12 either all of them, some of them to the SRP.

13 And the format, I think, has yet to be decided,  
14 whether it would be a combination of written presentation  
15 and verbal or some type of workshop format. So the latter  
16 two there are still in the stages of development and  
17 discussion of exactly how we'd like to proceed.

18 Could I have the next slide, please.

19 --o0o--

20 DR. PFEIFER: This is just a brief slide on how  
21 the formats for the various discussion papers have, more  
22 or less, evolved.

23 They all consider or include an introduction and  
24 some background information. The second bullet, which is  
25 very important, is the presentation of the topic and the

1 relevance to risk assessment for these compounds.

2           Then there's generally a technical summary and/or  
3 conclusions. And one thought is that for the various  
4 papers, these technical summaries will be folded into some  
5 type of final executive summary.

6           And then the final point, and this was not  
7 presented to the SRP last March, but it's something that  
8 the workgroup came up with, and it is very important, is  
9 at the end of each discussion paper the author comes up  
10 with as many questions as he or she feels need to be put  
11 out there for the development of the important guideline  
12 issues that are going to be addressed.

13           If I could have the next slide, please.

14                               --o0o--

15           DR. PFEIFER: This next slide is just  
16 highlighting the various groups or categories that are  
17 presented in more detail in the hardcopy handout that you  
18 have.

19           And I won't go through all these, but when we  
20 started out this project, we did prioritize these in an  
21 order to develop discussion papers underneath these  
22 various groups. And the reason we did that is we  
23 basically started, more or less, from more general basic  
24 type information that we felt needed to be presented,  
25 discussed for inclusion and discussion and development of

1 the more specific areas that were to come.

2           So the first grouping has several papers on the  
3 physiological, toxicological significance of  
4 cholinesterase inhibition. And then as we move down the  
5 list, some of the topics get more specific and more  
6 important as far as developing eventual guidelines.

7           PANEL MEMBER FUCALORO: May I ask a question at  
8 this point?

9           DR. PFEIFER: Sure.

10          PANEL MEMBER FUCALORO: Where in here will you  
11 discuss the additive effects of people being exposed to  
12 more than one toxin with the similar endpoint or --

13          DR. PFEIFER: The accumulative exposure, under  
14 miscellaneous. And if you look at the --

15          PANEL MEMBER FUCALORO: Of course.

16          (Laughter.)

17          DR. PFEIFER: And I can just say briefly how that  
18 evolved. If you look at the handout, the more detailed  
19 handout, under that you'll see there's going to be a paper  
20 authored by Dr. Ruby Reed in my group at DPR and Dr. Reed  
21 is a member of the U.S. EPA Scientific Advisory Panel on  
22 the cumulative guidelines that are currently being  
23 developed.

24          And so she has firsthand information on where  
25 they're going and the methodologies. And these guidelines

1 are due out in draft form, I believe, in December and we  
2 will look at those and consider them in the context of  
3 where we want to go. And Dr. Reed will subsequently  
4 write-up a discussion paper on that.

5           And I know in March there was, I don't know  
6 specifically, which panel members here brought this up.  
7 It may have been yourself, Dr. Fucaloro, but I know Dr.  
8 Byus, in subsequent discussions, wanted that topic added  
9 to our group. So that's one reason that we're including  
10 it.

11           PANEL MEMBER FUCALORO: Thank you.

12           CHAIRPERSON FROINES: As long as we're on this,  
13 what would you prefer, would you prefer that you go  
14 through the entire presentation and then take questions or  
15 take them as we go along?

16           DR. PFEIFER: Yeah, I think the former, because  
17 I'm going to turn it over to Dr. Rice now and let him go  
18 through and --

19           CHAIRPERSON FROINES: Go through the whole thing  
20 and then questions.

21           DR. PFEIFER: And then if you have some that  
22 would be great.

23           DR. RICE: Hi. I'm Dave Rice from OEHHA. Is  
24 that loud enough?

25           I'm just going to take a couple of minutes here

1 and present some information regarding the progress we've  
2 made, what we need to do and what we're doing right now.  
3 And if I could have the next overhead.

4 --o0o--

5 DR. RICE: It's pretty straightforward, referring  
6 to the list of all the individual discussion papers that  
7 you've been provided with in the handout. Of the 27  
8 papers, or 27 different discussion papers listed in that  
9 handout, we've completed final drafts on 19 of them, and  
10 they're ready for either SRP and/or external review. We  
11 have five drafts that are at various stages that have  
12 already been presented to the work group. And no  
13 revisions are in progress.

14 And we have three drafts that have yet to be  
15 presented to the work group, but they're scheduled to be  
16 completed by the first week or first meeting or so in  
17 January, I believe.

18 --o0o--

19 DR. RICE: On the next overhead it gives you an  
20 idea of what we still need to do, and obviously we need  
21 to, the first bullet, finish our discussion papers. We  
22 need to complete the review of those discussion papers by  
23 the Scientific Review Panel and/or external experts. The  
24 next bullet we need to, or actually we have already  
25 established risk assessment guideline categories for

1 grouping of the questions that have been developed as a  
2 result of the individual papers. And I'll talk about that  
3 more on the next overhead, but I don't want to go to it  
4 yet.

5 I will say that, you know, what we've come up  
6 with as a process is it's pretty clear that our guidelines  
7 are going to be a result of the discussions that come out  
8 of these issue questions that are at the end of each  
9 paper.

10 So we wanted to kind of formalize our approach to  
11 talking about those particular issues, and so we've  
12 established -- we revisited the topics that we have for  
13 the individual papers, taking a look at the questions that  
14 have come out of the individual papers and reprioritized  
15 the various topics based on that information and our needs  
16 in terms of risk assessment.

17 And, again, I'll talk about that a little bit  
18 more on the next overhead.

19 The next bullet we're going to go through those  
20 guideline categories after we've plugged in all the issue  
21 questions and consolidate those questions and eliminate  
22 duplications and set aside any questions that may not be  
23 particularly relevant to our needs.

24 We then also need to formulate the  
25 recommendations based on discussion of those issue



1 questions. We still need to determine really the scope  
2 and the format of our actual product is are we going to  
3 end up with two documents. One document that's going to  
4 be all the discussion papers and another document that's  
5 going to be guidelines, you know, being connected with  
6 some sort of executive summary or have one big document.  
7 We're just not quite sure what the final product is going  
8 to look like.

9           And then, of course, after we get past that, we  
10 are going to need to present our guideline recommendations  
11 to this panel.

12                               --oOo--

13           DR. RICE: The next overhead, which is pretty  
14 busy, but I'll try to get through it real quick, is this  
15 is just our grouping for the issue questions that have  
16 come out of the discussion papers. And we have four main  
17 headings, as you can see. We've got the relevance of  
18 cholinesterase inhibition to risk assessment. We  
19 obviously thought that was a most important question to  
20 ask here. Something that has come up out of our  
21 discussions is the next major heading and that's the use  
22 of human cholinesterase data, since more and more human  
23 data is being submitted in the area of pesticides in  
24 support of registration.

25           Our next major topic area is, you know, how are

1 we going to deal with the LOAEL/NOAEL determination, and  
2 the impact of analytical variability, biological  
3 variability, biological significance and what kind of  
4 uncertainty factors we need to apply.

5           And the last major grouping is the relationship  
6 of cholinesterase inhibition to other endpoints, such as  
7 endpoints we see in the functional observational battery,  
8 developmental neuro-toxicity, ocular toxicity,  
9 immuno-toxicity, endocrine disruption and structure  
10 activity relationships, that's really not an endpoint, but  
11 we included that there just so we can continue or finish  
12 our discussion on the topic.

13           And that's pretty much all I have. I guess if  
14 there are any questions.

15           CHAIRPERSON FROINES: Thank you. Could we have  
16 the lights.

17           PANEL MEMBER BLANC: So the relationship between  
18 the working papers and then this final slide is that  
19 multiple group papers would inform the same or overlapping  
20 topics.

21           DR. RICE: Exactly, and vice versa, I guess  
22 that's the overlapping part. A given set of issue  
23 questions from the paper may plug into different topics as  
24 well.

25           PANEL MEMBER BLANC: Well, just looking at the

1 outline of the discussion papers, one of the things that  
2 may come up as a possible source of unnecessary confusion  
3 may be times when you're using cholinesterase as an  
4 umbrella term in times when you're using  
5 acetylcholinesterase specifically and  
6 butrylcholinesterase, so you might want to just go back  
7 and make sure that you're consistent in your terminology.

8 DR. RICE: Certainly.

9 DR. PFEIFER: Yeah, I think when we use the term  
10 cholinesterases, it means all of them, and then we try and  
11 be specific. And I know in developing our risk  
12 assessments that question has come up. And generally my  
13 suggestion in some cases is to clearly define which  
14 cholinesterases you're talking about, just so there isn't  
15 any misinterpretation.

16 PANEL MEMBER BLANC: Right. Because, for  
17 example, topic 2C.2 Acetylcholinesterase in Neural  
18 Development. I assume you would be concerned about neuro  
19 target esterase and neuro development also, so that  
20 implies you're only looking at cholinesterase and others,  
21 and then you talk about acetylcholinesterase in topic  
22 2C.4, when I guess you mean cholinesterases. I mean, you  
23 should try to be consistent, because you're going to  
24 engender unnecessary confusion, I think. At least when it  
25 comes back to us, it may be confusing.

1           Now, also about that is just in how you've  
2 divided things up. For example, Topic 1C, which is  
3 Acetylcholinesterase in Different Brain Regions, and then  
4 the next one is Cholinesterase Inhibition in Blood and  
5 Peripheral Tissues. Is the implication that the  
6 peripheral nervous systems is going to be covered in 1D or  
7 that the peripheral nervous system is not a different  
8 brain region. So it's odd in that constellation that  
9 there is not a separate peripheral nervous system paper  
10 then or -- do you see what I'm asking?

11           DR. RICE: Yeah.

12           DR. PFEIFER: Not entirely on the latter. I'm  
13 trying to focus in on the consistency with the  
14 terminology.

15           PANEL MEMBER BLANC: Well, you're dividing up the  
16 physiologic significance of cholinesterase inhibition in a  
17 broad way. And so you've got one paper that's going to be  
18 on the central nervous system, I guess, because when you  
19 say the brain, I assume you mean the central nervous  
20 system.

21           DR. PFEIFER: Specifically the brain. And in the  
22 blood, I believe, the focus was on acetylcholinesterase,  
23 but sometimes its blood measures both butryl --

24           PANEL MEMBER BLANC: And so where would the  
25 peripheral nervous system be?

1 DR. PFEIFER: Pardon me?

2 PANEL MEMBER BLANC: Where would the  
3 peripheral --

4 DR. PFEIFER: Oh, the peripheral tissue such as  
5 the lung and diaphragm, that's one area.

6 PANEL MEMBER BLANC: So you're saying that topic  
7 1D would address the peripheral nervous system?

8 DR. PFEIFER: Well, peripheral tissues,  
9 specifically lung, diaphragm, because one of the areas of  
10 interest is developing formats methodological for and  
11 requiring that for submission for registering a pesticide,  
12 and as an indication of peripheral cholinesterase  
13 inhibition.

14 PANEL MEMBER BLANC: Well, I guess what I'm  
15 trying to say as you're going to be presenting it to us,  
16 there are going to be issues that are going to be  
17 classically related to sites of neuro transmission, and  
18 then there are going to be cholinesterase effects in ways  
19 that are not related to neuro transmission, I suppose.

20 DR. PFEIFER: Well, that one is related to neuro  
21 transmission.

22 PANEL MEMBER BLANC: However you slice up the  
23 pie, there will need to be some clarity for the people  
24 receiving these, so that they understand what's included  
25 and what isn't and to make sure that everything is

1 covered.

2 CHAIRPERSON FROINES: But I think that there's an  
3 approach that relates to the science and there's an  
4 approach that relates to regulatory demands. I think the  
5 generic term is the peripheral nervous system, and I think  
6 within that generic concept then there may be specific  
7 tissues that have more specific relevance. And it seems  
8 to me that it's in that order that one wants to address  
9 it. I think that's what Paul is saying.

10 PANEL MEMBER BLANC: Well, what I can't tell you  
11 that topic 1D is what it actually covers. All I'm saying  
12 is that here I'm looking at this title of what this  
13 working paper is on, and I have no idea what you mean,  
14 because I'm coming at it from a different disciplinary  
15 point of view.

16 DR. PFEIFER: Well, quite frankly, when I made  
17 this list up, I went back and looked at some of the  
18 titles. And I had to kind of clarify them a little bit  
19 too, because they weren't that specific from my  
20 interpretation, so I understand that.

21 CHAIRPERSON FROINES: But I think the 1C, when  
22 you say, again, the generic term is the central nervous  
23 system, the specific term is various brain regions. I  
24 think one wants to make sure that the broad title is the  
25 starting point and the details come below.

1 DR. RICE: I would agree. I think we need to go  
2 back and look at those, because we do discuss the CNS and  
3 the peripheral system in both of these papers or in either  
4 one of the appropriate papers. And we need to make sure  
5 that we address it completely and, you know, be precise  
6 about our title.

7 PANEL MEMBER BLANC: Because the problem is how  
8 will you know that you haven't missed a topic, because one  
9 person thinks they're doing it and the other group thinks  
10 that the other group is doing it based on --

11 DR. PFEIFER: There will be some overlap, but we  
12 tried to get pretty focused on, you know, this specific  
13 one.

14 PANEL MEMBER BLANC: You know, I'm actually less  
15 worried about overlap than I am about something getting  
16 not addressed.

17 DR. PFEIFER: We haven't missed very much, if  
18 anything, believe me.

19 CHAIRPERSON FROINES: But I think that this body  
20 is a body of scientists not regulators. And so to the  
21 degree that there are specific issues about registration,  
22 approval, regulatory considerations, then that needs to be  
23 a subset where you're educating the panel about those  
24 specifics, because you can't assume that scientists in  
25 universities or this panel or in general will necessarily

1 be knowledgeable about those more --

2 DR. PFEIFER: I hope I didn't, you know, mislead  
3 you on that, when I was talking about this peripheral.  
4 No, these papers don't get into, you know, any regulatory  
5 or registration type.

6 PANEL MEMBER BLANC: And then topic 4A  
7 Organophosphate Toxicity Heterogeneity in Humans.  
8 Conceptually, what is that addressing?

9 DR. PFEIFER: Variability in the human  
10 population.

11 PANEL MEMBER BLANC: I mean, is it narrowly a  
12 genetic variability or are you addressing age variability  
13 in responsiveness or --

14 DR. PFEIFER: I think both.

15 DR. RICE: As I recall the paper, we addressed  
16 just variability in humans as a broad stroke. And any  
17 sort of information we could collect on variability,  
18 particularly in terms of response, that that's what's  
19 included.

20 PANEL MEMBER BLANC: So it includes both  
21 sensitivity and susceptibility?

22 DR. RICE: Correct.

23 DR. PFEIFER: And then if you look at Group 8,  
24 these two papers are in the category of still being  
25 developed and there will be some information there that



1 will relate back to topic 4 and 4A.

2           PANEL MEMBER BLANC: Because you already had a  
3 question, I guess, about topic 9A, but if you think about  
4 looking ahead to see what are the errors in which we have  
5 to grapple at this end or are likely to be raising  
6 questions on individual chemicals as they come forward,  
7 these are the more difficult areas that we face and are  
8 likely to be areas of particularly intense concern.

9           DR. PFEIFER: You mean the human susceptibility  
10 and sensitivity?

11           PANEL MEMBER BLANC: Yes. They're generic. I  
12 mean they're not specific -- they're not as specific to  
13 this as obviously the issues about what does it mean to  
14 measure butrylcholinesterase versus acetylcholinesterase  
15 or any of these other questions. But nonetheless, they're  
16 quite relevant.

17           I would encourage you to throw a broad net in  
18 that particular evaluation, and look very closely at not  
19 just age and genetic factors, but also look at nutritional  
20 status and some of the other things that have been areas  
21 of concern, particularly in cholinesterase inhibition  
22 effects.

23           Time line to the panel. I mean, when would we be  
24 likely to need to be thinking about a workshop or  
25 discussion time or agenda time?

1 DR. PFEIFER: Well, we talked about this briefly  
2 this week, and based on the task in front of us, not so  
3 much the discussion papers, but discussions on developing  
4 recommendations of the guidelines and then having some  
5 type of external review, we're probably looking at the  
6 second quarter of 2002, probably at the end of the second  
7 quarter, so it would be close to June, I would think.

8 PANEL MEMBER BYUS: Your original time line was  
9 now, right. I'm not saying anything.

10 DR. PFEIFER: Actually, I looked at that.

11 PANEL MEMBER BYUS: It was a little optimistic.

12 DR. PFEIFER: No, I looked at that. And the  
13 fourth quarter of 2001 I said finish discussion papers,  
14 which, you know, we're probably a month behind there. And  
15 it said start formulating guidelines. And we've already  
16 started doing that, but I think there's, you know, going  
17 to be quite a bit of discussion and work ahead.

18 There are some papers that are quite important to  
19 this whole thing that are being revised, so that we can  
20 call them a final draft. And I think it's appropriate to,  
21 you know, where needed, that they be revised, because in  
22 our workgroup there is a lot of open discussion a lot of  
23 individual opinions presented about, you know, people's  
24 perceptions, concerns and scientific opinions that all, I  
25 think, added to the quality of these papers.

1           So, yeah, you're right, we probably were a little  
2 optimistic. But the idea of having, what I would call,  
3 experts outside the regulatory community pretty much  
4 review these, I think, would add a tremendous amount of  
5 credibility to not only the papers, but to the eventual  
6 recommendations, because obviously the people are going to  
7 take this information and compare what we have come up  
8 with directly with what the federal government has come up  
9 with and how to apply it.

10           And that has been, you know, my goal from the  
11 beginning to have it as best a footing on science to  
12 develop these as possible. And I think, like I said, we  
13 had Stephanie Padilla and Barry Wilson and Ginger Moser  
14 look at our papers, and I can tell you that their comments  
15 were quite favorable, but they were also very pointed in  
16 their critique of some of the things that they didn't  
17 agree with.

18           CHAIRPERSON FROINES: I have a number of comments  
19 that I'd like to -- some are substantive, some are  
20 procedural.

21           The first thing I think I'd like to ask you to do  
22 is, I think, there needs to be a Chapter 1. And Chapter 1  
23 needs to lay out the issues that will be dealt with in the  
24 subsequent list of papers and the overall objectives of  
25 the exercise in producing these documents. And I'm not

1 talking about an executive summary.

2 I'm talking about Chapter 1 should tell the  
3 reader, tell the public what are the issues that are going  
4 to follow in these, however many, documents there are and  
5 that will be addressed and what are the fundamental issues  
6 that we are -- why this is going forward?

7 In other words, to tell the reader in Chapter 1,  
8 in essence, the basis, the objectives for everything that  
9 is to follow. There needs to be obviously an executive  
10 summary produced separately than that. But, I think, at  
11 the outset, we need to inform everybody about why are  
12 there now 12 to 15 to 19 documents that are going to  
13 follow, and what are the very specific issues. And so  
14 that's the first point.

15 I think the last chapter obviously has to be, and  
16 I assume that that's what you were going to do, is I'm  
17 not -- I don't think I agree that the last chapter is  
18 cholinesterase issues, questions for guideline  
19 development. I think the last chapter has to be your  
20 recommendations for the guidelines.

21 DR. PFEIFER: That wasn't meant to be the last  
22 chapter. That's just in each individual paper, that's the  
23 last part that gets extracted out for using the  
24 guidelines -- developing the guidelines.

25 CHAIRPERSON FROINES: So the first chapter tells

1 everybody what it's all about. The last chapter tells  
2 everybody where you've come to. And in between you  
3 develop the scientific basis for that, so that they're  
4 basically -- this is basically a three-part per exercise  
5 as I would look at it. And I think that will help clarify  
6 it, because the current first chapter which I've read  
7 starts out going through the physiologic consideration of  
8 acetylcholinesterase, and then at the end of the document,  
9 it gets into various policy issues.

10           And so you kind of have a little bit of apples  
11 and oranges in the first chapter, and I think it's  
12 important to be able to make sure that people understand  
13 what the procedural policy, scientific questions are that  
14 need to be addressed and then get into the actual  
15 technical details.

16           The second thing that I wanted to say is I think  
17 that, as far as I'm concerned, obviously this is your  
18 process and you can invite external experts all you want  
19 to help you as you go forward, and I certainly would  
20 support that and encourage it.

21           I think in the end, I would like to propose a  
22 joint effort. And that is in the end, at the end,  
23 however, you may have gotten Stephanie Padilla to look at  
24 five chapters in the beginning or Barry or whoever, but in  
25 the end before the document -- the final draft review, I

1 think that should be, in essence, a joint effort between  
2 the SRP, OEHHA and DPR.

3           And that what we do is the SRP -- because this is  
4 going to help us do the review, and that's what I'm  
5 thinking about. I'm trying to think about how are we  
6 going to review 20 documents with this small panel. So  
7 what I would propose is that at the final draft review  
8 stage that we put together a list that comes from this  
9 panel, from DPR and from OEHHA.

10           And out of that list, we develop a final list of  
11 external experts who we want to review the document. We  
12 send it out and we get their comments back and then you go  
13 back and make changes, and then the final document comes  
14 forward.

15           So something like that so we are all participants  
16 in defining who the external experts are, because I think  
17 that will benefit this panel. And so we'll have  
18 confidence that we've come up with a list of names and  
19 OEHHA has come up with a list of names and so on and so  
20 forth.

21           DR. PFEIFER: I think that's fine. I mean,  
22 that's something I probably wasn't very clear on, but  
23 certainly, you know, I think that would be a good idea.

24           CHAIRPERSON FROINES: The third thing that I'd  
25 like to say, and this is not a criticism meant at all, it

1 is an attempt, on my part, to preserve the energy level of  
2 the SRP participants, and to, in a sense -- but more  
3 importantly that the role of the panel is to review a  
4 document in terms of its adequacy. And I don't know the  
5 exact statutory language, but I think we have to be  
6 careful to preserve our review function from our being  
7 intimately involved in the document development.

8           In other words, I want to keep Craig Byus from  
9 performing a staff function for DPR and OEHHHA, because  
10 that then makes it harder for him to be an independent  
11 reviewer when the document actually comes to us.

12           He may not agree, but I think that we just have  
13 to be careful. We also have to make sure we don't wear  
14 him out, by the time -- so when he comes here with the  
15 final document, he's able to be an objective thinker about  
16 it.

17           So I would suggest that during the document, when  
18 you're going through multiple drafts, and this is -- I  
19 mean, I'm just suggesting this. The panel has to decide  
20 how it wants to deal with the lead person. That's up to  
21 the panel. But I would suggest that the panel not be as  
22 deeply involved in the various chapters as one might  
23 think, because there may be multiple drafts and what have  
24 you, but that the panel more or less reserves itself to  
25 the final draft review, so that when we're having these

1 outside speakers do the review, we also have the leads  
2 doing the review at that point.

3           So that, in a sense, the SRP reviewers are in  
4 sync with the external reviewers, and that's a kind of  
5 dynamic process. And that's different than say Craig  
6 being involved in draft 3 of Section 2B.2.

7           And so I would say that the SRP leads would play  
8 their most important role at the final draft review when  
9 also the documents were going out to external reviewers  
10 would be my suggestion.

11           And so I think -- pardon me, I made some notes.

12           I think that covers it from my standpoint. I  
13 think the only other thing that is a matter of concern to  
14 me, and this is opening Pandora's Box, and I admit that  
15 I'm doing it, is when we have -- when the panel had the OP  
16 workshop last year, one of the key questions that we asked  
17 that really wasn't dealt with very effectively, and it  
18 came at the end of the day, was toxic effects associated  
19 with cholinesterase inhibitors, but that are independent  
20 of cholinesterase inhibition.

21           In other words, we have a whole spectrum of  
22 effects associated with cholinesterase inhibition, but are  
23 these compounds capable of causing toxicity via other  
24 mechanisms, even in addition to delayed neuro-toxicity?

25           And you haven't really got that in here. It



1 seems to me -- or at least, I missed it. But it seems to  
2 me that the sort of other toxic endpoints via other  
3 mechanisms is an issue of -- that we shouldn't not address  
4 those. Those are my comments.

5 DR. RICE: Well, with respect to the last  
6 comment, we agree completely and we do -- we are  
7 attempting to look at any other forums of toxicity for  
8 these particular compounds as we're reviewing the  
9 literature.

10 And in the -- I don't know what the best -- in  
11 the risk assessment guideline categories for the issue  
12 questions, the very last category, to a large degree  
13 addresses that, where we look at the relationship of ChE  
14 inhibition to other endpoints, and that means in terms of  
15 sensitivity.

16 CHAIRPERSON FROINES: Where am I looking?

17 DR. RICE: Oh, the very last overhead where we  
18 look at things such as ocular toxicity, immuno-toxicity,  
19 endocrine disruption, and, you know, the reasons down at  
20 the bottom of the list, so far we haven't seen any  
21 indication of any of these aspects of toxicity from these  
22 compounds to be anymore -- or to be more sensitive than  
23 inhibition of the different cholinesterases.

24 So, in a general sense, we're looking at that.

25 CHAIRPERSON FROINES: Yeah, be careful, because

1 you're making a judgment about -- you're doing risk  
2 assessment at the same time that you're doing -- by the  
3 sentence, by saying if you're considering sensitivity,  
4 you're making a judgment call there, I think.

5 DR. RICE: Right.

6 CHAIRPERSON FROINES: But I read this -- but this  
7 relationship of cholinesterase inhibition to other  
8 endpoints, I'm saying it differently. I'm saying  
9 relationship of cholinesterase inhibitors to other  
10 mechanistic pathways leading to other endpoints.

11 DR. RICE: Oh, I understand. And that's why I  
12 couched that, in terms of -- the risk assessment in terms  
13 of sensitivity.

14 DR. PFEIFER: I mean, obviously, the focus of  
15 this work group was on the inhibition of cholinesterase.  
16 So the question was are there other -- you can  
17 characterize types of systemic toxicity that are or are  
18 not related to cholinesterase inhibition. So that was  
19 basically the question before the authors. And so they  
20 went through the literature and looked at those aspects.

21 PANEL MEMBER BLANC: Well, perhaps the way of  
22 melding these two things together would be in the  
23 introductory section that Dr. Froines has alluded to, if  
24 you're in agreement with drafting such a section, that it  
25 would delineate both the terminology and the potential

1 mechanistic implications.

2           Because there are really three things that are  
3 embedded in what we're talking about. One would be  
4 toxicity related to cholinesterase inhibition at sites  
5 other than sites of neuro transmission, that would be  
6 inhibition of cholinesterase with effects that the  
7 cholinesterases have that are unrelated to neuro  
8 transmission.

9           The second would be inhibition of other enzymatic  
10 functions that are not precisely cholinesterases.

11           And the third would be toxic effects completely  
12 independent of enzymatic inhibition that it has a  
13 structural, functional relationship to cholinesterase like  
14 structures, I guess.

15           Those are three possible different path ways.  
16 And as you get farther away from anything resembling  
17 cholinesterase inhibition then there's less and less data,  
18 and less and less likely to be broad links, that there may  
19 be one acetylcholinesterase inhibitor which on an  
20 idiosyncratic basis, tends to be a sensitizer because of a  
21 side group, and can't really generalize to other  
22 acetylcholinesterase inhibitors, because it's a  
23 peculiarity of that particular one for all I know.

24           So I suppose as you get farther afield, it's less  
25 generalizable, where I wouldn't see any reason why this

1 shouldn't be a general pattern of effects.

2 Does what I'm saying fit into your -- does that  
3 correspond to your, sort of, categorization or one way of  
4 categorizing it or is there a space in one of these  
5 documents where those issues are delineated?

6 DR. PFEIFER: I don't know that we're considering  
7 looking at how you characterize other enzymatic -- I mean,  
8 we're considering looking at the inhibition of  
9 cholinesterase certainly as an endpoint. And then we  
10 wanted to look at other types of, what I would call,  
11 systemic toxicity and see if we could say that was related  
12 to cholinesterase inhibition or it was independent of  
13 cholinesterase inhibition.

14 And then the next question would be, are these  
15 other endpoints of toxicity as sensitive, more sensitive  
16 or less sensitive than the inhibition of cholinesterase  
17 for risk assessment purposes?

18 CHAIRPERSON FROINES: I understand that. I think  
19 coming from a toxicologic standpoint, one of the questions  
20 I'd be interested in then though is what are the  
21 mechanistic considerations that suggest, that underlie  
22 other systemic toxicity that might occur separate from  
23 cholinesterase inhibition.

24 DR. PFEIFER: And where known, that is addressed.  
25 If it isn't known, then --

1 DR. RICE: We do address those three areas that  
2 you talked about. We don't specifically identify them as  
3 such. But as an example, in one of the papers on  
4 butrylcholinesterase, there's a discussion of the  
5 potential stereo chemical role, if you will, that  
6 butrylcholinesterase may have in neurodevelopment, for  
7 instance, and/or in nervous system transmission, not an  
8 enzymatic role or actually an unknown role.

9 In the paper on immuno-toxicology,  
10 immuno-toxicity of the Cholinesterase inhibitors, there's  
11 a very large discussion of the effect of cholinesterase  
12 inhibitors inhibiting enzymes important in the immuno  
13 response that aren't cholinesterase, but other --

14 PANEL MEMBER FUCALORO: That are not.

15 PANEL MEMBER BLANC: Yeah, there are other  
16 esterases.

17 DR. RICE: Other esterases of unknown, you know,  
18 function and known function. And so we address those  
19 issues as we find out information in each of the topic  
20 areas.

21 DR. PFEIFER: But they are specific to the topic,  
22 which is, I think, what you were getting at, and not just  
23 other general toxicity.

24 DR. ALEXEEFF: George Alexeeff with OEHHA, just a  
25 point of clarification, now there's two ways one could

1 approach this overall issue. One is to develop guidelines  
2 for cholinesterase inhibitors. In other words, chemicals  
3 that cause inhibition, but that may or may not have the  
4 sensitive most sensitive health effect or the most  
5 important health effect, which is, I think, what you're  
6 referring to.

7           The other is to come up with guidelines on if  
8 you're evaluating cholinesterase inhibition, how you  
9 actually do that. You know, what would the procedures for  
10 evaluating that?

11           And I think what staff has indicated that they're  
12 looking at other endpoints, but at the same time that  
13 they're looking at these particular compounds to see how  
14 cholinesterase plays out in terms of other endpoints.

15           But I guess my question comes back with the panel  
16 in terms of just your expectations as to what you think  
17 this work product will look like, is it your expectation  
18 that, okay, if we're taking a particular cholinesterase  
19 inhibitor, what will be the guidelines in evaluating it?  
20 In other words, how will we look at cholinesterase and how  
21 will we make sure that there isn't some other endpoint  
22 missed?

23           That's why it's not clear, when you're bringing  
24 up these other endpoints, that by working out other  
25 mechanisms, which are important, we might normally do that

1 in our normal evaluation of any TAC. You know, we'd  
2 always like at -- for example, we looked at death and  
3 carcinogenicity was the endpoint.

4 So that's why, I guess, it was not clear and not  
5 to try to expand the scope of this series of work  
6 products.

7 CHAIRPERSON FROINES: Well, I think that's a good  
8 point. And that's why even when I raised it, I raised it  
9 with some hesitation. But I think that clearly there has  
10 been some debate and controversy, or however one wants to  
11 phrase it, about cholinesterase inhibition in and of  
12 itself. So that's a box that we can clearly recognize  
13 that we want to address from a risk assessment standpoint,  
14 risk assessment methodology standpoint.

15 But we also don't want to just look for the keys  
16 under the light-post either, because people have been  
17 looking at OP compounds in terms of cholinesterase  
18 inhibition for the last umpteen million years. And so we  
19 keep looking at that and should. But the question is, are  
20 there other keys out there in the darkness that we're  
21 missing, and that's what I think we can't simply avoid,  
22 because I think that could lead to an error in --

23 DR. ALEXEEF: I think that would normally be  
24 picked up on a case-by-case evaluation of the compound  
25 hopefully. Granted, there may be some overreaching

1 issues, but that would be pretty hard for us to look at  
2 all cholinesterase inhibitors and come up with a list of  
3 likely other noncholinesterase things that could also  
4 happen in the document, I mean, like this.

5           But I think that maybe we could somehow in, as we  
6 formulate the guidance, be clear that just because  
7 something inhibits cholinesterase, that's not necessarily  
8 what the ultimate NOAEL development will be based on,  
9 because that may not be the most important relevant,  
10 sensitive or appropriate endpoint.

11           DR. PFEIFER: Well, also not all the  
12 cholinesterase inhibiting compounds exhibit a lot of these  
13 other systemic toxicities, liked delayed neuro-toxicity,  
14 ocular toxicity and some of these other points.

15           PANEL MEMBER BLANC: Well, I mean let's come back  
16 to that as a good example. Let's talk about delayed  
17 neuro-toxicity in response to your question, George. I  
18 think that this panel, whenever organophosphate comes  
19 forward, is going to want to know if the appropriate tests  
20 were done that had evaluated its potential for delayed  
21 neuro-toxicity.

22           And to the extent that these documents illuminate  
23 what is the best way in which one assesses neuro target  
24 esterase effects, that is something that we'll be for.

25           The parallel to that would be if there is a



1 generalizable structure function effect that  
2 cholinesterase inhibitors have on an esterase, which is  
3 present in leukocytes and which can be related to antigen  
4 presentation. Then we need to know about that so that  
5 every time a cholinesterase inhibitor chemical comes  
6 forward, we say have the appropriate tests and structure  
7 function assays been looked at.

8           What I think there's less need for and less  
9 interest in the panel would be a sort of idiosyncratic  
10 miscellaneous effect of a peculiar cholinesterase, which  
11 has a very odd side group, which is associated with met  
12 hemoglobin emia, but in no way do the data suggest that  
13 the class, even a subgroup of acetylcholinesterase  
14 compounds, cause met hemoglobinemia. Is that helpful to  
15 you?

16           DR. ALEXEEFF: Yeah, and I think we've tried to  
17 address that. You can see how some of the topics are set  
18 up. I'm just looking at like 2C.3, Ocular Toxicity  
19 Associated with Organophosphate Exposure.

20           That's not necessarily only cholinesterase  
21 mechanism. Maybe it is, I don't know. I don't know the  
22 literature. But I'm just saying we could look at ocular  
23 toxicity, in general, since that is an effect that occurs  
24 and look for things that you're, you know, mentioning that  
25 may be there's some other generalized effect that occurs

1 possibly --

2           PANEL MEMBER BLANC: But look at 2C.4,  
3 acetylcholinesterases and the Immune System. The title of  
4 that suggests that the only esterases for which the  
5 discussion there would focus on would be  
6 acetylcholinesterase and the immune system.

7           I understand from your oral comments that, in  
8 fact, you'd be looking at other enzymatic effects of  
9 chemicals which are acetylcholinesterase inhibitors. And  
10 comes back to my earlier comment about being sure that the  
11 titles of your topics or the subtitles, you should make it  
12 clear how you're dividing up the pie, so that we're  
13 assured that everything that we want to be covered is  
14 being covered.

15           DR. RICE: We do need to be more precise, because  
16 a more appropriate title for that particular paper would  
17 be something like effects of cholinesterase inhibitors on  
18 the immune system. And that would take into account any  
19 effects it may have on other enzymatic processes.

20           CHAIRPERSON FROINES: I did not understand what  
21 you just said.

22           DR. RICE: What I said was changing the title.  
23 Instead of saying acetylcholinesterase is in the immune  
24 system, the effect of cholinesterase inhibitors on the  
25 immune system would not limit it just to

1 acetylcholinesterase, nor would it limit to --

2 CHAIRPERSON FROINES: But the question is the  
3 cholinesterase inhibitor operating via noncholinesterase  
4 inhibition mechanism may produce immuno-toxicity.

5 DR. RICE: I understand that.

6 PANEL MEMBER BLANC: It's not easy. To get the  
7 right wording it's not -- it's completely convoluted and  
8 laborious, but you can see the problem here.

9 CHAIRPERSON FROINES: So, for example, for 20  
10 years, I think it's getting 30 years now I've been  
11 interested in issues of degeneration, and I've always been  
12 a skeptic about neuro target esterase, because I think  
13 it's too simple a view of that process.

14 And so I, in my own personal professional  
15 scientific career, have been interested in OP compounds  
16 that have some potential or exonil degeneration. And so I  
17 continue to have that kind of interest, and I'm not  
18 pushing it on you, but it's just an area that I think we  
19 don't want to exclude, even though we recognize that we  
20 have these key questions around cholinesterase inhibition  
21 to answer.

22 Can I ask -- I want to ask Craig Byus a question,  
23 because I propose, basically, that the panel leads play  
24 their most dramatic role at the final draft review stage.  
25 And, actually, Craig can do as much as he wants in

1 between. That's clearly up to him as an individual  
2 investigator. But are you comfortable?

3 PANEL MEMBER BYUS: I was going to ask you for  
4 that guidance today, in actuality, and what level, how  
5 each detail Peter and I should spend during this process?

6 Let me say I think the process is going along  
7 well. I mean, I have all of the chapters. I was much  
8 more proactive in the beginning in reviewing these  
9 chapters than I have been lately, simply because of the  
10 amount of effort and time that it takes.

11 And I think it's going along well. I think  
12 there's a problem -- I see there are several problems.  
13 One is this sort of bottom up approach as opposed to a top  
14 down approach. We would like to see sort of a global  
15 overview and defining of the key issues, and then a  
16 working down from the top.

17 And their approach, this is my own opinion, it's  
18 been more from the bottom up, these guys are in the  
19 trenches working with this day to day all the time, year  
20 after year. And so they have a lot of procedural issues,  
21 which have a lot of scientific basis, and so they're  
22 looking at it pretty much, sort of, from the bottom up.

23 I think that's fine. I originally thought top  
24 down was better, but as I read these things, I agree  
25 there's sort of a dichotomy between what's in the titles

1 of these chapters and what's actually here, so that  
2 there's a lot of editorial work that's going to have to be  
3 done ultimately.

4           But I think the process is ultimately fine. I  
5 think that going from the bottom up will ultimately work  
6 out, bottom up will work out fine, if somebody at the end  
7 does what you suggest with Chapter 1, does a big global  
8 overview and really does do the editorial job that's going  
9 to need to be done to tie everything together.

10           And consistency, this was another problem I had.  
11 It's great to have all these people doing this, and I  
12 really applaud this, because I think it does bring in all  
13 of these other viewpoints.

14           But it makes it more difficult from an editorial  
15 consistency point of view to make the kind of document  
16 that we would all like to see here, as a university  
17 professor and whatever, so that's going to be one of your  
18 problems, I think, ultimately. So how you solve that, you  
19 know, it's going to be somewhat difficult, but that's what  
20 I foresee.

21           And then the other big thing is the policy  
22 issues. I mean, I really think the policy issues, when  
23 you have the science here, and it may be spread apart in  
24 various places, but really the science is good, the  
25 references are good. It's kind of the classic old

1 pharmacology coupled with toxicology, and a lot of these  
2 as you know -- as you said a lot of these issues have not  
3 been resolved. Relatively simple things you would think  
4 could have been resolved many years ago have not been.

5           And I think really the key thing is going to  
6 be -- one of the key things is going to be the policy,  
7 what you have developed as policies, and that's where we  
8 need to really -- I don't know whether -- so I would say  
9 to you, I agree about allowing them to develop this  
10 document as they want and -- but are they going to want  
11 our input before they develop the policy, that's where I  
12 see maybe we could put some input in --

13           DR. PFEIFER: Well, our goal --

14           PANEL MEMBER BYUS: -- before or after. But I  
15 mean that is the key thing, because you're going to come  
16 back and you're going to say butrylcholinesterase is  
17 irrelevant, and it means nothing. Now, that's what you've  
18 said in the past. Now, clearly, I would disagree with you  
19 with this.

20           So if that's your policy, that's where we're  
21 going to be -- and maybe that is the best time to argue it  
22 out, after you have developed the policy and after there  
23 is the document with the data here in front us that we can  
24 all look at.

25           DR. PFEIFER: I think our goal is to give you

1 recommendations, which will be guidelines/policy

2 recommendations, and then --

3 CHAIRPERSON FROINES: I would like to actually  
4 disagree with something Craig just said. I would almost  
5 like to avoid the word "policy", because that sounds like  
6 something that we should give a call to Paul Helliher and  
7 ask him what he wants to do or Winston Hickox, and I don't  
8 want to do that.

9 DR. PFEIFER: This is a guideline.

10 CHAIRPERSON FROINES: Exactly why I want to stay  
11 away from the concept of policy, because what I would like  
12 and I think this panel has an obligation to view it this  
13 way, is that based on the science comes recommendations  
14 for how to approach risk assessment, and then we can  
15 debate that.

16 We may have the head of Cal EPA may decide as a  
17 matter of policy to change all that. That's a different  
18 issue. I think ours should be based on the review of the  
19 science rather than a review of somebody's point of view  
20 on this subject.

21 So I think what we need to do is to have the  
22 forest, then we have the trees, and then we have the  
23 forest again with what --

24 (Laughter.)

25 PANEL MEMBER FUCALORO: This is Chapter one

1 little chapter zero.

2 (Laughter.)

3 PANEL MEMBER BLANC: You're the Lumber Jack?

4 (Laughter.)

5 PANEL MEMBER WITSCHI: Well, except it's going to  
6 be the second forest after the beavers have gone through  
7 it.

8 (Laughter.)

9 PANEL MEMBER FUCALORO: That's appropriate, we're  
10 talking about pesticide.

11 CHAIRPERSON FROINES: Well, we can get lost in  
12 any one of those three places. As we've seen, we can get  
13 lost pretty easily.

14 I had a question about where -- since I think  
15 that toxicokinetics are really quite crucial to  
16 cholinesterase inhibitors. Is toxicokinetics incorporated  
17 within these sections or is there going to be separate  
18 discussion of toxicokinetic issues?

19 DR. PFEIFER: Well, you have to understand in  
20 looking at these papers as well as all the other things I  
21 believe that Drs. Kellner and Moore in Topic 1A went  
22 through some of the toxicokinetics.

23 DR. RICE: Dr. Byus disagrees.

24 PANEL MEMBER BYUS: I'm trying to remember.

25 CHAIRPERSON FROINES: I read 1A, if that's -- I



1 wouldn't agree with that.

2 DR. PFEIFER: I know there is some papers where  
3 there's a lot of enzymatic, but I can't recall specifics.

4 DR. RICE: I can't recall specifically either,  
5 but I think it more -- it would tend to be towards the  
6 latter and come up on an individual case-by-case basis or  
7 topic-by-topic basis and more reflective, not directly in  
8 toxicokinetics, but, you know, exposure duration. So it's  
9 really not head on addressed as toxicokinetics, per se.

10 CHAIRPERSON FROINES: It's a major issue.

11 I would also caution you about the notion of  
12 adverse effects. I would be careful to not come in and  
13 state something shouldn't be done because it doesn't  
14 constitute an adverse effect, because a change may have  
15 physiologic implications that may result in adverse  
16 effects. And so I think that one needs to look at the  
17 issue broadly on that. That issue has come up here before  
18 with this panel. Do you know what I mean?

19 PANEL MEMBER FUCALORO: You mean something may  
20 not have a toxicological endpoint that anyone has seen,  
21 but one has seen a biochemical change?

22 CHAIRPERSON FROINES: And those changes may have  
23 implications for adverse effects.

24 PANEL MEMBER FUCALORO: They've not been  
25 identified.

1           CHAIRPERSON FROINES: And maybe adverse effects  
2 in and of themselves and we may not just know enough.

3           PANEL MEMBER FUCALORO: When you said it, I had a  
4 sense of deja vu. I guess you've said it before.

5           CHAIRPERSON FROINES: No, I think Paul's raised  
6 it before.

7           PANEL MEMBER FUCALORO: Well, someone has.

8           CHAIRPERSON FROINES: Paul.

9           PANEL MEMBER BLANC: I think that there was one  
10 of their sections that was -- at least one of their  
11 topics, I think, was trying to get at that which was 4B  
12 Evaluating Clinical Signs and Symptoms in Humans versus  
13 Animal Studies. I would just point out that it's very  
14 difficult to elicit symptoms from an animal.

15          DR. PFEIFER: We understand that.

16          PANEL MEMBER BLANC: You may want to think about  
17 how you word that as well. But I imagine that that was  
18 part -- that's driving that section to some extent, I  
19 suppose.

20          What John was just alluding to in terms of what  
21 is the clinical correlation of a biochemical abnormality  
22 perhaps, I don't know.

23          PANEL MEMBER BYUS: Again, I would like, John,  
24 some clarification on what you would like Peter and I to  
25 do with this document, because I was going to ask you this

1 and I appreciate you're input.

2 I mean do you want us to review it for the  
3 science, particularly? Do you want us to review it -- I  
4 mean, clearly that is the main point, but how editorial, I  
5 guess, is the best word to use, do you want us to be or  
6 should we be?

7 CHAIRPERSON FROINES: My concern is that I  
8 want -- I need to reserve your independent evaluation of  
9 their document. That's what we are required in a  
10 statutory context, that we need to tell them whether we  
11 think it's good or not, and that to over simplify it. And  
12 to a degree that we begin to become -- play a staff role  
13 and really work out the details of a document, I think we  
14 begin to have -- it becomes more difficult to have an  
15 independent evaluative position with respect to the  
16 document.

17 So I would -- but at the same time, we've also  
18 seen the lead as helping to facilitate the process. But I  
19 think that one has to be a little careful about that so  
20 that one doesn't get so deeply involved that you lose  
21 one's independent function. So I would basically leave it  
22 up to you and Pete's discretion, but I would suggest that  
23 the most important place of review will be at the final  
24 draft review. Although, I think one can give suggestions  
25 along the way.

1           PANEL MEMBER FUCALORO: Especially, if they sense  
2 things are going in the wrong direction, we certainly  
3 don't want at the end their to be major changes. But if  
4 they believe that there are problems, really significant  
5 problems early on, I think it's important that they get  
6 that information to the authors.

7           PANEL MEMBER WITSCHI: You know, I really would  
8 like to side with you and see what you said. If memory  
9 serves correctly, the whole thing started with a very  
10 simple question. This was one of the risk assessments,  
11 some data on cholinesterase inhibition and I've forgotten  
12 what species were not considered to be other elements.

13           And the panel asked why not? And the answer was,  
14 well, the EPA doesn't do it either or something along  
15 those lines and this really triggered the whole workshop  
16 and the whole symposium and the process.

17           And so clearly the panel eventually has to agree  
18 with the conclusions which are being drawn from the  
19 science. And I'm perfectly happy to draw some conclusions  
20 from the science. I would be very uncomfortable to go  
21 into all the detail, whether all the science is there or  
22 not, because that's not my field of expertise.

23           But what I really would like to see eventually is  
24 a document, that I have from -- I've seen so far, is going  
25 to be a very good document.

1           But what I really want to see is a document which  
2 spells out the issues, and you've come to some conclusions  
3 and then our task is whether we can agree with those  
4 conclusions.

5           CHAIRPERSON FROINES: I agree. I think it's --  
6 I've said it twice, I don't want to repeat myself, but  
7 it's important to preserve the independent evaluation of  
8 the panel. It's also important to preserve the energy  
9 level of the panel and both those things are significant,  
10 especially given the fact the we had four and today is the  
11 fifth meeting on SB 25, so people have been really dragged  
12 through the mud in a sense in that effort.

13          PANEL MEMBER BLANC: Or drive through the  
14 forests.

15          (Laughter.)

16          CHAIRPERSON FROINES: I'm not doing to well at  
17 metaphors today.

18          And I'm assuming that since Paul Gosselin or  
19 Keith haven't stood up and started to scream that this  
20 notion of having a joint effort with OEHHA and DPR and  
21 ourselves to find some of the external experts, so we can  
22 all feel comfortable with that, is --

23          DR. PFEIFER: That's perfectly acceptable. I  
24 mean, we're formulating a list based on people we know  
25 professionally in this field. But there are others that

1 you may not know of who -- and the other question that's  
2 come up, do we want to have each outside expert review  
3 every paper or let them pick papers or, you know, that's  
4 another question that I think we need to address.

5 CHAIRPERSON FROINES: Well, I would -- well,  
6 that's not -- this is something we'll have to work on  
7 together, because it's not a trivial issue, because on the  
8 one hand you might say well, we would pick people based on  
9 their expertise and who would be best at looking at a  
10 particular issue. That's the easiest answer.

11 But at UCLA we have a Department of Pharmacology  
12 with some people who have spent their lives on  
13 acetylcholinesterase. And that they are not necessarily  
14 toxicologists, but who they have such an incredible depth  
15 of science, that they could look at the science without  
16 necessarily knowing all the toxicology and look at your  
17 document and give vital input to it. So that it seems to  
18 me that who you actually ask to do the review is a  
19 creative undertaking.

20 So I think the answer to the question is yes,  
21 meaning, you know, it's to be worked out. It's an ongoing  
22 process.

23 PANEL MEMBER WITSCHI: I would like to call your  
24 attention to something that you probably don't know,  
25 because it's very exotic. And this is in certain

1 aircraft, there are once in awhile leaks of hydraulic  
2 fluid or engine oil into the cabin. And some of those  
3 contain organophosphorous compounds in trace amounts, but  
4 there is some concern out there among pilots and flight  
5 attendants that this might represent a toxic hazard.

6 DR. PFEIFER: I would agree with that. And  
7 there's also, as most of you may know, on international  
8 flights going to like New Zealand, Australia and Jamaica,  
9 they routinely either preboard or actually while the plane  
10 is in flight, fumigate.

11 PANEL MEMBER WITSCHI: But those are the lights  
12 they use. These are not organophosphorous compounds.

13 DR. PFEIFER: Oh, well, that's true. I don't  
14 know. I really would kind of take exception to being  
15 dosed while I'm going on vacation.

16 (Laughter.)

17 PANEL MEMBER FUCALORO: They have a sprinkler  
18 system with malathion.

19 CHAIRPERSON FROINES: Well, see that's what the  
20 Government has in mind when they started thinking about  
21 this new way of doing human experiments. They're going to  
22 use people on airlines as the study population.

23 CHAIRPERSON FROINES: Thank you very much. I  
24 think we're finished for the moment, unless somebody else  
25 on the panel has further comments?

1 And it's obviously an ongoing effort.

2 Congratulations.

3 DR. PFEIFER: George had a question.

4 DR. ALEXEEFF: I'll just ask my question. It  
5 sounded like the way you -- because David had asked --  
6 talked about the structure of the documents. It sound  
7 like the panel, basically in the end, wanted one document  
8 as opposed to one document with the science, another  
9 document discussing the implications of the science, the  
10 guidelines, it sounded like you wanted it more integrated.

11 PANEL MEMBER BLANC: Yes.

12 CHAIRPERSON FROINES: It's quite an undertaking.  
13 Congratulations so far.

14 DR. PFEIFER: Thank you.

15 CHAIRPERSON FROINES: So we have a little bit of  
16 time left. Maybe Andy can come back. But before Andy  
17 comes back, I wanted to raise a question that hopefully  
18 Peter -- Peter Witschi. Clearly, the situation has  
19 changed since September 11th. Airlines have cut back  
20 flights. There are significant security concerns. And  
21 the panel had some difficulty, because there are three  
22 people who are coming from Ontario, and United -- there  
23 are no current nonstop flights from Ontario to San  
24 Francisco anymore, strange as that may seem.

25 And so Craig and Roger and Tony had to go to



1 Oakland and take a cab across. And so that -- and when  
2 they arrived, they were in less than a good mood, to say  
3 the least.

4 And so the question for the panel is what shall  
5 we do about location of meetings and travel, as we start  
6 planning for next year?

7 PANEL MEMBER WITSCHI: Well, first of all, if  
8 those guys are unhappy sitting in a cab across the bridge,  
9 I'd encourage them to drive themselves.

10 PANEL MEMBER FRIEDMAN: That's even worse.

11 May I suggest that if we meet in the bay area --  
12 when we meet in the bay area, that we meet in Oakland,  
13 that would make their life a lot simpler and it's not that  
14 hard for us to get over at least not for me.

15 CHAIRPERSON FROINES: Well, Gary, it's  
16 interesting you say that, because I personally agree with  
17 you, I like going into Oakland, but the one member who's  
18 missing is Stan Glantz who hates the idea of having to go  
19 to Oakland. So there's no unanimity. I don't what Paul's  
20 position on this.

21 PANEL MEMBER FUCALORO: Is it because he's a  
22 snob?

23 (Laughter.)

24 PANEL MEMBER BLANC: Well, I don't think that  
25 there's any difference for -- any major difference between

1 if we're having a meeting, you know, at this location and  
2 having a meeting at the Oakland Hyatt or whatever it is.  
3 I think there have been times where we've had meetings at  
4 UCSF itself, and those have been for logistical reasons  
5 that would make it as hard to get here as to get to  
6 Oakland, but those have been the exceptions rather than  
7 rules.

8 But there have been one or two times meetings,  
9 because neither Stan or I -- there was no way to come  
10 otherwise because we had to be -- and you know we were  
11 only there for part of the meeting.

12 CHAIRPERSON FROINES: Jim should join us, I  
13 think.

14 But if we are in a situation like today, there  
15 wouldn't have been any substantive difference for me to go  
16 to Oakland or San Jose, if that would help and have people  
17 fly in and out of San Jose.

18 CHAIRPERSON FROINES: But you're coming from  
19 Davis, right?

20 PANEL MEMBER FRIEDMAN: I live up north and so it  
21 would be difficult, very difficult.

22 PANEL MEMBER FUCALORO: San Jose is tough.  
23 Oakland is --

24 PANEL MEMBER WITSCHI: What about Sacramento?

25 PANEL MEMBER BLANC: Yeah, Sacramento is a looser

1 for everybody.

2 PANEL MEMBER BYUS: Sacramento is another easy  
3 one for us to fly in.

4 PANEL MEMBER BLANC: No, Sacramento is basically  
5 your -- I mean, that's like two hours each way for -- I'd  
6 rather go to Ontario than go to Sacramento.

7 PANEL MEMBER FUCALORO: Is that right?

8 CHAIRPERSON FROINES: You would?

9 PANEL MEMBER FRIEDMAN: It's a long drive.

10 CHAIRPERSON FROINES: You can fly to Sacramento.

11 PANEL MEMBER WITSCHI: You can take the train.

12 (Laughter.)

13 CHAIRPERSON FROINES: I have done it a number of  
14 times.

15 PANEL MEMBER WITSCHI: You can take the train.

16 It's not bad, the train, actually.

17 PANEL MEMBER BLANC: I can drive to San Luis  
18 Obispo and take the train to LA, too.

19 CHAIRPERSON FROINES: Now, the fact of the matter  
20 is --

21 PANEL MEMBER FUCALORO: Oakland is the best.

22 CHAIRPERSON FROINES: Let me suggest something  
23 that Paul may be forgetting, which is if Roger and Tony  
24 and Craig couldn't get a nonstop flight from Ontario, that  
25 probably means they can't get a nonstop flight to Ontario.

1 So when you say you'd just as soon go to Ontario, you're  
2 not going to have a nonstop flight.

3 PANEL MEMBER BLANC: I can't get to Ontario and  
4 back in the same day anyway, by and large. So I always  
5 went down the evening before, if it was Ontario and then  
6 just flew back.

7 But I mean the last time I looked at it -- from  
8 here, I think that was the difference, in fact, is that  
9 the first flight up --

10 PANEL MEMBER ATKINSON: There are no flights,  
11 period.

12 PANEL MEMBER BLANC: No, but I'm saying in the  
13 old days where there was a flight to San Francisco, there  
14 was still never a flight early enough from San Francisco  
15 to Ontario to go in the same day. And so whereas to LA --

16 CHAIRPERSON FROINES: So not to prolong this, so  
17 what -- we clearly have a vote for Oakland is one option.

18 PANEL MEMBER BLANC: Then there's the more  
19 generic thing, which is that there has been a traditional  
20 commitment to alternate meetings between southern  
21 California and northern California, not every other  
22 meeting -- I mean, we've been doing it like -- we were  
23 doing it two up here, one down there.

24 It seems like we sort of strayed into four up  
25 here and one down there, instead of two up here and one

1 down there.

2 PANEL MEMBER FUCALORO: We noticed.

3 PANEL MEMBER BLANC: So I think that it's  
4 certainly time for us to have a meeting in southern  
5 California.

6 CHAIRPERSON FROINES: I think we should also  
7 consider --

8 PANEL MEMBER BLANC: That would certainly make  
9 their lives a lot easier.

10 CHAIRPERSON FROINES: -- trying to find a place  
11 at USC perhaps at the medical school or someplace in that  
12 vicinity, because then the people from Riverside can come  
13 a distance, and the people from the westside, like me, can  
14 come from a distance. But we should also clearly have  
15 meetings over in the Riverside area as well.

16 PANEL MEMBER FUCALORO: Speaking of lights, it is  
17 not quite a flight of fancy, but what is the legal  
18 constraints or requirements regarding being physically in  
19 the same room. I'm thinking of teleconferencing. Is that  
20 completely off the wall or is it something we could  
21 actually consider?

22 CHAIRPERSON FROINES: I don't know what the legal  
23 constraints are. I don't think it's as good a way of  
24 communicating as one --

25 PANEL MEMBER FUCALORO: It's not.

1           CHAIRPERSON FROINES: But if we could look at it  
2 as an option -- I mean, we need to -- I think what we  
3 would need to do would be to check into our various  
4 institutions about the facilities that are --

5           PANEL MEMBER FUCALORO: I believe I have the  
6 facilities. I think you guys do too, right?

7           PANEL MEMBER BLANC: UCSF certainly doesn't, not  
8 even remotely.

9           PANEL MEMBER BYUS: There's new Internet  
10 teleconferencing procedures now that are much more  
11 inexpensive that you can actually do on your own computer  
12 in your own office. I mean, it might be something to look  
13 into. I mean for certain issues, I mean, for example,  
14 like reviewing the findings today to meet a deadline. It  
15 seems we're always having meetings to just review, to get  
16 the findings out in a timely manner.

17          PANEL MEMBER FUCALORO: It seems to me the  
18 legal --

19          PANEL MEMBER BYUS: That would be easy to do over  
20 teleconferencing. You know, when an issue came up where  
21 we didn't have to have a full meeting and fly everybody  
22 all over to do something. I don't know about the legality  
23 though.

24          PANEL MEMBER FUCALORO: The public has to somehow  
25 be able to plug in, so to speak, I mean put a television

1 here or something.

2 CHAIRPERSON FROINES: So from what I here in this  
3 meeting, Peter is in Sacramento, so there's some  
4 advantages to him to stay and go to a meeting in  
5 Sacramento. Some people said Sacramento is okay. Paul  
6 doesn't care for it.

7 But what I'm hearing is that for the next few  
8 months, we should be planning meetings in southern  
9 California, to try to --

10 PANEL MEMBER FUCALORO: Well, I understand the  
11 next two meetings --

12 CHAIRPERSON FROINES: -- to balance things out.  
13 Oakland is an option, and that's probably all we have to  
14 really decide at this particular moment.

15 PANEL MEMBER FRIEDMAN: Can I just pursue this a  
16 little. Was the problem with the cab ride the Bay Bridge  
17 traffic tie up? Is that why it was a problem to get over  
18 here this morning, why you guys were in a bad mood?

19 (Laughter.)

20 PANEL MEMBER FUCALORO: Listen, the meeting was  
21 at 10:00, right? We've been up for six hours by the time  
22 the meeting started.

23 PANEL MEMBER FRIEDMAN: Oh, okay.

24 PANEL MEMBER FUCALORO: And there was no bad  
25 traffic between Oakland and here. In fact, the traffic

1 was beautiful.

2 PANEL MEMBER FRIEDMAN: I was going to suggest  
3 that BART was an alternative, because it picks you up at  
4 the Oakland Airport, but that's not the problem. But when  
5 we go to southern California, we often stay overnight, why  
6 can't the same thing happen when people come up here?

7 PANEL MEMBER FUCALORO: That's a point. I'm an  
8 honest man, I concede that that's a point.

9 CHAIRPERSON FROINES: I think we've gone as far  
10 as we're going to go on this particular topic.

11 So it's only 1:25. Andy, do you want to try and  
12 finish out?

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
14 SALMON: Can we take a five minute break?

15 CHAIRPERSON FROINES: If we can bring this as  
16 close to closure, I think we will have done a good job.

17 (Thereupon a brief recess was taken.)

18 CHAIRPERSON FROINES: Everybody should note that  
19 we are not going to vote on these chemicals today, because  
20 we're going to try and get as far along as possible. And  
21 one of the chemicals, carbon disulfide was not noticed, so  
22 we couldn't take a vote anyway on carbon disulfide. So we  
23 will finish this off and take a vote on a later date.

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
25 SALMON: Okay. So the next chemical that I'm going to



1 talk about is the methylene dianiline. The panel reviewed  
2 the derivation in March and there's a couple of changes  
3 we've made in response to comments by the panel. We more  
4 accurately described the disease seen in humans and we  
5 also made a point of mentioning the carcinogenicity.  
6 We've adopted this as a principle now that when a  
7 material, which is up for review for a chronic noncancer  
8 REL, is also, in fact, a carcinogen on the hot spots  
9 universe, that we should mention that in the REL summary.

10 We looked for evidence of any differential  
11 effects on infants and children and basically found  
12 nothing that gave us any indication.

13 So the endpoint is retinal toxicity. I mean, it  
14 was a possibility that this would have a differential  
15 effect, I suppose, since it's somewhat neurologically  
16 related. But we don't really, I think, know enough even  
17 about the mechanism to do anything other than speculate at  
18 this point, so we have to stay with the defaults.

19 --o0o--

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: The next one I want to present --

22 PANEL MEMBER BLANC: Can you just take note that  
23 you need to correct your footer in the process.

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

25 SALMON: I'm sorry about that. Unfortunately, the wrong

1 section break got deleted when we were in the process of  
2 -- thank you for pointing that out. I'm sorry. That is a  
3 typographical error, and hopefully we will be presenting  
4 phosphine in due course with a proper footer.

5           Selenium, again, this was one which the panel has  
6 looked at previously. The complexity here is that we are  
7 doing a root to root extrapolation. The critical effect  
8 is the induction of symptoms of selenium and excess in  
9 humans in dietary studies and epidemiological studies in,  
10 I think, China.

11           And the concern was that it's possible to inhale  
12 enough selenium possibly to induce similar symptoms by  
13 this root. So what we have done is calculated an overall  
14 intake based on the oral root using similar methodology to  
15 the U.S. EPA's reference dose.

16           And then we have made a number of assumptions in  
17 the root to root extrapolation, which we have clarified in  
18 response to discussion at the last meeting.

19           The other thing we've done is looked at the  
20 potential implications for children's health. And in this  
21 case, the key study being basically environmental  
22 epidemiological study does, in fact, include children as  
23 young as one year old. There is also in the database on  
24 the compound, a developmental study in hamsters. And so  
25 we do have some reasonable basis in this case perhaps

1 uniquely for feeling that the chronic REL should be  
2 protective of infants and children.

3 --o0o--

4 PANEL MEMBER FUCALORO: And, of course, the  
5 inhalation REL is 20 micrograms of selenium itself,

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7 SALMON: Yes, to the compounds, then the actual  
8 gravimetric amount would be adjusted to --

9 PANEL MEMBER FUCALORO: Grams of selenium?

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Yes. That refers to selenium.

12 PANEL MEMBER ATKINSON: On the next page, I think  
13 you should leave back in the vapor pressure of elemental  
14 selenium, ten to the minus three. It's a rather important  
15 number, because it means it's going to be at least  
16 partially in the gas phase in the atmosphere.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: So we should not have deleted that.

19 PANEL MEMBER ATKINSON: So leave the one at 20  
20 degree C and don't leave the one at 356, but leave the  
21 selenium at zero.

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: Okay.

24 CHAIRPERSON FROINES: Roger, what page are you  
25 on?

1 PANEL MEMBER BLANC: The very first page.

2 PANEL MEMBER FUCALORO: A92.

3 PANEL MEMBER ATKINSON: And on A93, the first  
4 sentence after, "Effects of human exposures," I think it  
5 would be wise to delete the word "gas" after CO2. It  
6 can't be a gas. It's got to be present in the particulate  
7 phase.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Yes. Okay.

10 PANEL MEMBER ATKINSON: I'll just throw another  
11 one at you. You didn't make any consideration of  
12 dimethylene selenide, which is volatilized bacterial or  
13 microbial degradation of sulfur that leads to dimethyl  
14 selenide. I don't know whether I'm really being facetious  
15 or not, but it's probably present in the atmosphere in  
16 some places.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: Yes, we're not -- I don't think we have any  
19 evidence of it being an issue for the hot spots program,  
20 but it's probably something that we should just check  
21 because these things do have a habit of appearing in  
22 strange places.

23 I mean, maybe we could ask whether anybody has  
24 got a hot spots measurement on that near a sewage works or  
25 something.

1           PANEL MEMBER ATKINSON: Well, the other place  
2 would be if you're trying to bioremediate high levels of  
3 selenium, you'll end up with dimethyl selenide.

4           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
5 SALMON: I'm not aware we have such a situation. We'll  
6 check into that.

7           The next one that we're going to talk about is  
8 sulfuric acid. And the panel reviewed this in some detail  
9 back in March. And the issue here is how do we  
10 accommodate the children's health impacts. The derivation  
11 that we proposed for the REL has not changed.

12           However, there's extensive epidemiological work,  
13 which interalia was reviewed by the air quality advisory  
14 committee, the corresponding panel for the criteria  
15 pollutants when they were looking at the criteria  
16 pollutants for SB 25.

17           And they actually have reviewed a number of  
18 epidemiological studies. It appears that the critical  
19 exposure, which results in exacerbation of asthma in  
20 children, is generally described as sulfate aerosol. But  
21 an important component of that response appears to be  
22 generic to acid aerosols of which obviously sulfate is a  
23 large component in some situations where exposure to the  
24 criteria pollutants is occurring.

25           But anyway, we felt that in view of this

1 important impact on children's health from sulfate  
2 aerosols that we should review that evidence in relation  
3 to our proposed chronic REL for sulfuric acid.

4           And one of the problems with the epidemiological  
5 data is that it doesn't show a clear threshold for that  
6 response. It sort of goes down, more or less, linearly  
7 about to a level at which the effects disappears due to  
8 sensitivity of the study as much as anything else.

9           But if there is -- the statement from the papers  
10 and from the reviewers is that if there is a threshold,  
11 it's probably something around two micrograms per meter  
12 cubed. This is the general consensus as to where the  
13 effects start.

14           And if taking that into account and taking into  
15 account that we believe that the asthmatic children, the  
16 most sensitive subpopulation that we're likely to have to  
17 deal with in a hot spots situation, we feel that this  
18 chronic REL, which was proposed on the basis of the animal  
19 studies in nonhuman primates, the proposed REL of one  
20 microgram per meter cubed is adequate in that it is  
21 sufficient, just about, to protect asthmatic children.

22           And because they are a highly sensitive  
23 subpopulation, we wouldn't expect to have a large safety  
24 margin, but we feel that this is probably a case where the  
25 proposed REL is appropriate.

1 PANEL MEMBER FUCALORO: You've mentioned this and  
2 I just want -- it bears repeating it, at least to me, is  
3 that you expect all atmospheric sulfuric acid pretty much  
4 to be in aerosol form.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: Yes.

7 PANEL MEMBER FUCALORO: You don't expect it into  
8 a gas form?

9 PANEL MEMBER ATKINSON: No.

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Not by the time --

12 PANEL MEMBER FUCALORO: Low pressure.

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

14 SALMON: Certainly not by the time it makes it over the  
15 fence, and into the --

16 PANEL MEMBER FUCALORO: Yeah.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: One of the reasons why I wanted, you know, to  
19 discuss this particular one with you and, you know, may be  
20 get a little bit of feedback, is that we're looking at the  
21 same database.

22 And at our proposed REL for nitric acid, which as  
23 I mentioned earlier, we're not bringing forward as a  
24 proposal at this point, and thinking that well, you know,  
25 it's an acid which is probably going to be turning up in

1 aerosol form in the environment, as a result emissions of  
2 nitric acid are indeed in nitrogen oxides from hot spots  
3 sources.

4           And we would basically anticipate that the same  
5 kind of constraints on what would be an acceptable  
6 exposure for children that we've identified for the  
7 sulfuric acid aerosols, is probably going to be -- it  
8 would probably be reasonable to assume that we should  
9 regard that as a limit for nitric acid aerosols, as well.  
10 And in the case of the nitric acid proposal, partly  
11 because, frankly, I think it's based on some older and  
12 less exhaustive animal studies in terms of the critical  
13 study.

14           That the nitric acid, the level we had originally  
15 put forward in the draft would not be protective of  
16 asthmatic children. So this is the reason why we pulled  
17 this one back. And what we're thinking is that we need to  
18 take account of this data on acid aerosols in relation to  
19 the nitric acid.

20           PANEL MEMBER ATKINSON: Nitric acid can be  
21 present in the gas phase quite easily. It's got a fairly  
22 high vapor pressure. So unless there is something to  
23 neutralize it, like ammonia, it will be present in the  
24 atmosphere in the gas phase.

25           AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF



1 SALMON: Well, I think this is a further reason why we  
2 need to spend more time thinking about nitric acid.

3 But as a starting point, we feel we ought to look  
4 at the impact of acid aerosols as possibly a constraint on  
5 what would be acceptable as a chronic REL for nitric acid.

6 PANEL MEMBER ATKINSON: You just used the words  
7 acid aerosol and nitric acid won't be present in on -- May  
8 not be present.

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: Depending on the nature of the emission.

11 PANEL MEMBER ATKINSON: Or on the other  
12 components in the atmosphere.

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

14 SALMON: Yes. That's something that we should perhaps  
15 consult with the Air Board as to exactly what's likely to  
16 be out there.

17 PANEL MEMBER BLANC: This may have come up the  
18 last time we discussed sulfuric acid, but the compound was  
19 involved in a couple of big releases in the east bay,  
20 which was a trisulfuric acid --

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: The oilum.

23 PANEL MEMBER BLANC: Yes, oilum breaks down to  
24 sulfuric acid?

25 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: I think basically, by the time, it's been out in  
2 the atmosphere and had a chance to react with a certain  
3 amount of ambient moisture, it's reasonable to regard it  
4 as being primarily the same as a sulfuric acid aerosol.

5 PANEL MEMBER BLANC: So in your major uses and  
6 sources, given the historical importance of these oilum  
7 releases, do you think you should have a sentence there  
8 about oilum breakdown.

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

10 SALMON: Yes we will add that.

11 --o0o--

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: And then the next item the --

14 PANEL MEMBER BLANC: One other question, I'm  
15 sorry. Is there any release of sulfuric acid in natural  
16 volcanic or thermal sources?

17 PANEL MEMBER ATKINSON: Yeah, it's released from  
18 volcanoes.

19 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

20 SALMON: Volcanoes, certainly. I think the biggest  
21 problem that I'm aware of from the sort of the geothermal  
22 type of sources is, in fact, hydrogen sulfide to reduce  
23 rather than to oxidize is safe. But certainly I think  
24 there are plenty of circumstances when sulfur oxides  
25 release from volcanic sources. The general ambient levels

1 of sulfur pollutants in California from both natural and  
2 anthropogenic sources is fairly low.

3 I mean, in the criteria pollutant universe,  
4 sulfur oxides are a large problem on the east coast due to  
5 particulate.

6 PANEL MEMBER BLANC: Sulfur containing coal  
7 burning.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
9 SALMON: Sulfur containing coal into a somewhat lesser  
10 containing fuel oil. Whereas, California has a habit of  
11 using relatively low sulfur oil for diesel and fuel.

12 PANEL MEMBER ATKINSON: It might be good to add a  
13 sentence or two right at the first page stating that any  
14 sulfur oxides emitted into the atmosphere will end up  
15 converted in that gas phase or through rain or cloud drops  
16 into the sulfuric acid.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
18 SALMON: Yes.

19 PANEL MEMBER BLANC: Well, because Mount Lassen  
20 was, but not extinct actually.

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
22 SALMON: Clear, there's a possibility for episodic  
23 excursions. It's not on a very large scale. I don't know  
24 that we can regulate against them.

25 --o0o--

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: Vinyl Acetate. This one was one in which the  
3 panel hasn't looked at in detail in March. And so this  
4 is -- here it is.

5 The proposed REL is based on historical legions  
6 of the nasal epithelium in rats, a long-term inhalation  
7 study. There's an observed LOAEL end and an observed  
8 NOAEL.

9 And we have calculated on this basis a proposed  
10 REL of 50 parts per billion. And a fairly high quality  
11 study in terms of the source data and not having to apply  
12 too many uncertainty factors. And the human equivalents  
13 concentration includes the RGDR calculations. And so the  
14 additional intraspecies factors on top of that is three.

15 And we have included an intraspecies uncertainty  
16 factor of ten for human diversity.

17 --o0o--

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: The chronic REL here basically doesn't have any  
20 very noticeable allowance for children's health. I think  
21 the statement which we have in the summary is -- well, we  
22 have this usual problem that we've got a somewhat irritant  
23 related sort of endpoint, but no data on children.

24 But on the other hand, at least here we do have a  
25 comparison REL, which is on a developmental study. So we

1 have a safety margin relative to that in the proposed REL.

2 And we are, for want of better information,  
3 relying on the uncertainty factors, both of intraspecies  
4 extrapolation and for the human intraspecies uncertainty  
5 factor to species to conclude that the proposed chronic  
6 REL would be sufficiently protective of children's health.

7 PANEL MEMBER BLANC: And the reason that you  
8 couldn't use a benchmark approach was because the -- or  
9 was it just too steep?

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Basically. Basically, it's too steep a dose  
12 response to get a very clear analysis. The other problem  
13 is just the way the data reported.

14 We have, at this point, a little bit of a problem  
15 converting the -- this table where it's reported as very  
16 slight, slight moderate, and severe, and then, you know,  
17 the incidents of those different levels. That's a little  
18 bit complicated to --

19 PANEL MEMBER BLANC: Translate.

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: -- to actually translate into something where our  
22 standard use of the benchmark doses software we expect a  
23 single parameter input. Maybe this is something where we  
24 need to, you know, think about how perhaps we could tackle  
25 that in the future as a method development issue, but we

1 don't really have the technology to do that well at this  
2 point.

3 CHAIRPERSON FROINES: Given where we are, there's  
4 nothing to preclude the panel from adopting the chronic  
5 RELs that you've presented today with the exception of  
6 carbon disulfide. So that unless there are major  
7 objections, it seems to me that we would cut down having  
8 to take up the issue again for these compounds at a later  
9 meeting if we did go ahead and vote. So what's the  
10 motion?

11 PANEL MEMBER BLANC: The motion is bearing in  
12 mind -- no, that's too wordy. Taking into account the  
13 changes agreed to in the draft document, the panel  
14 approves the specific chemicals presented, with the  
15 exception of carbon disulfide.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF  
17 SALMON: So it's the batch 2B chemicals that this motion  
18 refers to, not the batch 2A chemicals?

19 PANEL MEMBER FUCALORO: Right.

20 CHAIRPERSON FROINES: Is there a problem, George?

21 DR. ALEXEEFF: No. I just thought you might want  
22 to list the chemicals.

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

24 SALMON: It's shown on the slide.

25 DR. ALEXEEFF: And for the record, these Batch 2B

1 chemicals are acrylonitrile, beryllium, and compounds  
2 chloropicrin, diethanolamine, ethylene dibromide,  
3 isophorone, maleic anhydride, methyl isocyanate,  
4 4,4-methylene dianiline, selenium and compounds other than  
5 hydrogen selenide, sulfuric acid and vinyl acetate.

6 PANEL MEMBER FUCALORO: Is there a second for  
7 that?

8 CHAIRPERSON FROINES: Are you seconding?

9 Discussion?

10 All those in favor?

11 (Hands raised)

12 CHAIRPERSON FROINES: Vote is unanimous. The  
13 resolution is approved.

14 I should say that I think that vinyl acetate is  
15 more likely to exert its toxicity through acid aldehyde,  
16 but you guys don't agree with that. But I think vinyl  
17 acetate is more probable, is more benign.

18 So, Andy, you have one more slide, which is where  
19 do we go from here. And if you can do it in five minutes,  
20 we can --

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: I trust I can do it considerably faster than  
23 that.

24 So I'm just making sure I've got the right one.  
25 Okay, so the next steps for the chronic RELs. Well, we

1 have completed 2B, but we still have the 2A compound which  
2 we will bring -- we will notice and bring to your  
3 attention at the next meeting for appropriate, further  
4 instruction and or resolution.

5           We now have batched three. We have a second  
6 draft, which has yet to go through the public comment  
7 process. So we will be releasing the second draft for the  
8 period of notice and public comment, and also, of course,  
9 sending it to the panel in due course.

10           When we send it to the panel, we will include the  
11 public comments and the response -- our response to those  
12 comments.

13           And then the panel will, I assume, want to review  
14 the Batch three chemicals in groups of not more than about  
15 15 or 20 at a time.

16           It may be that the batches are a little smaller  
17 than that, because there are some materials in batch 3  
18 which, quite frankly, I don't think we're going to propose  
19 a REL for, because there is our further investigation that  
20 identified an either no-use in California or  
21 no-significant hot spots toxicity issues.

22           So I think for those things for which there is  
23 absolutely no use in California identified, I think we  
24 will probably not be bothering you with those ones. But  
25 there are, in fact, a couple of interesting chemicals in



1 there as well, so I hope it won't be too distressingly  
2 boring.

3 PANEL MEMBER BLANC: Thank you.

4 CHAIRPERSON FROINES: Thank you. Do we have a  
5 list of these chemicals, at this point, because we'll need  
6 to assign them?

7 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

8 SALMON: I will Email you a list -- the list which, you  
9 know, is potentially out there is the same as the first  
10 public comment draft list of things remaining. But as I  
11 say, we need to actually go through the list and review  
12 some of them before we have it absolutely finalized.

13 So what I can do is I can Email you the list as  
14 soon as we have it, which should be fairly soon.

15 CHAIRPERSON FROINES: So Email me the list and  
16 I'll take a resolution to close the meeting, before people  
17 walk out of the room.

18 PANEL MEMBER FUCALORO: Second.

19 CHAIRPERSON FROINES: We need to vote.

20 PANEL MEMBER BLANC: All in favor?

21 (Ayes.).

22 CHAIRPERSON FROINES: Congratulations, we did the  
23 entire agenda, and we're early.

24

25

1           (Thereupon the California Air Resources  
2           Board, Scientific Review Panel  
3           was adjourned at 2:00 p.m.)  
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