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3 APPEARANCES:

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5

SCIENTIFIC REVIEW PANEL MEMBERS

6

DR. JOHN FROINES, CHAIRMAN

DR. ROGER ATKINSON

7

DR. PAUL BLANC

DR. CRAIG BYUS

8

DR. ANTHONY FUCALORO

DR. STANTON GLANTZ

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DR. HANSPETER WITSCHI

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1 RIVERSIDE, CALIFORNIA, MARCH 5, 2001 - 9:10 A.M.

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3 DR. FROINES: We will call to order the March
4 5th, 2001 meeting of the Scientific Review Panel on Toxic
5 Air Contaminants.

6 The first item on the agenda is discussion of a
7 chronic RELs, the new chronic REL documents chemicals.
8 And so the first speaker will be Melanie and Jim Collins.

9 DR. GLANTZ: Before that, can I say one thing
10 about the meeting time? I'm perfectly happy to come to
11 beautiful Riverside, but I think when the staff schedules
12 the time for the meeting, they should be cognizant of
13 travel arrangements and airline schedules so that -- for
14 example, I had to get up an extra hour early to go to
15 Oakland because there were no flights out of San
16 Francisco that would have gotten here by 9:00.

17 I think it's reasonable to move the meetings
18 around, but I think that one ought to be cognizant of the
19 schedules so that you don't have to either get up in the
20 middle of the night or come down the day before or up.

21 DR. ATKINSON: Of course, we have the same
22 problem coming to San Francisco.

23 DR. GLANTZ: We can start at 10:00, 11:00, noon.
24 Whatever. Okay.

25 DR. BLANC: Thanks for sharing.

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1 DR. GLANTZ: Now, he told me to say this.

2 DR. FROINES: Just so it's on the record. We
3 will avoid further family bickering, however.

4 Dr. Collins.

5 DR. COLLINS: Good morning. I'm James Collins,
6 staff toxicologist with the Environmental Office of
7 Health Hazard Assessment. And hopefully the PowerPoint
8 presentation arrived here a couple light years ahead of
9 us.

10 This is chronic Reference Exposure Levels Batch
11 2B. It's part of the Air Toxics Hot Spots Program
12 guidelines. The chronic REL document methodology was
13 approved last year, and we have brought four batches of
14 chemicals to the Panel and there's probably there's
15 another 40 or so yet to come.

16 The chemicals in this batch -- to kill time,
17 I'll read them. Acrylonitrile, beryllium, chloropicrin,
18 diethanolamine, ethylene, ethylene dibromide, ethylene
19 glycol butyl ether, fluorides, isophorone, maleic
20 anhydride, methyl isocyanate, methylene dianiline, nitric
21 acid, phosphine, selenium, sulfuric acid, triethylamine
22 and vinyl acetate.

23 There are handouts of the slides, which I guess
24 we have to have on electronic backup. Prior actions on

25 the chronic RELs on Batch 2B included there was an

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1 initial draft of the technical support document that was
2 available for public comment in October of '97. A second
3 draft incorporated the public comments and new data and
4 was made available for public comment September 27th,
5 1999.

6 The methodology was approved by the SRP and
7 adopted by the Director of OEHHA on February 23rd, 2000.
8 Since then we've had Batches 1B, 2A completed and adopted
9 and now we're bringing Batch 2B.

10 The next page, pesticides in Batch 2B include
11 chloropicrin, ethylene dibromide and methyl isocyanate.
12 And we'll be discussing chronic RELs for use through
13 these compounds in their non-pesticidal applications.

14 Of the various chemicals, we received public
15 comments on three of them -- chloropicrin,
16 diethanolamine, and maleic anhydride, and those comments
17 and our responses were submitted to the panel and
18 Dr. Glantz has read those thoroughly.

19 The chloropicrin chronic REL, we have our
20 derivation on two slides. The study was an industry
21 study by Burley, Flare and Benson published in 1995.
22 They looked at both mice and rats. We based our chronic
23 REL on the mice. These animals were exposed six hours a

24 day five days a week for two years. The critical effects
25 seen were nasal rhinitis and bronchiectasis. The LOAEL

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1 was half a part per million, the NOAEL was .1 parts per
2 million.

3 The average experimental exposure was
4 approximately .018 parts per million for the NOAEL group.
5 We used the EPA's software for determining regional gas
6 deposition and came up with the factor of .21 which made
7 the human equivalent concentration .0038 parts per
8 million. We then applied an uncertain factor of 3 for
9 interspecies, 10 for intraspecies, with a cumulative
10 uncertain factor of 30 and a chronic REL of .1 parts per
11 billion or .8 micrograms per meter cubed.

12 Now is -- that's all we have. This is actually
13 what we were supposed to do on our PowerPoint
14 presentation, which we're still waiting for. And I have
15 no other comments other than we would like to hear what
16 the panel has to say about the various chemicals that
17 were assigned to them.

18 DR. FROINES: I'm a little confused. Are you
19 going to make a PowerPoint presentation?

20 DR. COLLINS: We sent it.

21 DR. MARTY: They're having technical
22 difficulties.

23 DR. GLANTZ: We have the printouts of the
24 slides.

25 DR. COLLINS: That's basically what I just went

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1 through was the handouts. I'm sorry. I thought this
2 thing would be --

3 DR. GLANTZ: John, I think we could forego -- we
4 have hard copies of the slides. They're very brief.

5 DR. WITSCHI: The first thing you learn as a
6 graduate student was never to check your slides in the
7 luggage in an aircraft, and I think the same applies to
8 PowerPoints or whatever it is.

9 DR. FROINES: I have -- there seems to me to
10 be -- we have this list of the assignments, and in
11 looking on your slide there seems to be one -- unless I'm
12 misreading it, it looks to me like you're -- that one
13 chemical was ethylene.

14 DR. COLLINS: Yes.

15 DR. FROINES: And there is no panel member
16 assigned to it.

17 DR. MARTY: Actually we didn't bring that
18 chronic REL forward, so that should have been deleted.
19 I'm sorry for that.

20 DR. FROINES: So --

21 DR. MARTY: We have not brought forward a

22 chronic REL for ethylene.

23 DR. FROINES: So that we can -- this was --
24 these overheads was to be your presentation?

25 DR. COLLINS: Yeah.

8

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1 DR. FROINES: So then we can proceed with panel
2 discussion.

3 DR. COLLINS: Yes. Definitely.

4 DR. FROINES: So Paul, the first chemical then
5 on the list is beryllium.

6 DR. BLANC: So in terms of the beryllium
7 document, one of the things that struck me about it was
8 that -- and this is understandable given the time line
9 that you just alluded to -- that for some of these there
10 seems to have been a bit more re-visiting of the
11 literature than for others.

12 For some of them it doesn't matter much because
13 the literature has been fairly static, but since for
14 beryllium the literature is quite active, I think that
15 this particular write-up would benefit from going back
16 and looking, and I'll transmit to you three different
17 papers that were not addressed that I thought were
18 relevant.

19 One is a review of the development of the
20 eight-hour occupational exposure limit that was posed to

21 apply to occupational environmental hygiene this past
22 year. And because it reviews a lot of the data and the
23 rationale, I think it's appropriate to address it, even
24 though it's the occupational standard and it talks a lot
25 about the 1940s data and ambient data, which I guess is

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1 from Lorraine, Ohio.

2 DR. COLLINS: The Isenbudd (phonetic) were
3 they -- the vicinity of that.

4 DR. BLANC: I always assumed that was Salem, but
5 I guess it was Lorraine.

6 DR. WITSCHI: It was Lorraine.

7 DR. BLANC: And second is a paper analyzing the
8 incidents -- well, it's a case control study but still at
9 Rocky Flats. And since they have a lot of hygiene data,
10 I don't think you had included the Rocky Flats data in
11 your review.

12 The third is a Japanese study which is from '97
13 and also has exposure data and incidents of lymphocyte
14 transformation in the population, working population.

15 So I'm going to give you all those. I think
16 that you need to double-check and see that none of
17 these -- at a minimum I think some of these would be
18 supportive of what you're doing, or if they have lower
19 implications you should address that.

20 The second thing is a generic comment and this
21 actually applies in other places. There are times
22 where -- it makes most sense to report everything in
23 micrograms and all of a sudden you're presenting
24 something as .0006 milligrams and everything else is in
25 micrograms. It would simply be more logical to express

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1 that as say 6 micrograms.

2 So if you look through there and I think this is
3 actually a generic comment that applies to some of the
4 other ones.

5 DR. COLLINS: We put both. Sometimes it may
6 be -- you mean consistently if there's only one put
7 micrograms.

8 DR. BLANC: Yeah. Translate it into micrograms.
9 And another thing about this one that I wasn't quite sure
10 if I understood the rationale. When you did -- actually,
11 leaving all this other stuff aside, when you did the
12 reference exposure level, you used an interspecies
13 uncertainty factor of one and then in parentheses you put
14 sensitive subpopulation. Now, you based it on the Price
15 study which was an occupational study.

16 Given the amount of work that has shown that
17 there are HLA types which are probably more at risk for
18 developing beryllium disease, this would probably be one

19 of the compounds for which interspecies uncertainty is
20 the most -- most likely to be and the occupational
21 population that was looked at wasn't just a population of
22 that one HLA type. So I wasn't clear why there was an
23 interspecies factor of one. It was as if the study you
24 were quoting was of children or asthmatics or something.
25 That's the only other time I've seen you use an

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1 interspecies factor of one.

2 Can you tell me why you did that?

3 DR. COLLINS: I think we just said there was a
4 very small percentage of the work population that got the
5 disease, and we felt that they might be the sensitive
6 population. They didn't get the HLA typing, but --

7 DR. MARTY: It looks like the REL is based on
8 the low observed adverse effect level in the sensitized
9 workers. There were eight out of 136.

10 DR. BLANC: But people get sensitized. That's
11 how they got the disease. But to say they got sensitized
12 because they were -- some of those people who got
13 sensitized might have been at increased risk to becoming
14 sensitized because of HLA type, and some might have been
15 sensitized because of the dose response relationship.

16 I don't think it's particularly valid to say
17 that that was a study of the sensitive subpopulation. It

18 was a study of a whole -- if anything, working groups are
19 usually healthier to start with.

20 DR. MARTY: I don't think we meant to imply the
21 study was only of people who were sensitive. It was a
22 study of a whole bunch of people that exposure
23 concentration that we determined was a low observed
24 adverse effect level was the median exposure of the
25 workers who were beryllium sensitized. So we considered

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1 that a LOAEL for the sensitive subpopulation, but you're
2 right that those people may not necessarily have been the
3 most sensitive.

4 We don't know what their history of exposure
5 was, for example. They could have had very high exposure
6 at some point which --

7 DR. BLANC: Triggered that.

8 DR. MARTY: Triggered the sensitization.

9 DR. FROINES: The -- as the data emerges on this
10 issue of subpopulation, sensitive populations, the
11 genetics is relatively complicated in there's actually
12 three categories. And so I think Paul's point about some
13 of the sensitization may have occurred in the population
14 which has called intermediate risk, so to speak, and that
15 may be a dose response issue.

16 DR. MARTY: Right. We could add an intraspecies

17 uncertainty factor, too. A number.

18 DR. BLANC: I think that would be the only thing
19 that would be reasonable unless you have some really
20 overwhelmingly convincing rationale not to.

21 DR. MARTY: The question would be is it three or
22 is it ten. Are we looking at -- Can we make the
23 assumption that these folks who got sensitized --

24 DR. BLANC: I think you should look at the data.
25 There are more recent articles by Lee Newman that you

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1 don't cite that don't include exposure data but certainly
2 address this issue of the genetics of the disease. I
3 don't offhand know what the right number would be.

4 DR. MARTY: Okay. We'll look at those studies
5 and come back with a discussion of what we think the UF
6 should be.

7 DR. FROINES: The thing that catches your eye,
8 if you've been involved with beryllium at all, is in fact
9 the lack of Lee Newman studies quoted here, and also that
10 there's quite a bit of genetic work coming out Los Alamos
11 that isn't quoted. So that somewhat more attention to
12 the lymphocyte (phonetic) proliferation results I think is
13 appropriate.

14 DR. BLANC: The only other thing I would caution
15 is that when you use the term subclinical, you refer to

16 this end point as subclinical because they had a
17 lymphocyte transformation SA positive and didn't have
18 radiographic changes of beryllium disease but they did
19 have pathology on biopsy. So some people might use the
20 word subclinical because they weren't symptomatic, but
21 it's not the same kind of subclinical as, you know -- I
22 would just be cautious with that word. It might actually
23 be the correct usage perhaps, but it may be implying more
24 than you have to.

25 I think Kay Chrysler would probably take

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1 exception to it, for example. So that's my first one.

2 The second one --

3 DR. WITSCHI: I have a few comments on
4 beryllium. The first one, since Tony is not here, on
5 page 7. Beryllium sulfate is really quite soluble in
6 water.

7 DR. MARTY: We have it as insoluble.

8 DR. WITSCHI: That's wrong.

9 DR. MARTY: Sorry.

10 DR. WITSCHI: Then the next page on effects of
11 human exposure, the last sentence of the first paragraph
12 is the total number of beryllium related disease cases
13 has declined. I would be a bit careful with that one. I
14 think not everybody would agree, and actually beryllium

15 has become quite a potent litogen.

16 DR. FROINES: Peter, what did you say?

17 DR. WITSCHI: Litogen, l-i-t-o-g-e-n. That's an
18 agent that promotes litigation. And so I'm not so sure
19 whether beryllium disease has really declined. Some
20 people would tell you we see more and more of it.

21 Then on page 14, to make a chronic oral
22 reference level is really some kind of -- I don't know
23 how to say this, you know, but it's been known since the
24 '50s that beryllium was not absorbed at all from the
25 gastrointestinal tract. Some of the early studies have

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1 really shown there's no absorption of beryllium if it's
2 given orally to anything.

3 And so to have an oral reference exposure level
4 is kind of -- doesn't make sense.

5 DR. BLANC: I think they are -- why don't you
6 just include that because we asked to you include other
7 reference levels? Does this have some meaning? Actually
8 that's why I didn't pay much attention to that because I
9 just thought (inaudible) EPA does, but it doesn't.

10 DR. MARTY: It does have implications. This
11 isn't just a comparative piece.

12 DR. BLANC: This last thing?

13 DR. MARTY: Right. If you'll recall from the

14 part four of the Air Toxic Hot Spots Guidelines, we have
15 a certain number of chemicals which we look at in the
16 risk assessment methodology via other routes of exposure
17 besides inhalation so when we do the risk assessment we
18 use these oral reference exposure levels to estimate
19 hazard from --

20 DR. BLANC: All sources.

21 DR. WITSCHI: That's not the problem. The
22 problem is there was a rat study and diversite shows no
23 effects and so on. I know the rat study. But the
24 problem is that it was already stupid to do the rat study
25 at the time being because some earlier evidence had

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1 conclusively shown that beryllium is not absorbed from
2 the GI tract. Period.

3 Admittedly those studies go back to the '50s,
4 but that's a fact. So even having done an oral study was
5 already at the time being some kind of nonsense.
6 Anyhow --

7 DR. BLANC: So what should be done to the
8 report?

9 DR. WITSCHI: At least add a paragraph and say
10 maybe it was nonsense to do an oral absorption study in
11 view of the facts it's a well known observation that
12 beryllium is not absorbed.

13 DR. BLANC: What do you guys have to say about
14 that? If it's not absorbed --

15 DR. COLLINS: It is poorly absorbed. I think
16 we're just following the EPA, and technically it could
17 be --

18 DR. BLANC: The trivial impact on your standard
19 overall because it's such a low level and that's the
20 no-effect level.

21 DR. COLLINS: But if it's a waste of space, it's
22 a waste of space. It is a freestanding NOAEL --

23 DR. WITSCHI: Sorry?

24 DR. BLANC: Wouldn't it make sense to say zero?
25 Just because the EPA does something --

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1 DR. COLLINS: We have two options. Either leave
2 it in there or drop it. Basically anything that isn't
3 mentioned is zero.

4 DR. FROINES: This is one of those that I have
5 a lot of problems with because under critical effects,
6 there isn't any. So we don't have -- we don't have any
7 toxicologic information that says there are adverse
8 effects associated with oral intake except for these old
9 1975 studies that show some weight changes and those
10 kinds of weight changes can happen for a lot of reasons,
11 as we all know.

12 So when we're left, we don't have -- our NOAEL
13 is based on no adverse effect, and I frankly have serious
14 problems with that methodology. I think it's better to
15 have some dose response information when one defines
16 NOAEL as opposed to defining a NOAEL from essentially a
17 negative study.

18 So I agree with Peter. I think it should be
19 deleted.

20 DR. BLANC: I certainly don't have any problem
21 with that. You know, also one very minor thing in the
22 very first table, also because you brought up the thing
23 about solubility, didn't we decide we weren't going to
24 present observed vapor conditions? So it has a vapor
25 pressure of ten tora to 860 degrees. Is that a great --

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1 DR. ATKINSON: Non-volatile for all of them.

2 DR. WITSCHI: The last thing I have --

3 DR. BLANC: When you're in the sun --

4 DR. FROINES: If you're in the sun, you don't
5 have to worry about beryllium.

6 DR. MARTY: Okay. We'll delete the oral REL. I
7 think the thinking was they did have some decreased
8 growth rate during between -- two and six months in the
9 rodents. So we were a little concerned that well, maybe
10 that is a generalized chemical stressor effect, but as

11 you point out that could be from a lot of things.

12 So -- and I agree. We're always have heartburn
13 over using a freestanding NOAEL.

14 DR. FROINES: In our recent 600 animal study, we
15 had all sorts of weight changes that went on that we did
16 complicated analyses about and in the end couldn't figure
17 out what was going on, and in terms of biological
18 significance.

19 DR. WITSCHI: Okay. The last comment I have is
20 about a year ago I reviewed the new ATSDR document on
21 beryllium. So I don't know whether it's come out or not,
22 but there is going to be a new one.

23 DR. FROINES: There is of course the new DOE
24 standard. Is that what Paul is talking about?
25 Department of Energy has a new beryllium standard that's

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1 about a year old I think.

2 DR. BLANC: No. I don't know if that's a
3 standard. It's not a standard. They have a program.

4 DR. FROINES: Standard. It was a standard. I
5 was on the Federal Advisory Committee and did it.

6 DR. BLANC: Anyway, there's a lot of literature
7 that you need to look at.

8 DR. MARTY: Okay.

9 DR. FROINES: The Genetics is absolutely

10 fascinating at this point.

11 DR. BLANC: So the second one that you asked me
12 to do was fluorides and my comment on the fluoride one is
13 a bit more diffuse and that is that -- do you have all
14 the stuff here about the fluorosis and the data and
15 the -- this lengthy table with every single observation
16 from the 1963 study and all of that.

17 My question is there's nothing -- there's some
18 very offhand or oblique reference perhaps to respiratory
19 issues related to fluoride and particularly in the
20 primary aluminum smelting industry. The problem with the
21 respiratory effects on the primary smelting industry is
22 it's not clear it's due to the HF. On the other hand, it
23 seems that to -- if you're not going to look at
24 respiratory end points from the aluminum -- primary
25 aluminum smelting industry, you need to at least say yes,

20

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1 we understand that there are all these end points but the
2 reason we're not going to work with them is because --

3 DR. MARTY: Could exposures.

4 DR. BLANC: There are other exposures. And it's
5 not clear this is the effect that this is causally
6 related to fluoride.

7 DR. MARTY: We can add that in.

8 DR. FROINES: Paul, can I ask one exposure

9 related question?

10 DR. BLANC: Let me ask one other question in
11 light of our discussion we just had.

12 Since fluoride is in the water, why isn't there
13 an oral -- why isn't an oral exposure route of issue here
14 to combine in your -- I mean there is one where I guess
15 it would matter if you were ingesting fluoride and
16 then --

17 DR. WITSCHI: Well, if I might add to this, if
18 you're talking about fluoride carries in the water, there
19 is an NRC report which you don't quote which addresses
20 exactly the issue of how much fluoride and is it good or
21 is it bad and all these kind of things.

22 It's about five years old, but this was one of
23 the Committee of Toxicology of Natural Resource Council
24 did quite an extensive study on fluoride which you might
25 want to look up.

21

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1 DR. MARTY: I think we were trying to focus on
2 inhalation studies which doesn't answer your question.

3 DR. WITSCHI: I have the same thing. Beryllium
4 which is a non-issue orally, you discuss the oral.
5 Fluoride where the issue is really oral exposure, there's
6 nothing there.

7 DR. BLANC: I mean it wouldn't be at the end

8 point respiratory, but since you're doing fluorosis and
9 its systemic affect.

10 DR. MARTY: Right. Okay. We can look into
11 looking at the developing a chronic oral REL.

12 DR. BLANC: Doesn't EPA have a chronic oral REL?

13 DR. MARTY: I don't know. I'll find out.

14 I'm also not sure where fluorides came out.
15 They should have come out when we did that analysis of
16 what would be -- what should be looked at by multiple
17 pathways of exposure. It should have come out as
18 glomming, as being particulate and not -- so I don't know
19 why we didn't do that.

20 Andy's pointing out that maybe part of the
21 problem is the nature of the airborne releases, if it's
22 fluorene gas versus fluoride salts. We would have to
23 look at that. That may have played into --

24 DR. BLANC: I think you made a comment that
25 everything was absorbable from -- by inhalation so you

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1 were going to treat it all the same early on in.

2 DR. MARTY: Yeah. We clearly have to work
3 something out for the oral issue.

4 DR. ATKINSON: On page 453 you should probably
5 specify HF by all the physical and chemical properties,
6 the molecular weight density, vapor pressure, solubility.

7 So I take it just those are specific to HF.

8 DR. FROINES: I was going to say that following
9 on Roger's comment, hydrogen fluoride has been a
10 controversial issue in southern California because of its
11 releases from petroleum refineries. And there have been
12 I think litigation and certainly public concern over
13 hydrogen fluoride release from refineries.

14 It wouldn't be a bad idea if there had been some
15 acknowledgement of the fact that the issue in California
16 probably is releases from those kinds of sources so that
17 the problems with some of the exposure, the exposures
18 statements is that the reader doesn't get a sense of
19 where the issue might be if there is an issue, and in
20 this case there certainly is.

21 DR. MARTY: We can look at the Cedars database
22 that ARB has to figure out whether the majority is from
23 refining. It's also emitted in the electronics industry.
24 So in the Bay Area, Silicon Valley, as well as the
25 refining. But we can make that -- by looking through

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1 their database to see. All we've done here is report the
2 total pounds per year. That doesn't give you an
3 indication of which facility.

4 DR. FROINES: I had a question for Paul which is
5 that there's a lot of literature or some literature

6 rather that's not quoted here on studies that have looked
7 at pot room asthma.

8 DR. BLANC: That's what I was talking about
9 before, and the controversy with the primary aluminum
10 smelting industry is that it's not clear if it's the HF
11 or not, but I think that -- as I said, if respiratory end
12 point is not going to be looked at least there needs to
13 be acknowledgement as to the rationale for not using
14 those data.

15 DR. FROINES: I think my impression is that pot
16 room asthma is not an IHE topic disorder and that
17 fluoride seems to be a good --

18 DR. BLANC: Again, you could make the argument
19 either way. I think that if you made the argument that
20 you were using fluoride as a respiratory end point and
21 you were going to take asthma in that industry as a
22 fluoride end point, you would be ahead of the data to an
23 extent.

24 So one way to have you taking it would be to
25 have one of your small analyses at the end which would be

24

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1 were we to use this as the end point, this is what we
2 would come up with; and two, to reassure yourselves that
3 you wouldn't be an order of magnitude or two lower in
4 terms of what you were coming out with.

5 But I think it would be -- I think it would be
6 potentially a problem if you used that as the end point
7 because there's not a consensus.

8 DR. FROINES: It's an interesting research
9 question actually because there's very heavy exposure to
10 PAHs, and we think PAHs have a role in at least
11 enhancement of allergic airway disease.

12 DR. BLANC: Anyway, those are my comments on
13 fluoride.

14 DR. FROINES: So you're okay on the REL?

15 DR. BLANC: I mean if you're going to use
16 fluoroses as the end point, those two caveats in mind.
17 Because obviously for your standard setting or action
18 taking, the oral issue is going to be much more
19 important.

20 DR. FROINES: So that's it for you.

21 DR. BLANC: That's it for me.

22 DR. FROINES: And Craig Byus isn't here and Gary
23 Friedman sent a note saying that he wasn't going to be
24 able to be here but he had no problem with the review.

25 I think that I'd like to hold on this one and

25

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1 I'll take a look at it as well so we can -- so we're not
2 just left with the one sentence in an E-mail.

3 DR. BLANC: Can I just make a couple of comments

4 about a couple of these things?

5 DR. FROINES: Sure.

6 DR. BLANC: On methyl isocyanate, the -- can you
7 give me a sense again since I don't have these memorized
8 by heart? You came out with a REL in the end of .5 parts
9 per billion on methyl isocyanate.

10 My general take on these RELs is that they seem
11 appropriately conservative. This was the one that struck
12 me as being a little perhaps on the high side, even
13 though it's in parts per billion.

14 Can you just refresh my memory? How would this
15 compare, for example, to your REL for chlorine or
16 chlorine dioxide or --

17 DR. COLLINS: I think they're all in the same
18 neighborhood. We haven't got phosgene yet. That's in
19 the next batch. I don't have the numbers memorized
20 unfortunately, but they're about the same one or some
21 micrograms per cubic meter.

22 DR. MARTY: .5 to one, I think.

23 DR. BLANC: Because I would say that this is a
24 chemical which is about ten times as acutely toxic as
25 chlorine. I just wondered if -- I just wondered if this

26

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1 1986 study was the best and most recent.

2 DR. COLLINS: The problem is they're all too

3 short. We would much rather have a longer term study.
4 We don't have it.

5 DR. BLANC: But this study was published both
6 the same year as Bopaul (phonetic) basically or year
7 after.

8 DR. COLLINS: Two years, right.

9 DR. BLANC: So was this study done -- there was
10 not other studies that occurred after Bopaul and nobody's
11 been doing --

12 DR. COLLINS: I think there were a lot of
13 studies. The problem is they're not long-term studies
14 and Bopaul was an acute problems. So I think there's
15 probably (inaudible) than just finding what the acute
16 effects were.

17 DR. MARTY: I think some of the studies after
18 Bopaul expose the animals for a short time and then held
19 them over for observation for a long time.

20 DR. BLANC: I read that. Let me ask it a
21 different -- come at it a different way then.

22 The interspecies uncertainty factor which is
23 only three here is because of your ability to use certain
24 extrapolating models?

25 DR. COLLINS: And which in this case actually

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1 raised the number. So it's almost paradoxical. Usually

2 it lowers it but there are a few chemicals for which the
3 RGDR is greater than one and this was one based on using
4 the EPA methodology and computer program.

5 DR. BLANC: For rats? If it has to do with the
6 species involved?

7 DR. COLLINS: Each. There's about four species.
8 Rat, probably mice. Rats, hamsters and one other,
9 rabbits I think they have, that they have extrapolation
10 numbers for or the programs. It was just put into that
11 program and -- we have just been unwilling to put in,
12 quote, modifying factors if we didn't have some sort of
13 way to do it, unless you say well, maybe ten days is even
14 too short to use a factor of ten for subchronic, but that
15 would be about the only way we could modify if we're not
16 going to go from our default assumptions.

17 DR. BLANC: So what would you do if the
18 subchronic was even more uncertain? Do you have a
19 protocol for greater than ten?

20 DR. MARTY: That would be a judgment call.

21 DR. BLANC: Well, I want to you take a long
22 hard look at it.

23 DR. COLLINS: I think that's why we have the
24 (inaudible), the major areas of uncertainty are the lack
25 of chronic inhalation exposure studies. Really this is

1 the real shortcomings, just so short.

2 DR. BLANC: Right.

3 DR. MARTY: You can see we're getting to the
4 chemicals now that have less and less appropriate data.

5 DR. BLANC: One other question. You said the
6 Toxic Air Hot Spots in California estimated that there
7 was .29 pounds release. At this committee we've already
8 seen that one of the breakdowns from metham (phonetic)
9 sodium.

10 DR. COLLINS: That was an accident.

11 DR. MARTY: We also -- that data is only for
12 facilities reporting under the Hot Spots.

13 DR. BLANC: I understand that.

14 DR. MARTY: So we did add in a sentence this
15 does not include estimates of emissions and breakdown
16 products from the use of metham sodium.

17 DR. BLANC: Which you would estimate could be as
18 high as X pounds is what is missing there.

19 DR. MARTY: Okay. I don't know if DPR can help
20 us out with that kind of information or not.

21 DR. ATKINSON: I think you should also change
22 that sentence to it does not include the amounts or
23 include MIC or methyl isocyanate formed as a breakdown
24 product.

25 DR. MARTY: Okay.

1 DR. ATKINSON: And then put at the end of the
2 sentence something like estimated to be -- well, it's
3 undoubtedly much greater than .29 pounds per year.

4 DR. MARTY: Undoubtedly. It is sort of a
5 regulatory quirk that this program, the Air Toxics Hot
6 Spot Program, can't apply to pesticides in their
7 pesticidal --

8 DR. BLANC: But it doesn't keep you from saying
9 how much it is in this document.

10 DR. MARTY: No, it doesn't.

11 DR. FROINES: Have you talked to DPR about this
12 particular chemical? Because hopefully their perspective
13 and your perspective is somewhat similar on this
14 compound.

15 DR. COLLINS: They were sent -- MIC -- several
16 of -- the three pesticides, they were sent to DPR for
17 review and we certainly got back comments on chloropicrin
18 and I don't know they looked at MIC but no comment.

19 DR. MARTY: They're aware of what we're doing.

20 DR. FROINES: Well, you have -- your reference
21 level obviously has implications to their regulatory
22 process as well, so that you've kind of in a sense,
23 whatever standard you set, one would assume that their
24 standard would be consistent with that.

25 DR. SALMON: They have reviewed this in some

1 detail actually.

2 DR. COLLINS: Andy Ruben reviewed this in great
3 detail, chloropicrin and also we sent ethylene dibromide
4 for their review. But again, we're talking about their
5 non-pesticidal uses. I don't know what --

6 DR. MARTY: Paul is pointing out that we can go
7 back and look at the metham sodium document and do the
8 comparison, I think to see that we're on the same page.
9 We assumed we were on the same page when we didn't get
10 any comments back from them.

11 DR. FROINES: It's an interesting issue because
12 under AB 1807, when chemicals come to us for review
13 they're required to have a range of risk associated with
14 them. So what happened with the MITC document, of course
15 it included the discussion on MIC but because it had been
16 classified as a HAP, it was therefore grandfathered in as
17 a TAC.

18 So at this point from DPR, there's no range of
19 risk and there needs -- and there clearly needs to be a
20 range of risk on -- our assumption is that over time
21 compounds that were included as HAPs will have range of
22 risks or risk estimates developed so that there's a
23 consistency with the requirements under 1807 so that the
24 MIC issue is germane to both because theoretically this
25 value would serve as that range of risk. It's not a

1 range obviously but it's a risk number, so that it has
2 implications for risk management decisions that get made
3 with respect to metham sodium.

4 DR. MARTY: That's why we sent it over to their
5 shop for review.

6 DR. BLANC: Does DPR want to say anything?

7 DR. FROINES: I think Paul said it in Melanie's
8 ear. Paul, do you want to comment?

9 MR. GOSSELIN: Nothing other than Andy's not
10 here.

11 DR. FROINES: This is Paul Gosselin from DPR.

12 MR. GOSSELIN: I believe we did take a look at
13 this document, and one of the things that we can do is go
14 back and make sure that what's in here and in the Hot
15 Spots document is compared to what we have written up in
16 our metham sodium document, which does include a
17 description MIC and some calculations as a component of
18 the overall breakdown of metham sodium to make sure that
19 we've covered a lot of the same issues and the same
20 ground.

21 DR. FROINES: Paul.

22 DR. BLANC: No. Nothing else.

23 DR. ATKINSON: Also on page 76 I just noticed
24 that's the conversion factor and the chemical properties
25 you've got too many micros.

1 DR. FROINES: Paul, you said you had a couple
2 questions. Are you --

3 DR. BLANC: On -- that was it on the -- I don't
4 think I have a question on Dr. Friedman's response.

5 DR. FROINES: So the -- so I'm next. I had no
6 questions about ethylene glycol butyl ether and I had no
7 questions about methylene Dianiline.

8 DR. BLANC: I had a comment about methylene
9 dianiline.

10 DR. FROINES: I had a comment about methylene
11 dianiline only insofar as it's one of these things that
12 I'm trying to find it here.

13 It's frustrating in a sense that since the
14 milking point of methylene dianiline is 92 degrees
15 centigrade, the amount of methylene dianiline that we
16 might find in the air in California is probably let's say
17 small euphymistically, and so it's not one of these
18 compounds that get brought forward in a toxic air
19 contaminant program that probably has limited relevance
20 to say the least.

21 DR. ATKINSON: I suspect that it's going to be
22 found in the updated gastros in the upper atmosphere. If
23 I remember rightly, there's actually a study of its
24 gasphorous chemistry. So it can't be done right. I
25 would have to check.

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1 DR. MARTY: Just sort of a generic comment on
2 the issue of chemicals that aren't very volatile,
3 sometimes they're emitted -- often they're emitted at
4 high temperatures and high pressures and that's how they
5 get out there and then their particle or air solidifies
6 (phonetic) and that's how the exposure occurs.

7 DR. FROINES: In general those exposures --
8 never mind -- can't lead to occupational exposures rather
9 than ambient exposures because those are not necessarily
10 long lived.

11 DR. MARTY: Unfortunately we generally don't
12 have a lot of information on what happens to them once
13 they're out there.

14 DR. FROINES: Paul had a comment.

15 DR. BLANC: This is a chemical which causes
16 colostatic (phonetic) jaundice. It's unusual in that
17 regard in terms of occupational liver toxins and you have
18 this phraseology about it -- in the very first sentence
19 of part four, several cases of human exposure of MBA have
20 clearly identified the compound as a heterotoxicant which
21 produces a condition resembling viral hepatitis.

22 I would probably get rid of that last phrase. I
23 would just say it's a hepatotoxic compound because they
24 identified the compound as hepatotoxic period because --

25 one of the things about it the pattern of toxicity is

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1 that it's -- it actually is colostatic enough that it
2 doesn't look like a viral hepatitis. And pathologically
3 if you had a lower exposure level, it wouldn't look like
4 a viral hepatitis either.

5 The only reason one would say that what it has
6 in common is that the liver enzymes might be elevated in
7 both, but it's a phrase you don't need to say and it
8 makes it --

9 DR. MARTY: It's not accurate.

10 DR. BLANC: It's not accurate.

11 DR. FROINES: On this compound -- are you
12 finished?

13 DR. BLANC: Yeah.

14 DR. FROINES: You know what happens in here, you
15 refer, for example, to the NTP chronic anobioesate
16 (phonetic). If a compound is identified as a carcinogen
17 in some form, it wouldn't be a bad thing to have a
18 sentence or two that gives the current status of
19 methylene dianiline with respect to its carcinogenicity
20 just so the reader knows.

21 We read this whole document, we see actually an
22 NTP bioesate, but when all is said and done we have no
23 idea what its carcinogenicity outcome is. And clearly

24 that's not necessarily something to do in great detail,
25 but at least you could inform the reader is this a

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1 compound that is an IARC (phonetic) 2B or 2A or something
2 to that effect just so we have some idea of its
3 carcinogenicity.

4 Because the implication if it's positive if it
5 were an IARC 2A, for example, would be that there might
6 be a risk assessment that would result in a considerably
7 different value and so that we don't understand the
8 compound in its entirety.

9 DR. MARTY: We can add that. I think at one
10 point we had those in there and then we ended up taking
11 them out. I don't know why. This is part of a series of
12 documents and we actually do, if I'm not mistaken, have a
13 potency factor for methylene dianiline in part two.

14 DR. FROINES: I think it is a carcinogen.

15 DR. MARTY: It is.

16 DR. FROINES: Maybe it would be related to
17 occupation as such. The -- so I have some familiarity
18 with glycol ethers, and I've always been concerned that
19 you find these erythro side effects but you don't find
20 anything in humans, and so there's a real -- seems to be
21 some real species differences, at least in the data
22 that's available to us, whether or not that means that

23 humans haven't had adequate exposure, but I don't know
24 what to do with that, Melanie.

25 It seems like it's not a major human hazard on

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1 the one hand, but there is some animal data, particularly
2 in rats for erythrocyte fragility, and when all is said
3 and done it's a dissatisfying chemical that we really
4 don't know much about its toxicity. And so -- but I
5 didn't see any reason to say well, okay, you should
6 ignore the animal data, but I've always been troubled by
7 the fact that this compound has a dichotomous science
8 with respect to it.

9 MR. MARTY: I would say that we had the same
10 problem. We went round and round on what to do about
11 that because there's very limited information, mostly in
12 vitro, of erythrocyte fragility as an end point using
13 humans erythrocytes. So it does appear that animals are
14 more sensitive in the literature.

15 DR. SALMON: The in vitro data actually
16 suggested that rat erythrocytes were 15 times more
17 sensitive than the humans in the fragility effect, but
18 our conclusion was that it was unwise to assume that
19 there would be so large a differential in favor of humans
20 in vivo, which is why we used the interspecies
21 extrapolation factor of one in this case, which reflects

22 our acknowledgement that it appears that humans are
23 relatively resistant to that effect, but we weren't
24 entirely comfortable with assuming that it wouldn't
25 impact them under any circumstances.

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1 DR. FROINES: In an air pollution context it may
2 not be a crucial issue. In an occupational setting it is
3 important because janitors have a fairly wide spread
4 exposure to this particular chemical, and so it's -- we
5 once did -- were going to do a study of this, of janitors
6 exposures to solvents, and EGBE was very widely used. So
7 it was something that needed some resolution and still --
8 so the issue as far as I know is still unresolved.

9 DR. SALMON: I think you're certainly correct in
10 pointing out the EGBE as a widely used chemical, and I
11 think it's also likely, I'm told, to become more widely
12 used due to its use to replace other glycol ethers and
13 other VOC chemicals. So it's certainly an issue.

14 Both we and the USEPA looked at this and, in
15 fact, our analysis isn't exactly the same as what the
16 USEPA came up with for this compound but it's certainly
17 similar that we are to some extent taking a similar and
18 caution slide on how exactly to interpret these data.

19 But the overall level that we produce as a
20 result of this is I think -- we thought this was a

21 reasonable compromise between the concerns and the
22 available data, anyway.

23 DR. FROINES: The triethylamine I'd like to hold
24 off on at this meeting and talk further about it later.

25 The one question I had about sulfuric acid I

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1 asked Melanie this morning, which is on the one hand we
2 have this risk assessment for sulfuric acid and my only
3 question is what's the relationship between sulfuric
4 acid, for example, is released from petroleum refineries
5 or in lead battery plants or what have you as compared to
6 sulfate that is in the atmosphere from a variety of
7 sources, and not so much in southern California but
8 certainly in the East coast.

9 The issue of acid rain is really quite
10 important, and I don't know if that's something that this
11 REL and the sulfate ambient standard there needs to be
12 some consideration of that or whether I'm just off the
13 wall on it.

14 DR. MARTY: Actually, it's -- you're not off the
15 wall. It's a really good question. The sulfate standard
16 is a 24-hour standard. It's 25 micrograms per cubic
17 meter.

18 DR. ATKINSON: Is that sulfate or SO-2?

19 DR. MARTY: It's sulfate. I just called our

20 criteria guys and asked them. Our SO-2 has a one-hour
21 standard, and this is in parts per million, .25 PPM and a
22 24-hour standard of .04 PPM. So that would be in vapor
23 gas phase.

24 So the sulfate standard for the 24 hours is 24
25 times our chronic REL, which is one microgram per cubic

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1 meter. It's based on human studies and this is based
2 on -- our REL is based on a chronic (inaudible) study.
3 So in the human studies, which are the basis of our
4 criteria pollutant (inaudible) standards, are in this
5 case looking generally at relatively short-term effects
6 at the present time. There's more and better data that
7 keeps showing up looking at longer term effects.

8 The other issue is sulfates are an important
9 part of particles, so we are actually under SB 25
10 reviewing the particle standard as we speak and looking
11 at whether we can subsume a sulfate standard into the
12 particle standard.

13 DR. BLANC: Melanie, what's the chemical fate
14 of sulfuric acid in terms of conversion to sulfur
15 dioxide?

16 DR. ATKINSON: It's the other way around.

17 DR. BLANC: Sulfur dioxide.

18 DR. ATKINSON: Sulfur dioxide is photo-oxidized

19 to sulfuric acid.

20 DR. BLANC: Then it's not a two-way street.

21 DR. ATKINSON: No. And sulfuric acid gets taken
22 up by particles, neither homogenously it nucleates by
23 itself, or partitions onto particles where its often
24 neutralized by ammonium.

25 The other thing, on page 115 your vapor pressure

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1 looks way off. I would have taken it to be about ten to
2 the minus six tor or so because it's very long for pure
3 sulfuric acid and that's consistent with this really high
4 volume.

5 DR. MARTY: Okay. We'll look at that.

6 DR. FROINES: So Melanie, is the implication of
7 what you just said is that this REL being you said five
8 times different than the sulfate standard?

9 DR. MARTY: No. It's actually -- it's 24
10 times -- the 25. The sulfate standard for 24-hour
11 exposure is 25 micrograms per cubic meter. This chronic
12 REL, which is for essentially chronic exposure, is one
13 microgram per cubic meter. So in that respect there's a
14 little bit of consistency there.

15 DR. FROINES: So we now have a California
16 ambient standard for sulfate of one microgram per cubic
17 meter. Is that what you're saying?

18 DR. MARTY: No.
19 DR. FROINES: I'm joking.
20 DR. ATKINSON: This is sulfuric acid.
21 DR. FROINES: I know. I don't know if we have
22 to think about this anymore. We can just go ahead.
23 DR. BLANC: Oleum (phonetic) is a form of
24 sulfuric acid, which is what?
25 DR. SALMON: Sulfurtrioxide.

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1 DR. MARTY: It's got Sulfurtrioxide added to it,
2 added to H₂SO₄, so it's actually much nastier than
3 sulfuric acid. Andy, say that last.
4 DR. SALMON: In effect it's a partial anhydride
5 of sulfuric acid.
6 DR. BLANC: When you refer to Oleum in passing
7 and the -- on the -- where is it? Sulfuric acid and
8 Oleum are absorbed as the salts of sulfate anide. You
9 see that in the last paragraph of section four? Which is
10 the first time you refer to Oleum. Should you have a
11 parenthetical explanation of what Oleum is then?
12 DR. MARTY: Sure.
13 DR. SALMON: It might be helpful, yes. We can
14 put that in.
15 DR. BLANC: And do you have any sense of how
16 much of the sulfuric acid that's handled in California is

17 handled as Oleum as opposed to handled as concentrated
18 sulfuric acid?

19 DR. SALMON: My understanding is that it forms
20 part of the production process in the usual process. So
21 at some point it all presumably passes through that
22 stage, but I don't personally know at what point it's
23 diluted down to 100 percent sulfuric acid or to aqueous
24 sulfuric acid. I think it's probably handled in bulk in
25 manufacturing plants and for large bulk transport in that

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1 form but then diluted for use and transport in smaller
2 quantities, but I don't know the data. We would have
3 to --

4 DR. MARTY: I can try to find out from the
5 Office of Emergency Services under their CalARP program.
6 They probably have reasonable figures on that because
7 Oleum is so much harder to handle.

8 DR. BLANC: Do you -- I guess what I'm asking is
9 are the releases in the Hot Spots Program that are
10 quantified as sulfuric acid, are those actually
11 releases -- or part of those releases Oleum that are then
12 quantified as pounds of sulfuric acid plus pounds of
13 sulfurtrioxide or --

14 DR. MARTY: I honestly don't know. I could see
15 if ARB can help us out on that. If I were to hazard a

16 guess, which is always hazardous, I would say it's
17 sulfuric acid and not Oleum.

18 DR. SALMON: The end user emissions would be
19 likely to be the acid because they would be usually I
20 think not handling --

21 DR. MARTY: The accidents are the Oleum.

22 DR. BLANC: Thanks.

23 DR. FROINES: So trying to move ahead, let's
24 move to Stan Glantz's three compounds, acrylonitrile,
25 nitric acid and phosphine.

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1 DR. GLANTZ: Well, I read through these and
2 they all seemed very reasonable to me. I always feel
3 inadequate when reading this stuff not being a
4 toxicologist, but there were no glaring problems that I
5 could identify.

6 DR. ATKINSON: On the --

7 DR. GLANTZ: Maybe someone else found some.

8 DR. ATKINSON: On nitric acid, I think on the
9 first page you need to state that it's also formed in
10 situ in the atmosphere in the photooxydation NR2.

11 DR. MARTY: That's probably pretty important.

12 DR. ATKINSON: Not totally dominant although
13 they're sitting by a Hot Spot. The vapor pressure looks
14 a little low. I didn't look at the number but I suspect

15 it's quite a bit higher than that of 25 degrees C. It's
16 a fairly low volume on it. I would guess it's about
17 eight tor. That would be a guess if I remember rightly.

18 DR. FROINES: Do you remember what your
19 carcinogenist number is?

20 DR. COLLINS: For nitric acid?

21 DR. FROINES: No, for (inaudible).

22 DR. COLLINS: I guess three times ten to the
23 minus four, but I'm just guessing.

24 DR. FROINES: It's okay. Don't worry about it.

25 We have a long agenda, so --

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1 DR. BLANC: I had posed the earlier question on
2 the interrelations between sulfur dioxide, sulfuric acid
3 and sulfates. In terms of the relationship between
4 nitric acid and nitrogen dioxide, you just mentioned
5 going the other way.

6 DR. ATKINSON: It's NR2 to nitric acid.

7 DR. BLANC: But in the paragraph here it says
8 that nitric acid will, quote, break down.

9 DR. ATKINSON: Pure -- 100 percent nitric acid
10 tends to get a little bit of breakdown to NR2, but in the
11 atmosphere it doesn't go that way.

12 DR. BLANC: I meant industrially where people
13 would be releasing it. Once it's released as nitric

14 acid, it stays as nitric.

15 DR. ATKINSON: Unless it reacts on surfaces.

16 DR. BLANC: Like cellulose surfaces.

17 DR. ATKINSON: Could be.

18 DR. BLANC: Would it react with water?

19 DR. ATKINSON: It looks like -- NO, it releases
20 nitrous acid. It depends which surface you're on. Some
21 might transport it to NO back react it to NO. So it's
22 quite surface dependent. Mainly it will just stick on
23 the surface and that's it unless it actually reacts with
24 it, unless it's a reactive surface.

25 DR. MARTY: Dr. Froines, the acrylonitrile unit

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1 risk factor is 2.9 times ten to the minus four and it's
2 an IARC 2A.

3 DR. FROINES: I'm surprised it's only a 2A.
4 It's clearly a human carcinogen.

5 DR. BLANC: Can I ask a question about the
6 acrylonitrile while we're here? All of the REL depends
7 on the NOAEL in the one study being 25 parts per million.
8 That would be if you look at page A-3, next to the last
9 paragraph is where that study is discussed. It says
10 rats were dosed with -- they were exposed. It says rats
11 exposed to acrylonitrile ventilation exhibited time and
12 concentration dependent decreases in the MCVS, CVNASP

13 (phonetic) which were partially reversible after eight
14 weeks of recovery. The ops concluded that the nervous
15 system of the rats (inaudible) following the oral or
16 inhalation of (inaudible) acrylonitrile but the NOAEL by
17 inhalation for 12 weeks was 25 parts per million.

18 In many of the write-ups you are fairly explicit
19 with the actual numbers of rats that responded and didn't
20 respond at the critical dose levels, but for this
21 particular write-up it's actually not possible to tell
22 why that is the NOAEL. It's kind of like take our word
23 for it that's the NOAEL.

24 UNIDENTIFIED SPEAKER: I actually have a table
25 for -- this is actually a secondary study, actually a key

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1 study that we did not put a table in here, but I do have
2 it and I can add that it if that would be helpful.

3 DR. MARTY: The key thing that we used for the
4 RELs Quas study (phonetic) 1980 and the Gunnier
5 (phonetic) study we did a comparative REL, but it
6 actually comes out higher, quite a bit higher.

7 DR. COLLINS: And I do have a table. I'm sorry
8 I didn't get it in there, but I will add it if it would
9 be helpful.

10 DR. BLANC: Because you use the nasal epithelia
11 (phonetic), but then you talk about it in comparison, I

12 guess. Is that right? For comparison. Right, but that
13 that comparison would be quite different if 25 PPM
14 weren't NOAEL but the LOAEL, I think, was my issue with
15 that.

16 So I just wanted to -- and since the
17 neurotoxicity would be actually what you would expect
18 would be the issue in humans and not nasal irritation, I
19 was particularly interested to see that that -- you truly
20 felt that the 25 PPM was NOAEL and not simply that the
21 number of rats affected had a P value of .07 in that very
22 clear, step-wise dose response and because the sentence
23 said there was a time and dose dependent effect.

24 DR. MARTY: We'll go back and check that study
25 and make sure.

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1 DR. BLANC: Aren't there studies where you've
2 actually used the slope to define to benchmark?

3 DR. COLLINS: If we have enough data, right.

4 DR. BLANC: Do you think there's enough in that
5 that one to do a benchmark?

6 DR. COLLINS: I don't know.

7 DR. MARTY: We can do that though.

8 DR. SALMON: We can certainly use the table.

9 DR. FROINES: The affect you find at 20 in the
10 Quas study is non significant so you define that as a

11 LOAEL.

12 DR. COLLINS: Actually, there's like -- I'm
13 sorry. I do have that data. There's actually they
14 looked at four different things. 20 parts per million
15 was not significant for two of the things they looked at
16 and it was for two others. So they did consider it a
17 LOAEL because there was a statistically significant
18 difference in the control of that level and it's not made
19 clear enough in the write-up, but I will put in that
20 data.

21 DR. FROINES: Because when you read your two
22 paragraphs, you would draw the opposite conclusion. And
23 then you would go down here to the NOAEL at 25 and say
24 why doesn't that become the dominating decision point.

25 DR. MARTY: We should move this paragraph that's

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1 underneath derivation of LOAEL up front because this is a
2 better description of the study.

3 DR. COLLINS: We can put in the table, the data.

4 DR. FROINES: The Quas study needs to be
5 improved. The description of the Quas study needs to be
6 improved if you're going to use it as the basis of
7 your --

8 DR. BLANC: Just from a toxicological view, if
9 all things came out equal in your benchmark approach and

10 the neurotoxicity was giving you something similar, I
11 would think that it would make much more biological sense
12 for humans to be using that if you could.

13 DR. FROINES: Well, we should go to Peter
14 Witschi at this point I think.

15 DR. WITSCHI: Okay.

16 DR. FROINES: We're going to give him a chance
17 to get settled.

18 DR. WITSCHI: Recover from the traffic.

19 DR. FROINES: And get his apologies in order so
20 we can --

21 (Laughter)

22 DR. BYUS: I'm working on it.

23 DR. WITSCHI: Chloropicrin I have two comments.
24 One is on page A-19, almost to the bottom of the last
25 paragraph, in the middle of the last paragraph.

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1 Microscopic pathology of 1.0 PPM was increased in lung
2 and kidney, and this is a very amateurish description of
3 pathology, and actually in many other places of many of
4 those documents I've seen the same thing.

5 I don't know where this comes from or who
6 translated or whether this was in the original study, but
7 you know something increased lung nodules, kidney cysts
8 size decrease, that's all nonsense. I wouldn't know what

9 to do with this. This particular study Burlay Flare,
10 that came out of a testing lab. So you probably took out
11 of their -- is just the way they described the lesions
12 but somewhere there must be a diagnosis of the lesions
13 they found and I found this in many of the documents in
14 some other places that the pathology descriptions are
15 really not clearly adequate.

16 DR. SALMON: Our normal procedure would be to
17 quote actually what the study authors told us. So --

18 DR. WITSCHI: Well, then I think you don't read
19 those studies completely because they might tell you on
20 the results and what they observed when they did the
21 pathology, but somewhere, somehow they must give you
22 pathology chemical diagnosis.

23 DR. SALMON: We can look for that.

24 DR. WITSCHI: Otherwise it would not be a good
25 study and I think this was a professional testing lab and

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1 I'll bet you anything somewhere they gave you the right
2 diagnosis.

3 DR. SALMON: Well, one would certainly hope for
4 that, but clearly we can't guarantee it's there but we
5 will look for it.

6 DR. WITSCHI: It might not be in the same place.

7 The other question I have now, this is a

8 lacrimate (phonetic) and a pretty potent one. Is there
9 any reason to believe that there is some other toxic
10 effects at levels below that cause lacrimation? Or would
11 lacrimation be the most sensitive end point?

12 DR. FROINES: As a chronic end point?

13 DR. MARTY: It's a chronic study.

14 DR. WITSCHI: What's -- my question is is there
15 any reason to believe there is something at lower levels
16 that cause the acute effects of lacrimation? I don't
17 know.

18 DR. MARTY: The study found effects and it's a
19 chronic study and --

20 DR. WITSCHI: On the effects of --

21 DR. MARTY: Well, the LOAEL is a half part per
22 million.

23 DR. WITSCHI: How would people react at half a
24 part per million?

25 DR. MARTY: That would be pretty lacrimating.

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1 DR. WITSCHI: That's my point.

2 DR. MARTY: The concentration would be very
3 irritating.

4 DR. WITSCHI: What would be at .1 PPM at people?
5 That would be lacrimating too, and yet in the chronic
6 study of 1 PPM we haven't found any lesions.

7 DR. BLANC: Actually, they have found lesions.

8 There's bronchiectasis which is a pretty profound.

9 DR. WITSCHI: At .1 PPM? Okay.

10 DR. BLANC: But they're not calling it

11 statistically significant. That's again I think a real

12 problem of the analysis of these data. It's okay.

13 Rhinitis, there's already a baseline of three out between

14 three of the six out of 50 in the baseline, so there's

15 some sort of rhinitis in these -- in this animal species,

16 but unless bronchiectasis is a congenital problem in this

17 species, and it doesn't appear to be since there's zero

18 out of 50 and zero out of 50, I would be inclined to take

19 seriously the six to ten percent incidents of

20 bronchiectasis at the lower level of exposure.

21 And you exclude that because the P value for

22 that finding is not statistically significant, but it

23 doesn't take into account the obvious dose response that

24 you're showing there.

25 DR. MARTY: We could probably attempt a

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1 benchmark concentration and see where it comes out

2 relative to the NOAEL which we pulled out of the study.

3 DR. SALMON: This might be a good candidate for

4 that approach actually.

5 DR. BLANC: It seems to be a nice linear

6 response, five out of 50 and goes up to 28 out of 50 when
7 you increase the dose by five times. And then it goes
8 from 28 to 44 instead of 28 to, I guess, 100 percent when
9 you double it again, but it's pretty close.

10 DR. FROINES: I think you'll find it a
11 statistically significant trend test.

12 DR. MARTY: It jumps quite a bit for .1 to .5.

13 DR. BLANC: Yeah. That's what toxins do.

14 DR. SALMON: We can certainly try the BMD
15 analysis and see whether it gives us a more satisfying
16 answer.

17 DR. BLANC: I assume when you said the
18 significance -- you didn't make clear you didn't combine
19 eight out of a hundred to see if that was different than
20 zero out of a hundred.

21 DR. COLLINS: We didn't, but we could.
22 Sometimes we tend to use one or the other section and not
23 both, but that would make it stronger with the number of
24 animals, and sometimes people are hesitant to combine
25 males and females.

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1 DR. BLANC: And there's no obvious reason why
2 they're -- they don't seem to be responding any
3 differently here.

4 DR. MARTY: That would be okay for this end

5 point.

6 DR. BLANC: Eight out of a hundred is -- this
7 is, by the way, another one where you should give the
8 number of pounds used in agriculture in section three,
9 the last part of section three. The other is only 1500
10 pounds used not agriculturally, but the amount used as a
11 fumigant.

12 DR. FROINES: Moving on, Peter.

13 DR. WITSCHI: Okay. That's all for this one.
14 Then the diethanolamine on page 25, again in the last
15 paragraph male rats displayed diminilation (phonetic)
16 beginning at 2500 PPM. Diminilation (phonetic) of what?

17 DR. FROINES: What page are you on, Peter?

18 DR. WITSCHI: A-25.

19 DR. MARTY: The diminilation, which nerves?

20 DR. WITSCHI: Of what. Yeah. Central?
21 Peripheral? What happened where? Okay.

22 On the next page, the last paragraph of six you
23 mentioned an inhalation study which is not published in
24 the peer review literature, and then for setting your
25 LOAEL or your level, then you rely on an oral study

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1 because that's the study that has been peer reviewed.

2 Don't you think there would be peers enough to
3 review the study that really matters, the inhalation

4 study? And just because something is peer reviewed so
5 (phonetic) literature doesn't, at least in toxicology
6 study, not necessarily guarantee that it was adequately
7 reviewed. It just happened to appear in the peer review
8 literature. And if you have --

9 DR. BLANC: Speaking as the former editor of a
10 journal.

11 DR. WITSCHI: Exactly. I know well how good
12 reviews are.

13 And so here we have a case where you go for
14 setting an inhalation standard from an oral study where
15 you could have an inhalation study, except it hasn't
16 appeared in some second class journal. It's still a
17 report. So I think there would be peers enough to look
18 at this report and the original data and make up your
19 mind and come out and say we looked at this study, and
20 since we're dealing with an inhalation value, we can go
21 by the inhalation study because it's a good one or a bad
22 one.

23 DR. COLLINS: I'm not clear they actually sent
24 us the entire study. We don't even know any other than
25 the first name of the guy on it. So maybe we could ask

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1 them to send it to us.

2 DR. BLANC: You're definitely peers if you're on

3 a first-name basis.

4 DR. COLLINS: No, no. It was A.O. Gamer et al.
5 I don't even know who the guy worked with.

6 DR. BLANC: The first name. Full name. Sorry.

7 DR. WITSCHI: We should take this attitude and
8 drop it entirely from the document.

9 DR. COLLINS: Let me go back and see what -- we
10 do have an -- we did a comparison on that one.

11 DR. WITSCHI: Okay. That's all I have.

12 DR. FROINES: Is the Gamer study a chronic
13 study?

14 DR. COLLINS: 90-day.

15 DR. WITSCHI: The point is what we are doing is
16 we are setting an inhalation standard from an oral study
17 when we do have an inhalation study, and this does not
18 make sense.

19 DR. FROINES: My only concern is that acute
20 versus chronic, irritation as a chronic end point.

21 DR. WITSCHI: Okay. The next one is maleic
22 anhydride, and it was about four or five years ago I was
23 on the TLV committee and we re-examined the
24 documentation, the ACTIH documentation to maleic
25 anhydride. I didn't keep my files and I don't know

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1 whether the revised document has appeared since. All I

2 do recall when we did the revision, there was a great
3 deal more information than is present in this document.

4 So I wouldn't want to say, with one exception,
5 anything about this document except you should go and try
6 and see whether you get the update of the ACTIH
7 documentation.

8 And the other one is even a better document
9 would be issued by the German Mark Commission. That's
10 the equivalent of the TLV commission in Germany. As far
11 as I recall, and again I apologize for having thrown away
12 my notes, the Mark report I think is available in
13 English. This is a real treasure chest of findings which
14 pertain to maleic anhydride.

15 The only other one I had is on page 74. You
16 bring in again an interspecies and uncertainty factor of
17 three, which is correct except there's one thing the data
18 showed. If you think that man is like a monkey, then for
19 your end point man is not the most sensitive species.

20 So if you take the data from the most sensitive
21 species and go an uncertainty factor of three and the
22 data clearly showed that primates are not the most
23 sensitive species, this is getting things done by rote
24 and not based on actual data.

25 DR. BLANC: But they're using the monkeys so

1 it's okay.

2 DR. WITSCHI: No. There is rats, hamsters
3 and -- yeah. My point is --

4 DR. BLANC: I see.

5 DR. WITSCHI: Okay. Rats more sensitive in this
6 study, rats are more sensitive than monkeys, but
7 calculating the REL and introducing it an interspecies
8 factor of three, you assume that man is more sensitive
9 than the rats are. This study shows you the opposite.

10 This is again -- we've had this problem before,
11 this issue before that some of those things are just
12 kicked in by rote even if the data tell you otherwise,
13 or at least the data should make you think otherwise.

14 DR. SALMON: One of the questions which we had
15 which you might want to comment on in relation to the
16 monkey data is that since we only have the rather small
17 number of individuals in the monkey study, what would be
18 the sensitivity and precision of that study to begin
19 with. So how confident can we be that there is less
20 affect in the monkey.

21 DR. WITSCHI: This one came up before too.
22 There are always reasons to be conservative. I know.
23 Sometimes the data not to be are strong, sometimes in
24 this case they might not be as strong, but to me it seems
25 to become an unconditioned reflex.

1 Anyway, this is not the first time we have had
2 this discussion. I've forgotten what -- we had it on
3 some other compounds too.

4 So much for the maleic anhydride.

5 DR. ATKINSON: I have a question on page 72,
6 the first paragraph. That sort of indicates that at
7 least the authors of the Leatoul (phonetic) assume that
8 all the maleic anhydride was in the particle phase; is
9 that right? Certainly given that vapor pressure and what
10 we know of it, it certainly wouldn't be expected to.

11 Besides, I have a further question, and this is just out
12 of ignorance on my part. What does "inspirable" mean?

13 DR. COLLINS: Respirable.

14 DR. FROINES: No. It means that capacity to
15 inhale it. It's a phenomenon of large particles, not of
16 small particles inspirable. You're talking about 40
17 microns and up, above -- with the question being where do
18 you stop being able to inhale.

19 DR. BLANC: You mean respirable is a small
20 subset of inhalable.

21 DR. FROINES: Generally respirable we think
22 about in terms of reaching the deeper part of the lung
23 and inspirable the opposite.

24 DR. WITSCHI: Inspirable is what you see in a
25 dust storm.

1 DR. BLANC: Does it -- doesn't it -- if you drew
2 a convenient diagram, does inspirable exclude the
3 respirable?

4 DR. FROINES: No. It wouldn't exclude it.
5 You're right. But the inspirable issue --

6 DR. BLANC: It's dominated by particles which
7 probably wouldn't penetrate deep into the lung just by
8 weight, maybe not by number, because a lot of small
9 particles.

10 DR. ATKINSON: My point on that is that if all
11 they were measuring was the particulate maleic anhydride
12 they may have been underestimating the top amounts.

13 DR. WITSCHI: I think this was one of the
14 reasons to try to get ahold of the TLV documentation
15 because as far as I recall this problem about the human
16 data is discussed in more detail in this document than it
17 is here.

18 DR. BLANC: There's a key name of Venables
19 Kathryn Venables (phonetic).

20 DR. COLLINS: On maleic anhydride?

21 DR. BLANC: I think that her dissertation was on
22 asthma anhydrides.

23 DR. COLLINS: V-e-n-a-b-l-e-s?

24 DR. BLANC: I believe so. Kathryn is the first
25 name.

1 DR. SALMON: She was the one who worked at the
2 Loma School of Hygiene.

3 DR. BLANC: I think that's what she did.

4 DR. SALMON: Yes.

5 DR. BLANC: You worked with her so you might
6 want to -- but that would be at least have a very
7 thorough literature review also.

8 DR. MARTY: So was there an issue about defining
9 inspirable and respirable, defining that in here?

10 DR. ATKINSON: I didn't know what it meant.

11 DR. SALMON: It sounds like we should address
12 more attention to the (inaudible) issue as to whether
13 they're capturing the vapor phase as well.

14 DR. FROINES: I think that the suggestions about
15 the literature review are important. If this stuff -- if
16 there is IGE antibody responses, that's not trivial.

17 DR. BLANC: I guess one interesting question is
18 in terms of the human intraspecies uncertainty factor,
19 which assumes that there are sensitive subpopulations, is
20 that multiplication factor high enough when the mechanism
21 is that there are people who are primed to be sensitized
22 to something as opposed to thinking about women or
23 children or the elderly where we're sort of thinking
24 about a normal distribution, the tails of the normal
25 distribution? Whereas in these other issues we're

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1 thinking about it by variant distribution where we --
2 that responsive population may be really far out there?
3 Is that something that you've grappled with
4 systematically?

5 DR. MARTY: Yes. Actually in the introduction
6 of our document we're talking about the methodology. We
7 do say that we certainly cannot account for AS incratie
8 (phonetic) responses. We don't have -- at this point
9 it's difficult to say whether or not the ten-fold covers
10 everybody, and that obviously is going to differ chemical
11 to chemical and we don't necessarily have the data
12 chemical by chemical to say whether that ten-fold
13 intraspecies you have is adequate.

14 We are looking at that constantly. We just
15 started on the project to try to look at that some more
16 using epi-data on the criteria, but it's a difficult one,
17 particularly where there's immunological response. Then
18 it's really difficult.

19 DR. BLANC: And the EPA does haven't a position
20 on this?

21 DR. MARTY: Not that I'm aware of. They
22 understand the issues and realize it's out there and it's
23 pretty hard to define.

24 DR. WITSCHI: I once had to look at so-called

25 sensitive populations in the context of some air

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1 pollution, also nitrogen oxide and where common
2 (inaudible) asthmatics are more sensitive. And I looked
3 at many of those studies which were done in humans and
4 actually it was very disappointing because I think it was
5 only one study, and not a very good one, which showed
6 that the most sensitive ones were only sensitive by a
7 factor of about 15 to 20, and most of them actually in
8 those studies the asthmatics were not demonstrably more
9 sensitive in control studies.

10 DR. BLANC: That's true for nitrogen dioxide.
11 It's not for sulfur dioxide, but for sulfur dioxide where
12 it's well established it's about an order of magnitude.
13 So a factor of ten would make sense, but that's not a
14 sensitization issue, it's a --

15 DR. WITSCHI: No.

16 DR. MARTY: Also in the sulfur dioxide
17 literature, if you look at asthmatics within asthmatics
18 as a group, there's at least a seven- or eight-fold
19 sensitivity.

20 DR. WITSCHI: But the (phonetic) was much less
21 than I thought it was.

22 DR. FROINES: You ought to --

23 DR. WITSCHI: Your inclination, but us

24 toxicologists are thinking of several orders of
25 magnitude.

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1 DR. BLANC: Believe me, ten-fold is meaningful.

2 DR. FROINES: It's worth asking Dale Hattis
3 about this question when he's out here because he's
4 got -- his new paper comparing toxicokinetic factors, the
5 toxicodynamic factors with respect to particulate I think
6 is extremely important because the toxicodynamic factors
7 are so much larger than the kinetic issues. So this --
8 whether ten is adequate is certainly a highly relevant
9 question.

10 DR. WITSCHI: Who is this? Sorry.

11 DR. FROINES: Dale Hattis.

12 DR. WITSCHI: Okay.

13 DR. FROINES: So where that sensitive group sits
14 in the --

15 DR. MARTY: Basically the ten-fold UF is the
16 simplification of reality.

17 DR. FROINES: We had a small workshop looking
18 at that question, if you remember, about a year or so ago
19 where one looked at the question of whether or not given
20 inter-individual variability as we understand it now,
21 whether or not at least factors of ten were adequate and
22 the answer I think was no. In this case it's even more

23 relevant. Let's go on to selenium.

24 DR. WITSCHI: Well, I got lost somewhere. And
25 I might be wrong, but you calculated the inhalation REL

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1 from human data, which were ingestion, converting
2 probable intake as milligrams per kilo body weight per
3 day into how much a person would inhale.

4 Now, in this case, if I'm correct, this is a
5 very, very conservative estimate because then the
6 inherent assumptions are that there is 100 percent
7 deposition what's in the air, 100 percent retention
8 what's in the air, and 100 percent absorption what gets
9 into the deep lung. Now, selenium is not exactly
10 volatile which means if you have selenium dusts if you
11 drive up to Owens Valley and past Owens and all those
12 kind of nice things, you know, we are exposed to dust
13 with different particle size and all these kind of
14 things.

15 Really am I correct in assuming that if you
16 would consider to what people are exposed by inhalation
17 and what form and particle size and retention and
18 clearance and all these kind of things, that this REL is
19 extremely conservative. I'm not saying it shouldn't be
20 there, I just would like to point out the inherent
21 (phonetic) to fluoride or with the gas. If you convert

22 from oral exposure to inhalation with something, you can
23 be reasonably sure that it gets into the deep lung and
24 that it's going to be a great deal absorbed, but that's
25 something different with something that might be particle

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1 bound or particle associate.

2 DR. MARTY: We can add a discussion of that.
3 It's the same issue every time we do a route-to-route --
4 cross-route extrapolation. We're making these
5 assumptions.

6 DR. WITSCHI: Because I think that the -- I
7 really would like to know by how much you think this
8 overestimates. I know you can't know either, but the few
9 simple things, average particle distribution in a dust
10 storm up in Owens Lake and retention, penetration,
11 clearance possibly, and I don't even know whether the
12 form selenium is in the air if it gets into the lung in
13 particles if it can be absorbed. I don't know.

14 DR. ATKINSON: Given the vapor pressure of .001
15 tor of elemental selenium, some of that I would assume to
16 be in the gasphorous, although you claim it's all by
17 particulate on the (inaudible) conversion factor. If I
18 remember rightly, from emissions from power plants,
19 coal-powered (inaudible) power plants, it is distributed
20 some in the gas space and some in particle, for

21 elementals.

22 DR. WITSCHI: Some must. It also smells, the
23 famous garlic smell.

24 DR. MARTY: I think we can add in a discussion
25 of the issues. I hesitate to even attempt to quantify

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1 what the difference in internal dose would be, but we can
2 have a discussion of that because it is going to totally
3 depend on how much is elemental, how much is the salt,
4 what the particle size distribution. And even if you
5 know the particle size distribution coming out of the
6 stack, there's all kind of stuff that happens after that
7 to change that.

8 DR. WITSCHI: Personally I would be happy just
9 by saying what I tried to formulate. This calculation
10 assumes 100 percent deposition and retention and all
11 these kind of things, and then for people who know, that
12 would be clear enough.

13 DR. MARTY: Okay.

14 DR. WITSCHI: And the bigger question probably
15 needs to be addressed in a workshop or whatever it is
16 because it's an interesting question. It's a very
17 interesting question.

18 DR. BYUS: You might really -- selenium is one
19 of these compounds in the National Cancer Institute

20 identified as a chemo-preventive agent and the data is
21 actually quite good in epidemiology but within very
22 narrow ranges. If you are sort of sub-selenium in your
23 diet increasing the selenium in your diet, which if I
24 remember comes primarily from the food you eat, from
25 where the food is grown, what kind of soil it is

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1 determines how much selenium shows up in the plant
2 material that you eat.

3 But they've shown a very marked chemo-preventive
4 in fact for most cancers, at this is at the very low end
5 clearly. If you could just -- you know how people are
6 when they read these documents. People think a little is
7 good, so more must be better.

8 I think it would be nice to point that out here
9 in this document in case lay people are reading it that
10 it is a very toxic compound and whereas it may be good
11 under very -- dietary supplementation at very low levels,
12 beyond that it could be very toxic. People are going
13 around to health food stores buying selenium tablets and
14 zinc and all the rest of these things and eating a lot of
15 it.

16 But the data is actually quite good. If you
17 fall below and supplement back up, that it is
18 chemo-preventive.

19 DR. WITSCHI: Not only in Owens Lake but those
20 in Kesterson (phonetic) Reservoir.

21 DR. MARTY: Tell that to the ducks at
22 Kesterson.

23 DR. BYUS: I believe there is a relatively
24 well-defined transport mechanism for it for finding
25 proteins in terms of mechanism. At least there's a lot

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1 of people that work on that.

2 DR. BLANC: Isn't selenium what was used in
3 cleaning guns? Isn't that like the major consumer use of
4 bluing or something that's got --

5 DR. BYUS: Bluing is not cleaning. It's just
6 the finish on the metal.

7 DR. BLANC: But people do that, treat it at
8 home?

9 DR. BYUS: They can. There's these home bluing
10 kits if you want to re-blue your gun.

11 DR. MARTY: And then there's the dandruff
12 shampoo.

13 DR. BLANC: You mentioned the shampoo, but I
14 think from poison control centers, that's where people
15 get -- you know, children get toxicity from drinking this
16 stuff that somebody has at home to --

17 DR. MARTY: We can certainly add that in.

18 DR. FROINES: I think that the issue that Peter
19 is raising is extremely important and in the long run
20 can't be dealt with by simply putting in something that
21 it says we're assuming 100 percent absorption.

22 I think that in the long run we're going to have
23 to address this issue, and I'll give you an example of
24 something that's closer to me. That is that clearly
25 there's an enormous debate in California about chromium

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1 six in drinking water and we're going to hear much more
2 about it, especially if Julia Roberts wins the academy
3 award.

4 DR. WITSCHI: Could we get her to the meeting?

5 DR. FROINES: We'll invite Julia Roberts to the
6 meeting.

7 (Laughter)

8 DR. COLLINS: Probably Erin Brokovich would
9 come. I don't know about Julia Roberts.

10 DR. FROINES: But these issues of where one is
11 defining systemic toxicity or gastrointestinal toxicity
12 is very dependent on particle size, clearance mechanisms
13 and so on and so forth, and we can't go on doing risk
14 assessments that have validity that assume 100 percent
15 absorption. It's just wrong and it's -- I think it's an
16 overly conservative approach to risk assessment, in my

17 view, my personal view, my humble personal view.

18 The fact of the matter is I think that chromium
19 six is a very good case that has a high public interest.
20 Selenium is also an important issue precisely because of
21 what Craig says which is that it's like boron, it's like
22 a lot of -- and maybe even chromium that has a beneficial
23 side and obviously a not beneficial side.

24 So I don't know whether that means we have a
25 workshop -- I suspect that that's something to consider

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1 how to approach the issue, but I think Peter is
2 absolutely right. It's not something we can just go on
3 for the future assuming -- making a conservative
4 assumption like that that then we all recognize are
5 inadequate, inaccurate.

6 DR. WITSCHI: Thank you very much to bring this
7 up because it was also my point with the rote uncertainty
8 effect and all these kinds of things. If risk assessment
9 is going to make progress and more importantly is going
10 to maintain credibility, then those things have to be
11 very seriously considered.

12 DR. FROINES: Well --

13 DR. WITSCHI: Because otherwise we are putting
14 ourselves in the position of crying wolf.

15 DR. MARTY: As a panel would you prefer that we

16 remove this selenium REL because of the cross-RAD
17 (phonetic) extrapolation issue? We are also
18 uncomfortable with cross-RAD extrapolation. There's some
19 chemicals where that's the only way you can get to an
20 inhalation route.

21 DR. WITSCHI: Well, you have to ask a different
22 question and this is -- there are no inhalation studies
23 with selenium around; right?

24 DR. MARTY: That were useful to develop.

25 DR. WITSCHI: That were useful. Yes. There's a

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1 reason for that one. Nobody saw fit to invest in the
2 cost to do a real inhalation study because nobody thought
3 there was going to be a problem. The absence of studies
4 sometimes does not mean people have overlooked something,
5 but the absence of studies can also mean that people have
6 given some thought to a particular problem and also
7 chosen some priorities. Priorities are necessary because
8 certain things it's too expensive or too complicated.

9 You might, for example, ask selenium has been
10 around as a carcinogen for a long time. Why has the NTP
11 never done an inhalation study? This did not come from
12 nothing, rather probably have said let's do an inhalation
13 study with selenium in the gases. You what?

14 DR. MARTY: I guess most of the concern has come

15 from dietary selenium for sure. Then there's the issue
16 of cross-RAD extrapolation for something that's going to
17 be a particle versus something that's an organic, that's
18 not -- that may be largely in the gaseous phase or vapor
19 phase. And I think there that the assumption of 100
20 percent absorption is a little better and you don't have
21 this issue of particle size.

22 DR. WITSCHI: Actually to go back to use of
23 cross-RAD studies, if I'm correct, memory serves me
24 right, some of them actually were invented in California
25 in Proposition 65 where Proposition 65 was driven by the

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1 fact that there are carcinogens around so somebody had to
2 do something about this. This was case in the beryllium.
3 Beryllium is a carcinogen, but they took the inhalation
4 studies to -- the evidence for beryllium as a carcinogen
5 is in inhalation, but Proposition 65 ran a study on water
6 and beryllium without considering that beryllium only
7 causes cancer probably by being inhaled and there's no
8 way it can get -- do this when it's in the
9 gastrointestinal tract because it's not being absorbed.
10 So this was a previous one which was done by rote without
11 really further thinking.

12 DR. BYUS: I believe for the cancer
13 chemo-prevention work, most of that work was done in

14 animals, a lot of experimental animals with dietary, and
15 then it was converted to humans. It was very close. The
16 dosages were very close between animals and humans for
17 the desired anti-cancer effect down at the very low
18 levels compared to this.

19 DR. FROINES: Melanie, I'd like to move ahead.
20 Can -- do you want to consider this within your own staff
21 context and come back to us only go deal with the loose
22 ends?

23 DR. MARTY: Sure.

24 DR. FROINES: Your call.

25 DR. MARTY: We'll discuss it more internally.

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1 DR. FROINES: Okay.

2 DR. MARTY: I don't think there's a fix. It's
3 either you have it or you don't for this.

4 DR. FROINES: It's clearly an important issue.
5 I think with chromium six, when one goes back and re-does
6 the risk assessment for chromium six via the oral route,
7 one is going to be using occupational studies because
8 that's where the occupational epi comes from. So in
9 order to get any kind of realistic estimate of risk, one
10 is going to have to have some size distribution
11 measurements and make estimates of what is the
12 gastrointestinal dose as a way of doing the risk

13 calculation so these are issues that are quite germane to
14 all this.

15 Let's take a ten-minute break.

16 DR. COLLINS: We'll get to isophorone after
17 this?

18 DR. FROINES: I'm sorry. That's right. Is this
19 a two-minute to five-minute discussion?

20 DR. BYUS: I have no major concerns with the
21 isophorone section. My -- I had one question though --
22 no, I don't have a question. That was on methyl
23 isocyanate. I'm sorry. I don't have any real concerns
24 about it. It's well done as far as I can tell.

25 DR. FROINES: Did you have any comments on

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1 methyl isocyanate? Because we had a lengthy discussion
2 before you came.

3 DR. BYUS: My only suggestion about the methyl
4 isocyanate -- several. One was that we should include
5 the estimates of emission and breakdown products from the
6 use of metham sodium. You covered that? Okay. Good.

7 It was also disturbing that most of the studies
8 were not -- nothing is done more than ten days, and that
9 was the other concern I had in trying to estimate this,
10 chronic RELs or sub-chronic RELs, whatever you call them,
11 acute, in that continuum. It just seemed that was a

12 major limitation that probably most people are going to
13 be exposed to less but for a long time. Those were my
14 two concerns.

15 DR. FROINES: It shows the high quality of this
16 scientific review panel that there was consistency
17 across.

18 (Laughter)

19 DR. BYUS: Okay.

20 DR. FROINES: You were the test.

21 DR. BYUS: I was the test. All right.

22 DR. FROINES: Let's take a ten-minute break and
23 we'll go on to the next topic which I think is children.

24 (Brief recess taken.)

25 DR. FROINES: Escutia.

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1 DR. FROINES: We have a time crunch. We also
2 don't have a quorum. Can Bill Walker go track down --

3 DR. FROINES: I should say that given our
4 discussions with Melanie last time and given the
5 discussion I had with Jeanette Brooks last Thursday in
6 Sacramento, we have an interesting future ahead of us.
7 We have some pretty interesting compounds and issues
8 coming forward.

9 We have a quorum. Now, I wanted to say one
10 thing, if the panel would agree, that some of the panel

11 members have to leave no later than 2:15 today to make a
12 3:30 plane out of Ontario. Roger has assured me that
13 2:15, 2:00 to 2:15 would be just fine. So we have to
14 stop then, say about 2:00 and 2:15 at the latest because
15 I think we'll lose a quorum.

16 We'll also -- so I would propose that around
17 noon that we take a short break and people go in and get
18 sandwiches in the cafeteria and then come back and we
19 continue on. Is that all right with everybody?

20 Okay. Melanie.

21 DR. MARTY: Okay. What I'm going to do for the
22 panel today is provide a brief overview of SB 25. You
23 guys have already seen this material. We're just going
24 to go through it quickly to remind you of the process
25 that we're going through, and then Mark Miller is going

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1 to give a presentation on children's unique
2 susceptibilities to toxicants. So the stuff you should
3 be looking now is over on the overheads.

4 DR. BLANC: So we shouldn't look at you.

5 DR. MARTY: Senate Bill 25 was passed in '99 and
6 essentially it has amended the existing criteria
7 pollutant and toxic air contaminants statutes to add
8 specific requirements including an air monitoring
9 network, which I'm not going to talk about or absolutely

10 has -- it requires ARB to look at their air monitoring
11 network to determine whether it's adequate to estimate
12 exposures to children. It also requires South Coast AQMD
13 to notify day care centers when the criteria of the
14 ambient air quality standards are exceeded, and it
15 creates a children's environmental health center under
16 Cal/EPA. It also for our purposes requires us when we
17 are looking at --

18 DR. FROINES: Is that in OEHHA.

19 DR. MARTY: No. It's at agency. So it's
20 actually at -- it's under Winston Hickox directly, the
21 children's health center.

22 In evaluating both the criteria pollutants and
23 the toxic air contaminants, the statute requires us to
24 look at exposure patterns that result in disproportionate
25 exposures in infant and children relative to adults. It

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1 requires us to look at special susceptibility in infants
2 and children. It requires us to look at effects of
3 exposure to pollutants with similar mechanisms of action,
4 and also look at the interaction of criteria air
5 pollutants and toxics when we are evaluating candidate
6 TACs or evaluating health impact stuff, existing TACs
7 that were listed under 2728.

8 DR. FROINES: What does that mean?

9 DR. MARTY: The last? If there are data
10 available -- this is all to the extent practicable given
11 the data limitations. But if there are data studies that
12 have looked at, for example, respiratory effects of
13 criteria air pollutants in conjunction with irritants
14 that are not -- that are toxic air contaminants, then we
15 would have to consider that information.

16 There's as you know very little information. So
17 we were required -- we are being required to review all
18 the (inaudible) air standards and there's no SRP
19 involvement there, but more importantly for this
20 committee we need to establish a list by July 1st, 2001
21 of up to five TACs that cause infants and children to be
22 especially susceptible and the panel must review the
23 report containing the justification for the chemicals on
24 the list.

25 The step that follows that, once you generate

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1 the list, the ARB is triggered to re-evaluate any
2 existing airborne toxic control measures for chemicals on
3 that list to see if it's adequate or if they can do
4 anything more. And in addition, if there is no ATCM for
5 a chemical that gets on that list, then they have to
6 develop one. And of course this may mean that we would
7 be providing them information on the health criteria

8 piece that may require us to re-look at either a potency
9 factor or a REL.

10 That's it for the overheads. Just where we are
11 today, a brief update, we have gone to the prioritization
12 process. There -- we have a document that will be
13 released to the public tomorrow. Given the time
14 constraints, we're having a 30-day public comment period
15 while we're giving the leads, the three leads from the
16 panel, the document. So we'll get input from the public
17 and from the leads at the same time.

18 We will respond to public comment. The public
19 comment period runs from tomorrow for 30 days. We'll
20 respond to the comments and give the entire panel the
21 revised document plus our responses to the comments. And
22 then the panel meeting on April 30th at UCLA is where we
23 will get the full panel discussion on the list that we
24 generated and on the justification for adding those
25 chemicals.

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1 We are -- in the document that's going to be
2 released tomorrow, we will have 11 TACs that were -- that
3 we suggest have reasonable data to determine that they
4 potentially differentially impact children, and we will
5 be looking for comment on -- out of those 11 which five
6 should end up on the first list and out of those 11 how

7 do people respond to the arguments that we make that
8 those 11 differentially impact children.

9 So that's where we are now.

10 DR. BLANC: So the mandate to you is to list up
11 to five. It's not to list no less than five.

12 DR. MARTY: It's to list -- right. The statute
13 reads up to five, and the only reason that up to five in
14 there is because it triggers ARB to do a whole bunch of
15 work and it would not be handleable to them.

16 DR. GLANTZ: What's going to happen at the April
17 30th meeting?

18 DR. MARTY: Well, we need to take comments from
19 the panel on our document which describes what we're
20 calling the top 11, and we need to take comment from the
21 panel on how you perceive which five should really make
22 it to the first list.

23 This list can get updated. It's not the final
24 list. So there are updates that will, of course, happen
25 to this list.

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1 DR. GLANTZ: So is that -- then does it come
2 back to the panel again for action or for approval or is
3 that the approval?

4 DR. MARTY: That's going to be -- unless you can
5 sneak in another panel meeting, we have to have the

6 document finalized May 28th because there's a 30-day
7 public review time built into it before the June 28th Air
8 Resources Board board hearing. It's an informational
9 item at that meeting. The Board does not need to vote on
10 it.

11 DR. BLANC: I would suggest then that when you
12 distribute copies of pre-public comment to the leads you
13 also distribute a copy to the rest of the panel.

14 DR. MARTY: Sure. That makes a lot of sense
15 actually.

16 DR. FROINES: I thought that there was also an
17 issue of the panel reviewing the methodology that you
18 used.

19 DR. MARTY: To prioritize.

20 DR. GLANTZ: I'm a little concerned to squish
21 all that into one meeting. We're just not going to be
22 able to do it.

23 DR. BLANC: Isn't that all we're going to do at
24 that meeting? Isn't that going to be the sole agenda
25 item?

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1 DR. GLANTZ: Yeah. Well, that may be the case,
2 but the problem is if you look at the history of this
3 body, we usually have something to say that then requires
4 some reconsideration or some work.

5 I really think we would want -- maybe we have to
6 schedule an extra meeting in the first part of May
7 sometime, but I would be very uncomfortable with that --
8 with us meeting, discussing it once and then never seeing
9 it again.

10 There are a lot of issues that are raised in
11 doing this thing and I'm all for being expeditious about
12 it, but I think it's going to be very problematic. We
13 could always schedule a meeting and cancel it if I'm
14 being too pessimistic.

15 DR. FROINES: Let me ask Paul Gosselin a
16 question. Paul, is there anything that's an absolute
17 necessities to come up in the April meeting from you all?

18 MR. GOSSELIN: The AZM discussion will continue
19 and that could go over to May or June. We're still
20 having discussions on one of the litigation issues, the
21 timing on that right now is not --

22 DR. FROINES: You mean metham sodium. So I
23 think we're okay in terms of having a meeting devoted
24 to --

25 DR. GLANTZ: I don't.

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1 DR. FROINES: But I agree. I'm not -- I just
2 want to make sure from Paul that that's the case, your
3 comments notwithstanding. So Stan, I think, is proposing

4 that a mid-May meeting be scheduled and then cancelled if
5 we don't need it.

6 DR. GLANTZ: Yeah. If we don't need the
7 meeting, then we don't have to have the meeting, but I
8 think that would be much better than to get to the end of
9 April, have a bunch of open issues or things that we want
10 to see again and then not have a meeting scheduled before
11 May -- because you're saying basically this all has to be
12 done by May 28th.

13 DR. FROINES: I don't think the court reporter
14 got the Paul Blanc groan. You may want to put some words
15 into that for the record.

16 DR. GLANTZ: I'm not lusting for more meetings,
17 but this is the first time we're doing this. We're going
18 to be setting a bunch of precedents and I think we want
19 to make sure that we adequately --

20 DR. BLANC: Well, actually I have a compromised
21 suggestion.

22 DR. GLANTZ: Which is?

23 DR. BLANC: Which is that the Chair designate an
24 executive committee to work on the findings. I assume
25 there would have to be formal findings.

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1 DR. GLANTZ: That's what the lead people do. I
2 just think -- I just think given every other thing that's

3 come before this panel, it gets discussed, things -- some
4 of the things that get done can be done immediately or
5 are little things that don't really need to come back,
6 but usually there's at least something substantive. I
7 think we want to give OEHHA time to think about it. And
8 since we need to approve it as a panel, there's no -- I
9 just think -- you don't have to come to the meeting if
10 you don't want.

11 DR. FROINES: Wait a second. No. I'm not
12 having this happen without Dr. Blanc being there. But
13 the question is -- Melanie, I assume that we have to --
14 let me just do a procedural thing. I assume that we have
15 to have findings from the panel, even if they're limited
16 to approval, although I would bet that it would be far
17 superior if the panel actually had some substantive
18 findings because I think this is going to be very
19 controversial potentially depending upon which chemicals
20 are on the list, and so I think that you probably would
21 benefit from findings so that Paul's point or Stan's, I
22 can't remember which, is important. In which case
23 when -- by what date would you want those findings? I
24 think that you would want them for the May 28th. Or
25 would you? Help on this.

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1 DR. MARTY: I think it probably would be useful

2 to have them by May 28th because that's the deadline that
3 we have for ARB's board process. Now, we can hedge that
4 deadline because it's an informational item and not a
5 regulatory item for the Board. In other words, the Board
6 doesn't vote on it. They have traditionally liked having
7 30 days even on the informational items, but I was told
8 Thursday, I think it was, that we could use a few more of
9 those weeks, that the Board would be happy with 15 days.

10 DR. GLANTZ: The other thing might be to
11 schedule a meeting -- the public comment period is
12 opening tomorrow for 30 days?

13 DR. MARTY: Right.

14 DR. GLANTZ: What about having a meeting in
15 mid-April? Move the April meeting up and then we could
16 see where we're at. We could decide then if we needed
17 another meeting.

18 I just can't believe -- we've never had anything
19 like this come to this group and go through in one
20 meeting, ever, that I can remember. So if we don't allow
21 for the eventuality, then we're going to all be like in a
22 mad dash. I would actually suggest we move up the April
23 meeting a week or so.

24 DR. MARTY: I think the problem with that scheme
25 is that doesn't give us any time to respond to the

1 comments and get the panel members the responses to
2 comments in time for them to review for the meeting. So
3 I actually prefer trying to get a mid-May meeting.

4 DR. FROINES: Well, I think that -- let me
5 suggest, formally suggest, that we plan a mid-May meeting
6 which may be cancelled. And I know that that's very
7 difficult for people but -- shall we take a vote or shall
8 we just plan it?

9 DR. GLANTZ: I think you could do that as the
10 Chair.

11 DR. FROINES: So far we've heard from Stan and
12 Paul. We haven't heard from Craig, Peter or Roger.

13 DR. BYUS: It might motivate us to do it all in
14 a meeting so we could cancel the one that we schedule. I
15 hope it would be a motivational factor rather than a
16 reason to continue discussion beyond what is prudent.

17 DR. GLANTZ: On the other hand, you don't want
18 to be in a position where you're jamming a report through
19 just to avoid a meeting. All I'm -- it may be that it
20 will be so wonderful and everything will be so obvious
21 that we won't need it, but then we cancel the meeting.
22 I'm not lusting for extra meetings to go to, but anyway.
23 It will encourage the panel to be expeditious, but I
24 think we need to do it right.

25 DR. FROINES: And it may be that Paul's right

1 that we can have an executive committee, but it would
2 probably be an executive committee that made a quorum.
3 So it would be five people that would be required.

4 DR. BLANC: Chair, you've heard the panel. Go
5 ahead.

6 DR. FROINES: I haven't heard any violent -- so
7 let's -- Jim Bierman will work on scheduling a mid-May
8 meeting. May is always a bad month for everybody, so
9 many things going on, but we'll just have to live with
10 that I think.

11 DR. MARTY: The other suggestion I have is since
12 Paul brought up the idea of sending the entire panel the
13 document tomorrow instead of just the three leads, if
14 people want to provide us with comment as soon as they
15 have their ideas formulated, then that would be really
16 useful because we could then provide a response to the
17 panel.

18 DR. GLANTZ: And that might take care of it, but
19 I just don't -- I just -- and then I'll drop this, but I
20 think we do not want to give even the appearance of
21 rushing this. I think we need to meet the deadline so we
22 need to move forward quickly, but I think we need to also
23 make it very clear that no edges are getting cut.

24 DR. BLANC: Your three leads are going to be
25 supplying you with written comments; is that right? Your

1 three committee leads.

2 DR. MARTY: I would hope that they would.

3 DR. BLANC: And who are the three leads?

4 DR. MARTY: It's Dr. Witschi, Dr. Friedman and
5 Dr. Glantz.

6 DR. BLANC: If those are CC'd to the rest of the
7 panel, which wouldn't normally be the process --

8 DR. GLANTZ: I think --

9 DR. BLANC: But so that we have a heads-up on
10 what your issues are.

11 DR. GLANTZ: We can do that, but I think again,
12 if you're interested in expediting this and given that
13 different people have quite different knowledge bases and
14 perspectives, and that's the whole idea of the
15 construction of the panel, I think we could all share
16 what we have to say with each other, but I think the idea
17 of having Melanie send the report to everybody, not just
18 the three leads, is a good idea. I think everybody
19 should look at it and give Melanie their feedback.

20 I have my own perspective and my own knowledge
21 base, which is different from the other people on the
22 panel, and I would personally feel much more comfortable
23 the more input we get.

24 DR. BLANC: I'm not arguing against that. All
25 I'm saying is since the non-leads may not be preparing

1 written comments, or they may be, it's optional, but
2 since your comments will be written.

3 DR. GLANTZ: They're not necessarily written.
4 The other documents I've been the lead person on, it's
5 usually just looking it over and talking to the staff
6 about it.

7 DR. BLANC: I see. Never mind.

8 DR. GLANTZ: But if it is written, we'll
9 circulate it. I think the idea of getting everybody's
10 feedback as quickly as possible --

11 DR. FROINES: The other thing we'll do will be
12 as we move -- Jim can work on developing the meeting
13 schedule. I think the other thing that I would do would
14 be to ask Eleanor in about two weeks from now -- pardon
15 me. As we move towards -- so we'll get the document
16 tomorrow or shortly, that we'll have Eleanor communicate
17 with each person on the panel and she can communicate
18 comments to OEHHA, or the panel members can communicate
19 comments themselves directly, either way.

20 In other words, we'll try to facilitate the
21 process. And actually, if Eleanor's contacting the
22 various panel members, that will put some fire into them
23 to move it along.

24 So we do -- so the point is that we do have
25 essentially two months before that April 30th meeting.

1 So we actually have a lot of time to give significant
2 feedback. So it's entirely possible that if we are
3 effective over the next two months that we can do it in a
4 day.

5 DR. GLANTZ: It's possible.

6 DR. BYUS: How big of a document is this? Is it
7 a large thing here or compared to a normal risk
8 assessment, Melanie?

9 DR. MARTY: There's an introduction that's about
10 40 pages and then there's 11 chemical summaries, but
11 these are already ID'd TACs and at least some of the
12 panel is familiar with all of those chemicals.

13 DR. FROINES: But there is one thing that's
14 interesting about these 11 chemicals and that is that the
15 science associated with the evaluation varies
16 dramatically, namely that they're not all OP compounds.
17 There are a lot of different criteria, scientific
18 criteria for, so that it's -- I don't know all the
19 compounds, so I'm just knowing from a little bit about a
20 couple of them that there's fairly wide ranging
21 scientific issues. So it's not trivial by any means, I
22 think.

23 DR. MARTY: Absolutely.

24 DR. BYUS: That's what I wanted to find out.

25 DR. BLANC: With that in mind, why don't we go

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1 forward with the next presentation.

2 DR. WITSCHI: Just one question. Of those 11
3 chemicals, is ETS among them?

4 DR. FROINES: She can't release the names,
5 Peter, until tomorrow.

6 DR. MARTY: I think I can address that question,
7 though. At the last -- at the December meeting there was
8 a discussion of whether we could list something that was
9 not already identified as a toxic air contaminant, and
10 the panel asked me to go back and make sure that was the
11 case with our attorneys, which I did do, and it was a
12 resounding no. You cannot list something that's not
13 already identified.

14 DR. WITSCHI: That's where we have the problem
15 right there.

16 DR. FROINES: Well, I wish Melanie hadn't done
17 that.

18 (Laughter)

19 DR. FROINES: If I say she can't release the
20 names and then you go into detail, sometimes that muddies
21 the water. So forget what you just heard. Let's take it
22 up later. This issue is going to be resolved, Peter.
23 Let's not take it up right now. Trust me.

24 DR. MARTY: The next presentation is by Dr. Mark

25 Miller who is working for OEHHA. Mark is a pediatrician

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1 by training and is working in our children's health
2 initiative. He's going to be talking about some of the
3 reasons why kids, infants and children, might be more
4 susceptible to some toxicants. He's going to have to
5 condense.

6 DR. MILLER: I have a lot of respect for you
7 working across all these disciplines here. It is
8 difficult.

9 What areas might we want to look at, kind of a
10 broad brush stroke of where children might be different
11 in exposure, absorption, blah, blah, and shelf life.
12 Kids are going to be around a lot longer.

13 DR. GLANTZ: Shelf life.

14 DR. MILLER: Long latency periods, it makes a
15 lot more difference to a six-month-old than it does to a
16 seven-year-old.

17 Just historically in the London fog air
18 pollution incident back in 1952, you can see on the
19 bottom line of those statistics, pre- and post-mortality,
20 pre- to incident and just afterwards, and periods with
21 the highest mortality were in the first year of life and
22 then in the older individuals, greatest increase there.

23 So what in the physical environment is different

24 in kids? Prematures in the neonatal intensive care unit,
25 they're exposed to all kinds of things that you would

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1 never be in the future life, that they have light in
2 their cribs all the time, they're exposed to all kinds of
3 gases, noises. An older infant is unable to remove
4 themselves from a hazard, that you might be exposed to a
5 noxious substance and pick up and move to another area.

6 DR. GLANTZ: Although I have to say when the
7 Chairman or President of Phillip Morris was asked about
8 this, they said the babies could just crawl into the next
9 room.

10 DR. MILLER: And of course you take his word
11 verbatim.

12 DR. GLANTZ: Absolutely.

13 DR. MILLER: Their breathing zone is at floor
14 level if they're crawling around as opposed to four to
15 five feet for most adults. School age kids, they're
16 playing soccer every day out on the fields, adolescents
17 are exposed to occupational hazards and they have
18 particular ones that are unique to adolescents.

19 We talked about some of this, but there's also
20 very specific stage-related activities as in mouthing of
21 an infant or eating of soil and other non-food items in a
22 toddler. Children have less varied diets. Breast

23 feeding is probably the most extreme example of that.
24 There's no other time in life, other than usually the
25 first year or two, when we consume large amounts of

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1 breast milk.

2 This is from the Air Resources Board and
3 illustrates where kids and adults, although painted in a
4 big picture because it's under 12 and 12 and older, where
5 they spend their time. What we know is that kids spend
6 more time at home indoors and less time other places
7 indoors, adults are working. They spend more time
8 outdoors and they spend more time at the higher level of
9 activity outdoors and they spend less time in transit.

10 Soil consumption, here's a good illustration of
11 a marked difference. These are means and high ends of
12 soil consumption, and on the left is young children and
13 on the right is adults. This is not the PICA child, who
14 are multi-fold higher in their soil consumption.

15 DR. WITSCHI: Sorry. What do the different
16 shades mean and what's atop the columns?

17 DR. MILLER: Pardon?

18 DR. WITSCHI: What do the two different shades
19 mean?

20 DR. MILLER: The purplish lighter color is the
21 mean and the red is high end consumption. So this is the

22 distribution of soil consumptions and it's in milligrams
23 per kilogram per day.

24 DR. FROINES: I have always had a problem with
25 the notion of a PICA child because that's a dichotomous

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1 concept. You either are or you're not. I actually think
2 children represent a dose response gradient, and there
3 are some who have very high exposure, unless somebody can
4 say that there's some behavioral issue that creates a
5 dichotomous relationship to ingestion of various things,
6 but I think the concept of the PICA, child by
7 oversimplifying it underestimates the exposure to a lot
8 of children.

9 DR. MILLER: Certainly I think if you looked at
10 it, you would probably see that there's kind of a
11 bi-phasic distribution and there are these kind of
12 regular thing and there's these way high outliers. And
13 it may be a very specific period. They might be that way
14 for three months and not at any other time in their life
15 sitting out there.

16 I think nonetheless this point that children --
17 the distribution of children is way higher than adults is
18 really the point that I wanted to make. I think you're
19 right.

20 DR. FROINES: Well, I think you get into a kind

21 of blame the victim problem too where if you sit and look
22 at it in a dichotomous way, you sort of say there are
23 these bad kids who eat newspapers with lead pigments in
24 them. I think that's just -- we have to be careful not
25 to oversimplify the issue.

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1 DR. MILLER: What we would like to do is not
2 blame these kids for being susceptible to toxicants but
3 try to protect them since we really can't do much about
4 that behavior.

5 So physiologically kids are different. They
6 double their weight in the first six months of life,
7 generally triple in the first year. At no other time
8 period are you growing at that kind of a rate. They eat
9 more, drink more, and breathe more per body weight. They
10 have increased absorption of some nutrients and some
11 toxicants. Calcium is absorbed at a much greater rate in
12 an infant than it is in an adult, and as well that could
13 go for lead where a toddler can absorb as much as 50
14 percent of ingested lead as opposed to an adult at 10
15 percent.

16 Mean water intake, same thing. We were up at
17 180 milliliters per kilogram per day in an under half
18 year of age child and down in the 20 to 30 range for an
19 adult in advancing years.

20 Where that water comes from varies by age, so
21 that formula is fairly unique to the first year or so of
22 life. Water as a direct water source is lowest in the
23 first year of life and higher -- and you can see tea,
24 coffee is different. Milk is mostly consumed by those
25 under 20 years of age, and one example that's frequently

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1 used is apple juice in young children and by calculations
2 by the NAS, they came up with about 16 times average
3 apple juice consumption in the toddler, young childhood
4 age group to the national adult average.

5 This goes across for non-liquid food items as
6 well. When you look at it in milligram per kilogram per
7 day, essentially across all the items the younger you
8 are, the more you eat. And that's based on your
9 physiologic need for growth.

10 So not only are you growing, but even each
11 system is growing and developing in a different time
12 framework. Even within an organ system there are
13 variations in the timing and development of different
14 elements that are growing and differentiating. In this
15 slide the red is diencephalon (phonetic) which peaks at
16 growth around birth whereas the cerebellum peaks
17 somewhere around a year and a half of age. So that if
18 we're looking at a toxicant that affects a particular

19 process in neuro developmental growth, if you were
20 exposed at a year of age, you might find certain results
21 from that exposure and a different part of the brain that
22 was affected if you were exposed at a year and a half.

23 We generally think in terms of kids as a younger
24 spectrum of children, but this is rate by weight of
25 reproductive organ growth, and all of them are taking off

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1 around between eight and 12 years of age, and our
2 rapid -- the period of rapid growth is the teenage years.
3 So if you had a toxicant that affected proliferation of
4 tissue during the growth of these organ systems, the time
5 that you would be concerned about is the adolescent
6 period.

7 So children are roughly double the surface area
8 to body weight, so they have increased absorption. They
9 have increased metabolic rate. They have increased
10 ventilation. This is just a graphic illustration of
11 breathing rates by age groups. The --

12 DR. FROINES: I would assume that you would
13 consider that the lung develops for the first 15 to 20
14 years.

15 DR. MARTY: There's a lot of alveolar
16 proliferation in the first three years and then you have
17 almost as much as alveoli in an adult except they're

18 smaller. So from three to about 20 they grow -- the
19 alveoli grow in size rather than number. It makes it
20 complicated to discern alveolar surface area per unit
21 body weight, but there's some indication that it's
22 actually the same in a three-year-old as it is in an
23 adult, that ratio of alveolar surface area to body
24 weight.

25 DR. FROINES: So lung function though tends to

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1 increase until you're about 20. So as a --

2 DR. MARTY: I believe that's right.

3 DR. BLANC: A little beyond that, actually.

4 DR. FROINES: So that's presumably -- okay.

5 DR. MILLER: Water and fat, total body water is
6 higher at birth than later in life. Total body fat is
7 lower at birth. And not only that, the adipose tissue at
8 younger ages has a higher water content within the
9 adipose tissue. Also, newborns and infants have lower
10 levels of serum proteins and also because they have
11 higher circulating free fatty acids in billiruben
12 (phonetic) which are a protein binding displacer.

13 What's the implication? Well, water soluble
14 chemicals have then a larger volume of distribution in
15 young children and potentially less clearance in a
16 neonate. Fat soluble chemicals have a smaller volume of

17 distribution, possibly higher clearance rates, and these
18 are pretty well understood from the pharmacological
19 literature.

20 DR. BYUS: Premature infants even have less body
21 fat, markedly less.

22 DR. MILLER: Well, I think that as well. Now
23 we're getting to the point that I would like to make is
24 that we are not talking about children and adults but
25 there are actually multiple time periods that there's

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1 such great differences across a lot of different systems
2 that you really need to focus in if you want to have an
3 idea what you're potentially dealing with as far as being
4 susceptible to toxicants.

5 Fat soluble chemicals, this is from a study from
6 the Netherlands looking at the toxic equivalent intakes
7 of dioxin and PCBs, and the point I want to make here is
8 that, and this is in breast fed infants, you take in
9 about 50 times the picogram (phonetic) per kilogram in
10 body weight in the first year than you do at any further
11 time in your life. That amounts to, depending to who you
12 go talk with and listen to, maybe 12 to 20 plus percent
13 of your total lifetime intake during the first year or so
14 by breast feeding. And this is not to have any
15 implications that breast -- in the studies, always breast

16 feeding comes out as the better thing to do and the
17 Academy of Pediatrics highly recommends it.

18 So does that mean anything? Should we even be
19 concerned about it? There are at least two very good
20 studies that corroborate that DDE and DTE in breast milk
21 is related to decreased duration of breast feeding, and
22 they're in totally different populations. So the DDE in
23 breast milk at birth, the higher you are, the less likely
24 you are to successfully breast feed for a longer period
25 of time. That is also supported by what we know about

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1 intake of birth control pills in your interfering with
2 breast feeding.

3 I've made a step there, presumably related to
4 low level estrogenic affects of those compounds.

5 DR. MARTY: In other words, it's a milk
6 production issue for the mother.

7 DR. MILLER: Children are physiologically
8 different in many different ways, including their
9 metabolic systems to detoxify chemicals, and I think
10 you've had a talk already about organophosphates in
11 particular is one that's been fairly well worked out
12 where the enzyme that's highly responsible for
13 metabolants is nearly absent in the very youngest age
14 groups. Excretion is less, glomerular filtration rate in

15 a premie is 5 percent of the adult. Glucular annotation
16 is decreased.

17 This is a beautiful slide by Chris Teal. It
18 looks at P450 enzymes in human livers and developmentally
19 shows -- these along the left side are the cresteil along
20 that axis is different SIP enzymes, and then it's
21 development over a time period that goes from 30 weeks
22 gestation to adults. So they're individual within the
23 different enzymes. They have different patterns. Some
24 are developed at birth and decrease, the neonatal ones,
25 and then there are other ones that you really don't have

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1 much activity until several months of age and are
2 involved in metabolisms of compounds like caffeine and
3 venoflin (phonetic) given the much longer (inaudible).

4 Renal clearance is decreased, tubular secretion
5 is decreased so that it plays a role, for example, in
6 pharmacologic literature for why we need to prolong the
7 timing of immunoglycocides in dosing or in penecillins
8 which are actively tubular secreted.

9 Neurologically --

10 DR. BLANC: So you're saying -- can you go back?
11 So you're saying that actually glomerular filtration per
12 kilogram of body weight is very high.

13 DR. MILLER: Based on -- adjusted for other

14 factors as well. No. Glomerular filtration rate is low
15 at birth.

16 DR. BLANC: But they don't have as many MLs to
17 filter either. So that's MLs per minute, not MLs per
18 minute per kilogram.

19 DR. MILLER: Per kilogram and by creatinine it
20 is greatly decreased and in a premature is less than --
21 maybe that should be per -- I'm not sure. That number.
22 I think that number may be per kilogram.

23 DR. BLANC: What you're saying is given the
24 amount of creatinine that they have is less, also that
25 their filtration is lower.

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1 DR. MILLER: Yes.

2 DR. BLANC: Of the creatinine that they have.

3 DR. MILLER: That sounds correct.

4 DR. BLANC: All right. That's interesting.

5 DR. MILLER: Development of the brain and
6 certainly probably other organs, but particularly in the
7 brain, it's temporally and regionally determined by a lot
8 of different processes. It's kind of a complex slide,
9 but you have the growth and development, the kind of
10 growth on the top and these developmental differentiation
11 processes on the bottom that are happening over different
12 time periods.

13 So that proliferation and migration is happening
14 really through a long period of time. Differentiation
15 and synaptogenesis is starting a little later and ending
16 maybe a little bit earlier.

17 At any rate, the functional organization is a
18 developmental process that is uni-directional. You don't
19 go back and redevelop something that should have happened
20 earlier.

21 One interesting example of implication from
22 that, which is unique time periods during which you're
23 going to see differential kinds of results of exposure,
24 is from thalidomide (phonetic). They noted that in fact
25 thalidomide is related to the development of autism, but

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1 when they looked at this data that showed that there was
2 increase in autism in kids that had been exposed to
3 thalidomide, they realized that in fact it was only
4 between gestational day 20 and 24. This is in humans,
5 that all of the kids with autism were exposed during that
6 period of time and nobody who wasn't exposed during that
7 period of time developed autism.

8 So there's a really unique small window for
9 what's going on in the brain during that time and it
10 correlates also with other known affects on the cranial
11 nerves that are also developing during that time period.

12 It does not correlate with the time period which is much
13 larger with the limb defects that are seen from
14 thalidomide.

15 DR. FROINES: It is interesting apoptosis starts
16 out very early.

17 DR. MILLER: And that's --

18 DR. MARTY: There's also -- you're going to see
19 it right here.

20 DR. MILLER: Synaptic pruning -- this kind of
21 correlates with that. Synaptic pruning, we develop
22 synapses something in the order of trillions, and
23 basically you have the most number of synapses that
24 you're going to have maybe around two years of age and
25 then you slowly prune back those. And during early

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1 adolescence you're having the most rapid decline in the
2 number of synapses, and it's probably not only related to
3 your activities. We all suspected this, but -- so if you
4 have something.

5 (Laughter)

6 DR. MILLER: Anyhow, so if you have something --

7 DR. GLANTZ: When do we continue to deteriorate?
8 Go back one. Very few.

9 DR. FROINES: The question is can you -- can
10 toxic chemicals move that process towards the right in a

11 premature aging context abiotrophy is premature aging,
12 and so it would be interesting to see.

13 DR. MILLER: I don't know exactly about pruning,
14 but certainly apoptosis there are toxic chemicals that
15 prompt apoptosis in massive amounts including ethanol.

16 Here is just a list of some of the different
17 areas of neuro development and these processes and
18 different chemicals that are known to interfere with
19 those processes. And some like ethanol affect multiple
20 of the processes.

21 DR. GLANTZ: When you say developmental
22 neurotoxicity, do you mean during pregnancy or what does
23 developmental mean in this context?

24 DR. MILLER: Presumably it means during the
25 entire time these processes are happening. That's how I

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1 interpret it.

2 DR. MARTY: Yes.

3 DR. MILLER: So that, in fact, as time has gone
4 on we used to say oh, well, the brain's growth and
5 development has happened by six, but now people are
6 showing all kinds of important activity like synaptic
7 pruning that's going on at least until 20 and probably
8 longer.

9 DR. FROINES: That's why I asked the question

10 about the lung. Do you consider affects that reduce lung
11 growth, for example, a developmental effect to the degree
12 that it occurs in people breathing air pollution from age
13 four to seven?

14 DR. MARTY: Yes.

15 DR. MILLER: I would. Those technical
16 definitions that people use sometimes are different.

17 DR. BLANC: What does pesticides mean in a slide
18 like this? I think it's an unfortunate choice of --

19 DR. MILLER: Probably is, but there are many
20 different pesticides that have been shown to prompt
21 apoptosis, and I could get you the reference from that
22 including chlorpirophos (phonetic), which is one of the
23 most recently hot topics in the news.

24 DR. MARTY: And also chlorpirophos impacts
25 differentiations in synaptogenesis.

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1 DR. MILLER: I agree. That's a bad use there.

2 DR. BLANC: It suggests a lack of sophistication
3 that probably is not what you want to suggest.

4 DR. MILLER: Maybe that's why it's underlined.

5 DR. BLANC: You don't say organic chemicals.
6 You're otherwise fairly specific in what you mean.

7 DR. MILLER: Yes. We'll make that correction in
8 that slide.

9 DR. GLANTZ: We could get Paul to come up and
10 tell us which one they're really talking about.

11 DR. GLANTZ: Paul Gosselin, yes.

12 DR. FROINES: Aside from the comments, Paul
13 Gosselin's watching that clock with some concern. So
14 let's move on.

15 DR. MILLER: What's the evidence that any of
16 these things make any difference? Well, this is from the
17 Jacobsens who have done a great deal of work in the PCB
18 exposures, and as you increase the PCB in the poured
19 blood in the maternal serum, it's more importantly than
20 probably the milk, but also in the milk you see a fall in
21 the verbal IQs at age 11. This already goes out 11 years
22 and it's related to various measures of inutero PCB
23 exposure.

24 There's a decrease in word and reading
25 comprehension, and in the highest PCB grouping there

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1 are -- you would be three times as likely to have low IQ
2 and twice as likely to be two years behind in reading
3 ability. These are not highly exposed individuals. This
4 is within kind of background level exposure of PCB. And
5 it correlates -- this is Michigan, I believe, data, but
6 there's also similar data from upstate New York and the
7 Netherlands that would agree with that.

8 This is minamata disease. This is just a
9 picture of the differential lesions or deposition of
10 mercury in the brain. The top is the adult and the
11 bottom is a congenital exposure. Aldicarb, the point
12 here is that this potent cholinesterase inhibitor is
13 found in hot spots and was used on bananas in Central
14 America, sometimes imported at ten times the legal limit.

15 What the EPA assessment said of the hottest
16 banana was that you could exceed your daily limit eating
17 one seventh of a banana, and a toddler eating one banana
18 equals an adult eating five -- and we all know that kids
19 go through phases and many of them eat many bananas daily
20 for long periods of time.

21 Carcinogenesis, I think this one slide probably
22 does it. In looking at the risk of breast cancer in
23 patients that were treated for Hodgkin's disease, there
24 was an increased risk for breast cancer in these. It
25 says a secondary tumor, but when they looked at it,

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1 almost all of those were treated for the original
2 diagnosis between 10 and 16 years of age. If you were
3 treated before -- and this is treated with radiation that
4 includes the developing breast tissue of the body --
5 those who were treated before 10 years of age and compare
6 those with the same treatments between 10 and 16 years of

7 age, the relative risk was nearly seven times as great.

8 That also would go along with some information
9 we know from exposures to the atomic blast in teens who
10 had also increased risk of breast cancer.

11 Vinyl chloride --

12 DR. GLANTZ: If I could just -- there's evidence
13 for that with secondhand smoke too, exposure.

14 DR. MILLER: Actually there was something on
15 there. Breast cancer risk associated with NAT-2 slow
16 acetylators is higher if you were exposed before 16 years
17 of age than -- we didn't miss it. Thank you for pointing
18 that out.

19 Vinyl chloride, this is animal studies by
20 Maltoni, and what you see is in angiocarcomas of the
21 liver and hepatomas, that those exposed in utero and as
22 adults essentially have no (inaudible) with one in a high
23 exposure adult angiocarcoma, but the -- really the tumor
24 load was in the dose exposed as a newborn.

25 These are adducts that are seen from vinyl

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1 chloride exposure. What we see here is that the number
2 of those adducts in the liver are greatly increased in
3 the pups exposed compared to the adults exposed, but in
4 the lung, which is not really the organ that we're
5 concerned of, they're essentially the same.

6 I think I'll end there, unless there any
7 questions.

8 DR. GLANTZ: We're going to do this in one
9 meeting?

10 (Laughter)

11 DR. GLANTZ: Okay.

12 DR. BYUS: Is this all?

13 DR. MILLER: What I would like to say though is
14 that we held a conference last spring to introduce OEHHA
15 staff to some of these ideas and had a great many
16 illustrious speakers from around the country that, at
17 least in part, many of those talks on the OEHHA web site
18 and at least one or two of the panels are up there as
19 well. And we are going to have the second of those
20 annual children's environmental health conferences in
21 April. I think it's the 22nd and 23rd. It's a Monday
22 and Tuesday.

23 DR. MARTY: It's the 23rd and 24th.

24 DR. MILLER: In Monterey. Again we've got
25 wonderful speakers coming. The first day is going to be

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1 devoted to pharmacokinetic and pharmacodynamic issues and
2 modeling, and the second day is specifically going to be
3 directed toward neurotoxicology with a specific interest
4 in looking at the use of neuro behavioral end points.

5 DR. BLANC: One of the areas that seemed to be
6 not particularly highlighted in this series of slides,
7 and it may be because it's maybe the most complicated, is
8 immunologic development.

9 DR. MILLER: It's really complicated and very
10 interesting.

11 DR. BLANC: Particularly as it might relate to
12 toxic chemicals that might serve as adjuncts in atopic
13 sensitization from ambient allergens.

14 DR. MILLER: One of the very -- there's not
15 that much work in that area. One of the very few people
16 who have done work was our speaker last year at the
17 conference, Steven Holiday from Virginia, and his talk is
18 on the web site and is very interesting.

19 DR. BLANC: An example of diesel exhaust where
20 there's been a lot of laboratory data looking at it as an
21 adjunct for sensitization.

22 DR. MILLER: And there's a great deal of
23 literature at least speculating on the balance of TH-1
24 and TH-2 related to various exposures with lymphocytes.

25 DR. BLANC: That's mostly related to infectious

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1 exposures. I haven't seen any of that related to toxic
2 mechanisms driving a TH-1 and TH-2 balance.

3 DR. MILLER: There's a guy Nork Strum from

4 Sweden who has written about that.

5 DR. BLANC: Can we anticipate in your document
6 we'll be dealing with immunologic related toxins as one
7 way in which one or more of these 11 may have gotten
8 chosen?

9 DR. MARTY: We have a section in the
10 introduction part which discusses, albeit very briefly,
11 this concern about immuno development imprinting of the
12 immune system and immunotoxins.

13 In terms of the 11 chemicals that were picked,
14 yes, there are some that impact the immune system.

15 DR. BLANC: And that might be what's driving
16 their selection.

17 DR. MARTY: It's part of -- it's folded into
18 other issues.

19 DR. BLANC: And can you name some of the other
20 disciplines that are particularly the most relevant
21 without getting into the chemicals themselves? I would
22 assume neurotoxins would probably be the driving force,
23 but if in terms of the balance between carcinogens and
24 neurotoxins is this going to be a carcinogen driven
25 document or a neurotoxin drive document.

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1 DR. MARTY: It's not carcinogen driven.

2 Although there are carcinogens on the list. Neurotoxin

3 is important in at least three of those chemicals and
4 it's the absolutely driver for two of them. There are
5 some chemicals where it's the respiratory system that's
6 the target and we're looking primarily at asthma
7 triggers. And then there are some where it's a real
8 gamish. There's immunotox, developmental tox, for some
9 of the compounds carcinogenesis, reprotox, and terrata
10 production.

11 DR. BLANC: Terratogenesis.

12 DR. MARTY: Terratogenesis. Thank you. It's a
13 real mix.

14 DR. FROINES: We need to close this off because
15 we're way beyond our time. Let's take a very quick break
16 and bring back sandwiches and we'll get started on the
17 pesticide issues as soon as we can.

18 (Lunch recess taken.)

19 DR. FROINES: We can quickly move to the
20 discussion on the cholinesterase inhibition policy
21 development. Welcome.

22 DR. PFEIFER: Thank you.

23 My name is Keith Pfeifer. I'm a Senior
24 Toxicologist with the Department of Pesticide Regulation,
25 and Dr. Anna Fan and Dr. Catherine Dowling and from OEHHA

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1 and I are going to share this overview on what we're

2 calling the cholinesterase inhibition project, and the
3 name of our grup, our interdepartmental group is the
4 cholinesterase work group.

5 Just briefly what we would like to cover with
6 you and give you an overview of what we've done and where
7 we are planning on going with this work group, as you can
8 see the first slide there, which I'll mention in a
9 minute, are the goals. We'll mention briefly the staff
10 participating. We'll go through the topics and the
11 prioritization related to cholinesterase inhibition we
12 plan to address. We have an outline of the process for
13 developing what we're calling discussion papers, and also
14 a time line for our work group activities.

15 Now, we thought that it would be appropriate
16 to -- let me just say a goal that we don't have up there
17 is for this group to come to consensus, and that's one of
18 our main objectives, and the information that we are
19 presenting here today is a consensus of our work group.

20 There are approximately 15 scientists combined
21 from OEHHA and the Medical Toxicology Branch of DPR
22 involved in this work group. I just wanted to mention
23 that at the outset that this is an extensive effort on
24 both our parts.

25 The first goal we felt is critical to this whole

1 project and that is to develop scientifically defensible
2 discussion papers on the interpretation and use of
3 cholinesterase inhibition data and related toxicity end
4 points in pesticide risk assessment. You'll notice there
5 was some indication earlier, I think, in some discussions
6 about an OP organophosphate policy development, and we
7 felt that cholinesterase inhibition does not just relate
8 to organophosphates but also includes carbamates
9 (phonetic) and other thyocarbamates pesticides, and so we
10 wanted to use a kind of broader term here.

11 DR. FROINES: Can I just interrupt you for a
12 moment? I want to alert the panel to the reverse of what
13 you just said, that you thought the focus on OP compounds
14 was too narrow so because of things like carbamates. The
15 reverse of that is also that an emphasis on
16 cholinesterase as an end point is too narrow with respect
17 to OP compounds.

18 So everybody with me on this? So let's keep
19 that as an issue to come up and discuss later.

20 DR. PFEIFER: I think we're fully aware that
21 there are other toxicity end points, but the end point
22 that makes organophosphates, carbamates and other
23 thyocarbamates unique is their ability to interact with
24 cholinesterase and the controversy, if you will, that has
25 ensued over the years of how to interpret this.

1 The second goal is to utilize the scientific
2 discussion papers to formulate Cal/EPA guidelines on the
3 use of cholinesterase inhibition data in pesticide risk
4 assessment. Just briefly, I didn't put a slide up on
5 this but the discussion papers that we're referring to
6 here we intend to present all information and data that
7 are currently available on the topics, and Dr. Fan and
8 Dr. Dowling will be going through those in a second.

9 We're asking the question what do those data
10 indicate, and what are the limitations and uncertainties
11 for the use of these data in risk assessment. Our goal
12 is to come out of these discussion papers with
13 recommendations for guideline development, and we hope
14 that the summary -- there will be summaries of each
15 discussion paper that can be combined some way into, if
16 you will, an executive-type summary.

17 That's all I have right now as far as an
18 introduction.

19 DR. BLANC: John, you see that document
20 eventually as being something which (inaudible) or some
21 formal acknowledgement by the SRP?

22 DR. FROINES: I think that the answer to that is
23 yes, and I think that that document would represent the
24 criteria that this panel would use in evaluating
25 pesticidal documents or other end points. We haven't

1 gotten to that yet. But the -- so Paul, it becomes in
2 essence the SRP document as well as the agency's document
3 because that's the criteria that we would use so that our
4 agreement with that policy is not only something to seek,
5 but it's an absolute requirement.

6 DR. BLANC: Okay.

7 DR. FAN: I will present this outline of
8 discussion topics for which we are developing our
9 discussion papers. For what we have now on the screen, I
10 do not expect you to be able to see that. I have a
11 two-sided one-page handout that I've put on the table if
12 you're interested, and then within the next minute or so
13 we'll be breaking each of these down into bigger bullets
14 so you can see them on the screen.

15 Overall this represents the topics and areas
16 that we are going to address for each of these bullets.
17 We'll have a discussion paper developed. We'll review
18 the information in literature, prepare discussion papers
19 on each of those bullets, discuss them with members, and
20 then based on the information gained from the discussion
21 and collection of these papers we will develop the
22 guidelines which can then be adopted for our use in our
23 policy.

24 As you can see, several of these bullets are
25 grouped into priorities. So we have numbered them

1 priorities one to nine with priority one being the
2 highest and nine being the lowest.

3 This is the initial outline that the work group
4 has agreed upon, and in the process of developing the
5 discussion papers we modified the outline as appropriate.

6 For priority number one, we will first look at
7 physiological function and toxicological significance of
8 cholinesterases. As we go through this, please note that
9 the bullets in bold, these have been presented last time
10 at the last SRP meeting. What we've done since then is
11 add on the bullets that follow the first bullet, the
12 first outline. So you add on the content for each
13 category or priority.

14 So for this priority one group, we would be
15 reviewing the cholinesterase inhibition overview and also
16 looking at USEPA's policy. As some of you may know,
17 USEPA has a policy document that it put up on the web and
18 it's dated August 2000. Then this part would also
19 include looking at the role in morphogenesis (phonetic)
20 and development, the immune system function role in drug
21 metabolism, and control in regional brain cholinesterase
22 inhibition.

23 DR. BLANC: So to clarify then, the implication
24 is that under overview of cholinesterase inhibition,
25 leaving the USEPA side out of it, the overview would

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1 include the role of cholinesterase in arastocoline
2 (phonetic) in neurotransmission I'm assuming since --

3 DR. FAN: That would be part of cholinesterase.
4 The basic, the principals, the background would be the
5 overview of cholinesterase inhibition, the different
6 cholinesterases and different effects, and then continue
7 on with the role of cholinesterases in morphogenesis.

8 DR. BLANC: In non-neuro transmission or in
9 other things.

10 DR. FAN: Right.

11 DR. BLANC: Okay. I got it. The way it's
12 worded it's -- the elephant on the table is the
13 neurotransmission that nobody is talking about, but
14 that's subsumed in that first thing.

15 DR. FAN: The first bullet is the inhibition
16 itself. The second bullet on would be cholinesterase's
17 role in --

18 DR. BLANC: In everything else. Okay. All
19 right.

20 DR. FAN: Priority number two, group two, it
21 would be looking at those responses and considering and
22 point selection. It would include the review of the
23 science, interpretation of functional observation of
24 battery studies.

25 DR. FUCALORO: Can you define that functional

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1 observation of battery studies?

2 DR. FAN: There is a specific battery.

3 DR. FUCALORO: Go on. I'm sorry.

4 DR. DOWLING: These are essentially behavioral
5 tests.

6 DR. FUCALORO: Are they quantified in some way?

7 DR. DOWLING: Yes.

8 DR. BLANC: Animal functional whereas the other
9 is the neurobehavioral as human neurobehavioral, I'm
10 assuming, mostly on the next one down. Was that still
11 animals?

12 DR. PFEIFER: That would be -- most of these are
13 done with animals. So these are actually dose response
14 quantification-type testing. So there might be some
15 overlap between those two.

16 DR. BLANC: Between the FOB and neurobehavioral?

17 DR. PFEIFER: The FOB is a specific --

18 DR. BLANC: Subset.

19 DR. PFEIFER: It would be kind of a subset of
20 neurobehavioral.

21 DR. FUCALORO: And why would you separate
22 neurobehavioral affects with neurobehavioral affects
23 versus cholinesterase in the first one?

24 DR. FAN: The first one is a review of what's
25 electric shock. The second one is to take the

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1 information to compare and correlate the neurobehavioral
2 affects and see how they correlate with cholinesterase
3 inhibition.

4 DR. DOWLING: As I'm sure you're aware,
5 Stephanie Padilla of USEPA has done very significant work
6 correlating cholinesterase inhibitions in different
7 areas, plasma, red blood cell, brain, and also behavioral
8 affects.

9 DR. FUCALORO: I see. I think I understand now.

10 DR. BYUS: So you mean red blood cell and serum
11 here or do you mean brain cholinesterase?

12 DR. DOWLING: All three.

13 DR. FUCALORO: I understand. Sorry.

14 DR. FAN: That would include looking at the
15 NOAELs established for the FOBs for systols of
16 (inaudible) of cholenisterase inhibition and then in
17 addition would also include other cholinesterase related
18 end points.

19 In the process we need to look at CNS versus
20 peripheral nervous system responses. In this case we
21 would be looking at (inaudible) 1999 and we will also
22 look at what EPA has said in this regard. USEPA has

23 proposed to use the cholinesterase information as a
24 surrogate for brain inhibition, so we have to take that
25 into consideration.

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1 Then for group number three those responses and
2 data analysis, we would be looking at the possible use of
3 benchmark DOSE approach versus the traditional way of
4 looking at the data used in the NOAELs. It would include
5 defining the criteria for the susceptibility for the
6 benchmark DOSE modeling and evaluation of the (inaudible)
7 approaches. (Inaudible) we would pick some of the
8 examples from the DPR demonstration database and try to
9 use to benchmark those approaches.

10 We will be looking at the approach using the
11 statistical significance versus the percent inhibition,
12 so statistical significance is the traditional way we
13 have been doing for the NOAEL identification and the
14 percent inhibition would be the benchmark those approach
15 whereby a certain percentage is predetermined as change
16 from the normal to be the point of departure.

17 So we would be reviewing procedures and policies
18 from other regulatory agencies in what is proposed by the
19 industry in order for us to use information and develop
20 our own consistent approach.

21 In terms of interpreting the data, we would be

22 looking at analytical variable in measuring
23 cholinesterase inhibition, how these would affect the
24 data that we see, and also how to interpret them so that
25 would be looking at sampling handling and methodological

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1 variabilities and also considering the intra-laboratory
2 methodology standardizations.

3 We would be defining criteria for performing
4 method analysis and also criteria for correlating between
5 the different cholinesterases. For these we need to
6 determine the impact of analytical methodology on
7 interpretation of cholinesterase inhibition data, how
8 that would affect us in determining the NOAEL and LOAEL
9 data.

10 Moving on to five, looking at human versus
11 animal data, first we would address heterogeneity in the
12 population, look at (inaudible) versus clinical signs,
13 those that would be observed from animal studies versus
14 those we may be only able to see in humans and considered
15 adequacy and subjectivity of the (inaudible) observations
16 and adequacy of study protocols.

17 DR. FUCALORO: Do you see the data analysis
18 development that you have here as being applied to other
19 types of studies within your department? In other words,
20 are you doing something here that is kind of systemitizes

21 your analysis procedures or am I just --

22 DR. FAN: If you are talking about benchmark,
23 those approach.

24 DR. FUCALORO: They already exist.

25 DR. FAN: Those could be applied to different

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1 end points, different chemicals.

2 DR. FUCALORO: So you're not creating anything
3 new here that could have a wider applicability.

4 DR. FAN: Benchmark, those approaches are not
5 really widely used, although people have tried to use
6 that. It's not really the established method and adopted
7 generally for use and therefore looking at --

8 DR. FROINES: It's not a conceptual problem,
9 it's a database related problem.

10 DR. FAN: Mainly it's not consistently being
11 used, so we're trying it out to see if we can use it for
12 cholinesterase inhibition data.

13 DR. FUCALORO: I see.

14 DR. PFEIFER: The benchmark doses were very
15 important. In a lot of studies you don't have a
16 no-effect LOAEL and so you're going below the
17 experimental doses.

18 DR. WITSCHI: I have a question. In four you're
19 going to give a hard look to the analytics, and from what

20 little I know or what Barry Wilson (phonetic) tells me,
21 quite a few MSAs are inadequate. Am I correct in that
22 one?

23 How is this -- if you develop criteria or come
24 to a conclusion what should be done, if it's to be done
25 right, how much is this going to impact on all your other

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1 endeavors? Because if you look at the large database,
2 are you going to take into content some or probably most
3 of those studies have not been done with adequate
4 methodology? And if so, why look at that?

5 DR. PFEIFER: The question you asked is
6 certainly provocative, and this number four was kind of a
7 pet of mine just because of the issues that come up in
8 our risk assessments doing pesticides and cholinesterase
9 inhibition.

10 I don't know that we will be able to come up
11 with criteria that will absolutely say we can't use
12 certain data. I think -- I mean previously generated
13 data. I think it's more of one historical perspective on
14 problems that have existed, and maybe we can't come up
15 with some criteria, suggestive criteria that would
16 improve the whole presentation of data related to this
17 end point. Maybe down the road it will achieve more
18 strength as a requirement. I can't tell.

19 But as you know, there's -- you get in data sets
20 from different labs, and a lot of the information on how
21 the analytical was run aren't forthcoming and so you're
22 almost at a point where you have to take the data for
23 face value. I think what we're trying to do is lay out
24 some of the limitations, maybe of the data and some of
25 the criteria that possibly could be required.

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1 But again, the most important aspect, at least
2 from my perspective here, is the variability that exists
3 in analyzing for cholinesterase, even if it's clearly
4 stated out how they did it and they've done it by an
5 acceptable method and et cetera, but when you get down to
6 making a decision on a data set where the low effect
7 level is the no effect level and you have a known
8 coefficient of variation or known variability, does that
9 enter into where you say this effect is more in the realm
10 of the variability of the analytical method. From my
11 perspective that's really critical.

12 DR. WITSCHI: I see the problem and I think it's
13 a big one, and I wouldn't -- certainly I wouldn't
14 advocate to go back to all the animal studies which
15 haven't been done since I don't know when and look at
16 them in this light, but the human studies -- and I think
17 we have a great amount of human data -- it might be much

18 more urgent to some extent to look at them according to
19 the criteria what is really correct measurement.

20 DR. PFEIFER: You mean a controlled human study?

21 DR. WITSCHI: Yes, and in other human studies.

22 Because you know as somebody once said, they're the best
23 animal to study toxicology. Man is man and there's a
24 large amount of information available which probably --
25 under five which deserves in view of those problems which

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1 surface now perhaps a more critical analysis that has
2 been done so far. I don't know whether I'm expressing
3 myself clearly, but --

4 DR. FAN: In terms of human data, the last REL
5 that was -- an evaluation of the California
6 cholinesterase monitoring program was done I think the
7 last REL was in the '70s, in OEHHA we have a plan to
8 update that and do an updated evaluation at a time when
9 we can try to get the human data, but we have not seen a
10 concerted effort in collecting that pool of human data
11 for analysis.

12 So I think at this point based on what we are
13 doing now for our own project we have to rely on animal
14 data.

15 DR. BYUS: I have one more just brief comment
16 about that as well. I think this is a very important

17 consideration. I think certainly the symposium
18 highlighted the potential problems with measuring serum
19 cholinesterase levels in humans, which was considerably
20 important, very important to all the details involved in
21 that, but I would hope that when you prepared this
22 document that you gave some -- not just listed the
23 weaknesses but gave some likelihood if various procedures
24 weren't followed, then these values would be abnormally
25 high or probably abnormally low and by what factor so

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1 that you would -- you could give more than just a listing
2 of the methodologies and what's good and bad with them.

3 DR. PFEIFER: So you would like some type of
4 quantitative uncertainty.

5 DR. BYUS: Some editorial, right. For example,
6 if the samples weren't kept cold, which is I believe one
7 of the repaired rapidly in the data, then it's likely
8 that you'll see no inhibition or inhibitions of 50
9 percent or more that show up as nothing, as no inhibition
10 whatsoever.

11 DR. PFEIFER: There have been some studies
12 published that we're accumulating.

13 DR. BYUS: Wasn't Barry -- his data seemed to be
14 very provocative to me, but I mean more than just an
15 analysis of the pros and cons but more of a -- I don't

16 know if editorialize is the right word, but try and give
17 some more meaning to what values might mean if various
18 procedures were not followed, which way is it going to
19 go.

20 Does no inhibition really mean no inhibition or
21 was it if the samples weren't kept properly and analyzed
22 properly that could be up to 30, 40 percent inhibition.

23 DR. FAN: Yes, that's a very good suggestion.
24 Berry Wilson actually helped us in gaining increased
25 awareness of the importance of this analytical procedures

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1 and variability that can occur regarding IES. I invited
2 him to IES.

3 DR. BYUS: I know you did. It seems to me you
4 could just call up whoever did the studies and ask them
5 did they keep the samples on ice or not. If they
6 didn't -- I'm just -- this is just sort of information
7 that is crucial --

8 DR. FROINES: Let's go ahead. I'm worried the
9 point has been made actually two or three times. Why
10 don't we go ahead.

11 DR. FAN: I think we will also invite his input
12 in the process. Thank you. Then we move to number six.

13 DR. FROINES: I think that we have to be careful
14 too, though, because we have both a scientific mission

15 and a public health mission and the two are interrelated
16 and we need to decide how to evaluate these variables and
17 to characterize how important the differences might be
18 and also to not get into the kind of world of
19 epidemiologists where one person does a study and 75
20 other epidemiologists say why it was a bad study and
21 doesn't prove anything. Then we end up with no
22 conclusions.

23 In the end we need to take studies and try and
24 reach reasonable conclusions to meet our public health
25 goals. So there has to be some balance within this

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1 process I think.

2 DR. FAN: I think that we're trying to get that
3 covered under five, priority five, the human versus
4 animal data.

5 To move on to number six, the dose response
6 assessment, it is a continuation of the data analysis
7 part. Here it would include looking at the control
8 versus the baseline values and we will review the
9 literature available and also identify examples from DPR
10 registration database that we could use. And we would
11 consider the route-to-route extrapolations considering
12 what other agencies have in their policy and now existing
13 approaches that we are using.

14 Then for seven, short-term versus long-term
15 exposure, we would look at the mechanism for down
16 regulation/tolerance development and (inaudible)
17 cholinesterase inhibitions in the absence and presence of
18 clinical signs or symptoms and also looking at the
19 short-term FOB NOAEL for the approach that we use, plus
20 insert a factor versus a long-term uncertainty factor
21 versus long-term. And again we'll see what we can use as
22 examples from our registration database.

23 Number eight, structure activity relationships,
24 we will look at what ILSI has discussed in its position
25 and consider the neurotoxic batteries (inaudible)

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1 neuropathy data and also look at the possible application
2 of SAR to cholinesterase inhibition as not independent
3 point.

4 And then to complete that, the intraspecies and
5 interspecies variability, we'll review what's in the
6 literature and also in particular information gained from
7 the workshop, SRP workshop that was held in October 2000
8 and also evaluate the selection of default uncertainty
9 factors.

10 DR. BLANC: Well, first of all, when you say
11 priorities, these are in terms of your working order but
12 not the order that they would be arranged in the ultimate

13 document.

14 DR. FAN: The outline, it would change.

15 DR. BLANC: Right. Because it would be a
16 logical flow in particular. So I'm assuming that, but --
17 so I'm going to take it on face value your priorities.

18 I think that this panel would probably rank the
19 issue of intraspecies variability a little bit more
20 highly than you have, particularly for cholinesterase
21 inhibition. If you're going to be putting this much
22 effort into it, is a factor of ten reasonable for an
23 intraspecies variability, particularly given the data on
24 varying affects based on age and nutritional status and
25 other factors.

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1 DR. FAN: I think the priorities the way we have
2 might be misleading if those are really of higher
3 priority, but those are really the background information
4 foundation that we have to lay down in terms of providing
5 the basis for us to gain information to arrive at, for
6 example, ten-fold effectiveness.

7 DR. BLANC: It may be helpful to you to break
8 out number nine into two separate issues because they're
9 actually quite different databases that may help you
10 answer that question. Clearly they are quite different
11 because the intraspecies is really dependent upon human

12 epidemiologic data whereas your interspecies issues are
13 going to be related to mostly looking at animal data as
14 it may relate to what limited human data you have.

15 So it's just -- I think they're going to be
16 apples and oranges.

17 DR. FAN: That's reasonable. I think that also
18 some of these at this point is arbitrary in terms --

19 DR. BLANC: I'm just piloting what I think -- it
20 comes at the very end and it's two little bullets, but
21 this is a biggie for us.

22 DR. FAN: Do you think that combining that nine
23 with five in a discussion would help to bring out that
24 point for you?

25 DR. BLANC: The first part of nine, yes, is

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1 really related to human versus animal. It has to do with
2 intraspecies variability. But the second part of nine,
3 which is the intraspecies, is really at-risk human
4 populations.

5 I think there was another question that came up
6 in the workshop which was -- I think Craig was the one
7 who had emphasized multiple routes of exposure or
8 combined exposures to different cholinesterases.

9 DR. BYUS: That's what I was going to say. The
10 one thing that's lacking here is additivity, synergy with

11 other cholinesterase inhibitors. I know it's a huge
12 question you find difficult dealing with, but it's
13 incredibly important, I think. It should certainly be in
14 here somewhere.

15 DR. PFEIFER: We wouldn't argue with that. We
16 are aware that us USEPA is working on the methodology to
17 look at that. In a minute we'll be talking about time
18 frames by which we hope to achieve some of these
19 discussion papers.

20 DR. BLANC: Where would it fit into these nine
21 discussion papers is what Craig is asking.

22 DR. PFEIFER: Well, what I'm saying is we're not
23 at this point in time going to be looking at that because
24 it's another huge area.

25 Now, if we can accomplish this project, what

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1 we've proposed here, I think it would be tremendous. And
2 we can subsequently look into these other areas,
3 different routes, aggregate as it's called, cumulative --
4 being exposed to more than one organophosphate -- but I
5 think our working group looked at the task ahead of us
6 and felt in order to do this justice we need to focus on
7 these main issues just related to cholinesterase
8 inhibition. We all know of the importance of the issue
9 of cumulative or combined exposures.

10 DR. FROINES: Go ahead.

11 DR. FAN: That concludes the outline. I think
12 we have the next slide showing members on the work group.
13 This is a joint project between OEHHA and DPR. So some
14 members from OEHHA are listed here on this slide and the
15 second one shows work group members from DPR.

16 So at this point we have assigned about 15
17 scientists to work on this project.

18 DR. FUCALORO: May I see the other list? I
19 don't know people here. PHMO means what?

20 DR. FAN: Public Medical Health Officer.

21 DR. FUCALORO: Do you have someone who is a
22 specialist in statistics? Is that necessary? I often
23 wonder about that seeing these things.

24 DR. PFEIFER: Not specifically, no.

25 DR. FROINES: I would actually broaden that and

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1 say is there somebody who has expertise in study design
2 as well as statistics because study design is really the
3 conceptual issue.

4 DR. BLANC: Why is the OEHHA staff all
5 toxicologists and none of them epidemiologists or is PHMO
6 person an epidemiologist? Who is going to look at the
7 human data? So you have one epidemiologist and 12
8 toxicologists doing this or 15 toxicologists.

9 DR. FAN: I don't remember the positions or the
10 titles of the other members from DPR.

11 DR. PFEIFER: There's no epidemiologists there.

12 DR. BLANC: I'm just trying to trouble shoot for
13 you because if you come to this panel with a document
14 which has been completely dominated by a toxicological
15 world view and does not have any
16 epidemiologic/biostatistical world view represented, I
17 think that it will fair less smoothly.

18 DR. FAN: We can add on as needed. These are
19 formal members who regularly participate. We often draw
20 resources from other members, epidemiologists,
21 statisticians on an as-needed basis. So if it's your
22 recommendation, we could include it.

23 DR. BLANC: Let me ask it in a different way.
24 What can we do to help make sure that the resources that
25 you need to be mobilized for you to do this project as a

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1 group are mobilized for you?

2 DR. PFEIFER: I think we've mobilized a lot of
3 people. The next area that I wanted to get into, maybe I
4 could explain kind of how we're going to review these.

5 DR. FROINES: I'd rather you went to the time
6 line now.

7 DR. PFEIFER: Okay.

8 DR. FROINES: I think that I have in a sense an
9 opposite view of Paul in that respect because I could ask
10 the question differently. I would -- from a risk
11 assessment policy standpoint, I want to know why we have
12 to develop an encyclopedia. I think we could approach it
13 by defining the five important questions and coming up
14 with answers to them and doing it in a short period of
15 time.

16 So I'm interested in how do we operate in a
17 timely way versus how do we deal with this problem as
18 though we were writing the Tora.

19 DR. BLANC: That just comes down from on high.
20 You don't have to write that.

21 (Laughter)

22 DR. PFEIFER: Dr. Froines, I can just briefly
23 answer Dr. Blanc rather than go through our outline that
24 was the next slide.

25 We fully intend through the development and

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1 review process to pull in people in our agency that have
2 expertise in certain areas as Anna Fan just mentioned.
3 So I think we know, and then just briefly at the bottom
4 there it's our proposal to have this -- these guidelines
5 out for review by the experts that are so determined
6 later in the process.

7 But anyway, I'll -- Caroline, why don't you put
8 up the time line. I won't go through each one of these,
9 but I can tell that you every one of these bullets here,
10 including the last one which is today, have been
11 achieved. Our work group has met four times since the
12 beginning of January and we're meeting again this
13 Thursday. We're planning on meeting every two weeks
14 until this project comes to some finality.

15 DR. FUCALORO: And who are the SRP members?

16 DR. PFEIFER: I was just going to mention that.
17 I would like to thank Dr. Blanc and Dr. Byus and
18 Dr. Witschi for becoming the SRP leads and will be
19 interacting with the work group on this project.

20 DR. WITSCHI: We were commanded.

21 (Laughter)

22 DR. FUCALORO: I had a feeling. I know what
23 volunteer means.

24 DR. PFEIFER: And we certainly welcome their
25 suggestions and input into this whole process.

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1 DR. FROINES: You can always decline. It's a
2 voluntary process.

3 DR. PFEIFER: And incidentally just in passing,
4 the second bullet on that first slide was begin writing
5 and reviewing draft discussion papers. The first topic

6 about the review of cholinesterase and the USEPA policy
7 was drafted last week and it will be presented and
8 discussed at our upcoming meeting this Thursday.

9 Our proposal for the second quarter, April
10 through June, finish writing the discussion papers,
11 present the draft discussion papers to our work group,
12 involve the SRP leads as they feel that they want to be
13 involved as far as the development and review of these,
14 and then in some as yet to be determined way present our
15 progress to the full SRP, whether it's in this type of
16 form that we're doing today or because of tight
17 scheduling and future SRP meetings it can -- the leads
18 can just provide an update, whatever will work out
19 subsequently.

20 Then the third quarter, basically again a
21 continuation and finalization of the discussion papers,
22 and in the third quarter we help to initiate the
23 development of guidelines for the cholinesterase
24 inhibition project.

25 In the fourth quarter, finalizing the discussion

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1 papers, development of the guidelines, and then our
2 mission, goal is to finalize these guidelines in some
3 form and present those to the entire SRP.

4 So needless to say it's a very ambitious project

5 but I think we've gotten a good start. I think everybody
6 involved from DPR and OEHHA are committed to doing a good
7 job. I think the product at the end of this process will
8 be one that will stand up to outside scrutiny.

9 DR. FROINES: So it's a year long process.

10 DR. PFEIFER: That's kind of the way it came
11 out. I know there was discussion in December about
12 getting this done earlier, particularly because of the
13 organophosphate workshop that was held, and I think that
14 would have been preferable from everybody's standpoint.
15 But as the work group got together and started scoping
16 out all these issues and the complexities involved, I
17 think things just kind of started falling into this
18 year-long activity.

19 DR. FROINES: Well, I'll tell you my concern. I
20 don't know how many LP compounds are going to come before
21 this panel in the next -- between now and the end of the
22 year. Two?

23 DR. PFEIFER: Azinphos (phonetic) and
24 chlorpirophos (phonetic) are the two.

25 DR. FROINES: I think chlorpirophos is an

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1 important compound.

2 DR. PFEIFER: Now, whether that comes this year
3 based on the scheduling --

4 DR. FROINES: See, I'm concerned about that
5 because this is the encyclopedia of cholinesterase
6 inhibition and that's all well and good, but you've got
7 15 scientists who then have their time taken up to some
8 extent in a way that prevents or limits in any case their
9 ability to develop documents for this panel to review to
10 deal with real organophosphate pesticides.

11 So I'm a little concerned that the danger is
12 that we end up doing this and the process of addressing
13 pesticides basically is impacted by that. I don't think
14 that's a good -- it may not be a perfect decision.

15 I think that the other thing is that at one
16 point Paul Blanc at a meeting some -- at least a year ago
17 developed a pesticide cholinesterase inhibition policy
18 himself and said that as far as he was concerned,
19 every -- any inhibition of cholinesterase represented an
20 adverse effect, and that policy is at least the stated
21 policy of this committee, although I don't entirely agree
22 with it.

23 DR. FUCALORO: Byus supported that.

24 DR. FROINES: That certainly was easily done.
25 So we have a contradiction; don't we? We have a

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1 contradiction that we could define a series of questions
2 which is what -- how do you want to deal with various

3 cholinesterase inhibitions and select it and go ahead.

4 We could be done by the end of this meeting.

5 On the other hand, we're going to spend a year
6 going through this in ultimate detail and it's not clear
7 to me that a regulatory agency should be spending all
8 that time. This might be something that you would give
9 to a university to develop broad guidelines.

10 By using 15 staff people from the regulatory
11 agency and OEHHA, I'm not sure that this is the most
12 efficient process that we should undertake. So I think
13 it's a little disturbing, frankly. I think it's very
14 well meaning and I applaud you for that, but I'm also
15 concerned about it as a process.

16 You could put two or three academic scientists
17 on contract and have them develop a document like this.
18 It happens all the time. So whether or not this is the
19 best way to do this and go about this, I'm not sure.

20 DR. FUCALORO: May I ask? There were roughly 15
21 names. I don't remember. There were probably more than
22 15 names.

23 DR. FROINES: Well, 15 names plus they have to
24 deal with epidemiology, plus they have to deal with
25 statistics. It's 25 names when you're all finished.

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1 DR. FUCALORO: All working full-time for a year?

2 DR. PFEIFER: No. That's one of the reasons it
3 got spread out is because people will be working on
4 specific issues and not all the issues. They have to
5 review what the other work group people wrote but they're
6 not working on --

7 DR. FUCALORO: How many toxicologists do you
8 have on staff? Is that a meaningful question?

9 DR. PFEIFER: Doing risk assessment right now?

10 DR. FUCALORO: Yeah.

11 DR. PFEIFER: There's ten in my group.

12 DR. GLANTZ: I was sort of struck with the same
13 point John was that this seemed all very good but an
14 awful lot of it. I notice that you prioritized these
15 things and it looked reasonable to me.

16 The question is in terms of decision making and
17 policy making, do we really need to go through all nine
18 of these things before you can get anything useful out
19 the other end?

20 MR. GOSSELIN: Let me if I can -- may I respond
21 to some of the points?

22 DR. FUCALORO: Don't start by saying may I
23 respond to some of the points. You might get an answer.
24 Go ahead. I'm sorry. Just kidding, Paul.

25 MR. GOSSELIN: I think to a great extent that's

1 something we've been thinking about too is staffing-wise
2 and resource-wise devoted to this project for both staffs
3 of the work we have to do. And I'll tell you, that's
4 something that I have to live with every day on producing
5 and making sure we're getting what we're legally mandated
6 to do.

7 But I think also the issue about the
8 expectations from the discussion at the OP workshop and
9 the form this document has might be something for
10 probably the leads to sit down with the staff as probably
11 the first order of business. And if this is sort of
12 overshooting sort of the scope of -- essentially it's a
13 communication piece for the panel and the agencies to
14 some of the -- how the science is looked at for a
15 cholinesterase inhibition.

16 If it's getting too voluminous for the
17 expectation that we need to conduct our business, then
18 maybe it can be scaled back. Typically we end up finding
19 that -- not in this setting but in a lot of settings --
20 usually our efforts because of these resource
21 implications come up short. So it might be easy to scale
22 those back and refine down to some of the format that --
23 and some of the priority topics that might be the most
24 important.

25 Maybe the way it was described in some of the

1 questions and then in a narrative as to the guidance,
2 maybe the discussion papers might turn into the product
3 that the panel would ultimately be looking for. But I
4 would suggest maybe as the next step the leads and maybe
5 a course of action to take a look at what staff went
6 through on this and maybe to scale back and prioritize
7 something that's workable.

8 But in the end because after the -- we complete
9 this and the panel -- we all reach agreement on this
10 thing, one, we don't want it to have something that's
11 vague and unclear. And also it is probably going to be
12 looked at outside the borders of this state as being very
13 important. So that's what I think the heightened
14 interest among the staff in putting a lot of effort into
15 it was taken under.

16 DR. FROINES: I don't see -- if you took the
17 workshop transcript -- Eleanor, do we have all the
18 overheads from the workshop.

19 UNIDENTIFIED SPEAKER: Still trying to get
20 Stephanie Padilla's overheads, but we have most of the
21 materials and there's a lot to work from from the
22 transcript itself.

23 DR. FROINES: Maybe you've already done this,
24 but I would have sat down. In fact, Eleanor and I are
25 going to do this. We were going to sit down and write

1 out what are three, five, ten questions that emerged from
2 that workshop that we think are important.

3 Then the question comes is what does it take to
4 answer those questions from a policy standpoint for risk
5 assessment. In other words, it seemed to me that we had
6 a workshop, and then as a basis of that we wanted to
7 develop a focused answer to some of the obvious
8 questions.

9 And the questions, let's face it, there are a
10 huge number of questions but there are some big questions
11 and a lot of little questions which isn't to say that the
12 analytical questions are little in terms of their
13 potential significance, but it's different than whether
14 you use blood plasma or neuro cholinesterase inhibition,
15 for example.

16 There are some bigger questions and there's some
17 littler questions, and one can prioritize some of the
18 issues from a policy standpoint. We're talking about
19 policy, the mix of policy and science. And clearly the
20 policy questions relate to the science, but they're also
21 a little bit different in some respects. So --

22 DR. BLANC: Maybe the solution to this would be
23 to have the format of this, of the working topics rather
24 than be discussion papers, to be more on the format and
25 length of what would typically be in the text of a

1 findings from this group so that -- write it as if you
2 were writing findings for us that would be essentially
3 flushed out bullets but not discussion papers.

4 You may need to do some internal discussion
5 within your groups to be able to agree on that, and maybe
6 the way to do that is you've said that number one was
7 already written essentially in draft form, and maybe the
8 thing to do is see how -- and perhaps working with the
9 two leads, seeing how that working paper, number one,
10 could be distilled into bullet findings and then this
11 whole thing could perhaps be telescoped instead of into a
12 year into three or four months so by the beginning of the
13 summer we had a series of sort of recommended policy
14 findings based on the -- both the presentations at the
15 workshop and other supplemental scientific literature.

16 For example, if you have both brain and blood
17 cholinesterase available from the same species or
18 equivalent species, it would be preferred to use blood
19 cholinesterase in hazard assessment. I'm not saying
20 that's what you would say, but a-la that rather than
21 having a whole big discussion of there were 13 papers
22 summarizing the entire literature, developing a
23 250-page --

24 DR. PFEIFER: I guess the question I would have
25 if I were outside looking at that as a scientist is

1 what's your basis for that?

2 DR. BLANC: You could give the references.

3 Reference, citations.

4 DR. PFEIFER: Just the references or not a
5 written justification, rationale for doing that?

6 DR. BLANC: Well, you could --

7 DR. PFEIFER: Because there's a lot of
8 references out there, some good, some okay, some
9 terrible. So --

10 DR. BLANC: I don't know. I don't know if it
11 would work. Maybe the way to try it is with this first
12 chapter and see how that could be. It was just a
13 thought.

14 DR. PFEIFER: The first one is the easy one.

15 DR. FUCALORO: Paul, are you making your
16 suggestion because you want it easier to read or easier
17 to do for them?

18 DR. BLANC: I thought it could telescope the
19 time and increase the utility and not do -- you know, if
20 Dr. Froines was feeling that this had sort of grown into
21 something that was too overblown, that would be
22 self-defeating to produce.

23 DR. FAN: If we do not have a technical support
24 document, we may be suffering from the same as the EPA
25 policy document whereby we already hear criticism that it

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1 doesn't have the support for the statements they're
2 making.

3 DR. BLANC: Okay. Fine.

4 DR. FUCALORO: But I'm suggesting, though, for
5 readability, of course, a good executive summary that
6 outlines things and draws conclusions right up front and
7 then a technical document of some detail and here's what
8 you're discussing would be behind it. I don't know.

9 DR. PFEIFER: We would have an executive summary
10 that would be focused on specific issues.

11 DR. BLANC: I was trying to address Dr. Froines'
12 concerns about sort of waylaying the regulatory apparatus
13 while this thing goes on, but --

14 DR. PFEIFER: To answer Dr. Froines' question
15 about -- I do have other people in my group that are
16 working on organophosphate that aren't directly involved
17 in this work group.

18 DR. FROINES: Between now and next March 1st,
19 how many organophosphates or other pesticides will come
20 to this panel?

21 DR. PFEIFER: Let me answer that by saying that
22 the limiting factor in bringing these before the panel a
23 lot of times is the scheduling for the SRP meetings and
24 the agendas.

25

DR. FROINES: No, that's not true. It may be

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1 that the document you prepared may not get to the panel
2 in terms of the panel scheduling it, but the document
3 being ready to go to the panel has nothing to do with the
4 scheduling of the panel. I object to that.

5 DR. PFEIFER: We can reschedule the order that
6 we -- that if the focus wants to be on organophosphates,
7 we can reschedule the priority for presentation.

8 DR. FROINES: I'm asking a specific question.
9 Between now and next March, how many organophosphates
10 will come -- how many pesticides will come before this
11 panel?

12 MR. GOSSELIN: We have two in the cue. I
13 believe three.

14 DR. PFEIFER: We have molinate (phonetic),
15 chlorpirophos (phonetic), AZM phos (phonetic), and then
16 some assessment of MITC that will be kind of revised.

17 DR. BYUS: I do think that I see this document
18 as serving two purposes -- one for the panel and one for
19 your own internal education.

20 Your own internal value for your agency as well
21 as for us and for your own agency, I can see the value of
22 involving a lot of scientists and a lot of your
23 toxicologists and taking some time to do this and educate

24 your own people over time. I think that is in fact
25 valuable, and I think you have hit all the major points,

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1 some of which are easy, some of which are not easy, and
2 some of which I can also appreciate the value of having a
3 lot of justification for what you're doing given the
4 people that you have to deal with all the time.

5 DR. FROINES: But I don't agree with you because
6 DPR has been dealing with organophosphate for about how
7 many hundreds of years? It's not as though --

8 DR. BYUS: Effectively or ineffectively?

9 DR. FROINES: Priority one is writing about
10 cholinesterase. They should have that already. They
11 should take it off the shelf and be able to put it down.
12 It's not as though this issue started today. The issue
13 of cholinesterase policy has been going on for at least
14 two years in front of this panel and so that we have to
15 be careful to say yes, we're going to develop this
16 wonderfully broad-based document that covers everything.

17 Well, I'm not so sure that that is the role of
18 15 regulatory scientists in a government agency to use
19 that time which keeps them from doing real pesticides
20 that real people are exposed to, and it's not clear to me
21 that he can't give you a contract to do it and you write
22 the document and his 15 people can continue to work on

23 pesticides. It's not clear to me that this is the best
24 approach given the fact that we expect to have some
25 pesticides actually come before this panel and be

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1 addressed.

2 DR. FUCALORO: I understand it's not all --
3 they're not working full-time on it, and then give us an
4 estimate of what would be the through-put, how would the
5 through-put be increased if these people were pulled from
6 that task.

7 MR. GOSSELIN: Another way to look at it, and
8 this gets into maybe going beyond what the panel is
9 expecting for this, but you're dealing with essentially a
10 set number of work hours devoted to this. Because I
11 think collectively between the two agencies we wanted as
12 much perspective from the different scientists, that's
13 why it was broadened out to a larger group.

14 There's a bunch of different ways to cut it. I
15 agree. We're not losing sight of the fact that we have
16 continued work to do and we're trying to manage this
17 without losing or slipping our work load, and I'm pretty
18 confident that that's not going to happen.

19 Let me make another suggestion also. It sounds
20 like the panel wants or is expected to have a more
21 general policy discussion on some of the major topics,

22 and it sounds like from the time line that staff are
23 going to be able to work with the leads and get those
24 written up by the end of June, which isn't far off from
25 the next couple of months, and formatting that into a

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1 format with the leads that might maybe strike at the
2 heart of some of the issues and might get to where the
3 panel and where we're going at.

4 DR. BLANC: Let me see if I hear what you're
5 asking. What you're asking is if you could scale this
6 down in a format that administratively you could deliver
7 a document to us for our June 11th meeting, would -- how
8 much would you have to scale it down?

9 MR. GOSSELIN: Or with the leads, discussion of
10 what those discussion papers and format would look like
11 might get distilled down to something closer.

12 DR. BLANC: I think what you're hearing from our
13 Chair is that the time line is the tail wagging the dog.
14 And if a document could come forward by our June meeting,
15 we could probably live with that in terms of it not being
16 so grandiose as to put everything else out of proportion.
17 Is that --

18 DR. FUCALORO: You mean the final product by
19 June?

20 DR. BLANC: A draft document by our June

21 meeting, and which obviously we would have some comments
22 on and you would have to refine. Am I misreading?

23 DR. FROINES: No. But I also think -- you see,
24 I would have approached this issue differently than has
25 been approached because I would have said what are the

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1 precise questions that need to be addressed. What are
2 precise questions that need to be addressed, what are the
3 major policy questions, and then what are the underlying
4 technical issues that need to be addressed.

5 I would have phrased them and said what does it
6 take -- what do we need to know to be able to address the
7 primary policy questions? I think that's a shorter
8 process than what you have defined, or at least is a
9 different way of approaching it. If I had to approach
10 this question, I would have taken the workshop
11 transcript, I think Stephanie Padilla's work actually
12 defines everything quite beautifully, and we could have
13 worked from that. This way we're reinventing the wheel a
14 little bit. That's my concern.

15 So I think we should have -- in a year, Paul, I
16 think we should have more than three pesticides,
17 especially since the draft document on one of them has
18 already been written. That means you've got
19 chlorpirophos, which I assume has been almost written,

20 and so that means you've got a third one, molinate
21 (phonetic), which is a re-write from a previous document.

22 So if you look at the reality of that, azinphos
23 methyl is written, molinate (phonetic) has been written,
24 and chlorpirophos is almost written. So it seems to me
25 that the development of documents to the degree that it's

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1 inhibited by a process of this size is a problem.

2 DR. FAN: If you'll refer to the bold bullets,
3 these are the ones that we have agreed on from the last
4 meeting. What we have done since the last meeting is to
5 add on two smaller subject bullets. So if we are adding
6 too much to that which the panel has agreed on, maybe you
7 want to take a look and let us know which of these we
8 should not include then. That would scale down the scope
9 of our technical support document.

10 DR. FROINES: I'm saying you haven't defined the
11 questions that enable you to develop a risk assessment
12 policy for organophosphate pesticides or compounds that
13 inhibit cholinesterase. I don't want to lose that
14 because as far as I'm concerned, the issue of
15 organophosphates and carbonates and biocarbonates and
16 other end points besides cholinesterase inhibition is
17 what this panel was interested in, and you have in a
18 sense decided that you won't pursue the things the panel

19 was interested in.

20 I don't agree with that either. That's
21 something that -- I won't accept the idea that other end
22 points, other OP compound end points is not an important
23 topic that we put together the workshop to address. The
24 other end point was in fact the worst part of that
25 workshop, it was poorly done.

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1 But the issue is still on the table. We didn't
2 ask you to change this to cholinesterase inhibition. We
3 were clear on that. We were talking about
4 organophosphate compounds with multiple end points.

5 DR. BLANC: John, maybe one way of bridging the
6 gap would be to take one of their headings, number four
7 or number five for example, and give an example of a
8 couple of the regulatory targeted questions that would
9 come under those headings because what they're saying is
10 there's been consensus on the headings from both sides
11 they understood, and that's also consistent with what
12 you're saying. You don't have a problem with the bold
13 topic headings but how you would approach them within
14 that.

15 So if you were going to give an example of a
16 specific question rather than bullet outlines of the
17 entire topic, what would they be? Can you come up with

18 any off the cuff?

19 DR. FROINES: So look at the relative merits of
20 the different cholinesterase measures. That's the
21 fundamental question that EPA has been trying to deal
22 with all this time. That's the issue we argued about.
23 That's the question that EPA thinks is a matter of
24 concern; right? Blood versus neuro cholinesterase
25 inhibition. That's what the debate has been about; am I

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1 correct or incorrect on that? Isn't that the fundamental
2 debate?

3 DR. FAN: That is, for example, is included in
4 what we put under physiological function and tox
5 significance, the role in metabolism. That would be the
6 role of the different estorasis (phonetic).

7 DR. PFEIFER: That --

8 DR. FAN: We felt that we are addressing what
9 you are asking, but if it is not, if you would help us
10 modify that, that would be useful.

11 DR. PFEIFER: That whole bullet one or priority
12 one and then the subsequent bullets, those are some of
13 the areas that we felt based on the workshop that needed
14 to be developed and again related to organophosphates and
15 all the other compounds.

16 DR. FROINES: But I think where we're

17 disagreeing a little bit is I think that I'm approaching
18 this document as a policy statement. I think you're
19 approaching it as a scientific statement. And I'm saying
20 that you need to define the policy questions that need to
21 be answered.

22 The science is what underpins it. You're
23 approaching this in terms of -- the reason you have 15
24 toxicologists is because the conceptual framework that
25 you've defined is a conceptual framework designed by

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1 toxicologists. It is not a conceptual framework designed
2 by policy makers. I think that's the difference.

3 I think that the questions about how one
4 approaches cholinesterase inhibition in a policy context
5 is what I'm trying to say. That's the way I would start
6 out writing the questions, then I would develop the
7 science within that particular context.

8 I think that it's a reflection of a different
9 kind of organization because in the end your policy
10 statement is what the agency lives by. It's not this
11 encyclopedia of science of which at the very end you come
12 you with some conclusions. I think it's sort of a
13 different approach.

14 DR. PFEIFER: I think you're absolutely right.
15 I don't disagree at all. It was intentionally designed

16 to do that because our group felt that that would be the
17 best way to eventually formulate guidelines and then
18 eventually regulatory policy.

19 DR. BLANC: I think Dr. Froines' problem -- I
20 don't want to speak for you too much -- is the eventually
21 in that phrase.

22 DR. PFEIFFER: I understand.

23 DR. BLANC: There needs to be some way of
24 cutting through this knot, and I'm going to resuggest
25 what I suggested before which is that since you have the

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1 first piece written, you say basically it's ready in
2 draft form. You have a draft of number one done.

3 DR. PFEIFFER: We have a draft of priority one,
4 overview of cholinesterase inhibition. Again, you're
5 absolutely right. We could have taken that off the
6 shelf. It was just putting together some previous
7 statements as a way of getting our process going, of
8 getting people used to reading the documents, presenting
9 them, but that's the only one that is at that stage.

10 DR. BLANC: So since that's at that stage,
11 wouldn't it be possible to see what are the policy points
12 that would derive from that, if there are any? So at
13 least you could see if what you're suggesting could --
14 how you would translate what you've done into the format

15 that you're suggesting and whether that's workable,
16 isn't that something that could be done fairly rapidly?

17 DR. FROINES: According to the conversation, the
18 first section does deal with the principal questions.
19 That's what you said. You said that the issue of the
20 cholinesterase inhibition is dealt with in priority
21 number one. And if that's true, then one can develop a
22 policy document from number one.

23 DR. PFEIFER: Well, it gives an overview, almost
24 a textbook overview of some of the basic terminology and
25 gets into a brief presentation of what USEPA had done and

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1 some of the limitations on that.

2 DR. BYUS: You say you're going to have the
3 discussion papers done by June for all nine things, and
4 then from there you're going to develop the guidelines
5 after that. Is that --

6 DR. PFEIFER: That was just thinking ahead.

7 DR. BYUS: It seems to me that the guidelines
8 could come fairly quickly once you did all the discussion
9 papers. I don't think you need six more months to
10 develop the guidelines. I think it sounds to me like
11 you're going to get all the discussions and all the
12 science done by June and present that to everyone.

13 I assume you'll have risk inclusions from that

14 which will virtually almost set your guidelines for you.

15 DR. PFEIFER: That's what we're hoping.

16 DR. BYUS: I would hope. I don't think it's
17 going to be that bad. I still hate to disagree with you,
18 John, but I still see the educational value for your
19 agency in doing this this way. If it were me doing this,
20 I would do it the way you said, pose the questions.

21 DR. PFEIFER: I understand exactly where
22 Dr. Froines is coming from on that point.

23 DR. BYUS: I think before you come up with
24 something that you can be happy with, that you can
25 justify to people, the stakeholders, whatever you call

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1 them, and the public and other scientists, you need to go
2 through this process. You're only asking to take between
3 now and June to do it. So I -- granted you might think
4 they might already have it, but you don't. I think this
5 isn't a bad way to do it, and especially because you're
6 working with OEHHA so closely. This is an excellent,
7 excellent thing. One way to get at a knotty, difficult,
8 complex problem is to take it every two weeks meet for
9 short periods of time until you've finally got it solved.
10 And so I think that's not a bad thing to do.

11 DR. PFEIFER: Dr. Froines, I fully understand
12 your perspective on that. And as a matter of fact, at

13 times previously I thought about doing it that way, but I
14 think knowing the scientists that are involved, that they
15 would -- if the question were phrased, then all the
16 underlying support would still lead to a lot of these
17 issues and they would probably want those developed in
18 the amount of detail to support that overriding question
19 eventually anyway. Does that make sense?

20 DR. FROINES: I understand perfectly because I
21 understand -- I know how to do toxicology and I know the
22 orientation of toxicologists. I think it is also
23 ironically an interesting issue because when Paul Blanc
24 says where is the epidemiologists and you say we don't
25 really have any except for Stratton, there is a practical

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1 point about no epidemiologists and that's a simple point,
2 but there's also a conceptual point because an
3 epidemiologist actually brings a different view to the
4 problem which is more about -- I'm more oriented in that
5 direction for this paper than I am from the toxicological
6 point of view that wants to deal with every detail and
7 that the conclusions come from putting together every
8 detail.

9 You hope in the end when you've done all those
10 pieces that you're talking about that your policy
11 framework will follow from it. That's not necessarily

12 true. You may get lost in the detail, and in some
13 respects the epidemiology, to use that policy-oriented
14 person, brings a different view to it.

15 DR. BLANC: John, again we come back -- I'm
16 really having trouble translating your critique into a
17 practicable approach. So what are you suggesting happen
18 from here, between now and either our next meeting or
19 between now and our June meeting?

20 DR. FROINES: I think what should happen is --
21 Keith, I also appreciate one thing that Craig and you are
22 saying which is when this document is finished and it's
23 well done, it will form the basis for evaluating
24 compounds of the nature that we're talking about and it
25 will justify the approach that's taken to those

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1 compounds. I think that's very important because
2 pesticides is a world that can become very contentious,
3 as with all know.

4 So having a strong scientific justification for
5 the policies that you develop I think is crucial. So
6 don't misunderstand us. I fully agree with the goal and
7 some of the reasons for those goals. I think at the same
8 time I would like to see in the interim, during this
9 period of time, a shorter process go on that says what
10 are the principal policy questions that we need to

11 address and lay them out and in a sense try and define
12 where we're headed as well as engage in this process
13 which is so detailed.

14 DR. PFEIFER: Could I just say one thing about
15 Dr. Blanc's concern about epidemiologists? We -- I'm not
16 sure if the panel knows Dr. Michael O'Malley. He used to
17 work full-time in our work for Health and Safety Branch
18 when I was there part-time. He's over at UC Davis and we
19 fully intend to include him at whatever point we feel
20 appropriate to review a lot of these because quite
21 frankly, I personally rely on his expertise and opinion
22 on particularly cholinesterase because he has such
23 extensive background and experience working out in the
24 field.

25 DR. BLANC: Well, what I would suggest as being

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1 the most effective way then of making sure that the other
2 thing happens in terms of the policy that we need to get
3 addressed gets addressed in this document is that if the
4 findings from -- the summary findings of the workshop
5 which you had already -- which you already have sort of a
6 brief set of sort of findings; isn't that right? That we
7 agreed to. Wasn't there a letter or summary or
8 memorandum that followed up on the workshop that
9 represented sort of our view?

10 DR. FROINES: But we had every intention of --
11 Eleanor was going to develop a short version of that.

12 DR. BLANC: Well, I think that if we as a panel
13 had seven to ten policy questions that we sort of send
14 back to them as you are developing your document, here
15 are the ten questions which we anticipate you will be
16 addressing in the targeted way, then at least that would
17 set the agenda and then there couldn't be a way in which
18 there could be some miscommunication about what it is we
19 wanted answered by this document.

20 Would that be -- and you could bring that to us
21 for feedback. It should basically summarize the
22 principal questions that arose from the workshop.

23 DR. FROINES: I'll agree with that. Let me put
24 it -- that means that we will take on that responsibility.

25 DR. BLANC: Yeah.

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1 DR. FROINES: Mainly myself, Eleanor and since
2 you're suggesting it, you. We've already assigned
3 Craig --

4 DR. BLANC: I understand.

5 DR. FROINES: -- and everybody else here today.
6 So we might as well give ourselves some work to do.

7 DR. BLANC: And that would be transmitted from
8 the panel to OEHHA and the pesticide people as here are

9 our questions and make sure that these get answered in
10 your document.

11 DR. FAN: That would be helpful. It seems like
12 there is one critical point that needs to be clarified
13 maybe in the process of getting the questions from you.
14 We can get that clarified. That's OPs versus
15 cholinesterase inhibition is what you're asking for from
16 us. From the transcript from the last meeting it said
17 that to come back to the committee with a risk assessment
18 proposal for how the two state agencies would like to
19 approach cholinesterase inhibition or assessment. So
20 that was the focus that we've been working on.

21 DR. BLANC: The point is well taken. We should
22 clarify beyond if there are non-cholinesterase OP effects
23 that we want comment on, in what context, in what context
24 do we see that as a policy issue.

25 DR. FROINES: I think that's well taken, but I

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1 think it really demonstrates the fact that we don't
2 always say things as clearly as we would like to because
3 we set up a workshop of which one significant piece of it
4 was trying to get a sense of other health end points with
5 OP compounds.

6 DR. BLANC: The question may be, for example,
7 are there generic OP effects other than cholinesterase

8 inhibition that should be addressed as a group or is it
9 so heterogenous that those non-OP effects must be taken
10 on a chemical-by-chemical basis only? And if that -- the
11 policy implication is -- if the answer is the latter,
12 then in fact it has to be dealt within each document as
13 it comes forward and there's no utility to having a
14 generic review of the question.

15 If your answer is yes, there are some
16 generalizeable non-cholinesterase effects related to OPs
17 and those are related to adverse reproductive outcomes
18 that are not -- do not appear to be mediated by
19 cholinesterase, that might be all you need to say in the
20 document; is that right?

21 DR. FROINES: And in fact, that's a very good
22 way of phrasing it because obviously we're asking issues
23 of policy about cholinesterase inhibition, but the
24 workshop dealt with the scientific issues, not policy
25 issues, associated with other end points, for example,

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1 chronic irreversible OP effects or carcinogenesis or what
2 have you.

3 So on the one hand the cholinesterase is a
4 policy question that we're formulating where as the OP
5 other end points is actually a health effects evaluation
6 and --

7 DR. PFEIFER: I agree. In our documents we do
8 address other non-cholinesterase inhibition mediated
9 effects, if there's evidence of --

10 DR. BLANC: They may be some that are generic or
11 there may be none that are generic. That's all I'm
12 saying.

13 DR. FROINES: Where the policy and the
14 science -- if you're talking about carcinogenesis or
15 reproductive effects, we can actually separate those out
16 for the purposes of talking. Where it gets a little more
17 complicated is where you think -- and here I'm not
18 talking about delayed neuropathy. I'm talking about the
19 notion that OP compounds may produce axonal degeneration
20 or other chronic neurologic effects, that then -- that
21 are different that are not cholinesterase mediated.

22 And then you would have to ask the question
23 okay. What are the policy approaches to looking at those
24 kinds of questions? So you actually -- if there are
25 chronic irreversible effects, then in fact policy

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1 questions begin to arise about your evaluation, but to
2 the degree -- but at this point I still feel that we
3 don't really know the answer to the first question, let
4 alone thinking about policy.

5 DR. PFEIFER: I can tell you quite emphatically

6 that's one area we're going to address, whether it was
7 clear out of this presentation --

8 DR. BLANC: Or another question to follow up on,
9 one of the things Craig was asking about, our policy
10 question might be are the laboratory deficiencies in
11 cholinesterase measurements such that when you have
12 several studies of the same chemical, some of which have
13 negative results and some of which have positive results,
14 should the negative results be discounted because of the
15 high likelihood of false negatives.

16 DR. MILLER: That was the point of the bullets
17 about meta analysis, exactly right on that.

18 DR. BLANC: Well, you might exclude them from
19 meta analysis, in fact, rather than the implication from
20 a policy point of view that meta analysis isn't
21 appropriate because some of them are simply invalid
22 studies or if the biosys conversely if there was some
23 kind of laboratory abnormality where there is none, then
24 you would take an opposite approach. Although it sounds
25 like that's not the issue, it's really the other way

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1 around.

2 DR. FROINES: It's not just a question of
3 heterogeneity. It's actually a question of exclusion.

4 MR. GOSSELIN: It sounds like that from the nine

5 issues that were going to be flushed out by June, the
6 format of it by being posed in a question format with
7 some of the issues that are being laid out and then with
8 the issues of staff, they're going to describe
9 scientifically, kind of get to kind of the heart that you
10 would be looking at, correct.

11 DR. BYUS: I still think it isn't going to take
12 you six months to come up with the guidelines after that.
13 I would suggest that you shorten it to three months and
14 spend, I guess -- you know what I'm saying? It seems
15 like once you put this amount of effort into the
16 document, you should be able to come up with the
17 guidelines in a few months. Granted there's going to be
18 political implications to this, but at least it should be
19 pretty well done when you finish the nine bullets.
20 You're going -- you know what all the key points are.

21 MR. GOSSELIN: That's what I was going to
22 suggest.

23 DR. BYUS: And you're going to be discussing
24 them all along. So you should be able to come up with
25 these guidelines pretty quickly after you put all this

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1 effort into this document, and I would suggest you speed
2 it up, at least by the end of the summer and bring it to
3 us by then.

4 DR. FROINES: Craig is trying to get back on my
5 good side.

6 (Laughter)

7 DR. FROINES: It may take -- I do think that --
8 let's leave that question open and see how it flushes,
9 and we'll try -- obviously we'll try and push it to speed
10 up, but at the same time the other point I really want to
11 emphasize that the scientific justification for the
12 policy that emerges is one that we all want to be happy
13 with and all want to live with and all want adequately
14 justified. So I don't think we should sacrifice anywhere
15 along the line if we have -- you know, but I think we
16 should also try and make it as timely as possible which
17 is what my message is anyway.

18 DR. PFEIFER: I think it will help having
19 Dr. Witschi and Dr. Byus involved because they can give
20 the panel and their own perspective on things that we may
21 need to emphasize.

22 DR. BLANC: You say that now.

23 DR. PFEIFER: Well, what can I say. Back in
24 January we were trying to get some leads and get a little
25 guidance. So now we have it and hopefully we can move

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1 forward on it.

2 DR. FROINES: The only hesitation on the leads

3 is we've got everybody so committed on different topic
4 areas it's hard to find a lead who isn't already
5 overwhelmed. So part of our slowness is trying to figure
6 out who isn't going to come back and say I absolutely
7 won't do it because I'm already overwhelmed.

8 DR. BLANC: Paul, I know that you had hoped to
9 have on the agenda one other item which was your
10 document.

11 MR. GOSSELIN: That was informational at this
12 point.

13 DR. FUCALORO: Which document? I have all my
14 comments. I read them. When are we going to finish
15 this? Today?

16 DR. FROINES: The obvious question that comes up
17 with azinphos methyl is what's the relationship between
18 this process we've just been debating and azinphos methyl
19 so when we do take it up -- we probably won't take it up
20 in April because I think that Stan -- whatever happened
21 to Stan? He disappeared.

22 We want to talk about that issue about where how
23 azinphos methyl fits into -- and also you might spend
24 five minutes and tell us where chlorpirophos fits in too
25 because the obvious concern is we're moving ahead on

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1 documents, we're moving ahead on policy, but the two are

2 slightly disconnected through nobody's fault, just
3 through the nature of the process.

4 MR. GOSSELIN: We weren't going to go into great
5 detail on the entire document but try to give an overview
6 on the talk section, the health section, and contrast it
7 to the issues raised on the OP policy because as we move
8 forward we want to make sure that it does go ahead on
9 parallel tracks.

10 DR. FROINES: The other key question about
11 azinphos methyl to take up is that clearly in some
12 respects it's being discontinued at least in some
13 applications. So we would like you to talk about the
14 significance of the changes that are occurring at the
15 national level vis a vis the current circumstances.

16 DR. BLANC: And Paul, the FIFRA item.

17 DR. PFEIFER: That I guess we're not going to
18 get to today.

19 DR. BLANC: We should at least -- since it's
20 officially on the agenda, just to hear what the plan is
21 for how it would be handled --

22 DR. PFEIFER: In a couple previous meetings
23 there was some questions about why we focused on a FIFRA
24 guideline, so I thought it would be very good to have one
25 of our staff toxicologists, Tom Moore, who came down.

1 DR. BLANC: Where is Tom? I apologize for --

2 DR. FROINES: Paul.

3 DR. PFEIFER: He's a data review person in our
4 branch and is very familiar with FIFRA and the reason for
5 FIFRA, the limitations of FIFRA and --

6 DR. BLANC: Maybe if you could distribute to us
7 copies of his slides, Paul.

8 DR. FROINES: Paul, question. Any second now
9 Stan and Paul Blanc are leaving. That still leaves us
10 with a quorum. We could proceed and have --

11 DR. ATKINSON: I have class in a few minutes.

12 DR. FUCALORO: You have class?

13 DR. ATKINSON: Yeah.

14 DR. FROINES: I'm sorry. I was about to suggest
15 we go forward on azinphos methyl and that kills that.

16 DR. BLANC: I'm going to make a motion we
17 adjourn then. Is there a second?

18 DR. ATKINSON: Second.

19 DR. BLANC: You're the chair. You have to say
20 "all in favor."

21 DR. FROINES: All in favor? I'm sorry. I
22 really apologize for this. This is very really
23 disappointing. This won't happen again. I guarantee it.

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