

MEETING
STATE OF CALIFORNIA
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL

TOM BRADLEY INTERNATIONAL HALL
UNIVERSITY OF CALIFORNIA, LOS ANGELES
417 CHARLES E. YOUNG DRIVE, WEST
LOS ANGELES, CALIFORNIA

FRIDAY, DECEMBER 5, 2008

8:00 A.M.

LINDA KAY RIGEL, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 13196

PETERS SHORTHAND REPORTING CORPORATION (916) 362-2345

APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Stanton Glantz

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison

Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT

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

Dr. Bruce Winder, Staff Toxicologist

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

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

ALSO PRESENT

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

I N D E X
--o0o--

		Page
1	Call to Order	1
2	Continuation of the Panel's review of the draft Reference Exposure Levels for acrolein, acetaldehyde, arsenic, mercury, manganese, and formaldehyde	4
3	Continuation of the Panel's review of the draft report "Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors	38
	Adjournment	212
	Certificate of Reporter	213

--o0o--

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

2 --o0o--

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

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY : All right. We have --

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

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

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

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

16 (Laughter)

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

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: No pressure, Elinor.

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

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

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

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

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

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

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

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

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

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: I have just one question. We have the
25 Reference Exposure Levels to finish off because you

1 guys had a few questions that we researched.

2 CHAIRPERSON FROINES: Right.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: So I assume that's going to go first, and then
5 the cancer document.

6 CHAIRPERSON FROINES: Yes.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Okay.

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

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: December 5th.

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

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

23 DR. VERDER-CARLOS: Thank you, John.

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

1 for Pesticide Programs Division.

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

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

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

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

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

17 DR. VERDER-CARLOS: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 OEHHA STAFF TOXICOLOGIST WINDER: No.

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

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

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

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
12 MARTY: The handout.

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

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

25 PANEL MEMBER BLANC: Okay. So Bruce, a couple

1 things about this wording here.

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

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

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

11 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

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

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

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

25 PANEL MEMBER BLANC: Analyzing NHANES?

1 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

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

4 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

8 OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

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

12 OEHHA STAFF TOXICOLOGIST WINDER: All right.

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

15 OEHHA STAFF TOXICOLOGIST WINDER: Per se,
16 okay.

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

19 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

22 OEHHA STAFF TOXICOLOGIST WINDER: All right.

23 Any other --

24 PANEL MEMBER BLANC: Or female adolescents.

25 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

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

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

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

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

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

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

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

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

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

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

25 So even though this -- that's why this

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

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

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

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

15 PANEL MEMBER BYUS: In that analogy.

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

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

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

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

1 PANEL MEMBER BLANC: He went out to that many?

2 OEHHA STAFF TOXICOLOGIST WINDER: He did.

3 PANEL MEMBER BLANC: Okay.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: But we rounded.

6 PANEL MEMBER BLANC: Rounded from what?

7 OEHHA STAFF TOXICOLOGIST WINDER: From the

8 96.71.

9 PANEL MEMBER BLANC: All right.

10 CHAIRPERSON FROINES: Where the 97?

11 PANEL MEMBER BLANC: It says Lucchini, et al.

12 of 96.71.

13 OEHHA STAFF TOXICOLOGIST WINDER: On this

14 screen, I've rounded it to 97 for purposes of

15 presentation here.

16 PANEL MEMBER GLANTZ: I would round it in the

17 document too.

18 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. Okay.

19 CHAIRPERSON FROINES: Especially when all your

20 other numbers are rounded.

21 OEHHA STAFF TOXICOLOGIST WINDER: All right.

22 Like I said, that's what I have for the revisions to

23 the manganese document. Now I have -- if we're ready

24 to move on, I have some for formaldehyde as well.

25 CHAIRPERSON FROINES: We talked about there

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

4 And did you address that?

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

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

15 We say that the:

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

20 And we say:

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

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

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

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

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

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

21 OEHHA STAFF TOXICOLOGIST WINDER: That
22 sounds --

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

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

5 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

6 CHAIRPERSON FROINES: Do you disagree?

7 PANEL MEMBER BLANC: No.

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

13 CHAIRPERSON FROINES: Is that okay with you,
14 Melanie?

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Yes.

17 CHAIRPERSON FROINES: Melanie says yes.

18 OEHHA STAFF TOXICOLOGIST WINDER: Okay. Now
19 that --

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

22 PANEL MEMBER BLANC: Thanks.

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

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

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

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

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

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

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

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

5 OEHHA STAFF TOXICOLOGIST WINDER: Pretty much.

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

10 CHAIRPERSON FROINES: It was what?

11 OEHHA STAFF TOXICOLOGIST WINDER:

12 Unproductive.

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

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

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

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

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

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

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

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

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

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

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

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

5 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

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

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

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: We'll bring up the point.

21 CHAIRPERSON FROINES: Look at Fred Kelly's
22 work.

23 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: So there's one more thing that I wanted to

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

3 CHAIRPERSON FROINES: Frank Kelly.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: Sorry.

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

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

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

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

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

25 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

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

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

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

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

17 OEHHA STAFF TOXICOLOGIST WINDER: With a HEC
18 adjustment.

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

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

1 and 3 for toxicodynamic. Is that combined --

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: That's a typo. It should -- toxicokinetic is 2
4 with a HEC adjustment.

5 PANEL MEMBER BLANC: Right.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: That's the standard because you haven't
8 accounted for all of the kinetic factors with the HEC
9 adjustment.

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

12 PANEL MEMBER PLOPPER: Oh, okay.

13 PANEL MEMBER BLANC: Good. All right.

14 PANEL MEMBER BYUS: You earned your hundred
15 dollars.

16 (Laughter)

17 PANEL MEMBER BLANC: At least.

18 PANEL MEMBER BYUS: That's a joke.

19 (Laughter)

20 PANEL MEMBER GLANTZ: It's not a joke.

21 (Laughter)

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: So that's all we had for the RELs.

24 CHAIRPERSON FROINES: Good.

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

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

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

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

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

16 What we did was we went back to the original
17 prioritization document, which was I think finalized in
18 '01 or '02, and we looked at chemicals that didn't
19 quite make the top five.

20 PANEL MEMBER BLANC: Right.

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

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

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

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

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

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

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

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

1 the determination.

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

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

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

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

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

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

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

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

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

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

19 CHAIRPERSON FROINES: -- something that
20 somebody will read.

21 (Laughter)

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

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

1 findings of the committee.

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

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

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

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

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

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

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

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

21 (Cell phone interruption)

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Sorry.

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

1 (Laughter)

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

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

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

9 PANEL MEMBER GLANTZ: Well, let's ask.

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

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

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

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

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

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

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

9 PANEL MEMBER BLANC: The wording of the
10 findings?

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

16 PANEL MEMBER GLANTZ: Okay.

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

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

22 PANEL MEMBER BLANC: Consensus.

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

1 PANEL MEMBER GLANTZ: I'll second that.

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

4 PANEL MEMBER BLANC: Can we --

5 CHAIRPERSON FROINES: It's an important
6 molecule.

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

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

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

18 PANEL MEMBER BYUS: Higher than adults?

19 OEHHA STAFF TOXICOLOGIST WINDER: And then it
20 dropped.

21 PANEL MEMBER BYUS: Higher than children?

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

24 PANEL MEMBER PLOPPER: Yes.

25 PANEL MEMBER BYUS: Okay.

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

3 PANEL MEMBER BYUS: Shift down?

4 PANEL MEMBER PLOPPER: Shift down.

5 PANEL MEMBER BYUS: Okay.

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

11 PANEL MEMBER BYUS: Okay. Thanks.

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

16 PANEL MEMBER PLOPPER: Mm-hmm.

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

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

25 PANEL MEMBER PLOPPER: Yes.

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

3 CHAIRPERSON FROINES: Did somebody second?

4 PANEL MEMBER GLANTZ: I did.

5 CHAIRPERSON FROINES: Is there discussion?

6 All those in favor?

7 (Ayes)

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Great.

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

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

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

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

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

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Well, they do use our Reference Exposure
9 Levels. The program was set up to look at the Hot
10 Spots program --

11 CHAIRPERSON FROINES: Sure.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: -- was the stationary part of it, and so the
14 districts all use the RELs and risk assessments.

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

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

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: We've actually sent the note in the past to the
24 secretary and -- secretary of Cal/EPA -- and cc'd the
25 Air Board. And actually, I think all the other boards.

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

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

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

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

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

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

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

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

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

5 CHAIRPERSON FROINES: That's exactly my point.

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

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

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

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

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

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

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

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

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

11 (Recess)

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

17 So Stan, why don't you start off?

18 PANEL MEMBER GLANTZ: Okay. Well --

19 CHAIRPERSON FROINES: Ready, Melanie?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Yes.

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

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

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

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

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

17 Now I may change my mind based on other
18 discussions.

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

1 about.

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

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

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

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

13 PANEL MEMBER BYUS: Anyone.

14 PANEL MEMBER GLANTZ: Anyone.

15 PANEL MEMBER BYUS: Anyone.

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

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

22 CHAIRPERSON FROINES: I think you should do
23 that.

24 PANEL MEMBER GLANTZ: Okay.

25 The first thing is: Before, the document

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

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

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

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

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: Sensitivity.

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

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

1 different points early in life.

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

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

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

15 And I think that clarifies it.

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

20 CHAIRPERSON FROINES: Can I ask a question?

21 PANEL MEMBER GLANTZ: Yes, sure.

22 CHAIRPERSON FROINES: Melanie, this is a
23 question.

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

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

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

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

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

13 PANEL MEMBER GLANTZ: No -- well.

14 PANEL MEMBER BYUS: No, it's not.

15 PANEL MEMBER GLANTZ: No, it's not.

16 (Laughter)

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

19 CHAIRPERSON FROINES: Sorry.

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

22 (Laughter)

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

25 The basic idea of what they do is that they

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

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

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

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

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

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

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

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

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

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

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

1 differently.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 You guys have any questions?

12 CHAIRPERSON FROINES: Questions for Stan?

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

17 So Joe, did you want to?

18 CHAIRPERSON FROINES: Please.

19 PANEL MEMBER LANDOLPH: Yeah.

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

25 I had some reservations about the use of the

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

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

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

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

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

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

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

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

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

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

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

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

19 CHAIRPERSON FROINES: Who?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Andy Salmon.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 PANEL MEMBER LANDOLPH: No. One more
22 sentence.

23 CHAIRPERSON FROINES: No matter what Stan
24 says.

25 (Laughter)

1 PANEL MEMBER LANDOLPH: One more sentence.

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

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

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

15 So now you can ask your question.

16 CHAIRPERSON FROINES: Well --

17 PANEL MEMBER GLANTZ: He forgot what it was.

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

21 PANEL MEMBER BLANC: Just clearing my throat.

22 (Laughter)

23 PANEL MEMBER GLANTZ: What did you say?

24 PANEL MEMBER BLANC: I was just clearing my
25 throat.

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

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

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

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: I knew you would bring that up, particularly
16 since I forgot to put it in. So I do have -- it's a
17 2008 paper, I think, 2007, where they nicely summarize
18 the issues around the fact that they really aren't
19 criteria, they are not set in stone, and some of the
20 arguments around it.

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

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

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

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

15 PANEL MEMBER BLANC: No, hold on.

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

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

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

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

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

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

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

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

25 What you mean is where effects only noted

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

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Exactly.

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

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

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

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

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

1 analysis.

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

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

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

15 PANEL MEMBER BLANC: Slope or something?

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

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

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

23 CHAIRPERSON FROINES: Joe?

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

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

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

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

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

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Yeah.

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

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Those analyses have been done by tumor type,
21 but the curve is different for each tumor type.

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

25 PANEL MEMBER LANDOLPH: Any difference versus

1 age?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Versus age.

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

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: That other tumors there are.

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Not a simple thing.

13 PANEL MEMBER LANDOLPH: Yeah.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

15 MARTY: We did refer to -- on pages 32 and 33
16 briefly -- to these other evidence in humans. We could
17 expand that discussion. We had more discussion of this
18 issue in our prioritization document in 2002. We could
19 pluck more from that and put it in here if you thought
20 it was appropriate.

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

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

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

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

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

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

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: Yeah. I think we have to be careful not to
20 have an exercise in, you know --

21 PANEL MEMBER BYUS: No, but --

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: -- writing a whole another document.

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

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

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

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Well, that's --

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

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

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

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

22 PANEL MEMBER BYUS: Okay.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Could I just make one comment? The purpose of
25 the analysis was to get a default policy in place where

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

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

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

9 PANEL MEMBER BYUS: I'll comment later.

10 CHAIRPERSON FROINES: Joe?

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

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

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

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

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

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

9 PANEL MEMBER GLANTZ: Oh, yeah.

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

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

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

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

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

1 historically on other documents.

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

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

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

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

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

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

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

1 you can add to what Joe and Stan said.

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

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

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

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

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

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: Yes.

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

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

3 CHAIRPERSON FROINES: Do it as you think best.

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

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

12 PANEL MEMBER BLANC: That's fine.

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

16 CHAIRPERSON FROINES: Another question about
17 this.

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

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

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

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: I can answer that in two sentences now, if you
5 want.

6 CHAIRPERSON FROINES: Please.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: The default uncertainty factors that we chose
9 and that EPA chose are the same, and the application to
10 those in risk assessment is the same.

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

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

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

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

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

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

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

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

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Yes.

23 CHAIRPERSON FROINES: Joe?

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

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

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

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

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

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

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

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

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

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Page 48.

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

5 CHAIRPERSON FROINES: That's right.

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

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Yes.

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

12 PANEL MEMBER LANDOLPH: I would second that.

13 CHAIRPERSON FROINES: Melanie, did you hear
14 that?

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

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

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

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

25 PANEL MEMBER BLANC: I mean is it on the EPA

1 website?

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

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

6 PANEL MEMBER LANDOLPH: Yeah.

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

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

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

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

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

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

21 PANEL MEMBER BYUS: Then we'll come back.

22 CHAIRPERSON FROINES: Can we take a short
23 break?

24 PANEL MEMBER BLANC: Please.

25 (Recess)

1 CHAIRPERSON FROINES: Let's go. Naphthalene.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: What I wanted to do -- I have about eight
4 slides just running back over what John presented last
5 time, kind of hitting the highlights of what changed in
6 this document.

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

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

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

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

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

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

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

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

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

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

1 that.

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

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

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

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

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

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: It could --

25 PANEL MEMBER BLANC: -- be used.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yes.

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

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Hopefully, somewhere in here.

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

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Yeah.

11 PANEL MEMBER BLANC: -- information.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: If it's not in here, I'll make sure it's in
14 here. But I'm pretty sure it's in here.

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

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

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: For the age-specific factors, yes.

23 PANEL MEMBER LANDOLPH: Yeah.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: But we routinely use epidemiologic data for

1 risk assessment. I know we say that in here.

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

5 PANEL MEMBER GLANTZ: Yeah.

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

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

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

14 CHAIRPERSON FROINES: What's the explicit
15 statement?

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

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

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

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

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: It could be. And generally when we use epi
3 data, we have typically used different models than the
4 LMS, although we have used all of the above.

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

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

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

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

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

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

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Yeah.

25 When we do a chemical-specific assessment,

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

5 PANEL MEMBER PLOPPER: Mm-hmm.

6 PANEL MEMBER BLANC: Okay.

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

9 PANEL MEMBER BYUS: I have a related question.
10 So if you used epidemiology data, would you
11 then use -- oh; sorry -- would you then apply the age
12 sensitivity factors for children, if the epidemiology
13 data was not generated in children?

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: Yeah.

16 PANEL MEMBER BYUS: Okay.

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

19 PANEL MEMBER BYUS: That's fine.

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

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

1 exposure occurred as children.

2 So there is a great human example.

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

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

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

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

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

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

25 The second point is that young animals and

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

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

9 PANEL MEMBER BLANC: Could you --

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: -- being adult, mature.

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

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

18 PANEL MEMBER BLANC: Yes.

19 PANEL MEMBER GLANTZ: So that's --

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

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Okay.

2 CHAIRPERSON FROINES: In what?

3 PANEL MEMBER BLANC: In the immunologic sense.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Okay.

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

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

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

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

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

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

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

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Close, right.

2 PANEL MEMBER LANDOLPH: Yeah.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: And we will apply these factors, as I mentioned
5 earlier, to all carcinogens except where there's
6 contrary evidence and regardless of the purported
7 mechanism of action.

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

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

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

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

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

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Yeah. We actually --

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: -- are leaving that a little open-ended.

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

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

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

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: We could do that. And also, we left it open

1 for case-by-case analyses.

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

5 PANEL MEMBER BLANC: Mm-hmm.

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

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

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

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

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

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

1 to take that into consideration on a quantitative
2 basis.

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

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

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

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Okay.

21 CHAIRPERSON FROINES: Yeah, but --

22 PANEL MEMBER BLANC: Algebraically.

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

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

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

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Yeah, that's fine.

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Okay. That's --

13 (Blank slide displayed)

14 PANEL MEMBER BLANC: I like that slide.

15 (Laughter)

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: That's all I was going to talk about.

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

23 And I wanted to let Martha start on her
24 slides.

25 I could talk about the response to comments

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

3 CHAIRPERSON FROINES: It's your call.

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

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Okay. We did --

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Oh, gosh, yes. Thank you.

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

15 I just want to explain what this was about.

16 And the way I read the document --

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

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

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

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

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

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

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

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

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Okay. And then there was the other handout

24 I --

25 PANEL MEMBER GLANTZ: Although the e-mails

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

5 (Laughter)

6 PANEL MEMBER BLANC: And the other handout?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: The other handout, I asked staff to give me a
9 few examples of risk assessments that OEHHA had already
10 conducted which compares the slope factors derived with
11 the benchmark dose and the linearized multistage.

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

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

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

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: We view them as the same numbers.

1 PANEL MEMBER LANDOLPH: -- to me. Yeah.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: If you use two different models, and you get
4 within a factor of 2 or 3, it's pretty good for risk
5 assessment.

6 We got comments basically from four
7 individuals, organizations.

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

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

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

22 They also thought that --

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

1 Did I misunderstand what you said?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Well, they typically start when the animals are
4 somewhere between six and eight weeks old for the
5 traditional bioassay.

6 PANEL MEMBER BLANC: Uh-huh.

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

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

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Actually, they're sexually mature animals. You
15 generally get them after they've been weaned and then
16 acclimated to your laboratory.

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

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

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: It might be equivalent to older teenagers.

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

1 use an age adjustment.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Right.

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

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

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: So then they also had in their comments that
10 the data were insufficient to say that there was
11 increased sensitivity for early lifestages because it's
12 only based on a subset of all the carcinogens.

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

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

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

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

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: Yeah.

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

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

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

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

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

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

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

4 So that's it in a nutshell.

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

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Uh-oh.

10 (Laughter)

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

13 CHAIRPERSON FROINES: I never say that.

14 (Laughter)

15 CHAIRPERSON FROINES: Is it Martha?

16 DR. SANDY: Yes.

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

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

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

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

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

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

14 And then some conclusions.

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

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

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

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

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

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

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

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

19 Because I think it's really an important
20 difference.

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

25 However, we do in the facility-specific risk

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

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

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

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

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

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

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

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yeah, it's pretty hard --

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

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

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

15 But I think you need to make it clear.

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

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Yeah. On page 50, we do have a statement and a
22 table showing what it looks like if you're going to do
23 the typical Air Toxics Hot Spots Program nine year
24 scenario. But --

25 PANEL MEMBER BYUS: What I'm getting at:

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

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Yeah.

8 PANEL MEMBER BYUS: Okay.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: We definitely do that.

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

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: A little more specific in here.

15 PANEL MEMBER BYUS: Yeah.

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

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: We actually did at the last meeting.

1 PANEL MEMBER BYUS: Okay.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: And I debated putting that second slide in, and
4 I didn't. So I probably should have. We did have that
5 in the last set of slides.

6 PANEL MEMBER BLANC: Is it in the document?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: It's in the document.

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

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Yeah, it's on page 50 --

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

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: Okay.

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

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Yeah.

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

1 difficult to answer because the slope factors --

2 PANEL MEMBER BYUS: I know.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: -- are based on chronic exposure.

5 PANEL MEMBER BYUS: That's the point.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Yeah.

8 PANEL MEMBER BYUS: So if you think it can be

9 used for short-term, then you should say so.

10 But if you don't, then don't say that it can't

11 be used for it, but say what you intended it to be used

12 for.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Okay.

15 PANEL MEMBER BYUS: And that's your decision,

16 really.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: Yeah.

19 CHAIRPERSON FROINES: But I think it's very

20 clear -- very important to make clear that there are

21 different agendas that you are pursuing, that you don't

22 want to turn this into every chemical we have to look

23 and see how long a person was exposed to it.

24 We need to have policy considerations drive

25 this as well as short-term exposure issues. Otherwise,

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

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

8 PANEL MEMBER BYUS: I don't disagree.

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

13 PANEL MEMBER BLANC: Also, the proportionate
14 impact --

15 PANEL MEMBER BYUS: Yes.

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

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

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Exactly.

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

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

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

7 PANEL MEMBER BLANC: Oh.

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

10 PANEL MEMBER BLANC: Sorry.

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

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

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

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

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

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

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

25 We considered human data and decided we didn't

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

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

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

14 CHAIRPERSON FROINES: Martha?

15 DR. SANDY: Yes?

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

18 DR. SANDY: Yes. Yes.

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

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

1 longer -- is sexually mature at ten weeks.

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

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

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

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

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

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

1 sense of the inherent susceptibility of the postnatal
2 lifestage.

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

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

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

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

25 PANEL MEMBER BYUS: As clarification, your

1 tumor response: Is it tumor multiplicity or tumor
2 incidence?

3 DR. SANDY: Incidence.

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

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

8 PANEL MEMBER BYUS: So it's incidence.

9 DR. SANDY: Incidence.

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

15 DR. SANDY: This is just incidence.

16 PANEL MEMBER BYUS: Incidence. Okay.

17 DR. SANDY: Number of animals with tumors.

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

20 DR. SANDY: Yes.

21 PANEL MEMBER BYUS: Okay.

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

25 CHAIRPERSON FROINES: It could change, which

1 tumors you're looking at.

2 DR. SANDY: Yes.

3 PANEL MEMBER BYUS: Okay.

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

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

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

16 DR. SANDY: Yes.

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

19 DR. SANDY: No.

20 PANEL MEMBER PLOPPER: -- they die.

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

25 PANEL MEMBER PLOPPER: Okay.

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

4 CHAIRPERSON FROINES: So you are saying --

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

6 CHAIRPERSON FROINES: -- duration is about the
7 same.

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

11 DR. SANDY: Right.

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

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

16 PANEL MEMBER PLOPPER: Okay. Great. All
17 right.

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

22 PANEL MEMBER PLOPPER: Okay.

23 DR. SANDY: Okay.

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

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

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

9 And we focus on the linear term which is q_1 ,
10 the slope parameter. It's representing potency. And
11 we compare the slope. So this is just reminding you of
12 where the q_1 s are. It's the slope that we calculate.
13 And we do a comparison.

14 And instead of focusing on a point estimate,
15 as Dr. Glantz was saying, we have actually come up with
16 a distribution of the value of q_1 . And this is just to
17 represent that.

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

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

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

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

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

15 So that was my question.

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

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

25 PANEL MEMBER BYUS: But --

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

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

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

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

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

22 DR. SANDY: That's --

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

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

5 DR. SANDY: Mm-hmm.

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

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

11 DR. SANDY: Mm-hmm.

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

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

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

24 DR. SANDY: Mm-hmm.

25 PANEL MEMBER BYUS: Am I making myself clear?

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

3 DR. SANDY: I think so.

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

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

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

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

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

21 PANEL MEMBER BYUS: I know, I know.

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

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

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

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

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

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

18 DR. SANDY: Okay.

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

1 multiple experiments in a study.

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

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

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

15 DR. SANDY: Yes.

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

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

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

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

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

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

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

18 CHAIRPERSON FROINES: That's interesting.

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

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

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

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

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

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

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

20 DR. SANDY: Mm-hmm.

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

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

6 Thanks for the comment.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Sure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 mixture distribution to get one representative
2 distribution across these chemicals.

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

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

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

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

19 PANEL MEMBER GLANTZ: Oh, good.

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

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

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

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Okay.

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

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

9 DR. SANDY: No. No.

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

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

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

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

19 PANEL MEMBER BYUS: Okay.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Sorry.

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

25 So for the single lifestage exposure

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

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

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

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

16 DR. SANDY: Correct.

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

19 DR. SANDY: Okay. Thank you.

20 PANEL MEMBER BYUS: It gets to the control.

21 DR. SANDY: Yeah.

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

24 DR. SANDY: Okay.

25 So we do have these examples in the document

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

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

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

17 And we have the same for the postnatal LPJ
18 ratio.

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

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

1 susceptibility.

2 So here we have a graph of -- it's a
3 cumulative frequency profile of each of the prenatal
4 multi-lifestage exposure studies ordered by the ASF
5 distribution.

6 So we have 22 different studies, and you can
7 see that some animals -- or some experiments, some
8 carcinogens, there is less sensitivity because they're
9 below the value of 1.

10 If something is 1, an ASF of 1, that means
11 there's equal sensitivity between the prenatal
12 lifestage and the adult and many experiments with
13 different chemicals where the ASF is greater than 1.

14 And here's where we have this cumulative
15 mixture distribution, both for the LP ratio which is
16 the line on the left --

17 CHAIRPERSON FROINES: What page is that last
18 slide from?

19 DR. SANDY: Just give me a second here. It is
20 on page --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Page 43 in the --

23 DR. SANDY: No, 45.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: -- main, and it's also in the appendix.

1 DR. SANDY: It's on page 39 in the Appendix J.

2 CHAIRPERSON FROINES: No, but in the text.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Page 43.

5 CHAIRPERSON FROINES: 43? It looks like 45 to
6 me.

7 PANEL MEMBER PLOPPER: There's two of them.

8 PANEL MEMBER BLANC: Go to the first part.

9 You're too far back. Go to the first section where
10 there's another page 43.

11 DR. SANDY: John, are you asking about this
12 slide right here?

13 CHAIRPERSON FROINES: No, the previous one.

14 DR. SANDY: The previous one. So that's
15 figure number 7 in the TSD, page 43.

16 CHAIRPERSON FROINES: The only reason I'm
17 asking is I just want to make sure that in the document
18 itself that it's readable because I can't read the
19 slide.

20 DR. SANDY: I know. And because the document
21 is in revision mode, it's --

22 PANEL MEMBER BLANC: It's smaller.

23 DR. SANDY: The print is much smaller.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: We could -- I see now. We could make this

1 figure bigger and put the legend on the next page.

2 That would help a lot.

3 CHAIRPERSON FROINES: Just as a general
4 matter, this stuff is complicated, as you know, so you
5 want to make sure that people can actually see what
6 they need to read. And it may be my age, but it
7 probably is not.

8 DR. SANDY: It's also having it in revision
9 mode that makes it -- shrinks it.

10 PANEL MEMBER BLANC: It's smaller.

11 CHAIRPERSON FROINES: Yeah. I just want to
12 make sure that everybody can read it that needs, wants
13 to read it.

14 PANEL MEMBER GLANTZ: All copies of the
15 document will be distributed with a magnifying glass.

16 (Laughter)

17 DR. SANDY: Now in Appendix J, it may be a
18 little easier to read. And that's -- this figure is on
19 page 39.

20 CHAIRPERSON FROINES: That's okay. You
21 answered my question. I don't want to prolong it.

22 DR. SANDY: Okay.

23 So back to this slide that's up. This shows
24 the cumulative LP ratio and ASF mixture distributions
25 for the prenatal experiments, and we've shown you where

1 the mean and median of the ASF mixture distributions
2 fall for the prenatal studies.

3 Okay. And here we have the postnatal ASF
4 cumulative frequency distribution. We have 55 studies
5 on here, and I know it's impossible to read.

6 In Appendix J, it may be a little more
7 readable. We also have presented it, as you saw it at
8 the last meeting, grouping the studies by chemical.
9 And you'll see there is variability, even among a
10 chemical such as EMU or benzidine that, depending
11 upon -- oftentimes, it's either gender differences or
12 the time of exposure within a given lifestage.

13 So if we go back to the prenatal, just a
14 second -- going forward -- the prenatal lifestage
15 window, you know, the sensitivity, we're looking at a
16 certain group of carcinogens here. You can see that
17 some of them, the ASF factor is a hundred, and some of
18 them is less than one. There is a great range of
19 variability.

20 And for some chemicals that require some
21 metabolic activation and are not long-lived enough to
22 be activated by the mom and get to the baby, those
23 enzymes in the in utero period may only be coming up in
24 the last couple days before birth.

25 So if the dosing occurred early in gestation,

1 then you're not going to see an effect. If it occurs
2 at the last couple days of gestation, then you may see
3 effects. And so that's how we have some variability.

4 PANEL MEMBER BLANC: And so this point about
5 chemicals which have more than one study or not only
6 being weighted as one, only being weighted once?

7 DR. SANDY: Each chemical is weighted equally
8 in our -- in coming up with our cumulative
9 distribution.

10 PANEL MEMBER BLANC: Right, so since like, for
11 example, benzidine or safrole will appear twice here.

12 How exactly -- and you're showing something
13 which wouldn't weight something -- which weights
14 something disproportionately because you're showing a
15 distribution -- maybe I don't understand what you mean.

16 If a chemical could only contribute -- I'm
17 sorry. If a chemical could only contribute its weight
18 once, and you're looking at a frequency distribution
19 and the median value of all of the observations, isn't
20 the chemical contributing its observation twice?

21 DR. SANDY: No. In this particular graph, we
22 haven't done any weighting. We've only just plotted
23 each of the studies for you in the cumulative frequency
24 profile.

25 PANEL MEMBER BLANC: But then, if you go on to

1 your next slide --

2 DR. SANDY: And as we go to the next one, this
3 one, we have weighted those two studies in safrole.
4 Those two studies got equal weight to the five studies
5 on ENU.

6 We weighted each chemical equally. So we have
7 22 -- or, sorry -- we have 22 studies, and we have 14
8 chemicals. We've weighted each chemical equally, and
9 for those --

10 PANEL MEMBER BLANC: Can you translate
11 "weighted" --

12 DR. SANDY: Okay.

13 PANEL MEMBER BLANC: -- into what you mean --

14 DR. SANDY: Yes.

15 PANEL MEMBER BLANC: -- because I could think
16 of a mathematical way of weighting it. I could think
17 of taking the average or the median value of the five
18 studies and using that as a single point in your
19 cumulative thing.

20 DR. SANDY: I should say that we sampled from
21 the distributions equally.

22 Here. Let me go back to the methods, and
23 hopefully this will help clarify this. To develop, for
24 example, the LP ratio mixture distribution, if you go
25 to that second -- well, the first bullet says we

1 have -- each chemical's equally likely to be sampled.

2 So we have all these distributions, and we're
3 equally likely to sample from a distribution, you know,
4 chemical X --

5 PANEL MEMBER BLANC: Okay.

6 DR. SANDY: -- we'll sample from one
7 distribution. Chemical Y, one distribution.

8 PANEL MEMBER BLANC: Yeah.

9 DR. SANDY: We'll take one sample. We'll do
10 that repeatedly but equally sampling from each
11 chemical.

12 But when you have multiple studies for a
13 chemical, we have an intermediate step where we create
14 a single LP ratio distribution for that chemical.

15 PANEL MEMBER BLANC: Well, then, why isn't
16 your -- why have the chemical appear more than once in
17 your cumulative chart? Why not just show us what its
18 distribution is for that chemical for the one time? I
19 mean it's very misleading.

20 DR. SANDY: I was asked by Dr. Glantz, and
21 Cathy Koshland liked it. They wanted to see, could you
22 please order these?

23 PANEL MEMBER GLANTZ: Yeah, the idea --
24 remember that the idea here is to just get a sense of
25 what the distribution of values is. And so some of the

1 studies were in males, and some were in females, for
2 example, and --

3 PANEL MEMBER PLOPPER: Different species too.

4 DR. SANDY: That's right.

5 PANEL MEMBER GLANTZ: And different species.

6 And remember, what they're trying to do here is come up
7 with a default value, not a value for a chemical.

8 PANEL MEMBER PLOPPER: So the idea is to just
9 sample all of these and --

10 PANEL MEMBER GLANTZ: Right.

11 PANEL MEMBER PLOPPER: -- try to understand
12 what would be the most protective default is what
13 you're saying.

14 PANEL MEMBER GLANTZ: Well, or not necessarily
15 the most protective, but some percentile in the
16 distribution. I mean you don't have a random sample of
17 chemicals here.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: So -- but to answer Paul's question, this
20 cumulative frequency profile is before they have
21 created the mixture distribution.

22 PANEL MEMBER GLANTZ: Right.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: So this is the individual studies that had a
25 prenatal component. And you'll see that some chemicals

1 appear more than once because there are different
2 studies. They haven't yet created the single
3 distribution to use in the mixture distribution.

4 PANEL MEMBER GLANTZ: Right.

5 The reason we did this, if you go back and
6 look at the earlier draft, there was a presentation of
7 the things ordered by chemical. And it just looked
8 random, and I found that hideously confusing. That is
9 still in the report in the appendix.

10 And I just think, in order to get some sense
11 of kind of what was -- you know, was the ASF bigger
12 than 1 or less than 1 most of the time in most of the
13 studies? That was the idea of this.

14 And what this is showing you is that if you
15 just look at all of the studies without their sampling
16 thing that, you know, there were some that actually it
17 seemed -- that the chemical seemed to be protective in
18 a few.

19 But in most of them, most of the studies
20 showed a ratio above 1, and it was, you know, and the
21 median was around 10 or whatever it is from this chart.

22 That's all that this is trying to do.

23 Then the next graph that they want to show
24 you -- I think it was the next slide -- is when they go
25 back and they weight all the chemicals equally by

1 randomly selecting one value for each chemical.

2 PANEL MEMBER BLANC: Okay. That may very well
3 be, but if you look at the way figure 8 is presented --

4 PANEL MEMBER GLANTZ: Which one was figure 8?
5 The other one?

6 PANEL MEMBER BLANC: They're all similar.

7 DR. SANDY: In the technical support document.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: This is figure 8. It's the postnatal.

10 PANEL MEMBER BLANC: Look at this. Okay.
11 There is the unweighted, raw observations.

12 PANEL MEMBER GLANTZ: Right.

13 PANEL MEMBER BLANC: Right, with a 50 percent
14 line drawn, a dotted line, at a value of 10.

15 PANEL MEMBER GLANTZ: Okay.

16 PANEL MEMBER BLANC: And with a notation, the
17 dotted line represents a default ASF for weighting risk
18 for carcinogen exposure between birth and two years of
19 age, see next section.

20 So I'm not saying you not have this figure,
21 but I think that you could make it a bit more explicit
22 in the title of the figure or in the legend of the
23 figure that this is unweighted.

24 Because it -- otherwise, why are you
25 showing -- if I just look at this, I see the 50 percent

1 median cutoff, and you're giving the value that you
2 eventually arrived at.

3 I mean you could see why it's confusing.

4 PANEL MEMBER BYUS: I wouldn't show the
5 50 percent value at all.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: It's not a 50 percent value.

8 PANEL MEMBER BYUS: It's meaningless.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: It's not -- all we did here was show you the
11 default, where the default lies.

12 PANEL MEMBER BLANC: Eventual default.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Right.

15 PANEL MEMBER BLANC: Which you haven't come to
16 yet, which you're going to come to in the future, after
17 weighting.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: Right. Of course, we were asked to put this
20 in.

21 PANEL MEMBER GLANTZ: I actually thought it
22 was helpful to put it in.

23 PANEL MEMBER BLANC: I'm not saying -- all I'm
24 saying --

25 PANEL MEMBER GLANTZ: All he's saying -- he's

1 not saying take it out. He's just saying explain it a
2 little bit better. That's all.

3 PANEL MEMBER BLANC: Well, you could even just
4 put the words postnatal ASF cumulative frequency
5 profile prior to weighting by chemical or without
6 weighting by chemical. Or something, you know, just to
7 make it clear that you're about to --

8 PANEL MEMBER GLANTZ: The reason I asked them
9 to put the dotted line on there was to show you that
10 all the weighting doesn't really change things very
11 much. But I think what he's suggesting is a good point
12 of clarification.

13 PANEL MEMBER BLANC: Don't change the figure.
14 Just change -- add a word or two to the title and a
15 word or two to the legend so that --

16 PANEL MEMBER GLANTZ: I think that's a good
17 idea.

18 PANEL MEMBER BLANC: The old -- you know the
19 old schtick about the figure should stand on its own,
20 blah, blah, blah.

21 PANEL MEMBER GLANTZ: Yeah.

22 CHAIRPERSON FROINES: I think that's actually
23 very important because what you need is, whether it be
24 lengthy or brief, but needs to be -- you need to be
25 able to understand it on its face.

1 PANEL MEMBER GLANTZ: Right. I think this
2 will clarify it. I think that's fine.

3 I mean I was the one who proposed to put the
4 dotted line in.

5 CHAIRPERSON FROINES: Otherwise the reader
6 doesn't know what to take from the chart.

7 The question is: What do you want -- what are
8 you trying to tell the reader? And that's where -- and
9 if you're giving different messages --

10 PANEL MEMBER GLANTZ: I think --

11 CHAIRPERSON FROINES: -- at different times --
12 let me just --

13 PANEL MEMBER GLANTZ: Okay.

14 CHAIRPERSON FROINES: And to the degree that
15 there are mixed messages, or rather that you want them
16 to take different notions away, it just needs to be
17 specific.

18 PANEL MEMBER GLANTZ: Well, no, I don't --
19 actually, I don't think there are mixed messages.

20 CHAIRPERSON FROINES: Right. That was a poor
21 use of --

22 PANEL MEMBER GLANTZ: Okay.

23 I think that the point -- the reason I asked
24 them to put the dotted line on was to make the point
25 that if you just look at the raw studies, and if you

1 do -- then do their fancy weighting, you get about the
2 same answer.

3 PANEL MEMBER BLANC: And I wouldn't be opposed
4 to the footer saying the reader will note that even
5 prior to weighting that the value comes out similar.

6 PANEL MEMBER GLANTZ: Actually, the dotted
7 line is the weighted estimate.

8 PANEL MEMBER BLANC: But it's coming very
9 close to the 50 percent cutoff.

10 PANEL MEMBER GLANTZ: Right. That's the
11 point.

12 PANEL MEMBER BLANC: So you could certainly
13 say that if you wanted to.

14 PANEL MEMBER BYUS: Do you know what I get
15 from reading this figure? I look at it, and what it
16 looks to me, what I get out of it is there's an
17 enormous variation in values, particularly for things
18 like DEN.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: Yes.

21 PANEL MEMBER BYUS: Enormous variation. So I
22 start to think, per chemical there's an enormous
23 variation. And -- particularly for certain chemicals.

24 So then I begin to wonder about the accuracy
25 of the method in what you're doing because if you look

1 at DEN, for example, on this figure 8, it goes all the
2 way from -- I don't know if this is a log scale, but if
3 you look at the top versions are over a hundred all the
4 way down to less than one.

5 So I don't know how -- so even though you
6 mathematically weight these studies, they're so
7 variable that I would wonder --

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: That's --

10 PANEL MEMBER BYUS: I mean if I were
11 criticizing this method -- say I was hired by
12 someplace, which I'm not; that was a joke -- that's
13 what I would say.

14 STAFF TOXICOLOGIST TOMAR: I would like to
15 make a point about DEN and ENU. Because DEN requires
16 metabolism. And the enzyme start around day 18 of
17 gestation, and this process is complete on day 30, and
18 we have seen what time is the exposure. Day one is
19 different than day 15. Day -- gestation day 16 is
20 different than 17 and 18 and 19 and 20.

21 ENU on the contrary does not -- it's simply
22 hydrolyzed. There, it depends on how good the DNA
23 mechanism is made.

24 CHAIRPERSON FROINES: I completely agree with
25 everything you just said. I think it's very helpful in

1 terms of clarifying Craig's remarks.

2 I would suggest that maybe, without -- if it
3 doesn't take too much work, to put a couple of case
4 studies, a couple of tables in where these issues --
5 that is, metabolism and the differences between species
6 are -- where you actually use the example and suggest
7 this -- some of these characteristics may be the basis
8 of the variability.

9 So that a reader who's pretty dumb can
10 actually look at something and understand with a clear
11 example of why there may be the variability. Because
12 otherwise, it's left to their imagination.

13 STAFF TOXICOLOGIST TOMAR: I that think once
14 Dr. Sandy started talking about DNA studies, it all
15 will become clear. But since the question came, I
16 thought --

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: We do have those case studies there right now
19 in Appendix J, and we can easily take these same kind
20 of figures and move them up into the main body of the
21 report.

22 CHAIRPERSON FROINES: Don't you think that
23 would be helpful? It would be helpful for me because
24 the word metabolism, you know, grabbed me, and all of a
25 sudden I thought to myself, oh, I know about that.

1 DR. SANDY: And in Appendix J, in addition to
2 these figures, we left in, as Stan mentioned, the other
3 box spots we showed you where you want to -- you guys
4 want to find a pattern.

5 But for us, we look at it and say, oh, because
6 it tells us the sex. It tells us the strain and the
7 species. There are differences, and the dosing window
8 too. So that's in the figure legend. We'll -- those
9 are the clues that may explain some of the variability.

10 CHAIRPERSON FROINES: Well, there are some
11 slight -- you know, I mean Stan's a statistician; I'm a
12 toxicologist. And so the way I look at it is a just a
13 little different than what he understands.

14 So I am just trying to make sure that we both
15 understand pretty much --

16 PANEL MEMBER GLANTZ: Right, but I think -- I
17 mean we spent a lot of time talking about this when I
18 met with them.

19 Because when I looked at the figure presented
20 the other way, where they were grouped by chemical, I
21 kept trying to figure -- and they had all the different
22 shapes, symbols, and colors and all that -- I was
23 looking at that, trying to figure out exactly what
24 you're asking about.

25 And really pressed them on why do we see these

1 differences, and why is this -- I mean they had a few
2 things, like the one you just heard where people had
3 some idea; but for a lot of it, it's like we don't
4 know. This is -- this is just variability that exists
5 that nobody quite knows why it's there.

6 CHAIRPERSON FROINES: Yeah, but --

7 PANEL MEMBER GLANTZ: Wait, let me finish.

8 Let me finish.

9 CHAIRPERSON FROINES: So -- I'm sorry. I'm
10 sorry.

11 PANEL MEMBER GLANTZ: And so the point is, and
12 the reason I wanted it presented this way, is because
13 this emphasizes the variability. Okay?

14 And that there is this variability, and that
15 is what then leads you to, you know, saying okay, we're
16 taking this default value when we can't explain all
17 this other stuff.

18 Because when you can explain all the other
19 stuff, then you're down to doing a chemical-specific
20 analysis.

21 CHAIRPERSON FROINES: But I just would say one
22 thing, and everybody else, I think, wants to talk.

23 All I would say is the -- having a study like
24 he's talking about, which is already in there, and a
25 conclusion that says we don't know, I'm perfectly happy

1 with that "we don't know" because that illustrates the
2 complexity of the issues we're dealing with.

3 So anyway, who else wanted to comment?

4 PANEL MEMBER BLANC: I just want to suggest
5 that we speed up and finish these slides so that our
6 transcriptionist can take a break, and we can take a
7 break, because clearly we're not -- clearly there's a
8 discussion to be had, but I want -- it's 20 to 12:00.
9 If you could finish.

10 CHAIRPERSON FROINES: Melanie, and -- we just
11 need to --

12 DR. SANDY: We're almost done.

13 CHAIRPERSON FROINES: How long do you think it
14 will take to get through these slides now?

15 PANEL MEMBER BYUS: If everybody is quiet.

16 (Laughter)

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: If everybody is quiet, Martha says five to six
19 minutes.

20 CHAIRPERSON FROINES: Okay, because --

21 PANEL MEMBER GLANTZ: In other words, three
22 hours.

23 CHAIRPERSON FROINES: Then we want to break
24 and come back for general discussion. But I have to
25 teach at 2:00 which means I have to leave here at 1:30.

1 And I would like us to come to a vote --

2 PANEL MEMBER GLANTZ: We can.

3 CHAIRPERSON FROINES: -- about that.

4 PANEL MEMBER GLANTZ: We can. So we'll all be
5 quiet for five to six minutes. We'll take a pool on
6 how long John will stay quiet.

7 DR. SANDY: One last point.

8 What this slide tells me -- I know there
9 are -- there's variability among -- for the same
10 chemical in different experiments. But the majority of
11 the experiments are showing that there's enhanced
12 sensitivity when exposure occurs postnatally. And
13 whether it's by a factor of 7 or a factor of 17, there
14 is increased variability.

15 So we also have the juvenile. We had fewer
16 studies. These are plotted as the others were, and
17 that dotted line is just the default factor.

18 That is 3, to show where that is.

19 And there's the cumulative LP ratio and ASF
20 mixture distributions and the mean and median of the
21 ASF.

22 PANEL MEMBER BLANC: So why -- I have to ask
23 this question. Why is it 4.5 and not 3?

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Because the -- I think there is some confusion.

1 The default ASFs are a policy choice. And we have some
2 discussion in the document.

3 What Martha is showing you is what the data
4 that we have are telling you about where the median and
5 mean lie in their mixture distribution.

6 PANEL MEMBER BLANC: So for one it's 10;
7 that's coincidence. And for the other it's 3.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Actually --

10 DR. SANDY: It wasn't --

11 PANEL MEMBER GLANTZ: The 10 is actually --
12 the median is 13 in that case.

13 PANEL MEMBER BLANC: Okay. Thank you.

14 DR. SANDY: So to summarize these results, we
15 have studies with 23 carcinogens, 20 of which act
16 primarily via genotoxic mechanisms, and 15 of those
17 require metabolic activation.

18 We see that carcinogens vary in age
19 susceptibility, and there is variability among studies
20 of the same carcinogen. We talked about this quite a
21 bit.

22 And it has to do with timing of exposure
23 within a lifestage. There's gender differences and
24 strain differences and species differences and other
25 differences we're sure of that we haven't

1 characterized.

2 Here, this is a different table than what
3 Melanie's shown you, the same idea. We have one
4 column, no adjustment for ASF.

5 So this is what we do, with no adjustment, ASF
6 of 0 for in utero and 1 for each of the other
7 lifestages, and you -- with our example here, you've
8 got a risk of 1 in 10 to the minus 4.

9 If we take the 50th percentile from our
10 analysis for each of those lifestages, so you have an
11 ASF of 3 for in utero, 13 for birth to 2 years, 5 for 2
12 to 16 years, and 1 for the remainder of life, you get
13 2.2 times 10 to the minus 4.

14 So it's -- you're increasing your cancer risk
15 estimate by a factor of 2.2 if you use the 50th
16 percentile.

17 If you use the 70th percentile from our
18 analysis for each of these lifestages, it increases by
19 a factor of 3. If you go up to the 95th percentile,
20 it's a factor of 16.

21 So this just shows you some of the ranges. So
22 we're not presenting the policy. We're presenting what
23 our analysis showed.

24 PANEL MEMBER BLANC: Is this table in your
25 document?

1 DR. SANDY: Yes, it is. It's in the Executive
2 Summary, and it's also in --

3 PANEL MEMBER BLANC: I suggest you change it
4 from 1.6 to 10 to the 3rd to 16 to 10 to the 4th so
5 that somebody can follow that because, believe me,
6 people are not going to catch that. Too subtle.

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

9 DR. SANDY: I'll do that. Thank you.

10 Then I can present the results of the case
11 studies very briefly, and Dr. Tomar can answer any
12 questions you have.

13 Here, for DEN, we plotted the potencies and --
14 the distribution of the potencies for each of the
15 studies. And we have grouped them by experiments where
16 the exposure occurred during the prenatal lifestage,
17 the postnatal, and the juvenile.

18 And then we created LPJ ratios which we're
19 showing here. The green is for the prenatal LPJ ratio,
20 so prenatal to juvenile. And the postnatal to
21 juvenile.

22 So you'll see that the prenatal, based on the
23 data sets we have, looked like they're much less
24 sensitive than adults to DEN.

25 But as Dr. Tomar just mentioned, DEN requires

1 metabolic activation, and many of these prenatal
2 studies, exposures occurred early in gestation when
3 there's no enzyme to activate DEN and that's why you're
4 not seeing any effect.

5 But a few of them, you do start to see an
6 effect because the exposure occurred in the last couple
7 of days of gestation when the enzyme is just starting
8 to come up.

9 So what can we conclude? Well, animals
10 exposed to DEN in utero are considerably less sensitive
11 than those exposed as juveniles based on this analysis,
12 and animals exposed to DEN during the postnatal period
13 are significantly more sensitive than those exposed as
14 juveniles.

15 We did the same thing for ENUs, so here are
16 the potency distributions for ENU with the different
17 lifestages. ENU does not requires metabolic
18 activation.

19 These LPJ ratio mixture cumulative
20 distributions look very similar. The postnatal one,
21 prenatal, when they're graphed like this, equal
22 sensitivity.

23 But when you actually look at the
24 distributions a little more closely, you see in the
25 second bullet here that the prenatal exposure's

1 associated with greater sensitivity to ENU than
2 postnatal exposure over all. But both lifestages are
3 sensitive.

4 So we conclude that early lifestages are
5 generally more sensitive than the adult lifestage to
6 carcinogens; and in the absence of chemical-specific
7 data, age-specific adjustments to potency are
8 justified, and that age-specific adjustment may vary
9 with lifestage.

10 Thank you.

11 CHAIRPERSON FROINES: Thank you. Great.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Time for a break?

14 PANEL MEMBER GLANTZ: Do you want to take a
15 break, or do you want to keep going?

16 PANEL MEMBER BLANC: Yeah, what about our --

17 PANEL MEMBER GLANTZ: Oh.

18 CHAIRPERSON FROINES: Should we break for
19 lunch at this point?

20 PANEL MEMBER BYUS: If you want to get done by
21 1:30, why don't we just take a break and not break for
22 lunch?

23 PANEL MEMBER BLANC: We can bring our food
24 back.

25 PANEL MEMBER BYUS: Oh, okay.

1 PANEL MEMBER BLANC: Let's take a 15-minute
2 break, bring our food back to the table, and start
3 again.

4 (Recess)

5 CHAIRPERSON FROINES: So we're going to start
6 again.

7 And the way we outlined it in the beginning
8 was at this point we're going to give the two Leads the
9 opportunity to say anything further they want to say
10 before we open it to the rest of the panel.

11 PANEL MEMBER GLANTZ: I don't have anything
12 else to say.

13 PANEL MEMBER LANDOLPH: Just a short comment.

14 In your page 35, where you talk about the NTP
15 bioassay, you might just want to add a short sentence
16 there stating if you use the NTP bioassay for risk
17 assessment alone, you can miss the prenatal, the
18 postnatal, and the juvenile stage.

19 So those are actually underestimates which
20 then gives you even more justification to use these
21 adjustment factors.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Okay.

24 CHAIRPERSON FROINES: I'm sorry. Peter was
25 talking to me.

1 PANEL MEMBER LANDOLPH: If you use the MTBE
2 bioassay, which starts about week 6 to 8 which is just
3 at the end of the juvenile or just at the beginning of
4 the adult, you miss the exposure for the juvenile and
5 the postnatal, so any calculations made using that are
6 underestimates because you don't have that early life
7 exposure, so this is even more justified.

8 CHAIRPERSON FROINES: Do you want to raise
9 your point now?

10 PANEL MEMBER BLANC: First Craig, I think, was
11 in line. No?

12 PANEL MEMBER BYUS: Well, I'm -- I started out
13 being highly skeptical, and now I'm completely
14 convinced of the quality and the excellence of this
15 approach.

16 So I think Leads and you all did a wonderful
17 job since improving the readability -- it was never in
18 the methods; it was just the readability of trying to
19 understand it. It is very complicated.

20 And again, I would just emphasize that you
21 state clearly what the purpose of the analysis is.
22 Because I think it's very important whether the overall
23 lifetime exposure, short-term exposure, what you really
24 want to use it for.

25 Because you're doing the analysis, and so even

1 though the numbers -- this may be used for other
2 purposes, you need to state clearly what in your mind
3 it's best used for.

4 And if there's limitations, you should perhaps
5 state that. But clearly, why -- what you think it
6 could be used for the most.

7 I'm particularly concerned about long-term
8 exposure versus short-term. Because the data was
9 really generated from the animal short-term exposures.
10 It wasn't generated --

11 STAFF TOXICOLOGIST TOMAR: Not all of them.

12 PANEL MEMBER BYUS: Not all. But the majority
13 of it from long-term exposure. And there may be some
14 mechanistic distance in terms of sensitivities is all
15 I'm saying.

16 And my only other comment would be the smoking
17 data with humans. I still think there has got to be --
18 now again, I don't know whether it is directly -- it is
19 in fact applicable and analogous with your radiation
20 experiment showing marked increase in sensitivity, if
21 there is, for human population, something that's very
22 large numbers.

23 I can't probably think of anything else
24 more -- with a bigger data set than that.

25 But other than that, I think it's very well

1 done, and I think it's not just clever but it's very
2 good science, and obviously lot of thought went into
3 it.

4 PANEL MEMBER BLANC: All right.

5 CHAIRPERSON FROINES: Paul?

6 PANEL MEMBER BLANC: I have a biological
7 question.

8 Day zero to day 21 in the small rodents from
9 which your data are based would be the equivalent of
10 what age period in the human?

11 STAFF TOXICOLOGIST TOMAR: That's the million
12 dollar question. Not too many people have answer for
13 that, but I'll try.

14 You have to divide the whole gestation
15 proportionately to rat or mice. But the thing is, the
16 different organs' still different in human.

17 PANEL MEMBER BLANC: Well, I'm not talking
18 about just gestation. I'm talking about from birth to
19 day 21, and day 22 to day 49.

20 STAFF TOXICOLOGIST TOMAR: That would be, in
21 my best guess -- there's no real data -- would be up to
22 10 or 12 years, and then from teens, from 12 to 18 or
23 12 to 21.

24 CHAIRPERSON FROINES: 0 to 21 days.

25 PANEL MEMBER BLANC: Like from birth to age 12

1 or so.

2 CHAIRPERSON FROINES: Is what -- at what human
3 age?

4 PANEL MEMBER BLANC: You just said 0 to 12,
5 didn't you?

6 STAFF TOXICOLOGIST TOMAR: Proportionately
7 because it's very difficult to --

8 PANEL MEMBER BLANC: Roughly.

9 DR. SANDY: I think what we're looking --
10 we've looked at -- sorry -- is the functionality.

11 So day 21 is the age of weaning, and we're
12 thinking -- I think this is in humans up to age 2 of --
13 for end of weaning time.

14 It's sort of what EPA has done. It's a
15 general assumption that you could -- that period when
16 the animal is still drinking milk.

17 CHAIRPERSON FROINES: So postnatal and 0 to 2
18 in humans.

19 DR. SANDY: That's what we have applied.

20 PANEL MEMBER BLANC: And adolescent is from --
21 and juvenile humans are from age 3 to age 16?

22 DR. SANDY: Yeah. That's what we've --

23 PANEL MEMBER BLANC: Well, I have to say that
24 that at face value is -- completely flies in the face
25 of what any sort of lay reader, but let's just say

1 anybody else would think reading the thing.

2 And I have to say that as I heard the
3 presentation I was completely flummoxed as to how you
4 could -- if you're talking about 40 percent of the
5 lifespan of the animal up to adulthood is 0 to 21 over
6 0 to 49, like 40 percent, right?

7 So unless there's something very biologically
8 strange about rodents -- maybe there is; I don't know.
9 But this age of weaning is only one -- is only
10 one thing.

11 I mean actually children in very primitive
12 societies may actually be nursed quite a bit beyond
13 two. I mean what in primate -- you're a primate guy,
14 aren't you?

15 PANEL MEMBER PLOPPER: Mm-hmm.

16 PANEL MEMBER BLANC: How -- what is the
17 primate weaning age?

18 PANEL MEMBER PLOPPER: Well, it's done
19 experimentally, just like it is for --

20 PANEL MEMBER BLANC: In the wild.

21 PANEL MEMBER PLOPPER: So it's usually six
22 months, six months of age.

23 PANEL MEMBER BLANC: In the wild?

24 PANEL MEMBER PLOPPER: Oh, in the wild? No,
25 that could go on for years. I mean that's sometimes

1 even what would be considered juvenile or young adults
2 in some species are still nursing, so.

3 PANEL MEMBER BLANC: Uh-huh.

4 PANEL MEMBER PLOPPER: It's like humans. I
5 mean, some places it's a long time. Sometimes it's a
6 short time.

7 PANEL MEMBER BLANC: So I have to say that I
8 don't want throw a monkey wrench in your entire edifice
9 here. That's a mixed metaphor, but this two-year --

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: 25 cents.

12 PANEL MEMBER BLANC: You know, up to two years
13 and then 3 years to 16.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

15 MARTY: Yeah. I know.

16 It's entirely a policy call to how you want to
17 use those weighting factors. And there is not a nice
18 little chart that says at day 22 that's equivalent to
19 whatever age in a human. It's very difficult, and in
20 fact it might even go by organ system rather than just
21 the whole animal.

22 So, you know, I know what you're saying. And
23 there is not an easy way to deal with it, and that's
24 why we just decided to do a step function: Zero to 2,
25 we're weighting by 10; 2 to 16, we're weighting by 3;

1 and above that, we're weighting by 1.

2 PANEL MEMBER BLANC: But you're asking us as a
3 Scientific Review Panel to say that the science behind
4 that finding is -- meets --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
6 MARTY: I think we're asking you to say the science
7 behind assuming there is increased sensitivity by use
8 of these default weighting factors, that the science
9 behind that is -- justifies using a --

10 PANEL MEMBER BLANC: Some type of weighting
11 factor, yes. But obviously that's not -- our finding,
12 doesn't our finding have to go beyond that?

13 You're actually proposing numbers, and you're
14 proposing ages to apply them. Is that not part of your
15 document?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: But it's a policy call. So, you know, if you
18 want to comment on the policy call, that's fine; you
19 can do that. It's okay with me.

20 But it is a policy call.

21 PANEL MEMBER BLANC: What's the science behind
22 the policy?

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: The science is that exposures early in life --

25 PANEL MEMBER BLANC: No, no.

1 What's the science behind using a two-year
2 human equivalent?

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Well, there's not. I just said there wasn't.

5 There's not a perfect answer to that. There's
6 not a perfect way to apply the uncertainty factors and
7 decide what number to use.

8 So that is why we said, okay, if there's
9 infants and toddlers up to two, that, you know, clearly
10 those are pretty early postnatal. So let's use that
11 10X for that age group.

12 Then we wanted to encompass puberty somehow,
13 so we went up to 16.

14 CHAIRPERSON FROINES: But your actual numbers
15 that you come up with -- the 13.16, I think it is, or
16 something like that -- is not 10.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: That's right. It's not 10 because 10 is a
19 policy call. 13 is a median of the weight that the
20 data were analyzed.

21 And we also discuss in there that it's not
22 easy to take a number from that data analysis in part
23 because of the limitations in the data themselves.

24 PANEL MEMBER BLANC: And if your median had
25 been 7, would you then have chosen the value of 10

1 because that was a policy decision?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: We may have, yes.

4 DR. SANDY: You may wonder, do you want to
5 pick the median? Do you want to pick something else?

6 PANEL MEMBER BLANC: Well, why did you
7 emphasize the median so much if you weren't going to
8 use it?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: We didn't really emphasis it. We just showed
11 it as part of the distributional analysis.

12 The little thing that you were looking at was
13 the policy call. And it -- maybe it shouldn't be in
14 that graph. But it was because we were asked to put it
15 in there.

16 PANEL MEMBER BLANC: No, no, okay. But I'm
17 trying to -- you see the position you're putting me in,
18 a little bit, which is you're asking me, on the one
19 hand, to approve -- to say use the best science, and I
20 want to echo the other comments that were made. I
21 think it's a very diligent, creative, and important
22 approach that you took.

23 And at the same time, you're asking the panel
24 to say and then when you get to a certain point in the
25 document, don't think about science; that's policy.

1 And you can either like the policy or not like the
2 policy.

3 That to me is very different than other things
4 we've been asked to comment on where it has seemed
5 less -- your whole effort has been usually to avoid the
6 substance or appearance of being arbitrary in a way.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
8 MARTY: Well, it's somewhat analogous to uncertainty
9 factors. Why do we pick half logs and logs?

10 Because there's a lot of uncertainty, yet we
11 know that there are these differences that need to be
12 accounted for. If you can't account for them with
13 data, you have to do something.

14 PANEL MEMBER BLANC: No, but you've also given
15 us good rationales for this is what standard we'll use,
16 this is what others have used, that if you use this you
17 get values which seem to make sense with observable
18 data.

19 I mean I think you're not doing yourself
20 justice. You've actually given us quite cogent
21 arguments why you used the uncertainty factors that
22 you've used.

23 PANEL MEMBER GLANTZ: Well, I think -- I mean
24 here's what I would suggest you do.

25 First of all, I think to say 13.16 is

1 ridiculous. I think -- I mean the way I interpreted it
2 is they rounded things off to one significant digit,
3 you know. If you take 13 and round it off to one
4 significant digit, given the uncertainties that --

5 PANEL MEMBER BLANC: Then why doesn't 3 round
6 to 0 or 1?

7 PANEL MEMBER GLANTZ: Well, I'm just telling
8 you the way I --

9 PANEL MEMBER LANDOLPH: Well, 3's kind of a
10 half a log of ten.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
12 MARTY: Exactly.

13 PANEL MEMBER LANDOLPH: That's justified.

14 And I agree with Stan. I mean the 13, I would
15 say given the uncertainty, which stands a couple orders
16 of magnitude for one chemical, 13, you might as well
17 drop to 10. It's reasonable. I could support that.

18 CHAIRPERSON FROINES: But I think, just to
19 support Paul on this, this notion of 0 to 2 as this
20 weaning period in humans, and then 3 to 16 relative to
21 the animal data leads you to -- it's -- it is a policy
22 decision to make those determinations. It's not
23 science.

24 PANEL MEMBER GLANTZ: Well, I think that
25 there's two different issues --

1 CHAIRPERSON FROINES: And I think what the
2 question becomes, Stan, that how is this going to be
3 phrased in the document?

4 Because do we really think that 0 to 2 and 3
5 to 16, you know, leads you to where you end up? And
6 that's -- or how does it lead you to where you end up?
7 It can't be argued on the basis of some scientific
8 merit, I think.

9 PANEL MEMBER GLANTZ: Well, I think that
10 there's two different issues that are getting mixed up
11 here that I think need to be treated separately.

12 One issue is: Why did you pick 10 instead of
13 13.28734? Okay? And I think that we've given you what
14 you can say. You know, the median is 10; given the
15 uncertainties, we're picking something to one
16 significant digit, the half log.

17 I think that's -- if you take your pre and
18 postnatal and juvenile periods that you presented, I
19 think you can very logically argue why you picked the
20 numbers you picked. That's one question.

21 Paul's raising a different question really,
22 which is: Why did you call -- you took juvenile rodent
23 studies, and how do you come to the ages that you
24 correspond those to humans?

25 So those are really two different -- the why

1 you use 10, I don't think that's problematic.

2 I do think this other thing, you know, he's
3 raising a good point. This is an area where I, you
4 know, just assumed there was a good logic for it
5 because it's not something I know.

6 But, you know, are you saying that there is
7 nothing in the literature that gives you some, you
8 know, rationale for why you -- you know, what you would
9 call a juvenile period in a human versus a rat?

10 PANEL MEMBER PLOPPER: I think what Melanie
11 said exactly what the problem is, is that there is
12 plenty of those sorts of comparisons for different
13 organ systems. And the problem is nobody has done it
14 for the whole organism.

15 And what I was going to suggest is that -- I
16 mean you've already got this very sophisticated
17 statistical expertise -- is to try to accumulate the
18 four or five -- obviously the two most important organ
19 systems would be respiratory system and nervous system.
20 That's where you focused most of the rationale so far.

21 And there's also one for lymphatic system,
22 whole lymphoid system, and try to come up with a
23 derivation based on what those -- the target organs
24 that you think are important for doing these analyses
25 and making these susceptibility measurements and look

1 at what's there.

2 I mean the one I know -- I've published four
3 or five for the respiratory system that compare all
4 kinds of species. They're all over the place. They're
5 in all the reviews.

6 So that -- and it's not -- and it's been used
7 -- it turns out that brain, nervous system in general,
8 respiratory system, and lymphatic system have almost
9 the same time frame. So it might be easy to do it that
10 way.

11 In fact, the same regulator's apparently
12 involved in postnatal developmental growth issues in
13 all three organ systems, and the time frame is almost
14 the same.

15 So maybe that would be -- and it's not that
16 far off of what you've got, but I would be picking
17 different time points knowing what happens with those
18 target systems.

19 That would be my suggestion. Then you don't
20 have this argument because you've already made the
21 argument you're going to use nervous system and
22 respiratory --

23 PANEL MEMBER BLANC: I think you're confusing
24 the noncancer health effects. I wouldn't necessarily
25 say here these are brain tumors and lung tumors.

1 PANEL MEMBER PLOPPER: Well, that's -- I'm
2 just giving this as an example. And I would suspect
3 that if you identified the three or four organ systems
4 that are the main tumor targets, that you'll find those
5 for those. That would seem to me to be a better --

6 PANEL MEMBER BYUS: Use that as a rationale.
7 I think that's an excellent idea.

8 PANEL MEMBER PLOPPER: Yeah.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: Okay.

11 CHAIRPERSON FROINES: Melanie?

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: There is some logic to that.

14 Here is part of the issue, that again we have
15 a subset of carcinogens people focused on back in the
16 '70s and '80s, these sort of prototype carcinogens,
17 so --

18 DR. SANDY: '60s and '70s.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Or '60s and '70s.

21 So in terms of what tissues these particular
22 subset of carcinogens target is not necessarily
23 representative of the universe of carcinogens to which
24 we want to apply the default factor.

25 That is one reason we had issues and trouble

1 with using the distributional analysis that we did to
2 pick the actual policy number.

3 So even if you could do that, I'm not sure --
4 you know, then would you pick a different number
5 depending on which tumors were produced by that
6 specific chemical?

7 I mean, I think it would get pretty contorted,
8 and that's why we stepped back, looked at the whole
9 picture, what it's saying, and said okay, we have to do
10 something to try to account for this susceptibility of
11 early life exposure.

12 PANEL MEMBER BLANC: Melanie, is an unstated
13 issue here that were you to apply your uncertainty
14 factor of 10 to age 0 to 7 you would be diverging from
15 the EPA, not only in the mutagenicity issue but in the
16 age range to which they apply their numbers?

17 Is that an --

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
19 MARTY: It is true that we would be diverging, although
20 we didn't really think about that specifically when we
21 were looking at this.

22 Pretty much everyone has talked about the
23 postnatal as really being most applicable to humans
24 at -- from birth to 2.

25 PANEL MEMBER BLANC: Who -- and they're

1 talking about that in writing, in articles that can be
2 cited and invoked with a rationale?

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: No, it's pretty much the risk assessment
5 community.

6 And I don't remember that EPA provided any
7 very specific justification when they did their
8 document, and I was actually on that SAP panel, so.

9 CHAIRPERSON FROINES: It does seem, if I'm
10 hearing Charlie and Paul correctly, that 0 to 2 may not
11 be the best number that should be selected.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Well then, I don't think there is enough
14 science to pick another value.

15 PANEL MEMBER BLANC: Well, there is -- sure
16 there is. You could say 40 percent of the preadult
17 lifespan of the rat is what this group of studies
18 applied to, so we're going to apply our finding to
19 40 percent of the preadult lifespan of the human. I
20 mean that's science.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: But it would make -- the assumption there is
23 that the organ development and tissue differentiation
24 and cell proliferation is identical in rodents and
25 humans in that time span, and it is definitely not.

1 So we did not want to specifically --

2 PANEL MEMBER BLANC: Do you have evidence
3 that --

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: -- make that statement.

6 PANEL MEMBER BLANC: -- 40 percent of the rat
7 is equivalent to 10 percent in the human?

8 I mean that's the decision you have made.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: No. And I think also you have to realize that
11 when we're talking about postnatal studies the mixture
12 distribution is a distribution because the studies
13 aren't all done with the same protocols, so some of the
14 exposures were day 5. Some of them were day 15.

15 PANEL MEMBER BLANC: I know, but you took that
16 into account by analyzing the data in the way you did
17 by doing the Monte Carlo, by being so meticulous. And
18 then --

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: Right.

21 PANEL MEMBER BLANC: -- at a certain point you
22 take this 90-degree right turn and make, you know, a
23 fiat to --

24 PANEL MEMBER BYUS: I have a comment that may
25 be an alternative. That's why I said about picking the

1 purpose.

2 If the purpose of your analyses is lifetime
3 exposure, calculating the potency and accounting for
4 these early stages, then it doesn't make any difference
5 because it's just lifetime.

6 However, if you want to use these age-specific
7 factors then in other studies to define other human
8 applicable or comparable exposure scenarios, then
9 you're going to have to get into this question.

10 So for lifetime, I don't think it much matters
11 other than if it's between rats and mice and humans.
12 So you don't have any problems with it. But if you
13 want to then apply to specific windows in human
14 exposure, then you're going to have to come up with
15 some rationale.

16 And I like Charles's idea of the comparable
17 organ-specific maturity factors, whatever you want to
18 call them, comparable relative to the tumors that
19 you're seeing a lot of.

20 And again, it doesn't really -- the fact that
21 it's carcinogen-specific doesn't matter because your
22 data is based on these carcinogens. So whatever tumors
23 you see a lot of, make the comparable organ maturity
24 calculations.

25 CHAIRPERSON FROINES: Craig, what I hear --

1 and Charlie should correct me if I'm wrong.

2 What I hear Charlie saying is if you look at
3 the neurologic system and you look at the respiratory
4 system, it doesn't appear that a 0-to-2-year period is
5 adequate because there is development occurring within
6 a longer time frame.

7 Am I getting you accurately?

8 PANEL MEMBER PLOPPER: There is a variety of
9 things. There's rates of proliferation, there's rates
10 of differentiation, there's initiation that go in
11 stages. And it seems like for now the nervous system
12 and respiratory system sort of track each other.

13 So there would be -- the same time frame will
14 have higher proliferative rates and lower proliferative
15 rates.

16 CHAIRPERSON FROINES: So does that mean --

17 PANEL MEMBER PLOPPER: Metabolism will be
18 functional and not functional.

19 CHAIRPERSON FROINES: So based on what you're
20 saying -- and presumably there are references to that
21 effect?

22 PANEL MEMBER PLOPPER: Yeah.

23 CHAIRPERSON FROINES: Could you, Melanie, come
24 up with some estimate that would help you not have to
25 make your argument solely based on a policy decision?

1 I don't know the answer to it.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: I think --

4 CHAIRPERSON FROINES: I'm just trying to help.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: I'm guessing no. I'm guessing no.

7 I mean one of the other issues that Martha
8 just reminded me about is that there's not necessarily
9 tissue concordance between species for specific
10 carcinogens. So then --

11 PANEL MEMBER PLOPPER: Oh, yeah.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: You know, then you're getting into -- like if
14 you're trying to base your age grouping by a specific
15 maturation of a specific system that was more
16 predominant, for example, in determining the postnatal
17 distribution, you still don't know whether that
18 carcinogen would impact that system in a human.

19 So it's pretty -- there's a lot of twists and
20 turns, making it pretty difficult to --

21 CHAIRPERSON FROINES: What do you think, Paul?
22 What would you propose?

23 PANEL MEMBER BLANC: Well, I think there's two
24 ways of going.

25 One would be for you to stick with the 2, and

1 then I'm going to urge the panel in its findings to
2 reject that and say that it should be applied to a
3 different age range.

4 Or for you to change your age range and come
5 to some age range that's more convincing.

6 And that -- the former might be a better way
7 because it would put you less at direct loggerheads
8 with EPA, and that might be a more advantageous
9 situation to be in.

10 I do think that this is one situation in
11 which, as opposed to our discussion this morning, I
12 don't think it's going to be possible to disentangle
13 the approval of the document from the draft -- from a
14 very close read of the text of the findings of the
15 panel.

16 So I don't think that we could come to an
17 approval of this document at this meeting because it
18 will for me depend on what the findings look like.

19 And although I think Craig's point is well
20 taken that in your calculations, for example, of the
21 70-year-old person the proportion -- the actual
22 numerical value changing from 0 to 2 being 10 versus 0
23 to 5 being a 10 or 0 to 10 being a 10 is not going to
24 amount to very much if indeed one of the applications
25 of this will be for nine-year exposures for risk

1 assessment. Then the proportional change, of course,
2 will be quite a bit more. So it does have
3 implications.

4 So I'm sensitive to the sort of difficult
5 situation you're in, you know, the sort of middle
6 ground between science-based estimates that support the
7 conclusion and then the more obvious policy decisions.

8 But if they are just policy decisions, then I
9 think we -- the panel could discuss among itself what
10 we think the policy should be or what -- actually,
11 that's not our role either.

12 We need to comment on whether the science
13 supports that part of the document or not.

14 DR. SANDY: The way I have thought of the
15 postnatal period in the animal and then in the human
16 from 0 to 2 is the rate of rapid growth that occurs
17 from birth until age 2. And presumably, you have that
18 with the rodents as well and also have this whether the
19 animal or human is still nursing. Age two is a
20 rough --

21 PANEL MEMBER BLANC: Well, the human is
22 nursing in a western society until age two. Primates,
23 we've just heard, will be nursing quite a bit longer
24 than that, and the human in the different -- so
25 biologically, why humans stop nursing at age two in Los

1 Angeles isn't, you know, is not a purely biological
2 thing.

3 And one of the reasons why I would suggest a
4 kind of step back from the precipice here is because,
5 you know, we may all be wrong and there may be actually
6 very obvious data out there that very strongly support
7 the two-year age human translation, and you'll find
8 that quickly, and everybody will be happy, and you'll
9 be able to insert a paragraph as to the pros and cons
10 and why ultimately you chose that, and everybody will
11 be ecstatic.

12 PANEL MEMBER LANDOLPH: And maybe also a
13 figure on page 35 below the mouse, maybe have a human?
14 This is not perfect. You just do the best you can.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: It's not doable.

17 PANEL MEMBER LANDOLPH: If it's not doable, or
18 there are other --

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Yeah. It's not doable.

21 DR. SANDY: Especially for the prenatal
22 period. There are so many -- each organ system, the
23 brain, the lung --

24 PANEL MEMBER BLANC: Well, the prenatal is not
25 an argument because you've never used that ultimately

1 anyway.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: But even in the postnatal, it is still
4 organ-dependent, species to species. There's not a
5 nice little correlation. So -- and, you know, I think
6 that we can look at the --

7 CHAIRPERSON FROINES: But Melanie --

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: -- the EPA's document, but I'm -- you know, I'm
10 not going to be able to tell you what their rationale
11 was.

12 CHAIRPERSON FROINES: Melanie, you're right
13 about that. You may be right about that.

14 What Paul is simply asking for is: How do you
15 justify that 0 to 2 then?

16 Am I correct? Isn't that what we're really
17 talking about? Because it's the underlying
18 justification that he's asking for, not -- and so that
19 seems to me to be the cutting edge.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Okay. The way it's been described when the EPA
22 did their document in 2005, as Martha just pointed out,
23 they looked at it as a period of rapid growth and
24 differentiation, 0 to 2. And obviously, there's not a
25 cutoff.

1 CHAIRPERSON FROINES: Did they have references
2 to that effect?

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
4 MARTY: Well, there's -- I mean you can -- we'd have to
5 look. I'm sure they had some references to it.

6 And then a relative --

7 PANEL MEMBER BYUS: It had nothing to do with
8 weaning. It has nothing to do with weaning, does it?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: No.

11 PANEL MEMBER PLOPPER: No. Weaning is not
12 part of that.

13 PANEL MEMBER BYUS: Weaning is not part of any
14 of that.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
16 MARTY: A slower period of development until puberty,
17 and then at puberty all kinds of things happen. And
18 that's why we wanted to also include puberty in that
19 second-fold factor.

20 CHAIRPERSON FROINES: That starts basically,
21 the juvenile period, at a relative early age.

22 PANEL MEMBER GLANTZ: Can I ask just one point
23 of clarification?

24 Would it be accurate for me to say that except
25 for this issue everybody's happy with the rest of the

1 document? Is there anything in the rest of the
2 document that people still want to talk about?

3 PANEL MEMBER BLANC: Well, I want to come back
4 to your rounding off. I'm going to buy the 13 to 10,
5 but the other value was 4 point what? What was the
6 other median value?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: It was 4.5.

9 But I will point out that we -- when we --
10 there's a section in the document, selection of the
11 default age sensitivity factor. And in that, we
12 discuss --

13 PANEL MEMBER BLANC: What page?

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

15 MARTY: Trying to find it. Page 48.

16 PANEL MEMBER BLANC: Yeah.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: So the second sentence is really kind of the
19 key sentence:

20 In view of the variability shown --

21 With those which Dr. Byus brought up earlier
22 with those distributions -- and the:

23 Uncertainty in applying conclusions from
24 a relatively small set of chemicals to
25 the much larger set of carcinogens that

1 are out there, it is probably
2 unreasonable to specify a default ASF
3 with greater than half-log precision.

4 So that is what we've got in there now:

5 Therefore, in the absence of
6 chemical-specific data --

7 Blah, blah, blah.

8 PANEL MEMBER LANDOLPH: You know, I would
9 accept that, particularly given that some of the
10 specific chemicals have a hundredfold range. That's
11 reasonable. I wouldn't want it any more -- that's a
12 rationale that's justifiable, and you can't get any
13 more precise than that.

14 I would accept that rationale.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: We didn't look at the numbers and then round
17 them down. We just said --

18 PANEL MEMBER BLANC: The nearest half-log.
19 We'll go to the -- you rounded to the nearest half-log.
20 Is that what you mean?

21 PANEL MEMBER GLANTZ: Yeah.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Yeah. If you look at -- yeah. 10 is somewhere
24 around the median. And so let's go half-log, you know.
25 It's just you can't --

1 PANEL MEMBER GLANTZ: So are you happy --

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: -- use the distributions --

4 PANEL MEMBER GLANTZ: -- with that, Paul?

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: -- to pick a number is what we're trying to
7 say. You can't use the distributions to pick a number.

8 PANEL MEMBER GLANTZ: Are you happy with that?

9 PANEL MEMBER BLANC: Not happy, but I
10 understand it now better.

11 PANEL MEMBER GLANTZ: Okay. So here's the
12 practical --

13 PANEL MEMBER BLANC: And I probably would say
14 we rounded off, therefore, to the half-log.

15 Because I actually had to think through what
16 do you mean by half-log precision? What you mean is
17 you rounded off to the nearest half-log so why not just
18 say we rounded -- therefore, we rounded off to the
19 nearest half-log?

20 That's what you did, right?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: We actually viewed them more as like an
23 uncertainty factor at half-log.

24 PANEL MEMBER GLANTZ: Well --

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: But yes.

2 PANEL MEMBER GLANTZ: You can say what Paul
3 says. That's fine.

4 (Laughter)

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Yeah. I mean if it were --

7 PANEL MEMBER GLANTZ: I'm trying to help you.

8 CHAIRPERSON FROINES: As a practical issue,
9 live with it. This is counting angels on the head of a
10 pin.

11 PANEL MEMBER GLANTZ: Okay. So here's the
12 question -- so I have the following question for
13 Melanie:

14 So basically, the only outstanding issue is
15 this issue of where do you draw the line between
16 postnatal and juvenile and juvenile and adult.

17 And I think the question is -- I mean the
18 point I think Paul raises is reasonable in that you're
19 not -- we're supposed to be approving science, and
20 you're just saying that there isn't science, or it's
21 all mushy and complicated.

22 So it seems to me that we have a couple of
23 options that we could have.

24 One thing is for us to not approve -- to say
25 that we don't -- that where you made that is a policy

1 decision, and so in approving the document we're not
2 making any comment one way or the other on the policy
3 decision because we're supposed to be approving
4 science, not policy.

5 CHAIRPERSON FROINES: No, I think we might say
6 something more affirmative and say we are -- we find
7 that the scientific information available is
8 inadequate; therefore, we recognize that OEHHA needed
9 to make a policy decision on this issue.

10 I don't know if Paul could live with that. Am
11 I being too Pollyanna?

12 PANEL MEMBER GLANTZ: Well, let me just finish
13 what I was -- that's one choice.

14 The other choice is to give it to, at the risk
15 of prolonging the torture here, is to let you guys go
16 back and look at -- I mean I guess a second option is
17 to say this is what the EPA did, and we're doing the
18 same thing they did, and cite the EPA.

19 The third thing would be, you know, to leave
20 this open and let you go back and see if you can come
21 up with a rationale for whatever -- and which may
22 involve changing those cut points, I don't know, but
23 something that addresses the issues that Paul is
24 raising.

25 I think those are the three options. I mean I

1 can live with any of those. What would be best from
2 your perspective?

3 CHAIRPERSON FROINES: This is not something to
4 ask Melanie right now. This is something to ask the
5 committee.

6 PANEL MEMBER GLANTZ: Well, except I think
7 that --

8 CHAIRPERSON FROINES: No, this is a decision
9 how the committee wants to approach the issue, not how
10 Melanie wants to approach it. No disrespect to Melanie
11 at all.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: My approach is thank you very much, we're done.

14 (Laughter)

15 PANEL MEMBER GLANTZ: Well, we can do that.
16 Okay.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: That was a joke, by the way.

19 (Laughter)

20 PANEL MEMBER BYUS: That's a joke.

21 PANEL MEMBER BLANC: I've already stated my
22 preference. My preference is to come to consensus,
23 which can't be done today.

24 And we have previously always found ways to
25 not have our findings contradict or undermine in any

1 way the documents that have come forward but have
2 always taken the approach of trying to amplify and
3 strengthen.

4 And I would not blithely want to diverge from
5 that, and I don't see logistically a way of solving
6 that at this sitting. And I don't see such great
7 urgency if this, as you point out, is the only thing
8 that's sitting between us. It would mean our next
9 meeting would be a very brief item of business.

10 I don't know that there's an administrative
11 reason. Perhaps Jim could tell us that there's some
12 deadline that's been missed --

13 CHAIRPERSON FROINES: There isn't.

14 PANEL MEMBER BLANC: -- in terms of a
15 legislative mandate.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: We missed that deadline a long time ago.

18 (Laughter)

19 PANEL MEMBER BLANC: Also, by the way, just
20 from a purely practical point of view, seeing a
21 document, the majority of which was no longer in track
22 changes, would make the thing a lot easier to look at.

23 And also, I would recommend that if we have
24 the opportunity that the Leads, working with our Chair,
25 come up with draft findings well in advance of the

1 meeting so that the committee can link closely the
2 wording of the findings to the wording of the document,
3 bearing in mind whatever version is coming forward to
4 us. Because I think the proof will be in the pudding
5 in terms of the findings.

6 That's my own personal view. I want to avoid
7 that kind of -- and it may, again, it may be that a
8 cursory review of certain written documents will come
9 up with a straightforward rationale that's supportable.

10 PANEL MEMBER GLANTZ: Are you doing a rapid
11 literature search, Melanie?

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: I'm looking at EPA's document.

14 PANEL MEMBER BLANC: Maybe Joe, because you're
15 the other Lead along with Stan, it would be important
16 for me to hear what you have to say.

17 PANEL MEMBER LANDOLPH: You know, with Stan,
18 we've worked through two revisions of the document,
19 transmitted a lot of changes. I agree with all the
20 work Stan had done.

21 So I think the document's in reasonably good
22 shape. But I would like to make you satisfied as well,
23 and I agree with your criticisms.

24 I could suggest that Charlie, who is really an
25 expert in this area, might work -- I'm making a

1 suggestion, and Charlie's looking irritated already.

2 But why not have Charlie work a little bit
3 with OEHHA?

4 CHAIRPERSON FROINES: I would say that Paul
5 was being very strategic. He said that you and Stan
6 and I -- I'm the new body. I would work on the
7 findings. And if that were the case then, given my
8 authority, whatever that may be, I would go to Charlie
9 and ask for his input.

10 PANEL MEMBER LANDOLPH: That's fine. And I'm
11 completely in agreement with that. Charlie's not
12 unhappy.

13 PANEL MEMBER GLANTZ: Well, are you saying --
14 so is what you're saying, John, that we would basically
15 approve, as we have before, approve the document
16 subject -- no. So you're just saying -- okay.

17 CHAIRPERSON FROINES: What's Paul saying?

18 PANEL MEMBER BLANC: No, I'm not saying we
19 would approve the document because I don't know what
20 the document will be. There are two or three forms it
21 could be in.

22 One could be staying with 2 and with no
23 further justification, staying with 2 with a
24 justification that's convincing, or saying, okay, it's
25 going to be 7 or 5 or 9.

1 CHAIRPERSON FROINES: The tension that
2 everybody feels is that Paul's scientific points are
3 clearly correct.

4 We also, however, want to be sympathetic and
5 supportive of OEHHA, and so delaying it makes everybody
6 uncomfortable.

7 My sense is that we will, if we do delay it,
8 we will come out with -- we will take a half hour to
9 finalize it at the next meeting, and we will all feel
10 satisfied with the outcome.

11 PANEL MEMBER GLANTZ: When is the next
12 meeting?

13 CHAIRPERSON FROINES: I mean we're trying to
14 be sensitive and supportive, but we also recognize that
15 there is a fundamental technical issue that needs
16 comment on; and Paul's said twice now three different
17 options that would work to resolve it, and we'll just
18 have to -- we might have to see which way we ultimately
19 agree would be the best outcome.

20 PANEL MEMBER LANDOLPH: So would you like Stan
21 to start working on the findings and send them to me,
22 and then I'll work on --

23 PANEL MEMBER GLANTZ: Well, we actually
24 drafted some findings up that you approved.

25 PANEL MEMBER LANDOLPH: Right.

1 PANEL MEMBER GLANTZ: But this point wasn't
2 addressed. The findings are quite simple, basically
3 part of it -- these were given to John, but this point
4 that Paul's raising wasn't in there.

5 But the findings were basically -- the first
6 part was just lifted verbatim from the REL document
7 about causality, that stuff that basically said we
8 concur in this two-step estimation and these default
9 values.

10 It didn't address -- this last point wasn't
11 addressed?

12 PANEL MEMBER BLANC: And I apologize. You
13 know at the last meeting we had, I had to go -- I was
14 there for the REL part but left before the concluding
15 discussion of the cancer document.

16 PANEL MEMBER GLANTZ: Did you find what the
17 EPA said?

18 CHAIRPERSON FROINES: Melanie, did you want to
19 make a comment at this point?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: I have -- not really. I mean, you know.

22 I'm looking to see what EPA said in their
23 document. It's a 250-page document. I can't find it
24 right this second.

25 But, you know, in all the presentations I

1 heard from them, the primary justification for the age
2 groupings were this rapid cell proliferation
3 differentiation 0 to 2, and then a relatively quiescent
4 period, as they termed it, up to puberty. And then
5 puberty --

6 PANEL MEMBER GLANTZ: And I'd like to make the
7 following suggestion to avoid having Melanie's head
8 explode: We don't have any other business. It's a
9 quarter to 1:00. You don't have to leave till 1:30,
10 right?

11 Why don't we stop for 15 minutes so Melanie
12 and the others can look through this EPA document
13 without us all sitting here staring at her and then
14 come back and see if we can't come to some closure on
15 this that everybody's happy with.

16 And if not, then we'll just put it over to the
17 next meeting.

18 CHAIRPERSON FROINES: But the thing that
19 concerns me Stan about that suggestion is that's --
20 what you're assuming is that the basis for resolving
21 this issue is going to be what EPA says.

22 PANEL MEMBER GLANTZ: Well, that --

23 CHAIRPERSON FROINES: And I'm not sure that
24 that's --

25 PANEL MEMBER GLANTZ: No, not necessarily --

1 CHAIRPERSON FROINES: -- as a matter of
2 science --

3 PANEL MEMBER GLANTZ: No, no.

4 I think I'd like to hear -- it would be
5 interesting to hear what they said and what the
6 rationale was. And it may be that if we hear that,
7 given the general difficulties that several people have
8 been talking about around the table, that we'll listen
9 to that, hear how they did it, and then say, you know,
10 that's probably the best you're going to do.

11 CHAIRPERSON FROINES: Melanie, is this -- if
12 there is something in the document, EPA document, is it
13 in your document? I think the answer to that is no.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: No. It's not in our document.

16 CHAIRPERSON FROINES: So that raises the issue
17 of the timing of whether we're not -- we can resolve
18 that.

19 PANEL MEMBER GLANTZ: Right. But why don't we
20 give them a little time where we're not sitting here
21 and let them just look, and come back in 15 minutes or
22 20 minutes and just see what they can find out.

23 CHAIRPERSON FROINES: Is everybody comfortable
24 with that? Paul, are you?

25 PANEL MEMBER GLANTZ: We don't have to vote on

1 anything, but I would like to hear what -- if they can
2 get this information, I'd like to hear it.

3 PANEL MEMBER BLANC: I am certainly in favor
4 of doing whatever will make the group that worked so
5 hard writing this not feel blind-sided or overly
6 frustrated due to the circumstances.

7 PANEL MEMBER GLANTZ: Why don't we recess for
8 20 minutes?

9 CHAIRPERSON FROINES: Okay.

10 (Recess)

11 CHAIRPERSON FROINES: We will reconvene right
12 now.

13 PANEL MEMBER GLANTZ: Give her ten minutes.

14 CHAIRPERSON FROINES: She just said she found
15 it. I thought she was asking to speak.

16 Melanie, are you asking to speak right now?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: I actually need five minutes.

19 CHAIRPERSON FROINES: Five minutes, we'll
20 reconvene.

21 (Recess)

22 CHAIRPERSON FROINES: Melanie, it's your call.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Okay.

25 This is from the US EPA's Supplemental

1 Guidance to Assessing Cancer Risk From Early Life
2 Exposure. And what they have in here is a little
3 different than what I remembered, but I can understand
4 now or remember a little better now what they were
5 talking about. And there was actually a lot of
6 discussion by the SAB about this and about the age
7 groupings.

8 Anyway, in here they describe that the
9 adjustments reflect the potential for early life
10 exposure to make a greater contribution to cancer risk.

11 The adjustment of tenfold is applied for the
12 first two years of life when toxicokinetic and
13 toxicodynamic differences between children and adults
14 are the greatest.

15 So that's work done by Gary Ginsberg, Dale
16 Hattis, Renwick, and others. And you can see, in fact,
17 in some of our other work where we looked at kinetic
18 differences, they are largest at infancy relative to
19 adults, and they drop off.

20 So they're focusing on both kinetic and
21 dynamic differences.

22 So then they didn't really have additional
23 data like Ginsberg and Hattis had put together for
24 choosing a good rationale for going from 2 to 16; but
25 they wanted to include that middle adolescence where

1 there is a more rapid period of development including
2 the physiologic changes in puberty, so that's why they
3 went up to 16.

4 And they didn't think that the full 10 was
5 applicable after the age of two because of the slowdown
6 in -- well, actually because there's not as large
7 differences in kinetics and dynamics.

8 So that's the rationale.

9 And there was a lot of discussion at the SAB
10 meeting about, you know, how do you pick an age group
11 and what -- how do you -- for sure to include puberty,
12 but should it be more than three at puberty or -- and
13 that's what they ended up settling on.

14 CHAIRPERSON FROINES: And is the
15 Ginsberg/Hattis work peer-reviewed?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: Yeah. And in fact, there is more work now
18 besides what is on --

19 PANEL MEMBER BLANC: Well, Melanie, I would
20 say that that's a very generic argument, and I would
21 think that -- I think your data analysis actually
22 contradicts that and is more supportive of the broader
23 early age range.

24 So I would kind of throw the whole thing on
25 its head. I think that the very important analytic

1 work that you did actually argues against the two-year
2 cutoff, unless there's something about the first half
3 of the life span of a rat up to adulthood that I am
4 missing.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Well, if you assume -- okay.

7 If you look at the toxicokinetic differences,
8 basically Ginsberg and Hattis looked primarily at drugs
9 and drug clearance and looked at metabolic pathways.
10 And you can see that in an infant chemical clearance
11 tends to be slower, so the half-lives range -- and we
12 also did the same stuff looking at environmental
13 chemicals -- and the half-lives can be up to, you know,
14 10-or-greater-fold for infants relative to adults.

15 Dynamic differences, they're going to be all
16 over the map because as you're growing and developing
17 you have different targets for toxicity.

18 So I don't think that the data that we
19 analyzed show anything particularly different in that
20 and certainly don't provide a cutoff point for humans.

21 PANEL MEMBER BLANC: Well, I would argue
22 contrary to that because in fact if you, by choosing
23 this period of time of day zero to day 21, were
24 diluting your effect which would have mostly been
25 between day zero and day 6, then why would you have

1 come up with a median that was not less than 10 but
2 actually greater than 10?

3 It should have been, if you were diluting out
4 the effect of this equivalent period of 0 to 2 -- which
5 it's hard for me to accept the argument that that's the
6 same as 0 through day 21 in the rat -- then you should
7 have come up with something considerably less than ten
8 if all the effect is really -- would have been
9 partitioned had you had studies which you didn't have
10 that were only from day zero to day 5 or day zero to
11 day 7 or whatever the argument is you want to make.

12 Does that make sense algebraically, what I'm
13 saying?

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

15 MARTY: And again, you know --

16 PANEL MEMBER BLANC: Let me ask another --

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: I don't think you can compare a rodent's -- you
19 can't make specific age comparisons readily between
20 humans and rodents and their various lifestages.

21 PANEL MEMBER BLANC: Well, let me ask you a
22 different question, theoretical, coming back to
23 something else we've talked about in terms of
24 indirectly supportive data, radiation data, that Joe
25 referred to before and my question about cancer

1 chemotherapy, delayed, secondary cancers:

2 If you have data that showed Adriamycin
3 administration in childhood leukemia between the ages
4 of three and 12 was associated with a hazard ratio of
5 10 for lymphoma, and the hazard ratio in adult-onset
6 cancer treatment with Adriamycin was a hazard ratio of
7 2 versus a hazard ratio of 10 -- and these are not in
8 two-year-olds; these are in three- to 10-year-olds --
9 would that -- how would you interpret that?

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Again, that's a chemical-specific example. And
12 if we had the chemical-specific data, we'd use it.

13 You can see that some of these chemicals, the
14 hazard ratio is more like 1000. So it -- there is --

15 PANEL MEMBER BLANC: I was just making the
16 argument about whether three to 10 was the same as
17 being an adolescent or not.

18 I mean what you're placing people between
19 three and -- you're saying people between the ages of
20 three and 10 are the same as people between the people
21 between the ages of 11 and 16. And I would say --

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Yes, we're lumping the groups. Yes.

24 PANEL MEMBER BLANC: Right. And I'm saying I
25 think people between the ages of -- children between

1 the ages of three and 10 are probably more like
2 children between the ages of one and two for the
3 purposes of what you're talking about here.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: Well, actually, I'll give you a flip example.

6 If you take girls treated for Hodgkin's with
7 radiation, it's 10 to 16 that's the much more important
8 age group and not three to 10. So there's a flip side,
9 and that's for breast cancer, and the risk ratios are
10 huge.

11 PANEL MEMBER BLANC: Mm-hmm.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: So we're lumping that whole group together,
14 knowing that there's going to be differences across
15 chemicals for susceptibility by early age.

16 PANEL MEMBER BLANC: But you're not comparing
17 two to 16 to one to two for Hodgkin's.

18 I'm just trying to make the point that,
19 biologically, if you ask anybody out there how they
20 tend to divide up youth and adolescence, they don't do
21 it one to two and three to 16.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: For sure.

24 PANEL MEMBER BLANC: So why -- what is the
25 rationale other than the EPA saying that's what they

1 like to do?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Well, it's not necessarily what they like to
4 do. I mean there are larger differences between
5 infants, toddlers up to two, and adults than there are
6 by the middle time period in adults for -- certainly
7 for drug clearance. That's pretty clear. And also
8 clearance of other chemicals.

9 CHAIRPERSON FROINES: There is a danger that
10 we're beginning to go a little bit around in circles on
11 this argument.

12 What's the -- what do we think is a compromise
13 solution to this?

14 PANEL MEMBER BLANC: I think the compromise is
15 for you guys to take a time-out to make an internal
16 decision. You have three different pathways you can go
17 down. Give us what your final decision is, and we'll
18 respond accordingly.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: So tell me what the three pathways are again.

21 PANEL MEMBER BLANC: One is you stick with
22 zero to two and don't provide any other supplemental
23 justification, other than this is policy.

24 One is that you --

25 CHAIRPERSON FROINES: And EPA does it.

1 PANEL MEMBER BLANC: And EPA does it.

2 One is that you stick with zero to two and you
3 have a pretty convincing rationale, a scientific
4 rationale or argument.

5 CHAIRPERSON FROINES: As good a rationale
6 as --

7 PANEL MEMBER BLANC: I would say tactically,
8 by the way, if you do that, also with some caveats like
9 we recognize that with additional data this may be
10 extended, you know, to age ten, and here's what
11 it would look -- here is how it would change, you know,
12 in a very small way, the cumulative life risk, some
13 kind of throw-out to that.

14 Or the third possibility is that you come up
15 with some widened age range.

16 I don't think any -- I'm certainly not --

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: With an appropriate rationale.

19 PANEL MEMBER BLANC: With an appropriate
20 rationale.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: We right now don't have a rationale for going
23 up to five or six or seven.

24 PANEL MEMBER BLANC: Well, you could say we
25 based this data on rat studies that represent

1 40 percent of the maturing period of the rat, and so
2 we're using 40 percent.

3 That to me is a more convincing argument than
4 anything you've said about one to two, frankly.

5 PANEL MEMBER BYUS: The other alternative is
6 using the approach that Charles suggested of organ
7 development.

8 I mean the reason there's a big difference at
9 two years old and drug clearance is because of renal
10 development. Strictly renal development -- and
11 clearance, renal capacity. Not the proliferative
12 capacity but --

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
14 MARTY: It's also hepatic --

15 CHAIRPERSON FROINES: That's Paul's second
16 alternative.

17 PANEL MEMBER BYUS: Oh, that's the second one?

18 PANEL MEMBER BLANC: Well, yeah, they come up
19 with a rationale. And it may be or two or it may be
20 three or it may be four or whatever. And then we can
21 respond to it appropriately. I mean I think it's --

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: We'll be back in a year and a half.

24 CHAIRPERSON FROINES: What?

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: No, I just said we'll be back in a year and a
2 half. Fine. That's what we'll do.

3 PANEL MEMBER BLANC: I think you've got a
4 really important document here.

5 I think it's important because it's original.
6 It's important because it's not the EPA. It's not
7 mouthing what they're doing.

8 To the extent that it's diverging from them,
9 you have excellent rationale for doing so. And you
10 haven't painted yourself into the corner that they have
11 with this mutagenesis stuff.

12 So if it takes another two months to shore it
13 up in a particular way that makes everybody happy, or
14 whatever it is, all the better. As frustrating as it
15 is.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: We'll look and see what's out there.

18 DR. SANDY: I was just going to say that I
19 don't think it's appropriate to say that zero days or
20 day one to 21 in the rodent is 40 percent of, you know,
21 this period of their life, and then we're going to
22 apply that to 40 percent of the human lifespan.

23 It's not a direct correlation. We just can't
24 do that. The animals are maturing earlier, and organ
25 systems and enzyme systems are changing. It's not

1 simple, and we can't just apply that.

2 PANEL MEMBER BLANC: Well, that's
3 conservative. If they are maturing earlier even, then
4 it goes to a higher age equivalent.

5 CHAIRPERSON FROINES: I have two comments.

6 One, does the panel -- I mean Paul's making a
7 recommendation which is up to us to vote. Another
8 alternative is to vote to approve the document right
9 now. So there are different potential options.

10 So at this point, I'm not going to phrase it
11 different options to vote, but is there general
12 agreement on his proposal, or do you want to continue
13 the discussion?

14 PANEL MEMBER GLANTZ: Well, my concern, you
15 know, based on talking to a couple of people in the
16 audience who know about these things who I said, well,
17 why don't you come up and address the panel and they
18 said no.

19 But I think that -- and listening to the
20 discussion here, my concern is that I think that this
21 is an area where there just isn't much data that leads
22 to a clean decision. So my concern is that we could
23 end up delaying without substantially improving the
24 document.

25 So I would, you know -- I mean I -- my bias

1 would be to approve it with the following -- well, no.
2 You asked what we thought; I'm telling you what I
3 thought.

4 Okay. I think we should approve the document
5 but, you know, with the -- subject to this section
6 being rewritten a bit to say that this is an area where
7 there is no clear bright line available to say that
8 this is what the EPA has done and their rationale, that
9 there are other rationales that we have talked about
10 that lead you to generally a similar conclusion, but
11 that this is an area where there is just -- the data
12 simply don't exist to draw a bright line. And that's
13 the best you can do.

14 CHAIRPERSON FROINES: I think that's a
15 reasonable argument with one -- where I would disagree
16 with you is I would prefer his proposal because it
17 gives us a chance to look a little bit more into the
18 science.

19 What I'm concerned about is having an
20 important section that says we're doing this because
21 it's our policy to do it, and that puts the panel in a
22 position of not being able to comment on the science.

23 PANEL MEMBER GLANTZ: No, I'm saying to take
24 the "it's our policy" out and rather replace it with an
25 explicit statement that this is a very different issue,

1 that there's not a clear answer; this is what the EPA
2 has done and why, but there's other -- you know, the
3 kind of stuff that has been discussed in the transcript
4 of, you know, this is a reasonable thing to do but, you
5 know -- but it is -- that's all it is, and that there
6 isn't some sort of bright line where things suddenly
7 change.

8 CHAIRPERSON FROINES: Well, I agree with you,
9 except I'm not prepared to vote on something that I
10 haven't seen yet.

11 PANEL MEMBER GLANTZ: Well, then what I would
12 hope we could do is have another meeting soon to bring
13 this to a conclusion.

14 CHAIRPERSON FROINES: We could have it a week
15 from now as far as I'm concerned.

16 Joe?

17 PANEL MEMBER GLANTZ: I mean I agree that this
18 is an important point. And I agree with what Paul is
19 saying, is that it is a very good document. It's
20 better than what the federal EPA has.

21 And we don't want to leave a loose spring
22 hanging that could undermine the whole rest of the
23 document. So I mean I do agree with that.

24 Just based on the discussion and talking to a
25 couple of the other people who are here, I think it's

1 going to be hard to come up with a nice clean argument.

2 CHAIRPERSON FROINES: Sure. This one isn't
3 going to be clean. We know that.

4 PANEL MEMBER LANDOLPH: I'm happy with most of
5 the document. I think it's an excellent document. I
6 wanted to congratulate you guys and gals for working so
7 hard on it.

8 CHAIRPERSON FROINES: Speak to the issue on
9 the table.

10 PANEL MEMBER LANDOLPH: Well, I want to put
11 that issue in context.

12 And I think I would go along with, for my own
13 personal point of view, a conditional approval of most
14 of the document, you know, what we've already reviewed
15 which is pretty good, and it's not going to change
16 except for the small comments they all make, and then
17 deal with the issue of Paul at the next meeting, that
18 he brought up and maybe have Charlie help EPA or
19 however they want -- OEHHA -- or however they want to
20 do that.

21 And I agree with your comments; it's difficult
22 to make these determinations, but lay that out cleanly.

23 It doesn't have to be a long section. I would
24 say three or four paragraphs would do it. Two pages
25 would be fine, overkill maybe. You don't have to make

1 a tome out of it.

2 PANEL MEMBER BYUS: I don't think it's such a
3 big issue, personally. I think it's important, but I
4 don't think it's a big issue. It's going to be up to
5 however people want to look at it, and I don't have a
6 strong feeling one way or the other.

7 But I would like the panel -- I think it's
8 important the panel reach a good consensus and
9 everybody feel good about it. I think that is very
10 important.

11 CHAIRPERSON FROINES: Charlie?

12 PANEL MEMBER PLOPPER: I agree with what you
13 guys have said. I think it's a great document, and
14 that my main concern would be that there isn't some
15 little systematic problem like this that can then be
16 used to undermine whatever findings you come up with
17 the next time somebody says yeah, well, they picked the
18 wrong time so it doesn't matter.

19 Let's just have a rationale, like Paul said,
20 and we don't have to worry about it.

21 CHAIRPERSON FROINES: Can -- everybody's
22 tiptoeing around the bush.

23 As the Chair, I am taking the position at this
24 point that we won't take a vote on the document at this
25 point, and we'll take the vote at the next meeting when

1 we have seen the document and everybody can unanimously
2 approve it rather than sort of saying, well, we'll give
3 it a tentative approval.

4 I think we should be clearer in our
5 articulation than that. But I'm -- I can be beaten to
6 death by Stan and others on this issues.

7 PANEL MEMBER GLANTZ: Okay. Well, the only
8 thing -- I'm happy with that. But I just want to make
9 sure as one of the Leads on this that the rest of the
10 document is finished --

11 CHAIRPERSON FROINES: Yes.

12 PANEL MEMBER GLANTZ: -- subject to the few
13 comments that were made here.

14 CHAIRPERSON FROINES: Yes.

15 PANEL MEMBER GLANTZ: So I'll work, and Joe --
16 we can work with Melanie to double-check all the
17 last-minute little corrections, but that's put to bed.

18 The only outstanding issue is this point that
19 Paul raised.

20 CHAIRPERSON FROINES: And --

21 PANEL MEMBER GLANTZ: And we'll have -- we had
22 had drafted findings which, I guess, didn't get
23 circulated. But we will also prepare a set of findings
24 that will include this point that will be circulated to
25 the panel well before the meeting too.

1 I just hope we can put this -- not have to
2 wait months and months and months.

3 CHAIRPERSON FROINES: Everybody around this
4 table -- I want to be clear -- everybody around this
5 table wants this to be over. And there's no doubt
6 about that.

7 (Laughter)

8 CHAIRPERSON FROINES: And secondly, I -- as
9 the Chair, I strongly apologize to Martha and Melanie
10 for delaying it one more time.

11 But I think in the long run everybody will
12 feel better about the outcome if we can make one more
13 half-hour-to-an-hour stab at it, and we'll be done with
14 it.

15 And I'm really sorry that it didn't get done
16 today, but the arguments that Paul raised I think have
17 merit, and we should address them and then go forward.

18 I want this to be seen in the most positive
19 light possible, if we can do that. Martha is nodding,
20 so I get a little positive --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: It depends on how extensive a justification you
23 want. I mean we could do this in a year.

24 PANEL MEMBER BYUS: Two paragraphs.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Two years.

2 PANEL MEMBER BYUS: Two paragraphs.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Two paragraphs?

5 PANEL MEMBER BLANC: First you have to
6 decide -- what I do want is a commitment in good faith
7 that you are going to have an open mind that it might
8 not be two years.

9 I don't want you just to walk out of here and
10 write a de facto justification for why you're sticking
11 at two years. I want you to look at it and to make
12 your argument.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: When I said two years, I meant it could take
15 two years to do the analysis.

16 PANEL MEMBER BLANC: No, no. Nobody is
17 saying --

18 PANEL MEMBER BYUS: No, no, no.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Or, you know, we can look at -- I can tell you
21 that lots of people have tried to make nice little
22 charts comparing --

23 CHAIRPERSON FROINES: Melanie, I would like
24 you to work out a meeting in two weeks to finish this,
25 if you can.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yeah.

3 CHAIRPERSON FROINES: Two weeks to a month.

4 PANEL MEMBER BYUS: Take you maybe two days.

5 PANEL MEMBER GLANTZ: Okay. Well, I think Joe
6 and I have this good sense of what people are looking
7 for, you know. We'll work with Melanie. We'll bring
8 in Charlie who actually knows what he's talking about,
9 and we'll come up with something.

10 PANEL MEMBER PLOPPER: Uh-oh.

11 CHAIRPERSON FROINES: And I'm going to be
12 reading the document as the person who signs it. So
13 it's not just the two of you and Charlie. If you don't
14 mind -- no disrespect intended, but I have to sign the
15 thing.

16 PANEL MEMBER GLANTZ: Okay. So are we all
17 done?

18 CHAIRPERSON FROINES: Are we done?

19 PANEL MEMBER BLANC: I move that we adjourn.

20 PANEL MEMBER LANDOLPH: Second.

21 * * *

22 (Thereupon the AIR RESOURCES BOARD
23 SCIENTIFIC REVIEW PANEL meeting
24 adjourned at 1:19 p.m.)
25

1 CERTIFICATE OF REPORTER

2 I, LINDA KAY RIGEL, a Certified Shorthand
3 Reporter of the State of California, do hereby certify:

4 That I am a disinterested person herein; that
5 the foregoing AIR RESOURCES BOARD SCIENTIFIC REVIEW
6 PANEL meeting was reported in shorthand by me, Linda
7 Kay Rigel, a Certified Shorthand Reporter of the State
8 of California, and thereafter transcribed into
9 typewriting.

10 I further certify that I am not of counsel or
11 attorney for any of the parties to said meeting nor in
12 any way interested in the outcome of said meeting.

13 IN WITNESS WHEREOF, I have hereunto set my
14 hand this December 15, 2008.

15
16
17
18
19
20
21
22
23
24
25

LINDA KAY RIGEL, CSR
Certified Shorthand Reporter
License No. 13196

