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AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

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PROCEEDINGS

CHAIRPERSON FROINES: So I will officially convene the meeting of the Scientific Review Panel on Toxic Air Contaminants for May 19, 2004.

And I'll note that all the members of the panel are in attendance with the exception of Roger Atkinson, who was not able to attend.

And so this is the first meeting of the panel in 11 months, and we have a very lengthy agenda. And so we'll try to move along as efficiently as possible.

So, Melanie, do you want to begin on formaldehyde.

SUPERVISING TOXICOLOGIST MARTY: Sure. The --

CHAIRPERSON FROINES: And let me just ask one question.

It's my understanding that Stan will only be here till noon; is that correct?

PANEL MEMBER GLANTZ: Eleven.

CHAIRPERSON FROINES: Eleven.

PANEL MEMBER GLANTZ: And then I'll -- if there's a phone, I can call in about 1:30.

PANEL MEMBER FRIEDMAN: I have to leave at noon.

CHAIRPERSON FROINES: Gary has to leave at noon and Stan has to leave at 11.

That leaves 1, 2, 3, 4, 5 of us. So it's still

a quorum. But it's a significantly depleted panel, so that --

PANEL MEMBER GLANTZ: They were -- the staff was trying to arrange a thing where I could call in on the phone. And I could call in about 1:30 till 3 to hear the -- you know, to hear the afternoon stuff.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER GLANTZ: The other thing is the part of the agenda that I think I have the most to offer on is the silica part. So you might want to take that into account.

CHAIRPERSON FROINES: Well, the silica will come up after formaldehyde. So we should be able to make that, I hope.

PANEL MEMBER GLANTZ: I might be able to stay --

CHAIRPERSON FROINES: I don't know how long Melanie and staff are going to present on formaldehyde.

So, anyway, everybody turn off your cell phones if any have them on, so we don't have the noise.

So, Melanie, formaldehyde.

SUPERVISING TOXICOLOGIST MARTY: Okay. The first agenda item is to discuss the formaldehyde petition.

(Thereupon an overhead presentation was Presented as follows.)

SUPERVISING TOXICOLOGIST MARTY: The Formaldehyde

Epidemiology, Toxicology, and Environmental Group, now called the Formaldehyde Council, petitioned the Air Resources Board to reopen the risk assessment for formaldehyde that was done under the Toxic Air Contaminant Program back in the -- until early nineties. The petition came to us in April 2002 with a number of appended reports for OEHHA to consider.

OEHHA reviewed the material in the submission and provided a response back to the Air Resources Board in November 2002. We reviewed the petition with the petition process in mind, which has specific criteria set out by this panel back in '89.

Andy will present to you what our recommendation was based on just the original submission using the criteria in the SRP process. He will also present a comparison of our cancer potency calculations with that from the petitioner, and a brief summation of newer epidemiology findings on potential links between leukemia and formaldehyde exposure in industrial cohorts and compare that to earlier findings on leukemia from earlier epidemiology studies. That latter part is if the panel is interested in that material.

Okay. With that I'm going to turn it over to Andy.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Okay. Thank you.

Well, I'll try and work through this as expeditiously as possible. So this is a presentation of the petition materials and our response.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: The petition made a specific request of OEHHA and the SRP that the 1992 risk assessment for formaldehyde be reassessed because of the appearance of what they described as new evidence, and requested review of this new evidence. The main item in this new evidence is a cancer risk assessment model which was laid out in a report produced by CIIT in 1999. And the petition claims that if this new evidence were accepted, it would change the cancer potency value and possibly the identification of formaldehyde as a carcinogen under environmental exposure conditions.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: The materials included in the petition included the CIIT report, various published papers -- included various published papers and government reports and also a PowerPoint presentation which was put together by the petitioners on the -- which it went through the development of the risk assessment presented by CIIT.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: In addition to those materials which were submitted with the petition, we received several other items after the petition was received but before OEHHA provided their response, including a copy of a report by the NAK Committee of the German government and various personal communications with Dr. Rory Conolly, who's the lead scientist with CIIT on development of their risk assessment. He was kind enough to assist us in understanding the materials that had been presented and to provide supplemental information that was necessary to interpret that. And he also in fact gave a slide presentation to ARB and OEHHA.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: In order to evaluate this petition, we basically turned to the SRP's criteria for considering reevaluation petitions and went through the various items.

The first item is: If the new evidence is accepted, what's changed and how has it changed? We examined the materials to see whether this would change the determination of health effects, the determination of threshold, all the derivation of a dose response characteristics, which in this case would be in the

carcinogenic potency.

The second requirement of a petition is that it describe the importance of the new evidence as it relates to the basis of the original risk assessment.

And the third criterion is that the petition should demonstrate peer review of the new evidence.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The OEHHA 1992 risk assessment identified formaldehyde as a carcinogen with a potential to impact humans. It found no evidence of a threshold. And it presented a calculated cancer potency value of seven times ten to the minus three per parts per million.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: OEHHA recommended denial of the petition on evaluating it against these criteria on case 1a: The evidence submitted with the petition does not change the determination that formaldehyde is a carcinogen.

The qualitative evidence presented did not include any new epidemiological studies or bioassays. There is in fact in the literature that we already knew about one updated bioassay which is in effect a repeat of an existing one with additional dose levels. But that in fact reinforces the original conclusion. So that doesn't

change the basis of evidence.

There was no evidence from supporting data presented which altered the qualitative evaluation.

And the overall interpretation of the data presented is that OEHHA's interpretation of the data on identification of formaldehyde as a carcinogen remains consistent with the recent determinations by IARC and by U.S. EPA and also consistent with the earlier OEHHA evaluations.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: On grounds 1b: The petition presented no clear grounds to review the threshold determination.

The proposed mechanisms examined both by OEHHA in 1992 and by CIIT consider the possibility of nonlinearity of the dose response relationships, but none of the models necessarily indicate an actual threshold.

And there was no new evidence presented on this point other than parameter determination in those proposed models.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: On grounds 1c: The petition did not provide any new epidemiology or bioassay data supporting a change in potency.

The petition argues that the CIIT report provides evidence for a change of potency. However, this is basically a reanalysis of existing data. And according to the terms that we see, that doesn't necessarily constitute new evidence.

And in terms of the analysis presented by CIIT, unlike the assertion in the proliferation which describes the OEHHA risk assessment as a default assessment, this is not in fact the case. The OEHHA '92 risk assessment did consider cell proliferation models and tissue-specific deposition models in that earlier risk assessment.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: On grounds 1c, continued also, the material submitted with the petition was not adequate to fully evaluate the CIIT model. Although I mentioned earlier, CIIT have been helpful in presenting us with additional materials and information to help us evaluate that model.

But even with this additional materials, we remain concerned that model uncertainty and uncertainty in parameter estimates and uncertainty on the relative role of mutagenic and proliferative responses, we are concerned that these are inadequately addressed in the CIIT report, and present a considerable level of uncertainty in their final risk estimate.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: On criterion 2, the relationship to the previous risk assessment, the petition failed to demonstrate details of how the new model would change the OEHHA risk assessment. And in fact, as I had mentioned earlier, it incorrectly describes the OEHHA assessment as a default method.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We also had concerns under heading 3 relating to peer review. Many of the critical calculations in the CIIT report have not been peer reviewed by publication or consideration by authoritative bodies. There were some materials which had been published at the time of the petition, but a considerable amount had not.

Since the petition was submitted, some new material has been published. But this is still not a complete peer review of the materials in the CIIT report. And, in fact, the material published in some respects is not exactly the same as what's presented in the CIIT report.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm now going to briefly compare the two risk

assessments, the OEHHA '92 and the CIIT '99.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The OEHHA risk assessment is based on the 1983 Kerns rat bioassay. It presented a preferred estimate of the -- of the unit risk as the upper confidence limit for lifetime risk as seven times ten to the minus three per parts per million. This used molecular dosimetry data, which was based on some experimental measurements of DNA protein cross-links, which you may find in subsequent slides abbreviated as DPX.

The OEHHA risk assessment considered both linearized multi-stage models and cell proliferation-based clonal growth models. And it also considered scaling factors based on either surface area considerations, breathing rate, and absorption ratio. And it also considered the impact based on either a systemic or point-of-application basis.

So there are several different bases considered in the risk assessment for all of these aspects of the calculation.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is shown diagrammatically in this model. We considered either an applied-dose or a tissue-dose model.

We considered linearized multi-stage model and cell proliferation models. We considered various bases for the scaling factor.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And, in fact, as you see in this table, we produced a range of estimates. And the one which was presented as the best estimate is within this range. It's somewhere in the middle of the range. It's actually a three-stage multi-stage model using a scaling factor which assumes systemic impact. And it uses the tissue-dose calculation based on DNA protein cross-links. And so this was the selected value from that range.

And this in fact compares with the EPA 1987 value of 15 times ten to the minus three per parts per million, which is within the range of estimates which OEHHA produced, although it's about twice the preferred value that was selected. The EPA model, in fact it is something of a default model. So OEHHA went beyond that approach in producing the estimate.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The CIIT model uses -- risk assessment uses a complex computational fluid dynamics model to assess the area and extent of deposition of formaldehyde in the

respiratory tract of both rats and humans.

They use the DNA protein cross-link data as part of the input to a complex nonlinear model, which they use to predict the extent of cell killing and then cell proliferation.

They used a two-stage clonal growth model, which is similar in form to one of the models that was considered by OEHHA. Although they used a different range of parameters for that input. They optimized the model parameters to fit human data, and then fit inferred parameters from the rat model and then put -- fed those into the human model in order to provide an intra -- interspecies extrapolation.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is roughly what their model looks like. The distinctive feature of their fluid dynamics model is that the areas of the respiratory tract they divided up into what they call so-called flux bins, which represent areas with similar rates of deposition. And then they run the whole deposition, cell killing and cell proliferation and clonal growth model separately for the -- for a number of these flux bins. And then in fact sum the cancer risk from each flux bin at the end of the calculation.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is -- the next two slides I'm going to compare the actual predicted dose response between these two models.

This first slide shows two curves from the OEHHA risk assessment. The upper curve, which is fairly linear in this range, in fact is the default model, which is rather similar to the one used by U.S. EPA. That upper curve is applied-dose model. Whereas the lower curve, which is, you can see, is somewhat -- somewhat nonlinear, in fact is the OEHHA value -- that's the one which the OEHHA preferred value is based. And that does use the tissue-dose calculation based on DNA protein cross-links.

So you can see that applying that model feature does have a significant effect on the overall risk prediction.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This -- I hope you can see the yellow curve on this. This is basically data from CIIT. It may show up a little better on the printed versions that you have. Or is it equally bad there? I'm sorry.

Is there any -- well, I don't know whether we can get the lights down at all.

I had hoped we would have a pointer, but we don't

seem to have a pointer here.

SUPERVISING TOXICOLOGIST MARTY: Thank you, Stan.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Anyway, the distinctive feature of this dose response is that there's a very strong point of inflection somewhere in the range around .5 to .7 parts per million. Theoretically the risk prediction rises very rapidly for levels above that range. And CIIT characterized that range as important for occupational exposures. But they claim that the lower risk range, which is in fact in this graph presented with the purple dots, is characteristic of environmental exposures, and the slope is much lower.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: An important point to note about this is shown in the next slide. This is the same environmental points as were in the previous slide, but with a different scale. And the important point to note is here, is that even with this model, the -- there is in fact a predicted dose response relationship. It's just less -- it's considerably lower. And we had some points to make about that.

But that's the -- the critical difference in the two predictions is that the CIIT model predicts a very, very strong point of inflection.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: From exposure at .1 parts per million, which would be in the environmental range, the CIIT estimate's in fact four orders of magnitude lower than the risk prediction from the OEHHA model.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The reason that they are so different is basically that the interaction of their fluid dynamic model, which predicts a highly nonlinear relationship between the applied dose and the deposition in various areas of the respiratory tract, so that much of the impact is in a few small areas of the respiratory tract in the lung. Whereas they're not predicting such a strong concentration in the human respiratory tract.

PANEL MEMBER FRIEDMAN: Could I interrupt?

What's DPX stand for?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: DNA protein cross-links.

So that the use of this fluid dynamic model and the way it interacts with the subsequent stages of the cell proliferation model is one reason why there would be a considerable difference. And in this case OEHHA used empirical DNA protein cross-link data, whereas CIIT

considered the DNA protein cross-link formation to be following this highly nonlinear and highly geographically-specific model which they developed.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Because of this deposition model which they used, the inputs to the two-stage cell proliferation model are nonlinear. So you basically have two interacting nonlinear models here. And the effect of this is that very small changes in the input values can make big differences in the risk prediction. And so those inputs can change both the slopes of the different phases of the dose-response curve, which you saw in the earlier slide which I presented which you couldn't read, and they can also make changes in the position of the point of inflection. So both of those features of that dose-response curve we regard as being highly uncertain because they're susceptible to changes in the parameter inputs for these highly nonlinear models.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm going stop here for a moment. And Melanie will --

SUPERVISING TOXICOLOGIST MARTY: Dr. Froines, I'm just wondering if you want to stop here and talk about the

information that was submitted to OEHHA in the petition, or if you want us to make a few comments on the new epidemiological studies which have been published since the petition was submitted.

CHAIRPERSON FROINES: Well, let me ask Gary about that.

Gary, do you -- would you like them to --

PANEL MEMBER FRIEDMAN: Yeah, I'd like to have them present that.

CHAIRPERSON FROINES: Go ahead.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'll continue then.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: One of the things which we've become aware of in fact since we considered the OEHHA recommendation to the panel about the petition is that there have been three important new epidemiological studies which have been published. These are shown here. And these include findings that might impact the basis and conclusions of a revised formaldehyde risk assessment.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Basically what these studies are, they are updates of existing cohorts which have previous -- about

which studies have previously been published.

The Coggon paper is an update with the extended follow-up and data revisions of an earlier cohort also studied by Coggon.

The Pinkerton paper describes an update and extension and reanalysis on a cohort originally published by Stayner.

And the Hauptmann paper describes update extension and revised analysis of the cohort previously reported on by Blair coworkers.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: One of the things that has been seen both in these studies and in earlier studies is that some studies have reported an enhanced risk of leukemia as a result of formaldehyde exposure. This slide presents the 11 studies that were examined in OEHHA in 1992, with the addition of the three new studies. And although none of these studies actually have a relative risk error range, which excludes one -- one of the studies earlier on comes very close -- but for the overall result none of them are actually clearly statistically significant. But nevertheless --

PANEL MEMBER GLANTZ: What is the measure of exposure that you're using here?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: It varies somewhat according to the studies. But it's usually some -- some combination of different values. In fact, sir, the recent papers do include consideration of several alternative measures of exposure. This is, if you like, the simplest and crudest overall value plotted here.

But I think what you can see is that, although none of the individual findings are actually clearly significant, and although one or two of the studies actually don't find an association, nevertheless there's a kind of weight of findings over on the side of there being some kind of an association.

So -- yeah, these are -- the axis here is just an ordinal scale. These values are ordered in terms of the increasing average or mean value for the risk ratio.

PANEL MEMBER FRIEDMAN: Can I interrupt there for a second.

Normally -- I mean it's preferable to express relative risk on a log scale, in which case the lower parts -- the studies that show a risk below 1.0 would be stretched out and might not give the same impression of the weighting that you described as being --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, I accept that. I fear this was put together in a little bit of a hurry. So if and when we come to

evaluate this in more detail, we'll obviously take your advice into account and make any such prediction. This is merely an attempt to say this is out there at this point. We don't pretend that we've been able to do an analysis of this.

PANEL MEMBER FRIEDMAN: It does show that those new findings fit into the --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. That I think is the point, that the new findings are consistent with the earlier findings, which were analyzed to some degree in the '92 report. So we're not talking about anything which is radically new here. But the new studies are larger, they use more up-to-date methodology.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And although the overall results are not so convincing, if you look at their more detailed analysis, both the Hauptmann and the Pinkerton study present a sub-cohort analyses, which include some values which actually are statistically significant. And the elements of selection which point to those statistically significant sub-cohorts basically include specifically myeloid forms of leukemia, either acute or chronic, as opposed to all the leukemias. So there's a biological

specificity in this effect.

And also there's an increase in the relative risk ratio when you look at either longer durations of exposure or higher levels of exposure. And particularly Hauptmann goes into some detail about examining the different exposure metrics and how those impact the statistically significant findings.

So I think what we're saying is that these papers are not showing us anything especially different from what went before in terms of the findings of this leukemia association in those two papers. But they do represent a more sophisticated detailed analysis, and there are some -- there have some statistically significant findings there.

Yeah, and the fact that there is a dose response, which is evident in the new analyses, is important.

The Coggon paper does not report an association with leukemia. Although, interestingly enough, they do report an association with lung cancer in that cohort.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So that's basically all I have. As I say, we're just describing what's out there at this point.

CHAIRPERSON FROINES: Can we get these lights.

PANEL MEMBER GLANTZ: Did you guys do a

sensitivity analysis on the CIIT model? I mean you said that it was highly nonlinear. But did you do any kind of quantitative analysis to see how varying the assumptions within a reasonable range would affect how their predictions compared to what you guys had done before?

STAFF TOXICOLOGIST MORRY: This is David Morry, OEHHA.

What I did is I got some parameters from Dr. Rory Conolly. And I attempted to reproduce the cell proliferation model -- part of their model, not the computational fluid dynamics part.

What I found is -- and I ended up with similar result to theirs using their -- the parameters they sent me.

What I found is if you -- there are two inputs to that model. One is the mutation rates for the changes of one cell type to another. And the other input is the rate of proliferation of the cells. What I found is that the model is far more sensitive to the rate of proliferation of the cells parameters than it is to the mutational parameters. So if you vary the parameters that had to do with cell proliferation only a little -- only a tiny amount, you get a huge difference in the cancer risk prediction that comes out of the model.

PANEL MEMBER GLANTZ: And what do you mean by

huge?

STAFF TOXICOLOGIST MORRY: Well, you can tweak it a little bit and it will just go astronomical in one direction or another.

PANEL MEMBER GLANTZ: But I mean how much would you --

STAFF TOXICOLOGIST MORRY: I did not do a quantitative sensitivity analysis of the model.

PANEL MEMBER GLANTZ: I mean I think an important question would be, you know, if it is that sensitive -- and those sorts of nonlinear models can be -- you know, how much would you have to change the input parameters to end up with risk results that were comparable to what OEHHA had come up with based on the earlier -- you know, the earlier analysis?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, obviously --

PANEL MEMBER GLANTZ: Does that make sense as a question?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Obviously that's doable because that's in fact what OEHHA did in '92, is that they ran a cell proliferation model using a different but still plausible selection of parameters and came up with risk predictions which were similar to, and in some cases higher and some

cases lower, but definitely within the range of the value that was selected eventually as the best value in '92.

PANEL MEMBER GLANTZ: But, see, the point I'm making here is it may be that there isn't -- if the model is indeed as sensitive as you're suggesting, it may be that there's not a difference -- you know, a big difference in terms of the estimated risks within reasonable parameter sets, which I think would be worth checking.

STAFF TOXICOLOGIST MORRY: If formaldehyde has a much -- has a smaller effect on cell proliferation than the one estimated, then the risk could be very much lower or very much higher. So by tweaking that parameter, the cell proliferation parameter, you can change the risk estimate by orders of magnitude. So changing the cell proliferation parameter in the right direction would make the CIIT model produce the same numbers that the OEHHA found --

PANEL MEMBER GLANTZ: Right. But the question is -- I mean it's true -- I mean if you just -- I'm sure you can pick some number that will make it do that. But the question is: If you pick values that are reasonable based on what we know about the biology, would that happen?

STAFF TOXICOLOGIST MORRY: I think that can be

done with, you know, biologically plausible cell proliferation rates.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's important to note that the CIIT model actually uses parameter values which are optimized in order to fit the bioassay data. So in a sense they're not using, quote-unquote, "independently determined biological parameter values". They're using values which, you know, fit the data the way they like the data to be fit.

And so, you know, the short answer is that there's probably several ways that you could do that depending on which -- you know, which angle you chose to look at the data from.

SUPERVISING TOXICOLOGIST MARTY: I'd just like to add one other issue to that. And, that is, that under SB 25 in California we're supposed to be considering children. And the cell proliferation rates would very likely vary by age. And there is no information on that in the CIIT model. And that would also impact whether the potency varies by age under their model.

PANEL MEMBER FRIEDMAN: Which way would it go? I mean if the cell proliferation rate was higher in children, would that make the potency higher?

SUPERVISING TOXICOLOGIST MARTY: Yes, it would.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: It would also possibly change the -- not only the slope of the curve in the different sections, but also possibly change the point -- the position of the point of inflection, which is potentially important because it's very close to the sort of division between the occupational levels and levels which are certainly plausible as being in the higher end of environmental range. And it could also change the relationship between, you know, the degree of -- the degree of difference between the low dose and high dose slopes.

CHAIRPERSON FROINES: Are there further questions before we turn to the leads for this issue?

Stan, are you satisfied with where you are?

Okay. The three leads on this issue are Gary Friedman, Joe Landolph, and myself.

And so why don't we turn first to Gary and then go to Joe.

PANEL MEMBER FRIEDMAN: John asked me to look at the three new epidemiologic --

CHAIRPERSON FROINES: I don't think you're close enough.

PANEL MEMBER FRIEDMAN: John asked me to look at the -- is that working? -- to look at the three new epidemiologic studies that were just presented here, and to see if I thought that that would indicate the need for

a new risk assessment by OEHHA.

And the original risk assessment acknowledged that the epidemiologic data were inconclusive and the risk assessment was based on, as we feared, extrapolation from animal models. And I think the situation was not changed -- has not been changed by these three new studies. They're also inconclusive in terms of whether you can judge that there's a causal relationship between formaldehyde exposure and leukemia or lung cancer or the others that were looked at in these papers.

So I think the situation remains the same, and I don't think the new epidemiologic evidence is sufficient reason to conduct a new risk assessment.

CHAIRPERSON FROINES: Questions for Gary?

The degree of succinctness is overwhelming.

Joe.

So -- well, just before we go to Joe, Andy, do you want to comment on what Dr. Friedman said, or David or Melanie?

SUPERVISING TOXICOLOGIST MARTY: Well, I hate to argue with an epidemiologist since I'm not one. But the one thing that struck us was that the -- particularly the Hauptmann studies appeared to be a pretty well conducted study. We had a number of folks at OEHHA who are epidemiologists read it. Of course this was, you know,

without the context of all the other information that these folks were reading it. But we were struck by the demonstration in our mind of dose response in the Hauptmann study, that they went to a great deal of effort to characterize exposure. Although, unfortunately, it's not described in that paper; it's described elsewhere. So we thought it kicked it up a notch.

CHAIRPERSON FROINES: Well let me ask you a question, going on his conclusion.

If you were to redo the risk assessment at this point, would you use the Hauptmann study as the basis for your risk determination or would you continue to use animal data? In other words, do you have sufficient confidence in the Hauptmann study that you would actually -- do you think that you would actually alter the basic information you use for the risk assessment?

SUPERVISING TOXICOLOGIST MARTY: I think -- we would certainly look at it closely in conjunction with all the other information on any potential link between formaldehyde exposure and leukemia, and we could make estimates based on that. Whether it would be -- we would also look at all of the animal data. And, you know, whether the epidemiology would be the basis for the number we chose, I really can't say right now because we actually haven't done that analysis. But we'd certainly look at

it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think the point is that we wouldn't have the data on which to base that choice until we did the reassess -- the risk assessment. But what I suspect would happen if we -- you know, if for whatever reason the panel were to direct us to do a formaldehyde risk assessment reevaluation, there is no doubt that we would look at these epidemiological data and attempt to produce some kind of probably highly uncertain risk estimate from them, and that we would at least be -- we would need to do something similar to what we've done in a number of other risk assessments, is to calculate a human value as best we can and see whether or not that's consistent with the animal data.

And if it is, then we might take that into account in predicting an overall risk value. But as to how much weight we would put on the human data versus the animal data, I don't think we can -- we can't answer that until we've done the assessment, which clearly we've not at this point.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: Well, I want to agree with Melanie, that I thought the Hauptmann study was very well done and impressively conducted and, you know, is

really a thorough discussion of limitations and strengths and so on. I think there were some inconsistencies in it. There was an association with the average and peak exposure levels but not with accumulative exposure. So there are some questions that were difficult to answer.

And I wanted to ask, in that nice slide that you showed, which I comment about the use of log scale, but still you did line up all the studies of leukemia, has there been a meta-analysis to show what the overall risk is based on all of these data?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There has been one put together by the -- I think by -- is it Dow Chemical? -- yeah, by an analyst from Dow Chemical. I'm not sure that what we have -- I'm not sure what we have at this point is, you know, a comprehensive academically validated meta-analysis. This is something which would need to be looked into.

PANEL MEMBER FRIEDMAN: I think it might be a worthwhile effort.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. I would certainly think that such an analysis would be required in order to consider the human data properly. And, as I say, I think if we were to be instructed to do a reevaluation, then that's clearly something that would have to be included in that

evaluation.

CHAIRPERSON FROINES: Yeah. I'm asking my questions basically not to create a difference between what Gary said, which I agree with, and OEHHA. I'm trying to get -- I was simply trying to get at the issue of, within the context of epidemiology, when is something sufficiently demonstrated that one feels confident that it would be appropriate to use for purposes of risk assessment?

And what I hear -- the question on meta-analysis an interesting one because, depending upon the results, one might argue that perhaps it is ready. But it's still sort of in -- it seems like it's in a gray zone. And one would like to see some more confirmatory data before one did that. But, again, maybe it's closer than -- maybe it's closer than I think anyway.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: For what it's worth, the Dow Chemical meta-analysis did not -- you know, it did not confirm the -- or they didn't regard it as showing evidence of a strong association that could be considered causal.

PANEL MEMBER FRIEDMAN: Did that include the Hauptmann study?

SUPERVISING TOXICOLOGIST MARTY: Yes, I think so.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I believe it did. But I don't know on what basis. I don't have the details of that.

CHAIRPERSON FROINES: Kathi.

PANEL MEMBER HAMMOND: It seems to me that in the -- you presented a one-point estimate and -- and constant set of limits of the entire data. But when you break it down by the exposure groups, that's where the dose response appears.

And also I was struck at the large -- the largest exposure group in the analysis in Hauptmann were statistically significant. And obviously those are smaller numbers. So, you know, the point estimate is higher. And that that's actually consistent with the Pinkerton paper as well.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER HAMMOND: But that was -- you know, so as it looked on the graph as you had it, it looked like they were not statistically significant and they all went under one. But I think when you look at the actual values and you stratify it by exposure levels.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. The overall analyses are not statistically significant. But there are several as a subgroup analysis, including the dose response thing --

PANEL MEMBER HAMMOND: Right. I think that's particularly important.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. Well, I think it has to be said that, you know, one of the reasons why people would probably think these papers strengthen the plausibility of the association is because of two things: There's the things like the dose response observed in Hauptmann and the time dose responses observed by Pinkerton. And the other thing is the indication of, you know, an apparent biological selectivity for the myeloid type of leukemia.

Now, this is obviously saying that -- you know, this evidence has more weight than what we had before. The question is, does it have enough, you know, to form -- and I think we're clearly at this point -- you know, we defer to Dr. Friedman's opinion on that, because he's the panel's expert. But, yeah, there's no doubt that the new data are more convincing than what we had before and would need to be considered were we to be instructed to do a reevaluation.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: I think the other question that, you know, is a big one in relation to formaldehyde exposure in leukemia is the one of biological plausibility. And there was discussion in the papers as

to whether formaldehyde can get far enough beyond the mucous membranes to get into the bone marrow and affect stem cells, and so on, and induce them to change into leukemic cells.

But we received some references, I think thanks to Eleanor, showing that there were stem cells in the circulating blood and that -- so if they're going from capillaries near the surface of the -- say, the nasal mucosa, they could be exposed to formaldehyde. So that I think that it is a biologic -- it is biologically plausible that that could induce leukemia.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There are also data showing appearance of chromosome aberrations, micronuclei cystochromes in exchanges in humans exposed to formaldehyde vapor.

So -- I mean another purely philosophical point of view is if you were in a position where you felt the epidemiological data were convincing, then, you know, plausible or not, you'd have to get used to it. And it would be up to the mechanistic analysts to explain an observation. I suppose while things are uncertain, then, you know, there's room for debate about plausibility, but --

CHAIRPERSON FROINES: We sent the references that Gary's referring to to the panel. And I've just -- but I

know that some people -- Kathi and Stan have been traveling, so they may not have it. So we'll get Peter --

PANEL MEMBER GLANTZ: What are those?

CHAIRPERSON FROINES: These are the references that relate to the issue of biological plausibility.

So if everybody's comfortable.

But I think, Peter, we should still have them for people in the audience. These are --

PANEL MEMBER GLANTZ: That was the thing -- that was the list of -- was that the list of references of first a list of characterization of -- yeah, I got those last week, I think.

CHAIRPERSON FROINES: Are those back there?

MR. MATTHEWS: No.

CHAIRPERSON FROINES: They should be. I think that --

PANEL MEMBER GLANTZ: Aren't there some other leads we haven't heard from?

CHAIRPERSON FROINES: Yeah, absolutely. But I just wanted to make one comment before going forward.

I think that the people misunderstand the term "limited" in the IARC evaluations. And it's one of these issues of the glass is half full or the glass is half empty. And I think it's important to emphasize that the term "limited" in terms of epidemiologic studies is

generally perceived as a positive statement about the fact that there is evidence of epidemiologic findings showing positive results. It is -- limited does not -- should not be taken as a negative statement. In fact, it's just the opposite.

And so that one question -- there are two issues: One has to do with the qualitative question of, is formaldehyde a toxic air contaminant? Is there evidence for its carcinogenicity? -- which is a "yes-no" question, a qualitative question. And then there's the quantitative issue of risk assessment.

And in your view would these studies -- may not be useful yet at least with the level of analysis that you've done to suggest that they should be used for risk assessment purposes. But do they add to the weight of evidence on the "yes-no" question of whether formaldehyde's a carcinogen?

SUPERVISING TOXICOLOGIST MARTY: I think the answer is yes, that they add to the weight of evidence that formaldehyde is a carcinogen.

CHAIRPERSON FROINES: Okay. Joe.

PANEL MEMBER LANDOLPH: We received a truckload of data on this one. I did read it all. And I was struck by a number of things. Of course the rat model leading to the concentration of formaldehyde in a nasal -- a specific

nasal area is interesting, and I had some questions as to whether --

PANEL MEMBER FRIEDMAN: Excuse me. Could you speak up a little louder.

PANEL MEMBER LANDOLPH: Sure. Sorry.

And I had some questions as to whether when you spread that over the mouth and the nose in humans and monkeys, maybe that would make the various regional-specific areas show a lesser risk. So it may be a little complication of going from a rat model to a human.

I liked intellectually the model. I think the model's intriguing. There's a lot of academic component to it. But I'm not convinced myself that there is enough new data, just on a data basis alone, to merit a reconsideration.

I would recommend that OEHHA take a leadership role in thinking about these models and determining whether they think they're worthy for implementation in the future, because I think this is a future science starting to break over us and I don't think we can ignore it forever.

Having said that, at the same time I still would urge caution, because certainly the linear ice multistage model is a conservative model; and I think before we

depart from that, there should be a very good reason for it. I'm concerned that the Conolly report is very intriguing intellectually, but I don't think it represents a substantial amount of new data as far as I can determine.

And I want to thank the presentation of Dr. Salmon and Dr. Marty.

I had the same feeling about this model because it's a very parameter-rich model as well as data rich. But the parameter rich bothers me a little bit. And particularly this being able to manipulate the cell division rates and cell death rates, as Dr. Morry so eloquently pointed out, can lead to large changes in the estimated cancer risk. So I have a natural skepticism about that, and I had it when I first looked at this model.

So I think I would urge you to take a look at the model and see whether in the future iterate a modified version of it might be useful in modern risk assessments, because I don't think we can ignore that new -- the new conceptual science breaking.

I'm extremely bothered by the fact there's a four order of magnitude difference between that model and the prior models. And I don't think that that four order of magnitude difference is based on the acquisition of new

data. I don't believe that. So that makes me even more skeptical of the application of the model at present.

So I guess my position would be one where I would say please look at the model, please look at the new science as it develops. But based on data alone, I don't think there's a necessity to do the reevaluation. If OEHHA comes up with a hybrid model or a version of this model which is reasonable and it's not so susceptible to manipulation by a parameterization, then I would urge you to begin thinking about applications of this in the future. But I would still urge some conservatism in this area to protect public health.

CHAIRPERSON FROINES: Okay. Questions for Stan -- for Joe?

PANEL MEMBER GLANTZ: I'll take the questions.

(Laughter.)

PANEL MEMBER BYUS: How was the drive from San Francisco to Oakland, Stan?

PANEL MEMBER GLANTZ: I got lost.

CHAIRPERSON FROINES: Okay. What I did was -- like Joe -- and Joe and I've had a number of conversations about this issue. This is a very complex petition, because you have dosimetry data that's been advanced, you have new approaches to modeling that have been advanced, there's new epidemiologic data. And so in my view, I

thought that the panel would benefit from expertise in the area of risk assessment and toxicokinetic modeling. And I knew that Dale Hattis in the early eighties, who is without doubt one of the three or four leading risk assessment experts in the United States -- and I think we would all agree with that -- had worked on formaldehyde in the early eighties.

So I contacted Dale and asked him to serve as a consultant to the panel. And he agreed. And he has written a report, which everybody on the panel here has, and is -- I think there are copies in the back for those that don't have it. And Dale was the person who actually provided the references that we talked about earlier with respect to Gary and the biological plausibility.

And I think that this, done in a relatively short time, is an extremely useful and informative document for us. And I think, however, that it has two implications. And one implication is that Dale Hattis is our consultant to this panel, so his findings have to have significant weight for the panel, I think. And in that regard Dale draws the following conclusions: And I'll read -- I won't read the whole document, but I'll read the three conclusions.

One is: "There are certainly elements of the CIIT model that represent potentially helpful advances on

the prior state of the art."

So that he is saying in that sentence that the CIIT model does represent new information.

PANEL MEMBER BLANC: No, I would disagree with that interpretation. He's saying it represents a new approach. It's not new information. I think that's a very critical difference. It's not new original data. It's a proposed hypothetical view of existing data. And I think that's critical.

CHAIRPERSON FROINES: We should discuss that. Because, yes, you're right. But the criteria don't limit us to deciding that the data has to be new. One can take a new approach, and one consider that a new advancement of the science.

PANEL MEMBER BLANC: I think it's more than just a semantic difference. So maybe we'll return to that. But I think it has to do with the difference between whether or not the OEHHA's scientific evaluation of the petition is appropriate scientifically from the panel's point of view, which is what we're being asked to comment on, as disassociated from the question of: That being said, how should the information that has arisen as a result of reviewing the petition be potentially applied to other activities that OEHHA can embark upon? For example, the way it's going to have to deal with formaldehyde and

the childhood risk assessment and ways in which it may more globally look at risk assessment models that involve nasal absorption and so forth.

I think those are two separate things.

CHAIRPERSON FROINES: Let me finish.

He also goes on to say: "There is some new science here. However, the analysis has not been carried forward far enough to be able to make an apples-to-apples comparison with the OEHHA/ARB upper confidence limit estimate."

And he then goes on to say that: "There is at least one additional helpful type of treatment of the CIIT data, some of which are new, such as the additional tumor findings reported here for the first time. This is an integrated treatment of the two pathways of carcinogenesis, reflecting both cell proliferation and mutagenic effects. This can be done..." and so on and so forth.

So I understand Paul's questions. But I think that at some level Dale is saying, is concluding that there is new information here. Whether that's methodologic or actual scientific data I think is something we need to discuss.

But having said that, the other conclusion that one would draw from this is that he is highly critical of

the CIIT approach at the same time. And I'm not going to go through and read that. Everybody can read it. And I talked to him this morning. And he felt -- and this is my notes from the phone conversation. He felt that, quote, "it's critical that the model be evaluated for uncertainties for the magnitude of the low dose linear component and include interactions with background cell replication rates and background mutation and stem cells susceptible to carcinogenic transformation."

He has questions, as Stan's raised, about the nonlinearity and the dose response relationship, but he hasn't looked into that portion of the data. And he thinks that that nonlinearity will go away if one develops an upper confidence limit on what is -- what CIIT calls their KMU, but it is in some respects similar to a Q start in our normal terms.

And he says that "the data is at this point not sufficient to arrive at a new upper bound risk analysis. It is not sufficient for a new estimate of the upper bound risks that could be associated with formaldehyde at environmental and occupational levels."

So that what Hattis is saying, I think, is in a sense two things: That there are new approaches, there is new toxicokinetic modeling, there is new risk assessment methodology, there's some new biological data on the one

hand; and on the other hand he's saying that there isn't sufficient evidence to develop a new upper bound estimate for the risk analysis. And so he's saying that based on the materials that he reviewed for this petition, that this information is not sufficient for estimation of the ultimate risk.

And so he would argue I think based on the two -- my discussion with him and the document, that, whereas there is new information -- and we can quarrel over the differences in that respect -- but that the data -- but that the methodology is not sufficient for evaluation at this point. So that would be his conclusion.

PANEL MEMBER FRIEDMAN: Well, could I -- there was something that you sent, I think it was a memo to the committee, in which you made three points. And I think one of the points you said was that there should be a new evaluation. And I didn't get that from our phone conversation. I think you said we may have this three-way conversation of the three lead people. And that one of the conclusions was, yes, there should be a new evaluation. And I didn't come away from the conversation remembering that.

CHAIRPERSON FROINES: Oh. Well, my view at this point is that there are a number of -- there may be four points that I would conclude.

The first and most significant point that I think we need to conclude is that there is no evidence submitted to date that would change our conclusion that formaldehyde is a toxic air contaminant, that our view in 1992 is the same as our view today. Formaldehyde is a toxic air contaminant based on the information in the petition and the new epidemiologic data and so on and so forth. So there findings are consistent with that.

I think we should also say that the CIIT petition does represent a new approach and does contain some new information. And I would argue as a person who does work in toxicokinetics that that would constitute relevant new information from the standpoint of risk assessment.

And so I would argue that there is new information. I would argue based on Hattis' review that that information is not yet sufficient to define a new risk assessment by OEHHA were OEHHA to take it up. So that the data is not -- the analysis done by CIIT requires extensive new work based on what Dr. Hattis -- what Dale Hattis says.

Fourth, I would say -- one of the things that was alluded to is that OEHHA is going to be looking at risk assessment methodology as part of the SB 25 process. So they're going to be looking at risk assessment methodology. And they have to look at some tier 2

compounds, and formaldehyde is a tier 2 compound.

So I could foresee a process in which CIIT developed their risk assessment model more fully, that they submitted that to OEHHA, and that while OEHHA was doing their tier 2 review following their risk assessment methodologic evaluation, that they'd look at formaldehyde within the context of the updated CIIT input -- formaldehyde industry input as part of their tier 2 process.

PANEL MEMBER FRIEDMAN: So we're not asking them -- according to what you're recommending, we're not asking them to do anything that they wouldn't ordinarily do under the SB 25 process, is that --

CHAIRPERSON FROINES: Well, I think they should respond and say that that would be appropriate if we took that approach. Because I've just listed basically a four-step approach. One is to acknowledge that there is some information, but that it doesn't affect our TAC determination; that there is more work to be done by CIIT to deal with some of the issues that -- Stan actually raised many of the same issues that in fact Dale did.

So I think it's not just Hattis' view. And that CIIT would then submit subsequent risk analyses based on what was requested; and that when OEHHA was dealing with their tier 2 compounds and was looking at the risk

assessment of formaldehyde in the context of SB 25, that they would then look at that new formaldehyde data from CIIT, which would be -- presumably have been submitted by them.

Gary.

PANEL MEMBER BYUS: Craig. Or Gary. Who do you want?

CHAIRPERSON FROINES: You see, Alzheimers comes on slow and --

PANEL MEMBER BYUS: I really do agree with you. I mean I find the model very, very interesting. I think it is a good -- it's a hypothesis model. I mean it's based on very sound science, and it's laid out in a very nice way. The problem is it hasn't really been validated sufficiently, is my feeling.

I mean the linear dose extrapolation for carcinogen model that everybody uses -- we all use has been -- was validated extremely well through many, many years. And this is actually a very good model, and it just hasn't been validated enough. It hasn't been tested appropriately. And it needs some more experimental validation before it can really be adopted. If it were -- for example, if this was shown to be sort of correct with proliferation models and distribution for a number of other chemicals, even though there would be no new data

for formaldehyde specifically, we would all say the model had a significant higher level of validation, and we'd be much more likely to agree with it in the context of a formaldehyde risk assessment here. But since it hasn't really been validated extensively, experimentally, it's of limited use in terms of changing what we already know.

But I do find, with you, that it is really new and it's a very nice model and it really needs a lot more work. Somebody should work on it because it's very, very interesting. And it may in fact be correct.

PANEL MEMBER FRIEDMAN: So to clarify, you're -- given that you see a lot of strength to this model, you're not recommending that OEHHA necessarily be the ones that perfect it, validate it, and so on?

PANEL MEMBER BYUS: No, not at all.

PANEL MEMBER FRIEDMAN: They should -- once it is perfected, validated, so on, then they can consider using it. But it's not -- we're not recommending that they have to do that?

CHAIRPERSON FROINES: I was being very specific. I was saying that this petition -- the material within this petition as far as I'm concerned is not ready for prime time based on Dale Hattis' evaluation.

And what I would say is that the industry should develop the model further and address the issues that Dale

raises, and there are -- I don't want to go through all the points in his document, but there are obviously the nonlinearity -- using an MLE model as opposed to an upper confidence limit. And Dale would argue that when you go to the upper confidence limit, you're going to lose some of that nonlinearity, and so on and so forth. We could go through it.

So the point is I'm saying it's not ready for prime time, but that I would urge them to pursue it further, and that when --

PANEL MEMBER FRIEDMAN: Who's the "them" that you --

CHAIRPERSON FROINES: The CIIT and the formaldehyde industry.

PANEL MEMBER FRIEDMAN: Okay. We just need to make really clear who "them" is.

CHAIRPERSON FROINES: And when -- but I would also argue that formaldehyde would be a good compound for OEHHA to look at in their tier 2 process, because they have to look at -- 15 chemicals?

SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: And so if you had new information that had been submitted when you're doing the tier 2 process, that one might consider incorporating that into a new risk assessment. And so it seems to me that

we're describing a process that would be -- if George and Melanie agree, that would be appropriate for down the road looking at how some of the uncertainties in the model have been evaluated.

PANEL MEMBER FRIEDMAN: May I just clarify that?

Well, let's say they then do this formaldehyde assessment for SB 25 a year from now and there's been no -- little or no progress on the things that need to be done with this CIIT model. Are you still recommending that they use it?

CHAIRPERSON FROINES: No. I'm not recommending that they use -- I'm not recommending they change anything. I think the burden is on the petitioner to come back and respond to the questions that have been raised, and then to -- and to the degree that they are responded to, then it would seem appropriate for OEHHA to incorporate them because they do represent a certain level of sophistication that might be relevant.

PANEL MEMBER FRIEDMAN: Okay. Well, that's the first clear statement that we're putting the onus on the petitioner. I want to make that -- I think that should be very clear.

CHAIRPERSON FROINES: Well, it's a -- I'm talking about a staged process and -- a staged process. And that the first step would be for the petitioner to take the

Hattis report and update their model appropriately, and then OEHHA could later consider that when they took up formaldehyde.

PANEL MEMBER BLANC: Maybe OEHHA could comment on this. But I would assume -- maybe I'll just wait until they -- maybe OEHHA could comment on this, but I would assume that if a version of this theoretical modeling approach appeared in the public peer review scientific literature in a published form, you would, as with other peer review studies, take it into consideration when you review formaldehyde as other compounds and as part of the SB 25 process. Isn't that correct?

SUPERVISING TOXICOLOGIST MARTY: Yes, we would look at all available information.

PANEL MEMBER BLANC: But you weight peer review published information somewhat more strongly than --

SUPERVISING TOXICOLOGIST MARTY: We do.

PANEL MEMBER BLANC: -- anecdotal or non-peer reviewed or non-published or proprietary information?

SUPERVISING TOXICOLOGIST MARTY: We do.

CHAIRPERSON FROINES: Are you comfortable with what I have proposed?

SUPERVISING TOXICOLOGIST MARTY: Yes. The only qualifying thing that I think I better say is we -- under SB 25 we need to revise our risk assessment methodologies

to incorporate considerations of age at exposure on potency of carcinogens as well as non-carcinogens.

We're in the process of doing that document. It's -- as soon as we're done with ETS, Stan, we'll be working harder on more of that document.

And we're also required to develop -- or to go back and look at 15 TACs per year under that statute. What we wanted to do is have at least some of those 15 TACs done when we put out the risk assessment revisions for public review.

Formaldehyde is a little more complicated, in part because of this type of information. So I wanted to avoid promising that the first batch of chemicals we look at is going to include formaldehyde. I think we can say that we'll try. But there are these unresolved issues with the model. You know, if they don't get resolved, we're not going to look at it until they do get resolved. So I don't -- the timing might be a little bit problematic.

CHAIRPERSON FROINES: Yeah, but I think that we have to be responsive to the petition as well. Insofar as if CIIT or, quote, "formaldehyde industry" comes back in, having addressed a lot of the issues, then it does seem to me that it's incumbent upon us to be responsive to that additional input. So to sort of say this one's more

complicated so we won't take it up as one of the 15, I don't -- I think that -- I think that you would need to be responsive to the fact that a significant -- I mean this is not trivial and an enormous amount of work has obviously gone into it. And so I think one has to be responsive to that.

PANEL MEMBER FRIEDMAN: Well, I agree with what you say. But isn't your first priority in this SB 25 process to look at risk to children? And if they don't consider formaldehyde as necessarily a greater risk to children as 15 others, then you wouldn't put that in the first 15, right?

PANEL MEMBER BLANC: Well, it actually was number 6, if I recall. It had just -- was just bumped out of the top 5. So --

CHAIRPERSON FROINES: Remember that formaldehyde was originally proposed as one of the top 5. And it was the recommendation of this panel that moved it down actually. And so that means as far as I'm concerned, and I think this is what Paul is saying, is that formaldehyde is still higher on the list than perhaps some other chemicals might be. So it would be appropriate to take it up.

SUPERVISING TOXICOLOGIST MARTY: It wasn't on the basis of its carcinogenicity primarily however.

CHAIRPERSON FROINES: I understand. It was on that paper from you know who.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think a subsidiary point is that we might well take it up early in the reevaluation process, but that it might take us a while to complete the reevaluation. So you wouldn't necessarily expect to see a final OEHHA reevaluation in the first crop of reports simply because this task is of sufficient magnitude that it could take quite a while.

CHAIRPERSON FROINES: Well, this process with formaldehyde's taken quite a while. And so I think it's going to take a while presumably for the industry to respond to the Hattis questions and those raised by it.

PANEL MEMBER BLANC: Well, does that mean that it will take industry longer to respond than it's taken the Air Resources Board to respond to the 1991 designation?

CHAIRPERSON FROINES: I don't understand the question.

PANEL MEMBER BLANC: Well, I mean -- I think earlier you said that it was designated in 1991. And has there actually been any regulatory action from the Air Resources Board or any program for reduction exposure or control of formaldehyde based on that?

CHAIRPERSON FROINES: As far as I know, there has

not been a control plan developed for formaldehyde up to the present.

Janette.

ARB AIR QUALITY MEASURES BRANCH BROOKS: We're currently in the process of developing a control measure for formaldehyde. And it's focusing on composite wood products, like plywood and particle board and medium density fiberboard. And we've gotten -- we've surveyed the industry. We're looking at the data. And we're looking at the technologies and the emissions from the Board itself and how those can be lowered. And that's where we are right now. We haven't gotten to the step yet where we're looking at regulatory concepts, but we're getting close.

PANEL MEMBER BLANC: Because I think it is very, very important that this discussion not be misinterpreted by the Air Resources Board as any indication from the scientific panel that there need to be any delay or slowing in the ongoing process from the Air Resources Board point of view. Again, reiterating what Dr. Froines said, which is that there's nothing in the information that's been presented that suggests that formaldehyde is not a toxic air contaminant.

CHAIRPERSON FROINES: Now, Jim just gave me a message that I actually don't think I want to follow,

because I think that the letter that I sent to Alan Lloyd responding needs to reflect what we've just been discussing.

Jim says the question before the panel is to make a recommendation to the ARB Chairman, Allen Lloyd, about whether the panel feels the information contained in the petition warrants reconsideration of the original risk assessment.

And I think that we could have a vote on that specific question, but I don't think it's what we're really talking about. I think we're saying -- we're saying that there is new information that's perhaps not ready for reconsideration, but we do think that, given -- if that new information were to be provided -- further information were to be provided, then it would be appropriate for OEHHA to look it up.

PANEL MEMBER GLANTZ: Well, I think -- I'd like to sort of differ slightly. I think we should answer the question "no," because that is the sort of bureaucratic or legal question before us. And I think we should say that there is not new information before us to warrant reopening the risk assessment. I think that's clearly -- the answer to that is clearly no. And I think that's all you need to write back to Lloyd.

I think that -- there is a transcript of this

meeting. I think people have -- several people have said there's some very interesting new information there, it's not sufficient to warrant reopening the risk assessment. But I think we've made it fairly clear to OEHHA and to the petitioners that if further information is developed and fed into the process, it ought to be considered very seriously. And I think that we've made it clear that we think formaldehyde is a high priority for the next phase of SB 25. So I think there isn't much more to say.

I think the letter back to Lloyd should be dealing with this narrow legal question of do we think that they put forward information to warrant reopening the risk assessment. And I think the answer to that is "no." But I think -- there is this transcript of this meeting. I think the panel's been pretty clear. And I think OEHHA has a history of taking what we say seriously. And I know that the formaldehyde people are going to listen to what you said. And I think that's all we need to do at this point.

PANEL MEMBER FRIEDMAN: I would like to make a motion that we do just what Stan said, just answer "no" and refer to the transcript for discussion of our thoughts about it.

CHAIRPERSON FROINES: Well, I just -- we'll take the motion in a second. But can we have some further

discussion on the point before we get to the motion?

PANEL MEMBER FRIEDMAN: Oh. Well, I made --

CHAIRPERSON FROINES: Make the motion.

PANEL MEMBER FRIEDMAN: I just did.

CHAIRPERSON FROINES: Okay. What is the motion? State it again.

PANEL MEMBER FRIEDMAN: That we send -- we answer Mr. Lloyd's question, "No, we don't think that further assessment" -- whatever the wording is --

PANEL MEMBER GLANTZ: I think that we should answer the question. Or, here, I'll make the motion.

PANEL MEMBER FRIEDMAN: Whatever he said, what should we do, the answer is no. But we should say that there was a lot of discussion and we indicated our thoughts, which we've indicated further work on the part of the petitioner and possibly OEHHA.

PANEL MEMBER GLANTZ: Well, actually I would suggest just writing a letter back saying, "No," and leave it at that. Yeah, because I think the rest -- because the transcript is there and the views --

CHAIRPERSON FROINES: I don't think that's being very responsible. I think that -- I personally feel that the evidence is very close to making the answer "yes" from my standpoint, and that --

PANEL MEMBER GLANTZ: Right.

CHAIRPERSON FROINES: So I think to answer the question "no" and stop is to -- it's not quite appropriate --

PANEL MEMBER BLANC: I think there are two separate issues. Maybe I can help solve this a little bit. One is the question of: What does the finding of the Scientific Review Panel need to consist of? And, secondly, how should the finding be transmitted to the Air Resources Board?

So I think that from the narrow point of view there needs to be a resolution passed by the Committee, which I would propose in the following wording: The Scientific Review Panel does not find that there is sufficient new scientific data on the part of the petitioner to require reopening of the previous risk assessment by OEHHA. That's the resolution.

You should accompany the transmission of that resolution with a text letter which summarizes some of the discussion and some of our recommendations and refers to the transcript. And I think that would be fine.

But I don't think we need to embody in a formal resolution other aspects. My only clarification would be that -- what I would suggest that you put also in the text of the letter is that, in essence, the Committee -- in coming to this conclusion the Committee felt that the

response of OEHHA to the petitioner had scientific merit. Because part of our Scientific Review Panel is we're commenting back on whether, you know, appropriate science was used on OEHHA's part in their activities.

So there was a scientific approach by OEHHA to the petitioner's information, reviewing it. And they came back with comments. And there may be difference in nuance of view on those comments, but I don't think we're seeing anything inappropriate about the scientific approach of OEHHA in evaluating the petition and responding to it. And I think that does need to be in our resolution perhaps. But I think the text of your letter should also reemphasize that.

So I don't know if you got the wording to my proposed resolution. Or, Peter, did you manage to write that down?

PANEL MEMBER GLANTZ: Well, I think the intent here is to -- I mean, as I said and I think what Paul said, is I mean I think there's two separate issues that are getting kind of confounded here. One is answering the fairly -- the specific legal question that's been put before us about whether or not the risk assessment should -- enough evidence has put before us to reopen the risk assessment. And I just think the answer -- and I think that's what the letter should say. But I think we

have clearly indicated to OEHHA and to the petitioners sort of a path to follow in the future. And in terms of further sophistication of the model and the other evidence, should the formaldehyde people want to bring that forward --

PANEL MEMBER BLANC: So, Stan --

PANEL MEMBER GLANTZ: -- and we've also said to OEHHA they ought to be considered seriously. So --

PANEL MEMBER GLANTZ: So, Stan -- so you don't agree with my compromise suggestion?

PANEL MEMBER GLANTZ: Well, I don't see what you're suggesting is that different from what I was suggesting.

PANEL MEMBER BLANC: Well --

CHAIRPERSON FROINES: I think it's very different.

PANEL MEMBER BLANC: What I'm suggesting -- well, let me clarify what I'm suggesting. I worded a specific resolution, which is actually now on the table and someone can second if they want. And I'm deferring to the Chair's discretion that in transmitting that resolution to the Air Resources Board, that I think the Chair certainly would be within his rights to also describe the context of that decision and refer to some of the salient points of the discussion as are reflected in the minutes of the meeting.

PANEL MEMBER GLANTZ: Well, I don't have a problem with that. I think -- again, I don't -- I don't have a problem -- John, if you think that it would be useful or fair or anything else to describe some of the discussion here in accompanying the decision, I don't have a problem with that. I think there's one fairly specific question we have an obligation to answer. And I think everyone agrees that the answer to that question is no.

CHAIRPERSON FROINES: I don't think there's -- I do not agree with you.

PANEL MEMBER GLANTZ: You don't think --

CHAIRPERSON FROINES: I don't -- I won't vote because I'm the Chair. But I think that the -- I don't think it's clear that there is not sufficient new evidence to warrant a reevaluation of the risk assessment. I've been clear on that. I think there is work to be done to look at that issue further. But I think that there is new information and I think that -- I'm not even clear that OEHHA has taken -- I mean what is OEHHA's position? Is it your position that there is not sufficient information to warrant reopening? Is that your position?

SUPERVISING TOXICOLOGIST MARTY: That is our position.

CHAIRPERSON FROINES: That is your position.

Well, people -- like-minded people can disagree.

So it's something -- we're going to take a vote on the issue. But I don't -- I think it's important that if we vote no, that we also give it a context, because as far as I'm concerned I couldn't accept saying just no.

PANEL MEMBER GLANTZ: Well, no -- and I don't --

PANEL MEMBER BLANC: But that's what I'm suggesting.

CHAIRPERSON FROINES: I understand that's what you're suggesting. I'm talking to Stan.

PANEL MEMBER BLANC: But I think Stan's agreed with what I suggested.

PANEL MEMBER GLANTZ: Yeah, well, I mean -- and I don't object to that either. I mean the way I interpret the discussion is that at this point on the table in front of us right this moment there is not sufficient evidence to warrant reopening the risk assessment. There are some very intriguing information. There's some interesting information. There is some information that if there is further development of the models, further validation of the models, sensitivity analysis, et cetera, et cetera, then at some point in the future they might be able to come back and present a better developed case that would in fact lead the panel to say yes.

So I think in saying no we're not saying, "This is the most ridiculous thing we've ever seen in our lives.

Go away and stop bothering us." I think we're saying right now we don't have enough information. But, as I said, I think that the transcript clearly outlines the areas that we fell short and clearly outlines a sort of road map for moving forward.

CHAIRPERSON FROINES: That's fine.

PANEL MEMBER GLANTZ: And I think that's -- and I think that the petitioners, who seem highly motivated on this, you know, I would expect will take what's in the transcript and try to deal with it. I think we've said to OEHHA that we think dealing with formaldehyde should be a high priority. They don't seem to disagree with that. And I think we've said that if better -- if the sort of preliminary information that's been put before us is more thoroughly developed and fleshed out to the point where -- you know, where people are a little bit more confident, then they ought to consider it. But I think the record's pretty clear on it.

CHAIRPERSON FROINES: Okay. I think that -- I mean my view is that there is new evidence, but it's not sufficiently developed and so we're -- we're in a gray zone. So I would agree with the notion to say no, but also I want to be able to say that there is interesting information that requires further development.

PANEL MEMBER GLANTZ: I don't have a problem with

that.

CHAIRPERSON FROINES: And I also think that this panel should say explicitly to OEHHA that were the information to be developed further, then we would expect to see one as one of the 15 compounds next year. Melanie kind of was a little wishy-washy on that issue. And I think we should be explicit about it. I think we should say formaldehyde should come up as one of the 15, because there is -- this isn't -- this is not a trivial situation. We do have a fairly major degree of work that's been provided that should be taken quite seriously.

PANEL MEMBER GLANTZ: I don't think anybody's disagreeing with that. I didn't think Melanie -- I didn't think Melanie said one --

CHAIRPERSON FROINES: Well, she was a little -- Joe.

PANEL MEMBER GLANTZ: What do you, Melanie --

CHAIRPERSON FROINES: No, no, no, no. We don't have to get -- no, we're back with Joe.

PANEL MEMBER LANDOLPH: Just, you know, from my own point of view. Again, it's an intriguing model. It's intellectually interesting. It's got a lot of cell division and mutation rates. But there are some things in it I think a lot of us are not comfortable with. The nonlinearity between .5 and one parts per million, which

is the relevant dose, where the risk goes up a hundred fold. That's worrisome. I don't know what that means, and that and this great influence of the cell division parameters on it. So I'm not convinced the model is anywhere near settled yet. It needs a lot more developmental work.

CHAIRPERSON FROINES: There's no question about that. The CIIT position has, since the late seventies, viewed the cancer risk assessment data consistently, that they really believe that as you go from 1 up to 5 up to 15, that -- that what really is going on is cytotoxicity and cell replication, as we all know. And that's the driving ideological feature. But it's not that simple, and that's what we're asking them to look into more carefully.

Kathi.

PANEL MEMBER HAMMOND: What I'm hearing -- excuse me. There are two issues -- two reasons that the petition should be considered. And one is this new epidemiology evidence, one is the model.

And we've been talking about -- I think it was clear from what Gary said, that -- but I just want to get some clarity here -- that there's not sufficient new evidence from the epidemiology to reopen the consideration. So we're really just talking about the

model. And it seems to me from what I've been hearing from everybody speaking about this that the model is insufficient at the moment to reopen the consideration. However, the model is intriguing and so we would want to encourage OEHHA to become familiar with the model, to be looking at it. Not to say, "Oh, well, we don't need to look at it now because the Scientific Review Panel said that we don't need to reopen formaldehyde."

So I guess what I'm hearing, but maybe I'm missing something here, is that the petition itself should -- we would not be supportive of it on the basis of a model either because the model's not sufficient yet to reopen. But we do think -- and then the burden lies with CIIT to further develop and validate the model to make it sufficient to reopen. The specific concerns about the model have been mentioned both by Dale Hattis and by Dr. Landolph. But we do think that OEHHA should be paying attention to this model and looking at it in more detail.

CHAIRPERSON FROINES: Is there a second to Paul's resolution? Because you said --

PANEL MEMBER GLANTZ: Okay. I'll second.

I'll withdraw mine or --

CHAIRPERSON FROINES: What you said and what Joe said and -- I've lost track. But I think there is a general consensus among the panel. So I think we should

move to voting, unless there's -- unless we're going to start repeating ourselves.

PANEL MEMBER FRIEDMAN: Was it stated when I was out of the room? I'd like it -- I was out of the room for a couple of minutes.

CHAIRPERSON FROINES: Well, we never go back.

PANEL MEMBER BLANC: I simply word it -- yeah.

PANEL MEMBER FRIEDMAN: You said that we'd say no, but the Chairman has the prerogative to explain --

PANEL MEMBER BLANC: That's not part of the resolution. But I also said that it was the sense of the Committee that the Chair certainly had the prerogative to place this in a letter in context. That's not part of the resolution. The resolution is as I stated it. I don't think people need to have it read back. And I heard Stan second.

I wonder if someone would like to call the question.

CHAIRPERSON FROINES: Is there discussion?

PANEL MEMBER BYUS: Just one more point, john.

CHAIRPERSON FROINES: Sure.

PANEL MEMBER BYUS: I'm very intrigued by the model. It's a very good hypothesis. Hattis has very good criticisms of the model based on certainty, et cetera. But I think it needs to be experimentally verified, not

just dealt with mathematically in terms of degrees of uncertainty. It needs to be done experimentally. We need to see some data verifying the validity of the model, particularly this nonlinearity flux point.

Now, how that is to be done, I could make a variety of suggestions. But that's not likely to be done in like six months or a year. But the model is a good one and it just -- and it gets the mathematical concerns the degrees of uncertainty needs to be dealt with and all the things that Dale Hattis suggested is the expert. But we need to do some experiments to provide some data to show that the model is in fact predictive. That's -- and that is likely to take a reasonably long time to do. So I just wanted to make that clear.

CHAIRPERSON FROINES: That's not an entirely trivial --

PANEL MEMBER BYUS: No, it is not trivial. But this model is intriguing enough that if it had some experimental backup, it could be adopted. But if it doesn't have the experimental data it's -- to my point of view is less likely to be --

CHAIRPERSON FROINES: Well, I think there -- to the degree that they addressed what Hattis has suggested, that we -- we might then agree to dis -- I mean for some of us it might be sufficient, for others it might not.

And so that's something to take up at a later time.

PANEL MEMBER BYUS: That's fine.

CHAIRPERSON FROINES: I think that -- I do think that -- the one thing that worries me about taking up new mathematical modeling is that you can open the proverbial Pandora's Box and everybody and his brother will start petitioning --

PANEL MEMBER BYUS: Without experiments --

CHAIRPERSON FROINES: And so the greater the validation of data -- new data, the better off I think is a general principle.

PANEL MEMBER BLANC: So it seems like we have come to consensus. I think it would be useful to call the question.

PANEL MEMBER FRIEDMAN: I'm sorry. I really would like to hear what we're voting on.

PANEL MEMBER BLANC: Could you read back.

CHAIRPERSON FROINES: Say it again.

PANEL MEMBER BLANC: Resolved that the Scientific Review Panel finds that there is not sufficient new scientific data to support the petition to formally reopen the prior risk assessment on formaldehyde.

PANEL MEMBER FRIEDMAN: Thank you.

CHAIRPERSON FROINES: And you understand that there's another proviso which is -- it's not part of the

motion?

PANEL MEMBER BLANC: And I'll say that again afterwards. Let's vote on the motion first.

CHAIRPERSON FROINES: Are we ready to take the question?

All those in favor.

(Hands raised.)

CHAIRPERSON FROINES: It's unanimous.

PANEL MEMBER BLANC: Then I would like the minutes to reflect the consensus of the panel that it should be the Chair's prerogative in transmitting this resolution to the Air Resources Board to summarize the discussion that occurred and the context in which this decision was made both in terms of what further work on the model might be done as well as what priority OEHHA should place on formaldehyde in its SB 25 follow-up.

CHAIRPERSON FROINES: We don't need to vote.

PANEL MEMBER BLANC: No, as long as --

CHAIRPERSON FROINES: Stan, this is a tricky issue. You had apparently significant comments on silica, and you're about to walk out the door.

PANEL MEMBER GLANTZ: Right. But I'll call back in at 1:30.

CHAIRPERSON FROINES: Well, should we take up then something else before --

PANEL MEMBER GLANTZ: I would suggest that.
CHAIRPERSON FROINES: Where's Jim?
Jim, is this going to work with Stan calling in?
MR. BEHRMANN: I think -- they claim so.
CHAIRPERSON FROINES: So 1:30.
PANEL MEMBER GLANTZ: I'll call back about 1:30.
CHAIRPERSON FROINES: So we'll hold off silica till 1:30.
PANEL MEMBER GLANTZ: Okay. I'm sorry.
CHAIRPERSON FROINES: That means we miss Gary.
So it's -- I guess we have to make a decision about which one --
PANEL MEMBER GLANTZ: You could discuss it with Gary, and then I could call in later. But I've got --
PANEL MEMBER FRIEDMAN: I don't have strong feelings about it. So --
CHAIRPERSON FROINES: Stan, do you have strong views? Would you -- I mean is it important for you to be --
PANEL MEMBER GLANTZ: I can just quickly say for the record if you want --
CHAIRPERSON FROINES: No, no, no, no, no.
PANEL MEMBER GLANTZ: Well, no. What it is -- and then I do have to run.
CHAIRPERSON FROINES: I don't think this is going

to work.

PANEL MEMBER GLANTZ: What, for me to call in later?

CHAIRPERSON FROINES: For you to make now a two-minute presentation.

PANEL MEMBER GLANTZ: Okay. I think I'll just call in and I can listen to the presentation. There have been some specific statistical issues about silica that I've looked at. I've had several discussions with OEHHA about them. And we'll just discuss them in the context of the presentation.

CHAIRPERSON FROINES: Is one of those issues the Berry comment -- most recent comments, I hope?

PANEL MEMBER GLANTZ: Yeah. Is that the one about the life table versus --

CHAIRPERSON FROINES: Yes.

PANEL MEMBER GLANTZ: Yeah, that's right.

CHAIRPERSON FROINES: Your input would be very valuable on that.

PANEL MEMBER GLANTZ: Okay. So that's --

CHAIRPERSON FROINES: So 1:30 then.

PANEL MEMBER BLANC: Out of deference to our stenographer, can we have a break?

CHAIRPERSON FROINES: Can we take a ten-minute break.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Let's move ahead. He'll be here momentarily.

Naphthalene.

SUPERVISING TOXICOLOGIST MARTY: Okay. The next item is discussion of the unit risk factor for naphthalene.

To my left is Dr. Joe Brown. He will be giving a presentation first on why we are looking at naphthalene and then on what we did to develop a unit risk factor.

Joe.

(Thereupon an overhead presentation was Presented as follows.)

STAFF TOXICOLOGIST BROWN: Thank you, Melanie.

I have a few background slides to start with here.

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STAFF TOXICOLOGIST BROWN: The first slide gives a little bit of background on the regulations naphthalene fall under: Toxic Air Contaminants Act, AB 1807; the Air Toxics Hot Spots, AB 2588; and also naphthalene as a PAH would probably also fall under SB 25.

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STAFF TOXICOLOGIST BROWN: Structure naphthalene.

This is the structure of naphthalene.

Naphthalene is a toxic air contaminant based on two criteria: It's a federal hazardous air pollutant, or an HAP, under the U.S. Clean Air Act of 1990. And, therefore, it's a TAC is a single substance. It's also a member of the class Polycyclic Organic Matter, POM. POM is separately a HAP and a TAC.

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STAFF TOXICOLOGIST BROWN: Industrial emissions of naphthalene are reported to be 360,000 pounds in 1997. Primary source is probably vehicle exhaust. Also occurs in wood burning. And it's a component of environmental tobacco smoke. The 12-hour average ambient air concentrations range from 348 to 715 nanograms per cubic meter in 1994 in California.

This is data from Atkinson in 1995.

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CHAIRPERSON FROINES: Can I just make one comment about that, Joe?

STAFF TOXICOLOGIST BROWN: Sure. Go ahead.

CHAIRPERSON FROINES: First is we've been -- we have sampled for naphthalene across 12 different communities in the Los Angeles basin, and we find values up to 6,000 nanograms per cubic meter. Distribution is very skewed.

And I should say for the panel that may not be

aware of this. If you compare the -- in Riverside, for example, where Craig's from, the average that we measure is around 580-600. But the point I wanted to make is that the level of benzopyrene, which gets most of the attention in this field, is around 100 picograms per cubic meter. So it's about -- in terms of our values, we tend to find that naphthalene is somewhere between 5,000 and 50,000 times greater than any other PAH that we see in the Los Angeles basin. So it's quite a dramatic exposure issue.

PANEL MEMBER HAMMOND: And just, you know, to add to that, we've been doing measurements in Fresno and seeing very similar results.

STAFF TOXICOLOGIST BROWN: It's a problem.

PANEL MEMBER HAMMOND: Yeah, year-round measurements there, too.

STAFF TOXICOLOGIST BROWN: This slide gives a little background on the non-cancer health effects. Respiratory effects seen in mice. Damage to the respiratory tract, including inflammation, epithelial changes, damage to ciliated and Clara cells of the bronchiolar epithelium, with neonatal mice being more sensitive.

There's also a report on hemolysis and methemoglobinemia in infants exposed to high doses of naphthalene. This was not by inhalation, but by oral and

dermal route.

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STAFF TOXICOLOGIST BROWN: There is a chronic inhalation reference exposure level, or cREL, for naphthalene established by OEHHA in 2000 of nine micrograms per cubic meter, or two parts per billion, based on respiratory effects in mice: Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia.

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STAFF TOXICOLOGIST BROWN: Carcinogenicity. There's an NTP 1992 study -- inhalation study in mice, giving some evidence -- that was the official conclusion -- of lung tumors in female mice.

NTP ran an inhalation study in rats in 2000. And this study showed clear evidence of respiratory epithelial adenoma in male and female rats; and olfactory epithelial neuroblastoma, a rare tumor, in male and female rats.

IARC in 2000 reclassified naphthalene as Group 2B, possibly carcinogenic to humans. Other relevant data include genetic toxicity. Studies in bacteria are generally negative. Studies in some mammalian cells are positive.

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STAFF TOXICOLOGIST BROWN: These are the bioassay

results of -- a summary slide of them. Across the top here you can see the concentrations used. These are generally six hours per day, five days per week. Here we have the results of the mouse study from 1990. Lung alveolar and bronchiolar adenomas and carcinomas. These are the quantal responses, the control, and the test concentrations.

The P values in this column here are the trend -- significance value for the trend test. And values for pairwise comparisons are given under the individual exposure levels, significance for that level versus the control.

So as you can see in the mice, we have a significant trend, but only a significant effect at the top dose.

Moving down to the female rats. The two nasal tumors, the nasal respiratory epithelial adenoma in the top row here, given a quantal response. Significant trend and significant effects across the board in pairwise comparisons.

And for the nasal olfactory epithelial neuroblastoma, there's a significant trend, but only a significant pairwise comparison in the mid dose.

For the female rats the nasal olfactory epithelial neuroblastoma gave a trend test, but only a

significant effect in the top dose. I should point out here that the numerators we use in these studies are generally the animals at risk. We don't include those animals that died before they had a chance to get the tour.

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STAFF TOXICOLOGIST BROWN: Now, the dose response methods we used were the linearized multistage model in the guidance we issued in 1985. This is a q1* by the MSTAGE -- in the MSTAGE program published by Crouch in 1992.

We also used the LED10 method put forward by the U.S. EPA in their 1996 proposed cancer guidelines and the latest version of their software to use this method, the Benchmark Dose Software version 1.3.2 of 2002.

We also used a multisite potency, a Monte Carlo method for combining two of the nasal tumors -- individual tumor potencies into a combined value.

We used interspecies scaling, body weights of human over body weight animal to the one-third power. And this factor was applied to the potency.

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STAFF TOXICOLOGIST BROWN: We use these inhalation elemetric relations to estimate the amount of naphthalene inhaled during the bioassays. The body

weights for the mice here and the rats were the time-weighted average body weights over the course of the bioassay.

And we assumed that inhalation uptake was equal in all species. We didn't have sufficient information really to differentiate that. We did look at potential pharmacokinetic differences and we didn't identify any.

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STAFF TOXICOLOGIST BROWN: This slide summarizes the potency values and the goodness of fit test for the multistage method analysis. You can see here, in the first column we have the animal potency in terms of per milligram per kilogram died, the human value based on the scaling, the human unit risk in terms of milligrams per meter cubed -- per milligram per meter cubed, and the goodness of fit statistic. And this statistic, the criteria was a value that equaled or exceeded .1 on a chi square goodness of fit test.

And here we have the various end points that we looked at: The female mice tumors and the various male rat nasal tumors; the combination of the male rat tumors, which is bold faced here because this is the value we actually used in the end, the 0.34 is the key value. But also we have the female nasal epithelial neuroblastoma value here on the bottom. They're all highly significant

good fits.

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STAFF TOXICOLOGIST BROWN: If you look at the next table, this is the result of the parallel LED10 analysis. And the values are almost identical. In this column we have the LED10; the human potency; the human unit risk value, where we had .034, by the multistage we had .031 by using this method. So they're virtually identical. And the fits are also excellent.

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STAFF TOXICOLOGIST BROWN: This just gives a picture of the LED10 methodology, which some of you may not be familiar with. The object here is to fit the observed data to any one of a series of dose response models. In this case, we use a quantal linear model.

And the critical values here are the 10 percent effect left, which is shown here, 10 percent over the background, and the lower bound on that level here. So in this case the unit risk -- and this was the dose in parts per million and the fraction of having tumors. Unit risk would simply be the slope of the line drawn between this point here -- and to keep my hand steady -- and the origin, or simply this value divided by this value here, which would be the slope of that line. Plus various correction factors would be added onto that.

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STAFF TOXICOLOGIST BROWN: Summary is that using either methodology, the 95 percent upper confidence bound on the unit risk value is in the range of .014 to .034 per milligram per meter cubed based on tumor incidence data and female mice and male and female rats from the NTP 1992 and 2000 studies.

The male rat was the most sensitive sex and species tested. And the NTP considered the rare nasal tumors to provide clear evidence of carcinogenicity for naphthalene. The potency and unit risk values for the combined nasal tumors are considered the best values for the purpose of risk assessment.

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STAFF TOXICOLOGIST BROWN: And on the next slide I summarized these values.

For the naphthalene unit risk and units of milligrams per cubic -- per milligram per cubic meter, .034 or 3.4 E minus 5 per microgram per cubic meter or 0.12 per milligram per kilogram per day.

The predicted risk at the high value noted by Atkinson here in 1995 would even be higher, based on Dr. Froines' statement, of 715 nanograms per cubic meter would be 2.4 E minus 5 lifetime risk.

SUPERVISING TOXICOLOGIST MARTY: We're going to

stop right here. That's all we have for summarizing what we did. We do have more slides touching on the key comments that we received during the public comment period and our responses.

CHAIRPERSON FROINES: Why don't you go ahead with those.

SUPERVISING TOXICOLOGIST MARTY: Okay.

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STAFF TOXICOLOGIST BROWN: Okay. The first comment summarized, the commenter objected to the adjustment of the numbers at risk for the early deaths in the bioassay results.

Our response was this is an appropriate method and also standard procedure according to OEHHA cancer risk assessment guidelines. The fact is we've been doing this for years, and I don't -- you know, we're sort of surprised at this comment actually.

PANEL MEMBER BLANC: Well, didn't you also make the point that this is also standard not just for you guys but EPA and everybody else?

STAFF TOXICOLOGIST BROWN: Yes. And also you get a better fit to the data if you do this.

PANEL MEMBER BLANC: No, I'm just saying I thought that was a convincing response.

--o0o--

STAFF TOXICOLOGIST BROWN: Another comment was the model chosen to fit the data for the LED10 method was inappropriate and the fit was poor. Well, this is related to the first response.

When the applied -- when applied to the data adjusted for survival the chosen model was the best solution, is a good fit. In fact, I showed the slide there of the degree of fit. And it was -- it certainly met the fit criteria. The key point is here you need to adjust the data properly.

--o0o--

STAFF TOXICOLOGIST BROWN: Third comment is: Naphthalene acts by a non-genotoxic mechanism, so the risk assessment should use the LED10 method with a margin of exposure rather than a linear low dose extrapolation.

The alternate method of the LED10 approach is to just apply essentially an uncertainty factor for that point of departure, I pointed out on the slide, rather than to extrapolate or get a slope and predict a risk.

Now, our response is: OEHHA's standard approach uses linear low dose extrapolation unless mechanistic data are only consistent with an alternate method. Data on metabolism, genetic toxicity and cytotoxicity are consistent with a genotoxic mechanism. Therefore, the standard linear approach is appropriate.

To our way of thinking you need to really prove a nonlinear approach. The default is the approach we've taken basically. And I don't -- I mean we haven't been shown data that convinces us that the approach is nonlinear. I know that's open for discussion.

PANEL MEMBER BLANC: Can you clarify something that confused me in the argument made in at least one of the submitted comments --

STAFF TOXICOLOGIST BROWN: I'll try.

PANEL MEMBER BLANC: -- which seemed to go -- maybe I misinterpreted the argument, but it was almost as if the argument was that it was genotoxic but not mutogenic and, therefore, it shouldn't be a nonlinear factor. I mean there was a lot of hand waving about how the mutogenicity data were equivocal in certain assays but that -- and then they cited as support of that that it seemed to induce chromosomal abnormalities without being mutogenic in mutogenicity assays and, therefore, it wasn't genotoxic.

And I wondered -- it seemed to be a somewhat confusing use of the language. And it would be useful for me to hear from OEHHA's point of view -- I would assume that you would approach something which caused chromosomal abnormalities as being genotoxic whether or not you could show it was mutogenic.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We do actually --

STAFF TOXICOLOGIST BROWN: I agree.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We do actually have some slides in a minute which we can -- where we can talk a little bit more about the genotoxic data. But certainly OEHHA's position is that, you know, these various kinds of endpoints all represent some form of genotoxic hazard and would be, you know, considered as evidence on the side of presuming a genotoxic mechanism for the purpose of the low dose extrapolation here.

As to the argument about -- in the comment, I must admit if I could figure out exactly what it was they were proposing, I would probably disagree with it. But --

PANEL MEMBER BLANC: Well --

SUPERVISING TOXICOLOGIST MARTY: I think it's important to note that in terms of assays for genotoxicity, you don't weight them all the same because they aren't actually measuring all of the same thing in terms of the mutation produced. So it's a false argument to say, "Well, we have, you know, ten negative studies and five positive studies. Therefore, it is not genotoxic."

PANEL MEMBER BLANC: That was only part of their argument. But the other -- wasn't there a part of their

argument was implying that it wasn't mutogenic; and, granted, it is genotoxic; but, therefore, because it's genotoxic but not mutogenic, you should do something different? Didn't they themselves in their own argument describe it as being genotoxic?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. And I think we -- and we disagree with the premise behind that argument.

PANEL MEMBER BLANC: So one of the things that I did think about, that OEHHA's reply perhaps to their criticism was that you could have even made the same argument that you made even stronger. I'm not undermining your rejection of their argument. But I thought that there was some more fatal flaw in their reasoning that didn't quite come through as strongly in your reply as could have been. But maybe I'm the only one who read it that way.

John, did you -- I mean you're near knee deep in this stuff. So did you --

CHAIRPERSON FROINES: I'm going to comment on it in a few minutes at some length. So we don't need to -- I'd rather give a longer presentation than to sort of deal with it in this context.

PANEL MEMBER LANDOLPH: I think this is rather straightforward. I think they were trying to define

clastogenic as nongenotoxic. To me genotoxic is an all-encompassing term. But clastogenic fits in there. And if this clastogenic, then it is genotoxic and then there is a linear no-threshold dose response curve, unless they can provide strong evidence to the contrary. And there is no evidence to the contrary for existence of a threshold whatsoever.

STAFF TOXICOLOGIST BROWN: Right, and that that's the only mechanism.

PANEL MEMBER LANDOLPH: And that's the argument, I think. So I think they're mixing -- they're not using the language properly, I think, is what I sensed.

PANEL MEMBER BLANC: Okay. Good.

So I didn't -- it's not something that I missed. Because when I read it I thought, "Wait, am I" -- you know, did something pass me by, did I sleep through that lecture or -- you know that feeling that you have? Okay.

--o0o--

STAFF TOXICOLOGIST BROWN: This slide just summarizes some of the metabolism on naphthalene. It's not surprising that it forms epoxides, diol epoxides, quinones, types of chemistry similar to other carcinogenic polycyclic aromatic hydrocarbons. So it's not implausible at least based on metabolism that something like this could be a genotoxic carcinogen at least based on

metabolic considerations.

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STAFF TOXICOLOGIST BROWN: This is a summary slide of the genotoxicity showing the individual assays and the results. You know, there are a bunch of negatives, there are some positives. I don't know if you want to comment on specific tests.

--o0o--

STAFF TOXICOLOGIST BROWN: There's also a few results on some of the metabolites, also positive results and negative results. It's a bit of a mixed bag. I don't know if you can take this and prove a nonlinear mechanism. Frankly, I don't think you can.

PANEL MEMBER LANDOLPH: Could you go back one slide for a second please.

STAFF TOXICOLOGIST BROWN: Sure.

This is without or with observation?

This is our IT.

PANEL MEMBER BLANC: Can you comment on whether or not the microsomal-enzyme-added salmonella test results are consistent with the salmonella mutogenicity on the next slide of the metabolite -- is, therefore, this -- yeah --

STAFF TOXICOLOGIST BROWN: They're only negatives.

PANEL MEMBER BLANC: No, the 1,2 -- the 1,2-naphthoquinone --

STAFF TOXICOLOGIST BROWN: -- metabolite is positive.

PANEL MEMBER BLANC: Is positive?

STAFF TOXICOLOGIST BROWN: Yes.

PANEL MEMBER BLANC: Is the 1,2-naphthoquinone not a metabolite that would be generated by the microsomal enzyme?

STAFF TOXICOLOGIST BROWN: Well, let's see. The naphthoquinone would be up in here. Let's see if I can point this out.

Right here. That's it right there.

PANEL MEMBER BLANC: I'm just trying to understand biologically why it wouldn't have -- but the only interpretation of why it's not positive in the Ames test as the parent compound is that the liver microsomal enzymes don't metabolize it to this limit?

STAFF TOXICOLOGIST BROWN: There's lots of reasons for something to be negative. But when you find something positive, you know, that's something I can respond.

PANEL MEMBER LANDOLPH: Yeah, you have to be very careful because when you're dealing with quinones you get redox cycling. And Bruce Ames and his colleagues had to

devise a special strain to capture oxygen radical damage in the first place. So that could be a very tricky issue, you know, the detection sensitivity of the various strains, because the reversion's very specific. So you could miss something.

STAFF TOXICOLOGIST BROWN: I don't think we're claiming we have a mechanism here. We're just claiming plausibility.

PANEL MEMBER BLANC: I mean, yeah, that's about -- the nature of my question is to plausibility, because if there was a straightforward answer, which is that the liver microsomal enzymes don't metabolize down this pathway, therefore the quinone metabolite is not produced in the Ames test unless you put in the metabolized compound itself, it won't -- the parent compound won't generate the metabolite question. Because when they test in the same assay the metabolite, it was positive for mutation.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think typically the conditions which you have in the standard salmonella reverse mutation assay not particularly conducive to picking up signals from this kind of metabolite, as Joe said. So the fact that it would be generated at perhaps rather simply low concentrations by metabolism in the petri dish with S9

could -- you know, that could be missed.

Whereas, if you were basically putting a bucket loadful directly in the actual assay in the metabolite, then, you know, perhaps the less sensitive test strain is adequate. But this is a common problem, as Joe was saying, with detecting this kind of response.

SUPERVISING TOXICOLOGIST MARTY: That's all we had.

CHAIRPERSON FROINES: Okay. I think that there needs to be some points made about this -- about the questions Paul's asking.

I think that this document -- I'm the lead from that point.

One of the problems with this document isn't anybody's fault. It's the fact that this is already a TAC. So we're not developing a document for a TAC determination. What we're doing is basically doing a risk assessment. And so one could have a very brief document that focuses on the risk assessment. I don't have any problems with the risk assessment whatsoever. So as far as I'm concerned, case done, the issue's over.

But I think that there is another issue here, that I'm very sensitive to for a number of reasons. And, that is, that I think in some respects it's important to have some information on mechanism because that goes to

the issue of biological plausibility, which Paul's been raising and Joe's commented on.

Now, in the first place we've done measurements throughout the Los Angeles basin in 12 different communities. And the first thing that one has to say is we find naphthoquinone in every place we look in Los Angeles. There is no place in all of southern California where you don't find 1,2- and 1,4-naphthoquinone, period. It's everywhere. And it comes from naphthalene.

So forgetting metabolism for a moment, we have to control naphthalene in the environment because it's formed when you combust fuel. So that naphthoquinone is always going to be present. It's hot-tube chemistry. You take a fuel and you put it in a hot tube and you produce naphthoquinones because you take naphthalene and you add oxygen as part of the combustion process, you get quinones by definition.

And the second thing is we now know from some work that's been published that if you take nitronaphthalenes that are formed in atmospheric chemistry, they degrade to naphthoquinones. If you measure what happens with 1,4-naphthoquinone as you go from the coast to Riverside, the amount of naphthoquinones increases. In other words, we're forming naphthoquinones from atmospheric processes.

And fourth, it's been known since the second world war that naphthoquinones are a metabolite of naphthalene. And I brought the papers to show it, that this issue of the metabolism has been known since Louis Fieser worked on naphthoquinone antibacterials during the second world war. And there are papers on naphthalene metabolism in 1953 in the biochemical journal. And so that it's not as though this is a mystery science. This has been something for which there have been dozens of papers developed over the last 50, 60 years.

Now, if we started talking here about -- so naphthalene ends up, in part at least, as naphthoquinone.

If we were talking about Butadiene, we would talk about Butadiene for about two minutes and then we would get into the mono and diapoxide because we would say the carcinogenicity comes from the mono and diapoxide. And so we wouldn't even bother to spend much time with Butadiene because we know we have to talk about a metabolite.

But somehow with naphthalene we don't -- we get to this issue of its metabolism late in the discussion as though it's a mystery process. Well, it's not a mystery process. It's a very well documented process.

So that we should be talking about the metabolize of naphthalene almost immediately because it's the same bio-transformation or atmospheric transformation. So

that's what I want to say.

Now, once having said that, the other thing that's true is naphthoquinone binds with glutathione and causes a DNA damage, and may be much more potent when it's bound to glutathione. So that there are two toxic elements that get formed. One is the glutathione conjugate which can be excreted, but also is itself capable of redox chemistry and electrophilic activity.

And so --

PANEL MEMBER BLANC: That's unusual, isn't it?

CHAIRPERSON FROINES: Well, not with quinones. Quinones -- people should need to know more about quinones, because they're ubiquitous and they don't get enough attention, although they have supertoxicity.

So, anyway, they do do redox chemistry. But we developed an assay from measuring the electrophilicity of quinones. And it turns out in our assay that 1,4-naphthoquinone is the most electrophilic of the quinones that we've measured so far. So you have electrophilicity that is binding with thyols and DNA bases as well as the redox activity that Joe's been talking about.

So, bottom line, to answer your question, naphthoquinone is genotoxic. And there's plenty of evidence to show it. For example, here's a paper by --

there are -- Steve Rappaport, who we all know, has all these albumin adducts that he's been looking at.

Here's a paper, it talks about a change in function mutations in P53. That's a 2002 paper.

Here DNA strand scissions by quinone -- by the same quinones.

In other words, there's an enormous literature. And somehow one gets the impression that there's no literature. So we get this document that talks about -- that it's not genotoxic that we get yesterday on E-mail, which is another issue. But the fact of the matter is they don't talk -- everything that I've just said, they don't say one word about in their document. It's as though it's selective reading of the literature.

Well, the fact of the matter is that it's very likely that the toxicity of naphthalene occurs because of naphthoquinones, and naphthoquinones produce reactive oxygen species. They're genotoxic. They react with biol groups, and so on and so forth. And we could spend hours talking about this science.

So that to me the issue is -- should be obvious. And the fact that it's not means that we're either not looking at the literature properly or that people are selectively looking at the literature, or whatever the devil the reason. But I think that we can predict the

toxicity of naphthalene. I mean naphthalene produces cataracts. You didn't put that on your slide, but we know that. And so on and so forth. And those are naphthoquinone metabolized.

So that the bottom line, as far as I'm concerned, is I think it would be helpful if you had put a bit more in your document, because I think the evidence is so strong. But I think that the bottom line is that we need to treat naphthalene very seriously given its -- one, given the fact that it produced brain cancers, where in the entire history of the NTP bioassay they had never seen a control animal with the same tumors. So I don't know how many control animals they looked at over the years, but it must be 700,000 to 800,000. And they've never seen that brain cancer.

I chair the NTP -- chaired -- past tense -- chaired the NTP Committee that reviewed naphthalene for NTP. And our committee voted 9 to 0 to list it as reasonably anticipated to be a carcinogen. So our committee was made up of academics and others from around the country. So that vote was clear. And the reason for the vote was the uniqueness of the brain tumors that were seen with naphthalene.

PANEL MEMBER BLANC: John, can you --

CHAIRPERSON FROINES: So I'm done. I just wanted

to -- I obviously have a big stake in naphthalene because we do research on it. So I'm just full of -- I could talk for hours. But I'll stop here. But the point is I think we need to stop thinking -- we don't think of benzo[a]pyrene as the carcinogen. We think of a whole series of other kinds -- whether it be quinones or diol epoxides or what have you. And we should treat naphthalene the same way, I think.

Joe.

PANEL MEMBER LANDOLPH: Yeah, I agree with everything you said. I think the other thing, you know, you might want to incorporate into the discussion is -- as you well pointed out, Dr. Brown, naphthalene has some hematotoxicity. And I was sitting here thinking, you know, that's exactly what Benzene has, and they both make quinones and they both redox cycle.

And then as you go from Benzene to naphthalene up to the higher congeners like benzopyrene, obviously you make a quantum jump because those are able to, you know, metabolize by P450 to diol epoxides and very efficiently form DNA adducts, whereas Benzene and naphthalene don't. Benzene's always been considered an outlier. But they act more by virtue of redox cycling.

The higher polycyclics will also make quinones which can redox cycle. So they can do both things.

Naphthalene and Benzene are missing the very strong DNA adduction properties. But they're acting through degeneration of these redox cycling quinones along the ways John also mentioned.

PANEL MEMBER BLANC: So I guess --

CHAIRPERSON FROINES: And for ARB, we have a method for measuring quinones -- for measuring quinones across the Board in the air. And so one of the things that ARB should consider is should you be measuring quinones in your monitoring program, because they're out there.

PANEL MEMBER BLANC: So, John, part of this discussion in a way is reminiscent of our discussion of Metam-Sodium and whether or not the OEHHA needed to consider up front in that document Metam-Sodium and its breakdown products, if you recall that discussion.

What I'm not -- I don't hear you going as far as to say that this should be called -- that this document should be on naphthalene and 1,4-naphthoquinone, are you?

CHAIRPERSON FROINES: Huh-uh.

PANEL MEMBER BLANC: So what you're saying rather is that in appropriate sections, including the introduction, there'll be more emphasis on the importance of the quinone breakdown product and that it be made clear that this occurs not only in -- as a metabolite and

biological systems, but as a photo-chemical or atmospheric reaction by-product as well as a thermal breakdown product in the combustion engines?

CHAIRPERSON FROINES: I'm basically reacting or responding to this naphthalene is not genotoxic argument, which we've gotten a number of comments including this document that came in the mail yesterday. And it doesn't address the main issues as far as I'm concerned. And so I'm -- what I'm really saying is we need to I think have in the document something that says -- that refers to some of this literature that says, yes, there is more evidence.

Now, Joe's added some, because I hadn't seen that slide before. Because he's took some of the naphthoquinones and actually looked at some of the genotoxicity data. And I don't know references those are to.

So I think that we just could very easily and briefly just strengthen the case by acknowledging that there are pathways that have relevance.

SUPERVISING TOXICOLOGIST MARTY: We'd be happy to do that.

STAFF TOXICOLOGIST BROWN: Sure. Easy.

CHAIRPERSON FROINES: But I didn't have any comments on the risk assessment in a negative sense.

So I would make a motion that we approve --

PANEL MEMBER BLANC: Do you think the risk assessment adequately takes into account by its design, because of the animal data that it uses, the quinone metabolite, or does it underestimate the risk by not looking at pure quinone?

CHAIRPERSON FROINES: I think -- I think that the uniqueness of those cancers is such that there's nothing else you could do but use that. I would -- so, example, if they had come in and wanted to use the mouse data, I would have been unhappy with that. They didn't. They came in -- I think that the tumor endpoint of consequence is the rat tumor endpoint. And so, therefore, that's what one should use for the risk assessment.

And, you know, as Joe and I both said, you know, you've got this redox cycling and you've got electrophilic activity which is more direct genotoxicity. And so that would just muddy up the waters, I think, to try and look at that. I don't think we really have the data to do it anyway.

PANEL MEMBER BLANC: I have one small comment, which I wouldn't even make except that it's generalizable to other situations that you may be in when you're running these reports, and I want to make sure that the terminology is consistent.

There's a part where you're talking about the

non-cancer health effects. And you're dealing with susceptibility to, you know, a med hemoglobin degeneration, and you used the term "hypersensitive" to this effect. And I would suggest that you don't use the word "sensitive" as people may misinterpret that as implying that -- susceptible is probably a better term.

CHAIRPERSON FROINES: By the way, there's also -- for Janette's and ARB's purposes, there's a fair literature that's developing on using naphthalene as a marker for jet fuel exposure. And I have those references with me in case you're interested in taking a look at them. Because they are -- clearly airports are something that we need to spend some focus of attention at this point. And there's -- I have -- there are quite a number of articles that I piece together on the jet fuel issue.

So I make a motion that we accept the document, recognizing that some small changes will be made.

Is that a --

PANEL MEMBER LANDOLPH: I'll second it.

CHAIRPERSON FROINES: Do we generally put -- Jim, do we generally say recognizing or acknowledging that small changes will be made in the resolution?

MR. BEHRMANN: Yes.

CHAIRPERSON FROINES: Or do we just --

PANEL MEMBER BLANC: Yeah, yeah, yeah.

CHAIRPERSON FROINES: Rather than just voting on the document?

PANEL MEMBER BLANC: Yeah, yeah.

CHAIRPERSON FROINES: Okay. Further discussion?

All those in favor?

(Hands raised.)

CHAIRPERSON FROINES: Unanimous, 4 to 0.

So what time is it?

PANEL MEMBER BLANC: Time for lunch.

It's 12:20.

CHAIRPERSON FROINES: It's 12:20?

So we should take lunch and then come back and start silica about what time?

1:30.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: Why don't we get started.

Melanie, I think we'll just assume that Stan will call in at some point. He probably has traffic problems getting back.

You know, I know you people in northern California have traffic problems, whereas we don't in southern California.

SUPERVISING TOXICOLOGIST MARTY: Okay. The next item for discussion is our chronic reference exposure level for our respirable crystalline silica. This was done under the Air Toxics Hot Spots Program.

So we'll be, in addition -- additional chronic REL for risk assessments conducted under that program.

And Jim Collins and Andy Salmon will be giving the presentation.

(Thereupon an overhead presentation was Presented as follows.)

STAFF TOXICOLOGIST COLLINS: So, first of all I'd like to go for the prior actions we've had on chronic reference exposure levels.

The technical support document for determination of non-cancer chronic reference exposure levels, an initial draft was available for public comment October 1997. The second draft based on revisions of the first

was available in September 27th, 1999. We then presented the guidelines in the first 22 chronic RELs to the panel. And after the panel's endorsements the OEHHA Director adopted the methodology and the chronic RELs on February 23rd, 2000.

In addition, there were three chronic RELs that we had in existing TAC documents that were incorporated. Those were acetaldehyde, perchloroethylene, and diesel exhaust.

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STAFF TOXICOLOGIST COLLINS: Subsequently, we looked at several other batches of chemicals. We had something called Batch 1B in which there were 16 RELs adopted in April of 2000. Batch 2A had 22 RELs adopted in January of 2001. Batch 2B, 12 RELs at the -- in December 2001. And then there were some individual chemicals, carbon disulfide, phosphine, triethylamine, and fluoride, that were adopted in 2002 and 3. So we have a total of 79 chronic reference exposure levels adopted so far.

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STAFF TOXICOLOGIST COLLINS: The Hot Spots Act was passed in 1987. And respirable crystalline silica was listed as a Hot Spots chemical in 1988. The annual emissions from stationary sources in California is estimated to be approximately 3 million pounds. Some of

the sources and emissions are sand and gravel mining, glassware manufacture, diatomaceous earth processing and cal signing and other sources. A chronic REL was requested by the ARB in 1998, and some air districts requested the same thing in 2000. There's a large amount of occupational data from human workplace exposure available in peer review literature.

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STAFF TOXICOLOGIST COLLINS: Is he on?

Several investigators are also concerned --

PANEL MEMBER GLANTZ: Hi. This is Stan.

STAFF TOXICOLOGIST COLLINS: Hi, Stan.

PANEL MEMBER GLANTZ: I can hardly hear you.

STAFF TOXICOLOGIST COLLINS: Okay. We're on the fourth slide.

PANEL MEMBER GLANTZ: Okay. The fourth slide of what?

STAFF TOXICOLOGIST COLLINS: Of the silica presentation.

PANEL MEMBER GLANTZ: Okay.

STAFF TOXICOLOGIST COLLINS: It's the -- the first bullet is listed as a Hot Spots chemical in 1988.

PANEL MEMBER GLANTZ: Okay.

STAFF TOXICOLOGIST COLLINS: Okay. The last bullet: Several investigators are concerned that the risk

of silicosis at the workplace -- current workplace standard of 50 micrograms per cubic meter --

PANEL MEMBER GLANTZ: You're kind of coming in and out. I can't hear you.

PANEL MEMBER BLANC: Well, there's nothing we can do about that, Stan.

STAFF TOXICOLOGIST COLLINS: How's that?

Okay. Next slide.

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STAFF TOXICOLOGIST COLLINS: Now, although we're going to dwell on silicosis as determined by x-ray and by autopsy today, I'd also like to point out that the American Thoracic Society stated that studies from many different work environments suggested exposure to working environments contaminated by silica at dust levels that appear not to cause roentgenographically visible simple silicosis can cause chronic air flow limitation and/or mucous hypersecretion and/or pathologic emphysema.

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STAFF TOXICOLOGIST COLLINS: Silicosis is an irreversible, progressive fibrotic disease of the lungs caused by inhaling crystalline silica. Some of the cohorts of workers that have been studied are gold miners in South Africa, gold miners in South Dakota, diatomaceous earth workers in Lompoc, California, tin miners in China,

granite workers in Vermont, hard rock miners, Ontario, Canada, and industrial sand workers in the United States.

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STAFF TOXICOLOGIST COLLINS: For this REL we used standard benchmark concentration method with the U.S. EPA's BMDS software, which Joe Brown mentioned earlier. The original method of doing RELs was the NOAEL/LOAEL approach. But wherever data are available and we can use a benchmark concentration, we attempt to do so.

As our key study we used a well-conducted epi study of gold miners in South Africa, and we also calculated RELs for several other cohorts which included South Dakota gold miners, diatomaceous earth workers, and Chinese tin miners.

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STAFF TOXICOLOGIST COLLINS: The key study was a study by Hnizdo and Sluis-Cremer, published in 1993. They had a cohort of 2,235 white South African gold miners, who had spent I believe a minimum of ten years doing underground mining. And they found among that cohort 313 cases of silicosis as diagnosed by x-ray criteria.

The LOAEL for this cohort was approximately three milligrams per cubic meter-years of cumulative dust exposure. So a person exposed to one milligram per cubic meter a year for three years would have that exposure, or

someone exposed to half a milligram per cubic meter for six years would have that exposure.

The NOAEL was the lowest group, which was zero to two milligrams per cubic meter of cumulative dust exposure. That dust contained according to the authors 30 percent crystalline silica.

We then took the data, which were about six or seven data groups, which I'll show you in a minute, fitted a model to it, and came up with a BMC01 of 2.1 milligrams per cubic meter-year of cumulative dust exposure or .636 milligrams per cubic meter year of silica exposure. The BMC01 is a lower confidence limit on an amount of silica -- cumulative silica exposure that would give a one percent incidence of silicosis.

These miners were exposed eight hours a day, five days a week. We assume in their eight hour work shift they inhale approximately one half of their 20 cubic meter daily air intake. The exposure duration for this cohort ranged from 9 to 39 years and the mean was 24.

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STAFF TOXICOLOGIST COLLINS: We then calculated if they were working for 24 years what was their average worker exposure. And we divided the 636 by 24 and came out with 26.5 micrograms per cubic meter for the BMC01. We then extrapolate that to an equivalent 24-hour,

7-day-a-week exposure, which is 8.75. And then we applied various uncertainty factors.

A LOAEL uncertainty factor is not needed in the BMC approach. Since the people were exposed on the average of 24 years, we did not need a subchronic uncertainty factor. Since we looked at humans, we did not need an interspecies uncertainty factor. But we did use an uncertainty factor of three for intraspecies since, among others, women, children, and elderly were generally not found working in the mines. And the cumulative uncertainty factor was three and, therefore, the chronic REL based on this study was three micrograms per cubic meter.

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STAFF TOXICOLOGIST COLLINS: This is a fit of the Probit model to the data. The P value was approximately .99. Several other models adequately fit the data. We took this one because the Probit model is a well used model and the fit was quite good.

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STAFF TOXICOLOGIST COLLINS: From some of the other studies we also obtained estimates which were similar to the original estimate. Steenland & Brown studied the home state gold miners in South Dakota. They found 170 cases of silicosis out of over 3,000 miners.

And using a BMD method, we ended up with an estimate of 4.

Hughes, et al., studied the diatomaceous earth workers in California. There are 81 out of 1,800 miners had silicosis.

The two values are based on an interpretation of their data. If they're really looking at a NOAEL, which they thought they were, the estimate of the BMD would be ten micrograms per cubic meter. We believe that their lowest score was probably a LOAEL, in which case he thought that three micrograms per cubic meter would be a more reliable benchmark for those.

Finally, Chen looked at 3,010 Chinese tin miners. Over a thousand of these miners had radiographically -- were radiographic silicosis. And we ended up with an estimate of six micrograms per cubic meter from that cohort.

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STAFF TOXICOLOGIST COLLINS: Some of the strengths of this REL we believe are the availability of several long-term studies of inhalation in workers at varying exposure concentrations, with adequate histopathological and radiologic analysis and adequate follow-up; a dose response for silicosis in several studies, which enabled us to do the benchmark concentration; the observation of a NOAEL in some studies

including the key study; and the power of the key study to detect a small effect, something on the order of a one-percent incidence.

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STAFF TOXICOLOGIST COLLINS: On the other hand, the weaknesses. There was a limited follow-up in some of the supporting studies. There was a general underestimation of silicosis by radiography alone. Generally a lot more cases are -- maybe 50 percent more cases are found on autopsy. There's a lot of uncertainty in the exposure estimation, especially in the early years when the cohorts were exposed. And the variability and the toxicity of various forms of crystalline silica.

How does this silica REL affect children? Is there a potential for differential impacts? While there is no direct evidence in the literature on differential effects of silica in infants and children relative to adults; however, there is evidence that particles are more -- can be more deleterious to children's health than adults. So we know -- specific interest information on the silica particle, however, in general particles tend to be more damages. OEHHA included an uncertainty factor of 3 to protect sensitive subpopulations, particularly infants and children.

SUPERVISING TOXICOLOGIST MARTY: That's the end

of the presentation on actually what we did. And we have several more slides on comments.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. I'll take over the presentation of the comments here.

We received a series of comments. The authors of these comments are listed here. Several of them are consultants engaged by the American Chemistry Council's Crystalline Silica Panel and there are some independent commenters also.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The first comment was that a chronic reference exposure level for silica is not needed.

Our response to that is that we believe it is needed based on the fact that we were asked to generate one by the California Air Resources Board and the air districts, and thinking that they're in good position to know that one is useful for their purposes.

Bring up the next slide please.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Part of the reason why they argued for the REL being unnecessary was this second comment, that there is

no silicosis due to ambient silica.

We're not arguing that there is a problem with occurrence of silicosis in the general population of California due to exposure to ambient silica levels. And one of the points we wanted to emphasize is that the reference exposure level, which is above the ambient levels generally found in California as we noted in the report, the REL is defined as a level at which effects are not expected to occur in the general population.

CHAIRPERSON FROINES: Andy, what -- I don't remember. But what are the ambient levels that are generally found in California?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: In the appendix to the report I think we list -- list levels up to about --

STAFF TOXICOLOGIST COLLINS: The very back of this.

CHAIRPERSON FROINES: Pardon me?

SUPERVISING TOXICOLOGIST MARTY: We have some data generated through the Air Resources Board for three areas in California. It's on page 36 of the report, the very last page. The means were two-tenths micrograms per cubic meter, six-tenths, and 2.3 for those three areas.

The ranges went up to 3.46 in the highest area, 1.15 and 1.44 in the other two areas.

CHAIRPERSON FROINES: How were they measured?

SUPERVISING TOXICOLOGIST MARTY: This -- okay. I may have to call ARB up here. But in talking with the ARB, these were x-ray diffraction analyses of particulate matter captured in typical PM10 samples. So it was not PM10. It was the crystalline silica fraction of that PM10.

STAFF TOXICOLOGIST COLLINS: We have the report, if you'd like to see it.

CHAIRPERSON FROINES: We have what? I'm sorry.

STAFF TOXICOLOGIST COLLINS: I have the report, if you'd like to see it, with us.

CHAIRPERSON FROINES: No, I just want to get an order of magnitude.

So this is the database?

STAFF TOXICOLOGIST COLLINS: No.

CHAIRPERSON FROINES: This is it?

STAFF TOXICOLOGIST COLLINS: Oh, no, no. There's a lot of other things. I mean, again, you know, you have -- this is not an exposure analysis for California as much as it is a risk assessment for silica. So there's other data available, which is not presented in the report.

SUPERVISING TOXICOLOGIST MARTY: There's one study that was done in Lompoc that was actually

specifically done because of the concern of a diatomaceous earth -- there's a mine close to the town and there's actually a cal signing facility in the town. And there was on the order of 30 or 40 samples taken, and only 3 of them were above the limit of detection, which was about half a microgram per cubic meter. So there's an additional set of data. None of those data have been published to my knowledge. But there aren't a whole lot of samples that are -- or there hasn't been a lot of monitoring for crystalline silica per se.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There's a number of other values listed in the appendix. The point is that most of these higher values are basically near source measurements of some kind. There are not a great many measurements of what you would call general ambient backgrounds.

PANEL MEMBER BLANC: Well, I think you'll be coming back to this, won't you, because one of the recurring criticisms was that the REL is close to background. So I assume that -- I think you should finish your presentation of your responses. I want to see whether that was one of the things that you're going to address. And if not, we can go back to this issue.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, our basic point is that we're not arguing

that the -- we're not arguing for a REL which is below the general ambient background. It's above what we believe the general ambient background to be in California.

And the other thing is the REL is not a standard for application to general ambient backgrounds. It's a standard to be applied in the assessment of emissions which are modeled by a facility. So what the REL is addressing would be an increment to whatever is present in the background.

The way the Hot Spots Program works, normally you would be running the emission inventory through some kind of dispersion model and predicting what the additional exposure resulting from the occurrence of that emission would be at that science.

So we're not in any case arguing that we're trying to -- you know, we're not advocating something which would result in regulating the silica level back down to background. And the assertion in some of the comments to that effect is misguided.

CHAIRPERSON FROINES: I think we should go ahead with the comments. I just want to say that it would be interesting if somebody could tell us though what sort of the South Coast or Bay Area Management Districts might do with a number like this. Because there are -- local air districts may view it as a regulatory value, whereas

that's not necessarily what you intended. So let's come back to that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, we can ask -- probably we should ask the Air Board to address the regulatory implications.

Anyway, on the next comment. This comment is that OEHHA should use the denominators from the exposure duration classes identified in the life-table analysis which was presented in the paper by Hnizdo and Sluis-Cremer to define the ratio of cases to subjects at risk in calculating the benchmark dose concentration.

--o0o--

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: On the next slide I've got a table of the actual numbers so you can see what this is about.

Basically what Hnizdo and Sluis-Cremeer did was they used a life-table analysis, which is a form of time-dependent analysis, in order basically to provide, firstly, a greater sensitivity to detection and quantitation of the effect. And, secondly, to give some idea of the time cost of development of the symptoms in the cohort over the duration of the study.

And what we were doing by contrast was we were basically using a cumulative incidence value, which was the number of cases in each cumulative dose group which

had developed silicosis versus the total number of individuals in that dose level group.

Now, what you can see here, the third column from the left is from the life table. In effect what you have is a moving snapshot of the cohort as the time progresses through the study, and as you build up, exposure in milligram per meter cubed years of cumulative exposure. So all of the members of the cohort here had some exposure in the range zero to two, in other words with a midpoint of one milligram per meter cubed. Whereas, as you increase the value of the midpoint of the cohort, so you find fewer and fewer members of the cohort actually reached that level of cumulative exposure.

So in fact only 197 members of the cohort actually experienced between 10 and 12 milligram per meter cubed years.

So in other words, this number at risk in the life table is a sliding scale moving through the cohort. Whereas, what we're doing is we're not doing the time-dependent analysis at all. We're doing a simple cumulative exposure at the end of the study basis for the benchmark dose.

And one of the reasons for that is that we are concerned about whole-life incidents. And the cumulative incidents in this case lasted for an average of 24 years,

which we considered to be appropriate to form a basis for judging the effects of a chronic exposure. But we did not make any further adjustment to time beyond that.

In other words, we're not doing a time-dependent analysis at all, mainly because we have absolutely no information about how the lesion progresses or how the appearance of the lesion would progress for time scales outside of the duration of the study. And that to us was a big uncertainty. We felt it didn't justify an attempt to use a time-dependent analysis.

And I want to point out in looking at these figures, that contrary to the implications in some aspects of the comment we received, all of the members -- all 2,280 members of the cohort are represented in the groups which we entered into our benchmark dose model. They're in that model at the eventual cumulative dose level which they achieved during the time course of the study. So if you add up the numbers in the right hand, the fourth column, which are the numbers at risk which we used, then you get the total size of the whole cohort.

PANEL MEMBER BLANC: What about the 55 -- what happened to the other 55 people, the difference between 144 and --

STAFF TOXICOLOGIST COLLINS: Oh, I'm sorry. I couldn't get the last line on the slide. That's all.

They were all back in that --

PANEL MEMBER BLANC: There's one more row?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There's an above -- there's a 13 and above category.

PANEL MEMBER BLANC: Okay. And so -- it's okay to take some time for questions, right? Because this was a major point of back and forth.

If one did the other way around and was looking at the 2218 entire cohort, you would be including within the same group some people who had been exposed to, you know, .05 of silica for 20 years and some people who had been heavily exposed, but you're only counting first year of their exposure and they couldn't possibly have silicosis yet?

STAFF TOXICOLOGIST COLLINS: Ten years is a minimum.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, there's a ten-year minimum.

PANEL MEMBER BLANC: But in any event, there could be people there who were 10 years and people who were 30 years or so?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Within each band of cumulative exposure there could be people who racked up their cumulative exposure

during a period of 10 years and there would be people who took up to 30 years to achieve that same cumulative exposure.

But one of the conclusions of Hnizdo's analysis was that the cumulative exposure was a respectable exposure metric to use for assessing the appearance of symptoms at least during the course of the study. So we stayed with that exposure metric within the study.

PANEL MEMBER BLANC: And I know it's somewhat out of order. But if Stan is still on the line --

PANEL MEMBER GLANTZ: Oh, yes.

PANEL MEMBER BLANC: I wonder since he was going to address this topic, even though it's slightly out of order, it would be kind of good to --

PANEL MEMBER GLANTZ: You know, you must be using a different microphone, because I had no trouble with Andy at all. So could you use his microphone, because you're just dropping in and out.

PANEL MEMBER BLANC: Well, let me speak like this, Stanley.

Can you make your comments on the life-table analysis issue at this time?

PANEL MEMBER GLANTZ: Yes. Well, I've -- as I mentioned this morning, I have looked at this and talked it over with the staff. And I think what the OEHHA people

are doing makes sense. And I think that the alternative analysis, which seems to be being proposed by the commenters, doesn't make sense because I think it's kind of a cross between what OEHHA did, which is a sort of dose response and a life-table analysis. And as I understand what the commenters are suggesting, they want -- if you look at this -- is the slide still up there?

PANEL MEMBER BLANC: Yes.

PANEL MEMBER GLANTZ: Yeah, it seems to me they're saying that you should be dividing the second column -- or the third column by the second column. And the third column is the sort of inverse cumulative density function. And the first column is like an incidence rate. And so that just doesn't make any sense to me at all.

So I support the kind of analysis that OEHHA did. I think it's sensible and it's very straightforward.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I want to make clear, we're not arguing that the life-table analysis used by Hnizdo and Sluis-Cremer, and advocated by Dr. Berry's comment -- we're not arguing that's wrong as a life-table analysis for cohort study. What we're saying is it's not what we chose to do and not what we considered appropriate for the dose response analysis that we made.

PANEL MEMBER GLANTZ: Right. And I think that

that's the point. I think that the -- what OEHHA is trying to do here is get an estimate of the dose response curve that accounts for the cumulative lifetime exposure by using the data in the life table, but analyzing it a little bit differently. And I think that that is a fairly direct way to do it.

And I think if you go back to the life table, you've got the problem of the magnitude of the dose and also the temporal history, which isn't really being considered if you do it the way the commenter suggested.

So, again, I think -- you know, the assumption which is implicit in what OEHHA did is that the effect should be proportional to the integrated dose -- the dose integrated over time. But I don't think that's an unrealistic assumption and it's something that's certainly used in lots of other compounds.

PANEL MEMBER BLANC: Stan, Paul here again. Would there be a problem also if -- even if one did the other -- the other approach, that there would be an absence of independence between the different ratios, because you'd be counting -- for some things you'd be counting the same people twice, wouldn't you? Or --

PANEL MEMBER GLANTZ: Well, I suppose -- I hadn't thought about that. I suppose that's true. I mean I just could not quite figure out why the approach that they were

advoc -- I could not get the approach they were advocating to make sense to me. I mean maybe that's why.

PANEL MEMBER BLANC: Because I think one of the problems that I sensed in the back and forth was that the OEHHA staff were struggling with trying to put into words the rationale in a simplistic enough way that any reader -- that would be transparent to any reader. I mean I think that --

PANEL MEMBER GLANTZ: Well, maybe what they should say is what I -- which I don't think -- as I recall, I don't remember reading in the report, is to simply say that they are -- you know, they're including time in the analysis in that they're looking at the integrated dose over time.

And then they're looking at the number of people who receive that temporally integrated dose and the number of cases developed among people who received that temporally integrated dose. And maybe making that explicit will kind of resolve the controversy.

PANEL MEMBER BLANC: Well, I think also they need to say that not only -- that the alternative is not an alternative. The alternative is -- it's not something we -- we chose to do it this way instead of this way is the way it comes off. And really what you have to say is were you to do it the other way, you would get the wrong

answer. And the reason you would get the wrong answer is A, B and C. And I think part of that is in fact that they're not independent -- you would be violating the assumption of independence of observations.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The way that they were suggesting we should do a time-dependent analysis has a number of defects, including --

PANEL MEMBER GLANTZ: Please stay close to the microphone.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Sorry.

The method which they were advocating we use in order to do a time dependent dose response calculation has a number of defects, one of which, as you point out, is the lack of independence between the different values. But the other issue which we -- were we to attempt to make a time dependent analysis is the question of how we would extrapolate from the study duration to a whole-life exposure. So those are two issues which we didn't feel that we had -- they're issues which in theory could have been solved if we had access to the entire individual data, as far as the independence is concerned.

If we had access to every single case time-duration report, you know, for the raw study data,

one could address that methodologically. But one could still not address the issue of how to extend out the expected time cost to represent a whole-life exposure. So we felt that the basic approach of using a time-dependent analysis of incidence was inappropriate in this case.

But as you point out, we are using a time-dependent exposure measure. But we elected not to attempt to use a time-dependent incidence measure.

PANEL MEMBER HAMMOND: It would seem to me that you would want -- what they're looking for is something like person years at risk. And as you say, you need a lot more data on them individually. And that's -- but that's not what they proposed either. They're kind of in some sort of crossways between --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think what they were trying to do was advocate some simple fix that would accommodate their objective of having us use the life-table data and also coincidentally would -- in their perception I think it would result in a higher reference exposure level.

However, I would like to point out that subject to all these caveats and concerns and the fact we felt it was inappropriate to use time-dependent analyses in this case, nevertheless, if you make all these simplistic assumptions and then adjust or attempt to adjust for the

study duration versus whole-life exposure, in fact you come up with numbers from both the Hnizdo and Sluis-Cremer data and also the Chen data which we analyzed as a supporting study -- and Chen does also do a time-dependent analysis -- if you make simplistic assumptions in order to extend those to a whole-life value, you come up with numbers which are not greatly different from the number which we propose using our long time dependent analysis.

In other words, we're not pretending that we've covered the temporal element here. But it doesn't in fact make, you know, a huge difference with these data sets.

PANEL MEMBER GLANTZ: So would it -- I mean that's actually a very important point. I mean would it be useful to actually present those calculations as part of the final response to comments?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We can certainly do that. Yes, we --

PANEL MEMBER GLANTZ: Yeah, I think that would be a good idea, because I think -- as I understood Kathi's comment, what they were trying to do is sort of halfway in between. And to do it properly you would have to do it the way you were saying. And if that sort of analysis leads you to essentially the same conclusion, I think that would be worth having in the record.

I do think though one should, where at all

possible, strive toward the simpler approach. And I think that the approach you have is pretty straightforward and defendable.

PANEL MEMBER BLANC: Another way in which you might be able to explain the pitfall of treating the data in the way that the critics have proposed is through an analogy -- by presenting an analogy.

For example, if you have a toxicologic study and you had one -- and you have 50 rats that were exposed at two parts per million for six months so that their exposure was one part per million year and you'd had another group of rats who were exposed at four parts per million for six months so that their exposure was two parts per million years. It would be as if saying -- and you saw no tumors in either of those two groups, and then you saw them in the higher group -- that you would say that you had no tumors in a hundred mice at one part per million year because, you know, the ones that had two parts per million year certainly had one part per million year. And then to then use that same 50 rats again, and you couldn't do that, right?

So I mean -- that may not be the right analogy. But I think that you may need to revert to some kind of analogy to explain to the reader why the reasoning is false.

PANEL MEMBER HAMMOND: That may be. But I think the other way is -- more directly in terms of what you have done, is to say you've taken each person, saw what their cumulative exposure was and put them in the appropriate bin, and that's how you did the calculation. I think it's a straightforward way to say what you did do as opposed to --

PANEL MEMBER GLANTZ: Yes, I agree with that. And I think it would make the report clearer and more defensible.

CHAIRPERSON FROINES: I agree with Paul though, notwithstanding Kathi and Stan's doc. I think that the -- the approach that OEHHA's taken, which you want to be particularly clarified, is relatively clear. I think Paul's analogy is actually very useful about the inappropriateness or the inadequacy of the alternative view. I think that's the one that for me was the most confusing. From a toxicologic standpoint, what you did here was very clear. But the alternative was less clear to me.

PANEL MEMBER HAMMOND: I think that's because it doesn't really make sense.

CHAIRPERSON FROINES: What?

PANEL MEMBER HAMMOND: I think it's because the alternative presented doesn't really make sense because

it's part way towards something else.

CHAIRPERSON FROINES: Well, it may be me and it may be them, but I don't know which.

PANEL MEMBER HAMMOND: But I think that it's a -- actually since I'm new to this process, you can correct me on this -- but I'm thinking that in the document that's the statement you want to be clear and say this is what it is. And in response to the comments, that's where you can go through these other possibilities and what they mean. But I think if you try to defend all of the -- it would be confusing --

PANEL MEMBER BLANC: Yeah, yeah, I agree. I mean what I -- for the analogy piece I would say that that would be something you might do in a response. But for the -- in the document you want to be clearer. I think it is clear to say that in this method of analysis each person appears on the analysis only once, whereas alternative analyses would have people appear more than once in the same analysis. I mean I think that you should say in the main body of the --

CHAIRPERSON FROINES: I think that -- yeah, I think that we're agreed, that those comments should be in the response to comments, because you don't want to add a lot of discussion to your basic document. It makes it messier.

PANEL MEMBER BLANC: But it could have been clearer in the basic document than it was.

PANEL MEMBER HAMMOND: I think the basic -- yeah, I think the basic document does need to say straightforward that each person is put into bin that they -- not that colloquial.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We can clarify that certainly. And we can add to the response to comments as well.

I think we mentioned calculation on the Chen data as part of our response to comment. But we can expand on that a bit if you want to see that.

PANEL MEMBER BLANC: Well, you know, that actually -- by the way, the -- I agree with Stan that putting a couple of lines actually in the body of the report that one does as an alternative, a life-table analysis that assumes people go on to live X number of years, you know, although not the basis of this evaluation as a -- you know, as a comparison yields the following. And you've done that in other documents before. And I think that that in the body of the text is often illuminating in the same way that using multiple studies and showing what they yield is appropriate to the body.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. Shall I get on to the next comment then?

Okay. Can I have the next --

STAFF TOXICOLOGIST COLLINS: That's it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. Now, the next comment relates -- the next comment relates to the composition of the dust to which the workers in the study by Hnizdo and Sluis-Cremer were exposed.

The initial report by Hnizdo gave the silica content of mine dust as 30 percent. However, a reevaluation of the exposure data by Gibbs and Du Toit subsequently suggested that Hnizdo had incorrectly calculated the percentage of silica, and that according to Gibbs the percentage of silica could be 54 percent, not 30 percent.

If I can have the next slide please.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We looked at this and, taking into account the comment that there is some question as to the validity of the percentage silica estimate given by Hnizdo and Sluis-Cremer, we actually looked at a considerably larger body of data, some of which was also referred to by Hnizdo, but some not. And this basically gives a series of different estimates of the percentage of silica in mine dust over the relevant period for the study and also

subsequently.

What we saw was it was actually quite a considerable range of estimates, with the estimate from Kielblock, which is a very large and fairly recent study, covering a number of different mines. And so the Kielblock report is extensive and it's based on very extensive data. But that produces a low estimate of 15 --

CHAIRPERSON FROINES: What were the location of those mines?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's all in South Africa. All these are -- yes, these are all South African mine estimates. And they're all similar sorts of mines.

Basically we have a range of estimates, from the low end of 15 percent with Kielblock, to the high end of Gibbs and Du Toit at 54 percent. So we felt that rather than relying on any one basis for estimating the percentage of silica, it would be better to look at the overall database, and not take only the highest values suggested by the commenter nor, conversely, should we take the lowest value from Kielblock. So we chose a number somewhere in the middle, which coincidentally is 30 percent, which is what we had to begin with. But we're now basing that 30 percent not merely on the individual report of Hnizdo, but on the full range of data that was

available for our consideration.

PANEL MEMBER HAMMOND: John, do you want this -- this is so complex, there's so many things. Should we ask questions at this point?

Okay. Are you done with that?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER HAMMOND: Okay. I'm concerned actually about this.

Could you tell me what is the median year that people started work in the study of these workers?

STAFF TOXICOLOGIST COLLINS: I think it was 1938.

PANEL MEMBER HAMMOND: 1938 is the median year?

And is there any reason that people think that the percent silica would have changed through the years? Is there any evidence that there's like going through different scenes or --

STAFF TOXICOLOGIST COLLINS: Oh, I would guess the more recent determination could have been more accurate.

PANEL MEMBER HAMMOND: That was kind of my point, whether this is an analytical issue or whether it's a true temporal change in composition.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think it's fair to say that the dust levels

have probably been reduced. But I don't think there's any --

PANEL MEMBER HAMMOND: No, but the composition --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm not aware of any data suggesting that the composition has changed. And the geological formations which they're working through are basically similar throughout the period. They're basically --

CHAIRPERSON FROINES: But it's not quite that simple, because the tools that one uses will generate different percentages of silica. It's not simply what you're actually mining, but it's actually what ends up being earth wise to --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There may be differences. But we're not aware of any data either to say they are or say what they would be.

PANEL MEMBER HAMMOND: I guess -- and the years that you've given are the years for which the samples were taken that yielded the percentage that we've listed; is that correct?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Samples --

PANEL MEMBER HAMMOND: For instance, Rendall, '56 to '72.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes.

PANEL MEMBER HAMMOND: But that 22 percent represents samples collected in those years, '56 to '72; is that correct? Am I understanding that correctly?

SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER HAMMOND: That Rendall, '56 to '72.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER HAMMOND: Okay. Because what I'm struck by is that -- I mean is -- in the data in the top line, is that including the data -- Rendall's data? The data points that Rendall used, are those also included in the Hnizdo --

STAFF TOXICOLOGIST COLLINS: I don't think so.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No. It is a separate -- it's a separate determination. Hnizdo refers to Rendall's supporting data.

PANEL MEMBER HAMMOND: Okay. Because I'm quite struck -- if we leave out the top two lines, you know, I mean that it looks to me as though most of the data is actually lower and that in fact --

STAFF TOXICOLOGIST COLLINS: In the cohort the last -- exposure in the dust was 1971. The first year was about 1940.

PANEL MEMBER HAMMOND: Right. And I think that the methods that were used to do -- examine the methods were used for the analysis of the crystalline silica?

STAFF TOXICOLOGIST COLLINS: Not in an extent, no.

PANEL MEMBER HAMMOND: Because I would be quite concerned about, you know -- I would think that the analytical methods would become more accurate over time. And notwithstanding John's concern, which I think is quite an issue as well, but if I look at that data, if I were to make an assumption, I think I would be saying that probably the composition is 20 percent silica, something -- I mean it just -- now, I haven't looked at the whole data and all those papers.

But because someone puts another number out and then -- you know, that's twice as high as the number you've had and then you've got all -- all your other data were lower -- and all the reported data are lower, now that you can average them and then come out with the same number, well, I'm not sure that's really the same thing. I think the truth may lie by looking deeply at what's there. And it may be that the dust in the past was actually only 20 percent silica. And you may actually be overestimating the pass rather than underestimating the pass --

CHAIRPERSON FROINES: Well, one of the questions I have is when -- what's the timeframe for analysis of the samples? In other words, what methods are -- basically I'm asking what methods are being used to do the analyses? Because if you're analyzing -- if you've got data from the -- you know, the people analyzed with infrared way back when as opposed to x-ray a fraction, you're going to get very different numbers potentially.

PANEL MEMBER HAMMOND: Well, that's what I'm asking. I think we actually need to look -- one would need to look at the methods used and take that into account in terms of how you weight it and look at that.

PANEL MEMBER BLANC: Well, isn't the -- this is a related comment. But the big argument that the criticism used was that the Hnizdo and Sluis-Cremer analysis was not acid washed and that the Gibbs and Du Toit estimate was on acid wash specimens, but what you're a little bit vague in in your response is whether the other three analyses were acid washed. So that at least on the four estimates it's comparable methods.

PANEL MEMBER HAMMOND: Except that also my understanding when you acid wash is that the acid wash is taking away organic material. So you're taking -- you're actually taking away from your denominator.

PANEL MEMBER BLANC: Well, I know. But I just

wonder if they're comparable to start with. We need to talk about, you know, the interpretation of that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think most of these determinations are using the -- this method -- this gravimetric method, which I think involves both cal signing the dust to remove organic material and then acid washing it to remove soluble minerals.

PANEL MEMBER BLANC: Well, see, that's part of the problem. I think you have to be more confident in your response. You institutionally. I think that the report needs to be -- I think in one hand, in the body of the report the reader is never really prepared for this issue when it later comes up in discussing specific data.

There's an allusion to how crystalline silica is measured or not measured, but it's not discussed in sufficient detail in a neutral way early on: Here are the major methods that are used; here are their strengths and weaknesses; and in the United States x-ray diffraction is used and these other places it's just by weight, inferring that the only thing left after, you know, five different steps must be silica because anything else would have been eaten away or dissolved or whatever.

And, therefore, you know, a test done by this method is, you know -- and if you do that, other data has

shown that it is 95 percent homologous with data that will be used in the United States based on x-ray diffraction.

Because, after all, if later on it's not this method that's used here for the silica quantification and if there's some, you know, error or difference systematically, you need to know that because you're making all of your inferences based on this study. So that's one thing I would suggest.

The other thing is -- let's assume a scenario where Gibbs and Rendall and the second Hnizdo and the Kielblock all did use exactly the same methods and you have those papers and you know the end. Then what I would suggest is rather than making the argument which is "Well, we don't really know so we're going to use the first value of 30 percent," in which unfortunately you've been boxed into a corner by Dr. Hnizdo because her responses are so inadequate and you've then invoked these inadequate responses.

And then what you do is you say, "Well, we're going to use her 30-percent data anyway because everything else comes out near to it." Why not instead of that -- if these are all using similar methods and you believe that the method is valid, why not take the ends, calculate a pooled percentage and use that. And even if it comes out to be 28.9 percent or 31.2 percent, you'll be on such

stronger ground rather than trying to defend this position which sounds so indefensible, you know, back and forth and back yourself in a corner.

PANEL MEMBER LANDOLPH: Yeah, I had the same feeling, because I was reading through this. That's obviously an issue that comes up. I just averaged the most -- 26 percent if you average all those values.

PANEL MEMBER BLANC: Assuming it's the same end. But it may not -- it's a weighted -- you need a weighted --

PANEL MEMBER HAMMOND: Well, and not only that it has to be -- make sure it's the same methods, the analytical methods. You have to check all that out, you know.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER HAMMOND: And if they're different methods, you need to look at what are the biases of the method? Is it known to be high or low as you look at that?

PANEL MEMBER BLANC: And the other thing is -- am I assuming that you actually have in hand Dr. Rendall's doctoral thesis?

STAFF TOXICOLOGIST COLLINS: I don't. Hnizdo -- we have Kielblock's, we have Gibbs and Du Toit.

PANEL MEMBER BLANC: So you need to get the thesis and you need to cite the thesis. You inappropriately say this is an unpublished document. But a doctoral thesis is the equivalent of a published, you know, thing in a way. It has a citation. I looked on World Cat and couldn't find it. So the South African libraries may not be in the system. I looked in, but -- you know, if somebody had a doctoral thesis from Columbia, I'd be able to cite it.

So you need it. It's critical enough to what you're arguing. It makes you seem sloppier than you are. It just doesn't -- you don't do yourselves enough credit when you do something like that. So --

PANEL MEMBER LANDOLPH: They have any error bars presented in any of those publications? Those would be useful to present too since obviously you're being harassed to find that number. Although the methods may be so different, it may overwhelm the error bars, but it would be useful to have it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, I think -- well, if we were to do a weighted mean, then we would be able to present those data as well. So clearly that's something we should look into.

CHAIRPERSON FROINES: Well, what's your sense of those studies in terms of the methodologies used at this

point?

SUPERVISING TOXICOLOGIST MARTY: I think we need to look into it more to really get a better sense.

PANEL MEMBER GLANTZ: Would you speak closer to the microphone.

SUPERVISING TOXICOLOGIST MARTY: We need to look into it more to get a better sense of the comparability of the methods that were used as well as the sampling size, how many samples did they actually take, and so on, and use that information to do a weighted mean.

I'm not sure it will be too much different than 30 percent, but it would certainly strengthen the argument.

PANEL MEMBER HAMMOND: But it might be 20 percent.

PANEL MEMBER BLANC: And also you should -- and you should not include the Hnizdo first-line data in that because you already know that those were -- or you have reason to believe that those were not acid washed. And that's their whole argument. So then don't use them. Use these other ones and average them if that's what it takes, if they're all -- assuming that they're all comparable.

PANEL MEMBER LANDOLPH: I like the fact that your numbers from the four studies actually came out pretty close. They're not dramatically off for the REL. There

was very good agreement there.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. The next comment is the -- well, the comment was that the studies which we cite as supporting studies are not sufficiently reliable to be used.

We disagree. We recognize that the studies have limitations, particularly things like length of follow-up, which would result in under-estimation of the effect because of the progressive onset of disease after association of exposure.

But nevertheless we feel that in spite of these imperfections it is useful to include them as supporting studies in the narrative. But obviously we give them less credence than we give to the Hnizdo and Sluis-Cremer study for that reason.

--o0o--

CHAIRPERSON FROINES: Sorry. Would you repeat the last sentence you said again. Somehow I didn't connect with a --

PANEL MEMBER GLANTZ: I can't hear again.

STAFF TOXICOLOGIST COLLINS: Last sentence.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. I'll repeat what I -- what I said basically is that we recognize that the supporting studies have limitations. But we considered it was appropriate to

include them in the report as supporting studies. And that we obviously give them less weight in determining what we should recommend as a REL than we give to what we consider the more reliable study, which is that by Hnizdo and Sluis-Cremer.

So we're not discounting them, but we're not weighting them as heavily in our overall consideration. We're just looking at them for supporting evidence rather than as a primary source of a recommended number. Okay.

PANEL MEMBER BLANC: Have you gone back to -- this is sort of a long shot. But when these publications came out in the journals in which they came out, were any of them accompanied by editorials? Especially the Steenland one.

STAFF TOXICOLOGIST COLLINS: I don't recall. I can go back and check.

PANEL MEMBER BLANC: I think you should double check. Because if they were, I think you might cite the editorial comments that were made at the time.

CHAIRPERSON FROINES: Well, we know there was an editorial on silicosis in the American Journal of Industrial Medicine. I can't remember, was it Ian Greaves or Harvey Checkoway wrote it?

STAFF TOXICOLOGIST COLLINS: Or was it Cocce?

CHAIRPERSON FROINES: It was not very long ago.

STAFF TOXICOLOGIST COLLINS: There was I think Cocce -- somebody from italy wrote on a -- C-o-c-c-e.

CHAIRPERSON FROINES: No. But Harvey or Ian wrote editorials on this issue in the American Journal of Industrial Medicine in the last three or four years.

STAFF TOXICOLOGIST COLLINS: You mean "Greaves on Not So Simple Silicosis," that article?

CHAIRPERSON FROINES: No, I'm talking about an editorial.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, we can try and track -- we'll try and track those down.

CHAIRPERSON FROINES: But they specifically talked about the dose response relationship to Silica.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I know -- I'm pretty sure Checkoway has written several things on that topic. I seem to remember seeing both editorials and published papers. We'll look for those.

CHAIRPERSON FROINES: I have a little trouble with what you said. Because when you say you don't give it as much weight or you weight it -- that sounds like something quantitative, when I think you actually mean it in a very qualitative descriptive sense.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes.

CHAIRPERSON FROINES: And so that in part one would like to know what the limitations were that made it -- because some of those studies that you quoted were actually quite good studies. And so when you say that they are -- they're problematic, or imply that, I think that even -- you know, Ken Rosenman studied from me a few years ago and so on and so forth.

A lot of -- there was some very good work on this. So it's not clear to me that -- I thought that using other studies was a very good device actually, very useful. And so what I'm worried about is creating a transcript where you're saying that they had such limitations that you gave them less weight. And I'm not sure you really mean that.

PANEL MEMBER HAMMOND: I think actually you did say it, but I think it doesn't come across as strongly, that the important thing is the limitations of the studies you identify are limitations such that they would underestimate the effect. You say that. I think that's a very important point.

I mean it shouldn't be buried in there, you know, so that -- in fact, anything, you know, the effect is stronger than what you've got. And even with that you get to the same number.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, I think it's true to say that the limitations we're talking about -- and, Jim, I don't know whether you can back me up on this. But it's my impression that among the specific limitations which we're concerned with for I think both the Steenland and the Chen study is length of -- is length of follow-up, which specifically will underestimate -- we're not saying that they're poorly executed or not good studies. We're saying that they would produce a less good number for our purpose.

PANEL MEMBER HAMMOND: But, no, no, don't say it that way. I would say that they end up -- they're going to under-count the number of cases of silicosis because they don't continue to follow to death.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, exactly.

STAFF TOXICOLOGIST COLLINS: And that's certainly the case of the gold miners in Ontario.

PANEL MEMBER HAMMOND: Right. No, I know. But the point is that clearly it's a direction and it's a direction that underestimates them.

STAFF TOXICOLOGIST COLLINS: Um-hmm.

CHAIRPERSON FROINES: Go ahead.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Okay. The next comment suggested that we had some incorrect values in some other parts of the document where we cite NOAELs and LOAELs. There is one case where we had quoted the mean of an exposure band rather than the upper limit when sizing a NOAEL in the Hnizdo and Sluis-Cremer study. So we have corrected that. But that doesn't have any bearing on the recommendation for chronic RELs since we weren't using the NOAEL approach to derive that.

The other NOAELs and LOAELs which we were accused of having got wrong were those which we simply -- we were citing another author. And we consider that we're correct in citing those as given by those authors.

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SUPERVISING TOXICOLOGIST MARTY: We have -- the last important comment that we wanted to discuss, which is coming up -- next slide, Jim.

Thank you.

--o0o--

STAFF TOXICOLOGIST COLLINS: We just wanted to say that in particular we want panel input on to this one. It gave us heartburn, and we thought that the commenters had valid points that were in our estimation difficult for us to deal with.

PANEL MEMBER HAMMOND: I think -- Oh, you should

go ahead -- sorry -- first.

CHAIRPERSON FROINES: Before you go to that, can I go back to the issue of the percent silica. The more I think about it, the more I think that the 54 percent is an overestimate based on the notion of acid washing. And that in some respects this notion of -- we had everything that went from 15 to 54 percent and, therefore, we took 30.

I think -- I mean you do address the hydrochloric acid issue. But I do think it's important for us to recognize that acid washing is not without its impact and we need to be quite serious about that, because we may be overestimating the percent silica as a result of that.

Don't you think, Kathi?

PANEL MEMBER HAMMOND: I think that's what I tried to say earlier. I was trying to say exactly that earlier. But I think that one has to look at every one of those studies, look exactly how they did it, and think to yourself -- you know, get an analytical chemist to look at it and say what is the effect, how close is it? If there's an error, is this over or underestimating each study, you know. And I would actually make a table that ends up, you know, comparing these that tells you what the methods are.

CHAIRPERSON FROINES: I think a little more work

needs --

PANEL MEMBER HAMMOND: And I think laying it out carefully. And also to the degree one can know the error in which the samples were collected as well as the method that was used for the analysis, and if the bias is high or low in the percent silica. You know, and I think putting that all out there and then systematically looking at it.

And, you know, what it comes -- I don't think taking an average of several numbers, six of which are very good and two of which are terrible, is a good idea. You know, I think you evaluate them. And if six of them are good, you look at those and may take the average of those, unless you see a temporal trend.

CHAIRPERSON FROINES: Paul's out of the room and I want to go out of the room. And so can we take a five-minute break so that we have a whole panel here for this discussion. Because obviously --

PANEL MEMBER GLANTZ: Yeah, this is Stan. I'm going to have to leave -- I mean I'm happy to take a five-minute break, too, but I'm going to have to leave at 3:00.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Okay. Let's get going.

Melanie, go ahead please.

SUPERVISING TOXICOLOGIST MARTY: Okay. The next

slide deals with the size fraction that the reference exposure level should be applied to in a risk assessment scenario. In the draft that went out for public review and also went to the panel, we simply put crystalline silica respirable, meaning PM10 fraction. That encompasses a larger size fraction than was actually measured in the epidemiological studies where they -- the measurement method essentially used a PR4 sampling device.

So the criticism is that you're counting too much silica if you're relying on the silica fraction, that is, PM10; and that, therefore, you are overestimating the health risk.

We were trying to figure out how best to handle that, because in fact that's probably right. We know that for regulatory purposes in California we define respirable as PM10. The occupational community typically views it as what is measured in their devices where PM4 is the median size captured. And then we also in California look at PM2.5.

So we thought we'd put in PM10 just to get the reactions from those folks who know a lot more about this on the panel in terms of how much they think that might overestimate the total silica exposure. And some of the thinking is the ideas for silicosis, that you have to actually get all the way into the alveolus. That may not

be true for some of the other effects of crystalline silica. COPD, for example, where you can reach the bronchioles and the smaller airways and have some toxicity in those airways.

So that's one of the considerations that you really should be looking at, just the tinier fraction of PM10. We don't have data on the size distribution of the particles in any of the epi studies. We don't have data on the size distribution of the particles that will be emitted from some of the facilities of concern in California. So it's hard to have any information that would allow for a correction factor to be applied in a risk assessment.

And most of the measurements we have, at least of background levels, are, as I said earlier, based on PM10 and looking at the fraction of PM10 that is actually crystalline silica.

So with that I will turn it over to the panel.

CHAIRPERSON FROINES: Kathi.

PANEL MEMBER HAMMOND: This is the area I think that I'm most concerned with in the document. Let's see, first of all -- well, I don't think one should refer to the occupational measurements as PM4. I think that -- and I think that it's not true that it's -- the mass median diameter is four microns. That's an incorrect statement

as well. What it is is that 50 percent of four micron particles will pass the size selector, which is a different statement. A hundred percent of the particles could be one micron in size and it would still be respirable. So it doesn't tell you the size distribution of the particles. It tells you the distribution -- the percentage of each size that's allowed to pass.

The occupational respirable samplers are designed to simulate what penetrates to the deep lung, to the alveolar, and, therefore, are most relevant for silicosis, and I think that's where they were first developed in that. And it's important to be aware of that so that they are, as you have said in the document, a health-based collection method. It's a broader size cut. Whereas as the PM2.5 and PM10 attempt to be a vertical size cut. If you could do it absolutely perfectly, it would be excluding everything greater than PM10 and including everything less than PM -- no -- 10 microns in size.

So I think it's important to, you know, keep aware -- keep the terms straight. So it is confusing.

But the term "respirable particles" is the internationally recognized term in general for this distribution that relates to what penetrates.

Given that in different settings there are different distributions of particle size, you really can't

take -- there's no place to take from a PM10 to the respirable particles, as you well recognize. But I'm afraid that adopting a number that comes from a PM -- from the respirable particle data literature and the epidemiology and just saying PM10, well, it would certainly be protected. But I think there is a real risk that you'll be including many larger particle sizes.

And just to say, when I served on the TLV Committee many years ago, we were very much grappling with this issue of how we take data that was collected, is slightly different, but the data were collected as -- was nominally total particulate, but it was probably closer to a -- something like a PM20 but what was collected on a total particulate, and then applying it to if we were to go to the inspirable sampling methods, you know, are the inhalable sampling methods.

So there are a lot of issues going on here. And other people are grappling with of how to go -- data collected epidemiologically in one size fraction, how do we apply it to another size fraction that's more appropriate for sampling. It's a big issue.

One of the ways to deal with that is simply -- simply -- it's not simple -- but to go out and collect a lot of data side by side. So, for instance, collecting PM2.5, PM10, and respirable samples side by side in a

variety of locations and seeing what those -- how those relate would be one very important piece of getting information, and understanding what's going on.

And my understanding is that to the degree we have information about silica, not necessarily crystalline silica, but it may well parallel that, that silica in the course fraction, in the PM2.5 to PM10 range, is in fact has much more silica than PM2.5 does. So we know there's a difference there.

And the respirable particles are, you know, kind of quasi, a little more like the PM2.5, although there are some problems within that.

So I think you really need to -- one needs to get data, if at all possible, to do some side-by-side sampling. Or, alternatively, to say that this REL applies to respirable particles as defined by the occupation literature, and not to try to impose the PM10 and PM2.5 standards, because in fact that's the most biologically relevant size cut in the first place. So maybe bending things around to other ways.

And there really is no reason that -- those samplers can be designed. There's no reason you can't have those. They do -- you can do respirable size sample. But you do run into sensitivity issues, but you can adjust those. People know how to set those -- design those

samplers to do the right size cut at different flow rates. So you can actually do that. But it's not simple. I mean there's work that would have to be done. But I think if it's worthwhile setting a REL, it's worth getting it right.

CHAIRPERSON FROINES: Are you suggesting size distribution studies or are you suggesting --

CHAIRPERSON FROINES: I can't hear.

CHAIRPERSON FROINES: I'm not a hundred percent clear on what Kathi just recommended in terms of this --

PANEL MEMBER HAMMOND: I was recommending specifically -- I mean one could do size distribution studies. That would be a way to do it.

I was suggesting -- since PM10 and PM2.5 are the samplers that are out there and readily available to ARB, so those are what are seen as the two choices that you have as I understand it, that one would want to sample with those two and with the true respirable by the occupational definition samples; all three of those side by side, in a variety of locations, to see how they relate to each other.

Now, it's actually true that if you did -- if you did a full-size distribution, you would be able to calculate that.

CHAIRPERSON FROINES: But I think that that's

really not feasible, because, yes, you can go out and make measurements, but those -- and one can do then a statistical analysis on the data that you have and say, "We can live with that"; but as we all know, the size distributions can change dramatically and so it throws that data into question about --

PANEL MEMBER HAMMOND: My primary -- you know, my primary recommendation is not that. My primary recommendation would be to say that the REL should be applicable to respirable particles as defined occupational because what's the epidemiology data is and it's the size distribution that's appropriate for the health outcome under consideration. Because the other ones that you've mentioned, COPD, are not part of the -- they're not the basis of the REL.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER GLANTZ: This is Stan. I'm going to have to sign off now. But I have said the main things I had to say on this issue.

CHAIRPERSON FROINES: Thanks, Stan.

PANEL MEMBER HAMMOND: Bye.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I'm going to try to build on what Kathi said with perhaps a practical solution that would apply with what she's saying. And, that is, that if

the document recommended that the way in which the REL should be interpreted in practice would be that if PM2.5 data are available which meet or exceed the REL, then the REL has been met or exceeded; and if PM10 data are available which meet or exceed the REL, then it is incumbent upon the interpreter of the data to then obtain repirable dust-sized collection consistent with the comparable approach. So that you would have an algorithm. Because clearly if you had PM2.5 collections that exceeded the REL, then that's at least -- a particle size that's at least comparable as far as you can tell with --

PANEL MEMBER HAMMOND: No, you would -- the PM2.5 would underestimate.

PANEL MEMBER BLANC: I understand that. I'm saying -- so it's got to be at least -- the PM2.5 would underestimate. It would be too conservative, right, because --

PANEL MEMBER HAMMOND: It would be insufficiently conservative.

PANEL MEMBER BLANC: It would be insufficiently -- yes, that's what I'm saying. So if you had a PM2.5 results which were higher than the REL, you'd say you've certainly exceeded the REL.

PANEL MEMBER HAMMOND: Yes, there's no question.

PANEL MEMBER BLANC: If you have PM10, which

exceed the REL, then you're obliged to obtain respirable range --

PANEL MEMBER HAMMOND: Either control it to bring the PM10 below --

PANEL MEMBER BLANC: What's that?

PANEL MEMBER HAMMOND: Either control it to bring the PM10 below the REL or measure the respirable.

PANEL MEMBER BLANC: Well, we don't suggest the control strategies. The REL is just an action. But it's like an action level. What I'm suggesting is sort of an action level strategy given the realities of what people collect, which is either PM2.5 or PM10.

One of the weaknesses of your response was it actually never mentioned PM2.5 in your responses. It was as if that didn't exist. It was as if the choice was PM10 or nothing. So people are going to have some PM10 data, they're going to have some -- you know, air districts are going to have PM2.5 data now. And if they wanted to do as a screen, then 2.5. But the 2.5 is under than the PM -- it doesn't -- no, that's not true. Take that back.

Anyway, you could develop a logical algorithm rather than trying to pretend that PM10 is the same particle distribution and box yourself into that. And I know it would be unusual. It would be the only REL that, you know, talked about things in that way. But it's an

unusual circumstance.

PANEL MEMBER HAMMOND: But basically what that would come down to is -- if the PM2.5 value were greater than the REL, you know you have a problem.

PANEL MEMBER BLANC: Right.

PANEL MEMBER HAMMOND: If the PM10 is less than the REL, you know you're okay.

PANEL MEMBER BLANC: Yes.

PANEL MEMBER HAMMOND: And the problem -- but if it's something other than that, that's where you're going to have to go to get more detailed information.

CHAIRPERSON FROINES: But I think it's extremely important to recognize that the PM10 data is not an adequate measure vis-a-vis the REL. And, you know, the South Coast Air Quality Management District and the Bay Area Management District and these people who want bright lines want bright lines. And you cannot use a PM10 sampler to measure silica, period.

So Paul's -- I agree and disagree with Paul's comments. Paul says if you are at the PM -- if you're at the REL using a PM10 sampler, you may be overestimating it. I think by definition you will overestimate it. And you have no idea how much you're overestimating it by. So, therefore, you can't use it. There's no quantitative validity whatsoever.

PANEL MEMBER BLANC: Suppose it was negative?

CHAIRPERSON FROINES: If it's negative --

PANEL MEMBER HAMMOND: But, no -- if PM10 had a silica under the REL, you're okay.

PANEL MEMBER BLANC: You're okay.

CHAIRPERSON FROINES: If it's under the -- if the PM10 silica were under the REL, that's okay. But I don't know what it tells you.

PANEL MEMBER HAMMOND: That's it. But I think -- but I would be -- personally, I'd be afraid that that may not happen because of natural material, but that's larger. But if that happened, it would be great.

SUPERVISING TOXICOLOGIST MARTY: Well, maybe I can make this really simple and just say for our -- the purposes of our REL we will set the REL for occupationally respirable -- respirable as defined occupationally. And the rest of the problem really doesn't fall on OEHHA. It falls on ARB and the districts to figure out how they're then going to estimate the emissions from these types of facilities that are in the appropriate size fraction.

CHAIRPERSON FROINES: But I think -- Okay, I think that's fine. But I think you have to say, and you'd have to be very clear in your document, and tell people how things change the cube and so on and so forth, so that everybody's clear on -- you get people who are engineers,

are not necessarily aerosol scientists, who need to understand it at a very relatively, you know, primary level.

PANEL MEMBER BLANC: Couldn't you do that as an appendix that's part of the document, you know --

CHAIRPERSON FROINES: Sure.

PANEL MEMBER BLANC: -- an example of how you might use this practically or something?

SUPERVISING TOXICOLOGIST MARTY: Well, we could -- yeah, what we can do is discuss the issues with using PM10 or using PM2.5. And in fact --

PANEL MEMBER HAMMOND: And why they're limited.

SUPERVISING TOXICOLOGIST MARTY: -- the comments that we got did a pretty good job of discussing what the problem with PM10 is.

PANEL MEMBER BYUS: But you do say up here it will not result in a serious overestimation. And that's not correct. I mean you say it in your document, you say it up here. The tone is completely incorrect, and you really have to fix that.

SUPERVISING TOXICOLOGIST MARTY: Yeah. Okay.

So we'll take that back. Well, in the final draft of the response to comments, the response to that comment will now be very different --

PANEL MEMBER BYUS: Okay.

CHAIRPERSON FROINES: And Paul's suggestion is a good one. It does clearly have a limitation at the PM10 level. And I can tell you -- I think we all can tell you that there's no quick fix, and that's the problem. And so I think -- I personally think that the -- you know, that your studies that range from 3, 4, 6 -- I don't know how much a 2.5 measure sampler is going to underestimate, but I think the 2.5 sampler is the best solution to the problem that we have at a practical level, understanding that it's an underestimate.

PANEL MEMBER HAMMOND: Yes, it's this much. That is the area between those two curves.

CHAIRPERSON FROINES: No, I understand. I mean --

PANEL MEMBER HAMMOND: And it depends on what the actual size distribution is.

CHAIRPERSON FROINES: Absolutely.

SUPERVISING TOXICOLOGIST MARTY: I have to say, the more we thought about it, the more we disliked our own response to the comment.

PANEL MEMBER BLANC: Now, does this finish up your part of the things you wanted to respond to here? Is this the end of your slides?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER BLANC: Because I think that there are a few other things that should -- need to be cleaned up.

CHAIRPERSON FROINES: So now we should -- we've actually finished the formal presentation. So we'll go to the leads, who have been silent so far, namely Blanc and Hammond.

Paul, go ahead.

PANEL MEMBER BLANC: Well, one thing -- one comment that was made is that it's a problem really to use a study from coal miners in this document. And I would agree with that. I think you have enough data without the data from those Chinese coal mine --

STAFF TOXICOLOGIST COLLINS: Tin miners?

PANEL MEMBER BLANC: I'm sorry. There was a coal mine study, too. I forgot where that was from. I'll come back to the tin mines in a second.

They have both exposures, so I don't know how you could interpret a coal mine study. So I just would take it out.

The second comment is on the tin miners. Since tin miners get a radiographic -- get radiographic changes related to tin as well as radiographic changes related to silica that's called stenosis, it doesn't have physiologic implications. But it seems that it would add a margin of

error into the -- an element of error into interpreting those results. I haven't read the paper that you used. I don't know how they discussed that in there.

STAFF TOXICOLOGIST COLLINS: I don't think they did.

PANEL MEMBER BLANC: And I was surprised that the consultants who had gone through this with a fine-tooth comb didn't raise that as an issue.

And then in terms of other cohort studies, was there -- the slate studies from England -- slate worker studies, did those not have the data in a format that were --

STAFF TOXICOLOGIST COLLINS: I'm not sure. Who did those? I'm not familiar with those.

PANEL MEMBER BLANC: There were classic studies on silicosis in slate miners in Wales.

PANEL MEMBER HAMMOND: I think they didn't have much exposure --

PANEL MEMBER BLANC: Well, maybe that's why. But I didn't see it -- I didn't see it dismissed as saying, "Well, you know, we looked at that study and I wasn't as" --

STAFF TOXICOLOGIST COLLINS: I don't think we did.

PANEL MEMBER BLANC: So could you -- you should

pull -- I'm sorry I don't have a citation to give you.

SUPERVISING TOXICOLOGIST MARTY: We'll find it.

PANEL MEMBER BLANC: The second major thing that I think needs to be brought up to speed in a document, even though you have a section where you say why is it that you're not going to look at lung function, you're only looking at radiographic changes. I think that you should cite the recent American Thoracic Society statement on burden of airway disease related to occupational exposures, in which an analysis of COPD in relationship to dusty trades, which would include silica exposure jobs, is -- should be alluded to in passing. I don't think you need to have a whole section on --

STAFF TOXICOLOGIST COLLINS: Something more recent than 1997?

PANEL MEMBER BLANC: It's 2004 or 2003.

So that needs to be cited. And if you look at the references there, those will probably include some other references that are relevant. There's actually a pretty detailed reference from somebody named Oxman, I think, on dust years of exposure and obstructive lung disease, which includes a lot of silica exposure. And I think you need to allude to that literature even as you're saying we're not going to deal with this.

I think another issue that needs to be raised is

that you're inherently conservative in the other direction by relying on ILO-graded x-rays that are one over one, because an ILO-graded chest radiograph that's one over zero is, more probable than not, disease.

An the ILO system was not invented as a clinical diagnostic tool and it's not to be used clinically diagnostically. It's to be used in epidemiologic studies. And, therefore, it is quite controversial. Although there have been statements saying that one over one is disease and one over zero is not disease, from a public health protective epidemiologic analysis point of view, one over zero is abnormal, and you're using one over one. Now, I'm not telling you to go back and redo everything. But it is a point towards saying, "What we've done, if anything, is not overly conservative." And I think you need to make that point.

Another thing that you need to say at some point in a general sense -- or at the same point where I think you need to say that the ILO is not a clinical tool is that, in fact, in this day and age silicosis is typically diagnosed by high resolution CT scanning, which is far more sensitive than plain chest x-rays.

And one of the reasons why in these studies when they do autopsies on people who had, quote-unquote, "negative" chest x-rays or chest x-rays that were less

than one over one is because it's acknowledged that chest x-rays are not sensitive to detecting disease, and that by CT scanning a lot of those people would have disease.

And all the argument about, you know, just because somebody has silicosis at autopsy, is that really a disease? I mean that was a sort of fallacious argument. Now, you don't have to get into that. You did that in the responses. But I think from the other point of view, you need to -- there needs to be some few sentences at least about that.

Another point that I think is important, and it relates to your very brief discussion about children or at-risk groups, but this also is relevant to the use of a threefold safety figure rather than one to one, you never discuss anywhere in this document the effect of silica on macrophage function and the risk of tuberculosis related to silica inhalation.

It's been very well shown after the South African mines that people without evidence of silicosis by chest x-ray but who have heavy burdens of silica by inhalation are at increased risk of TB and their increased risk of TB and atypical TB multiplied with their HIV status.

So if you want to make an argument that there are high risk groups for ambient silica exposure or at least in biological plausibility, I think that the issue of the

impact of silica on macrophage function and immune defense systems has to be included.

In fact, if you have heavy silica exposure and are PPD positive, you know, that was a reason to prophylax with INH. You didn't have to have silicosis by your chest x-ray, you just had to have a history of silica exposure. So unless I've gotten the criteria wrong, those criteria have been evolving over time. So I think that's important.

Then, finally, the -- because this could come back to haunt you in other areas, I think the discussion on the background incidence of chest x-ray abnormalities graded by high or low criteria, which you get into, and you didn't put a slide up, but the critique that the no-effect-level dose in the diatomaceous earth workers was in effect -- was a low effect level because they treated it as the value.

But in fact, you know, a 2-over-20 chest x-ray shouldn't be abnormal. And then you sort of say, "Well, we realize that smoking and age are related to ILO criteria." Then you say that the incidence based on, you know, the chest -- the general chest analysis is two percent in North America. There are real problems with that paper and that analysis.

And this is going to come back and bother you in

other situations. You have accepted on face value an analysis which was extremely flawed. And, in fact, the Castellan study, which you cite, is the only study that's ever been done intentionally to test the hypothesis, you know, "What is the incidence of ILO-read abnormalities in non-exposed people?" And his value was .2 percent or some number like that.

You need either to go -- you need to go back and read the original articles, including Castellan. And don't just cite that supposed meta-analysis on face value. I'm going to give you a couple of articles that are relevant.

STAFF TOXICOLOGIST COLLINS: Is that Blanc and Gamsu?

PANEL MEMBER BLANC: Yeah. And a second one.

This is going to be extra work for you guys. But, in fact, it's going to be useful for you I think in other situations. And I think it's just worth it for the Agency to come up with a -- now, you may come to a different conclusion than I have in reviewing that literature. But at least you've got to invest the time to do it because it's quite an important issue.

And I don't agree with your conclusions. I don't -- a) I don't -- except for asbestos exposure where clearly smoking was related to ILO-graded opacities in a

multiplicative way with asbestos. There's no other occupational data that suggests that when it's been analyzed correctly.

So that's the bulk of my comments.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Thank you.

One very small point. I think we recognize what you're pointing out, that the ILO grading that we were using as a trigger point is a relatively severe effect. And that is certainly factored into our decision to use a BMDO1, recognizing that the effects that we were using as a benchmark is by any reasonable standards a fairly severe effect, as opposed to a BMDO5, which is, you know, defaults for -- or standard for mild effects, which is of some significance.

PANEL MEMBER BLANC: Okay. You actually didn't say that as clearly in the document, because basically what you say is "We know that silicosis is an effect." But you didn't say, in fact, "This is not just silicosis. This is hit-you-over-the-head silicosis."

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: That's something we ought to clarify.

PANEL MEMBER BLANC: Right, because were we to use silicosis defined by one over zero or silicosis defined by CT scanning, which in clinical practice is what

people would use, we would -- you know, that would be a -- probably a milder disease. And by the time it's one over one, you know --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's incontrovertible.

PANEL MEMBER BLANC: Right. Now, that is one reason why the silicosis -- you know, you say there is one study where you're using silicosis where the majority of the silicosis is from death certificates. But I would make the argument that silicosis by death certificate is even worse than one over one, because for somebody to get silicosis on their death certificate -- I thought the argument was completely not convincing from the outside critique that -- you know, who cares if there's silicosis on the death certificate. You know, that's over-reported, because they lived in mining districts. I mean every study that's ever been done shows that death certificates underestimate occupational disease.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We hope that the REL would be protective before things got to that point.

CHAIRPERSON FROINES: Kathi.

PANEL MEMBER HAMMOND: I agree with several of Paul's points, I mean particularly -- the way I was going to say it is simply that I think that by using the

criteria that you used, you are underestimating the true effect. And I think that that needs to be said clearly. It is in the document, but I think it -- I think it needs to be very clear that there's -- that there is kind of an underestimate, but this is -- if you feel it's true, and I would defer to what Paul says and what, you know -- that if that's the best that we can do now, that's the best we can do. But I think we should be clear that we understand that the effects can be greater.

The other thing that I found confusing going through the document is whether or not you were doing just silicosis or other lung disease. And I think it's just silicosis. It's all being done that way. But you have a sentence, for instance, on page 6 which says, "At one microgram per cubic meter silica the excess lifetime risk was estimated to be 1.6 cases of lung disease other than cancer for a thousand workers." And then you go to a table that is silicosis.

And, you know, I think if it's just -- maybe again you might want to say there are these other diseases you think are associated. And you may not be being protective. That may be something -- there may just be insufficient data to protect from COPD. But I think that at some point you may want to just -- and, again, Paul may know now to do that better than I. But somehow

specifically address there are these other diseases and the reasons you've not addressed them, which may be the lack of data.

But then through the rest, as I say, we're doing just silicosis. And we're kind of doing just silicosis as it's pretty far along the way, and so we're underestimating the true number of cases.

And that's how I would see it.

PANEL MEMBER BLANC: I have an algebraic question for you, too.

When you go from a work exposure to environmental exposure, you have a mathematical adjustment that you do for the hours of exposure being 40 hours a week to being 7 days a week; isn't that correct?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The way it works, we actually weight the hours during the day more strongly. Because what we do is we actually assume that during your work time you inhale 10 of your allotted 20 cubic meters, rather than saying it's 8 hours out of the 24.

PANEL MEMBER BLANC: Right. So here's my point about Sluis-Cremer and Hnizdo. And maybe Dr. Hnizdo can clarify this for you. I do not believe that the underground miners in South Africa worked from 9 to 5, 5 days a week. I really don't think that's true. I think

at a minimum there was a 6-day work week. Now, whether it was a 12-hour shift or a 10-hour shift, she could clarify for you. But I do think it's going to impact a little bit your number.

STAFF TOXICOLOGIST COLLINS: We have a clarification from her. And I think she made everything equivalent to an 8-hour work shift. And I'd have to dig that up for you. But I'll -- if I find that, I'll send it to you.

PANEL MEMBER BLANC: You mean in her years of exposure, in her dust years of exposure? I mean what do you mean she did it?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Her calculation is a cumulative dust exposure.

PANEL MEMBER BLANC: So that if you worked a year in the mines, that was like one and a quarter years of a normal person?

PANEL MEMBER HAMMOND: An American.

PANEL MEMBER BLANC: Of an American person? I'm sorry.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think, in essence, what we're -- the impression we have from Dr. Hnizdo is that they, so to speak, normalized the actual hours of exposure that were thought to have occurred, as if a standard shift would have been

in operation.

PANEL MEMBER BLANC: I think you need to clarify it, because -- I mean the fact that I've changed --

STAFF TOXICOLOGIST COLLINS: It's in the text. But, okay.

PANEL MEMBER BLANC: -- it's not going to change your calculation. I mean if she -- depending on how she did that, it changed your calculation. Now, it's not going to change it by 50 percent. But, you know, it could change it by 10 percent or something, I mean --

SUPERVISING TOXICOLOGIST MARTY: Yeah, she went through the job classification and had average hours in the dust by job classification. But the biggest number on the table is eight. So if in fact it was ten six, days a week, I'm not sure that she adjusted for that.

PANEL MEMBER BLANC: You may want to -- I mean one way or the other I think you should have a footnote that says, "We took this into account" or, you know, "We didn't take this into account" or, you know --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It sounds like we need to have another phone call to Dr. Hnizdo.

PANEL MEMBER BLANC: I'm going to see her next week. So I could --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Warn her we're coming.

CHAIRPERSON FROINES: Can we move along?

Kathi, are you finished?

PANEL MEMBER HAMMOND: (Dr. Hammond nods head.)

CHAIRPERSON FROINES: Are there comments from Craig and Joe?

Now, the question I would have is -- I have no more -- I don't think we need more comments.

The question is -- there have been a lot of suggestions made. And we have two choices. One, we can vote on accepting the document, the REL, as proposed pending changes. Or we can say that we'll postpone the approval pending the changes and take a look at the document again.

PANEL MEMBER HAMMOND: I don't -- first of all, what size fraction are we talking about for the REL? What particle size fraction is the REL applicable to? Is it PM10, PM2.5, respirable occupational defined?

CHAIRPERSON FROINES: Well, the REL has nothing to do with that.

SUPERVISING TOXICOLOGIST MARTY: We would make the change of respirable per -- NIOSH respirable.

PANEL MEMBER HAMMOND: Okay. Because I think that would be -- that's like the --

CHAIRPERSON FROINES: The issue on the

respirability and the PM10 is an issue for -- actually for ARB once they've cleaned up their language that I think Craig or Joe mentioned. But basically I think the REL will -- I don't think there's anything that's been said that would change the REL as proposed.

PANEL MEMBER BLANC: I think that there's enough substantive issues here that we need to see another version. I think this is across the threshold to a follow-up version. And I think you feel the same way probably.

SUPERVISING TOXICOLOGIST MARTY: Yeah, and particularly since we're going to try to do a better job on the exposure issue. That could change the number. I don't know if it would change substantially, but it will definitely change.

CHAIRPERSON FROINES: So let's then -- we won't take a vote. We will take it up as an agenda item at the next meeting in July? Jim --

MR. BEHRMANN: We have --

CHAIRPERSON FROINES: -- what are we thinking right now in terms of the next meeting date?

MR. BEHRMANN: Jim Behrmann, panel liaison.

The two days that we've identified were July 21st and 23rd. But I think that may be somewhat dated and the panel needs to check their calendars again.

CHAIRPERSON FROINES: Okay. But we're planning to have a summer meeting at some point.

And so would you think you would be ready for them, so we assume that it would come back in July?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, we'll try and do that. I think we can do that.

CHAIRPERSON FROINES: Okay. Thanks, folks.

So we will hold on that. Is that acceptable to you guys?

Okay. The next item on the agenda is Department of Pesticide Regulation. And I want to limit the discussion today on this issue.

And, Tobi, you want to sit -- in case there are some questions, do you want to sit here.

Basically everybody on the panel has received the little document that Jim and I prepared that sort of lists the history of the relationship with DPR. I suspect Kathi hasn't seen it yet because she's been traveling. Joe's seen it. Craig has seen it. We have three panel members not here. And I don't know about Paul.

So if -- I'm here.

Have you seen the document I'm talking about?

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: Thank you.

And so this is background. And I'm not going to say anything more about it at this point.

There are clearly unresolved issues that exist between the panel and DPR. And I would propose to the panel that I or a small group of panel members meet with Secretary Tamminen and Director Helliker and talk about some of those issues. And that would be my proposal for what we in part take up -- talk about today.

The second issue is -- Tobi's going to mention, is she's looking for some leads for sulfur luoride. And perhaps she could give us an update on the timing of when that's coming forward.

The third issue that we've received is the request for a discussion on the prioritization process, which I'm going to take the -- what of the Chair? What do you call it -- the prerogative of the Chair and postpone that till July, because we have -- as I say, we have three people missing. And I think we should take that up when we have a little larger number of people.

So at this point I'm really only asking for two things. Can I get agreement on a meeting with the Secretary and the Director to talk about the issues that you would feel comfortable with that happening? Paul at one point had said he thought that it wasn't useful to write more letters. And so I'm suggesting that a meeting

between principals that could discuss some of the issues that exist between the parties.

PANEL MEMBER BLANC: Sure.

CHAIRPERSON FROINES: Everybody talks a lot, and then all of a sudden you get nothing back.

PANEL MEMBER HAMMOND: Do you want acclamation?

PANEL MEMBER BLANC: Who are you thinking would come from Cal EPA for that?

CHAIRPERSON FROINES: The Secretary.

PANEL MEMBER BLANC: And would there be someone from OEHHA?

CHAIRPERSON FROINES: Yes.

PANEL MEMBER BLANC: And who would that be?

CHAIRPERSON FROINES: I don't know.

PANEL MEMBER BLANC: What level would you like?

CHAIRPERSON FROINES: I don't know. I think what I need is flexibility from -- I think that the issue of whether OEHHA attends or not is something that this panel should suggest their views.

PANEL MEMBER BLANC: I think it would be very helpful to have somebody from OEHHA there because it might facilitate communications and workload, avoid duplication, and provide encouragement.

CHAIRPERSON FROINES: I don't want to exclude the ARB. But I think OEHHA and DPR would be the -- because I

think that there is specific interaction that occurs between those two agencies. And my sense is we don't want to make it larger than it really needs to be for this discussion.

PANEL MEMBER BLANC: Although, you know, one thing about the ARB and one of the things that has been a theme that's come up repeatedly has been the time line of data monitoring and the integration of data monitoring with proposed toxicity evaluations, where one thing -- you know, one substance is being sampled and another substance is being discussed in terms of a toxic air contaminant.

And so however it is -- I mean there definitely should be something on your agenda. And it would be I think important to have -- if the person isn't at the table who ultimately, you know, is in charge of the actual field sampling, there should be some form of communication for that --

CHAIRPERSON FROINES: No, I think that should be a subsequent meeting where we talk -- at the meeting that I'm talking about we talk about the larger issues and then have more detail on some of the issues that are very important but not necessarily --

PANEL MEMBER BLANC: You're saying some of this other stuff is the sine qua non; and then if you don't have that, then none of the rest of it really matters.

CHAIRPERSON FROINES: Well, I think that since the discussion is about the relationship between the panel and DPR, what we don't want is other departments or other agencies to kind of be there and, therefore, in a sense inhibit what should be a smaller discussion, I think.

PANEL MEMBER BLANC: A free and frank exchange of --

CHAIRPERSON FROINES: -- ideas.

PANEL MEMBER BLANC: -- ideas?

CHAIRPERSON FROINES: And we'll take up the risk prioritization process.

So hearing no objections, I'm going to go ahead with that.

Tobi, bring us up to date on the sulfurofluoride issue.

DPR ASSISTANT DIRECTOR JONES: We have a draft risk assessment that has gone through external peer review by OEHHA and ARB, currently considering those comments.

I had originally laid a tentative schedule in communications with ARB and OEHHA back in December of looking at possibly fall for presenting to the SRP. So we have some -- we have some steps before that in terms of public comment, a public meeting, and that sort of thing.

CHAIRPERSON FROINES: There's one thing that -- as most -- as everybody on the panel knows, and probably

most in the audience don't know, is there was a question raised about the fact -- there was some question raised about my participation in the development of the naphthalene document, and whether a person on this panel should be engaged in the development of a document prior to pursuing it from a peer-review standpoint.

In other words, if I'm too deeply involved in, say, naphthalene, does that mean that my ability to serve as a peer reviewer on the SRP is compromised? And so that issue's been raised.

That would -- if that issue were to be an important question, it would raise serious doubts about the ability of the panel to have leads working with the agencies.

And so, Jim, is it -- my impression from the Secretary's office is they do not consider that an issue because we are a standing committee as opposed to a UC Office of the President peer review person. In other words, if OEHHA or DPR goes to the UC to identify two or three peer reviewers, then that would be relevant to that regulation. But for a standing committee it's not relevant. So my impression is that we should go ahead on the assumption that we can still appoint leads.

Is that fair?

MR. BEHRMANN: Yes, you can still appoint leads,

especially in the case of pesticides, I believe.

What you were referring to are the CalEPA guidelines for peer review, which provide that in the case of where an author has been involved in actually drafting a document, that person obviously could not be appointed as an outside peer reviewer for it.

But I think that's a separate issue from how this committee as a standing committee uses the idea of leads.

CHAIRPERSON FROINES: Okay. So we'll proceed, Tobi, on the assumption that we're free and clear to keep doing things the way we've been doing. Because we have been doing them for -- since 1983, and so -- but obviously the kind of litigated world has changed since 1983, and so you never know where you're going to be.

So we need to appoint two people, one of whom would be interested in the exposure issues and the other would be a person who would have the health effects side.

Now, in terms of the health effects side, what's driving the risk assessment? Is it epidemiologic data or toxicologic information?

DPR ASSISTANT DIRECTOR JONES: Toxicological data.

CHAIRPERSON FROINES: Tox data.

So do we have any volunteers, assuming this is --

PANEL MEMBER BYUS: I have a question.

CHAIRPERSON FROINES: Paul and Kathi just finished being leads. So they theoretically have get-out-of-jail-free cards.

PANEL MEMBER BYUS: Relative to that question, whatever happened to the cholesterase inhibition document -- that inhibitor document that you were all preparing, of which I was a lead on for some year and a half ago or two years ago -- year and a half ago?

CHAIRPERSON FROINES: This is going to guarantee that you're the assigned person, you know.

(Laughter.)

PANEL MEMBER BYUS: No, no, no. I'm sorry. I was the lead on that document. But I wanted to know where that document is.

CHAIRPERSON FROINES: That's my point.

PANEL MEMBER BYUS: Okay.

DPR ASSISTANT DIRECTOR JONES: The project has not died. But as far as the document relative to this committee, I will refer back to the Chair and communications that my Director has had with the Chair and correspondence.

PANEL MEMBER BYUS: I didn't know that --

CHAIRPERSON FROINES: As far as -- the correspondence from Director Helliker basically said that that was one of the areas that they would no longer

interact with the panel on. And so that's where that is. That's clearly one of the issues that we would still like to be involved in and so would like to talk about that further.

So does that mean that you'd be willing to serve as the sulfurofluoride lead?

PANEL MEMBER BYUS: Sure, I suppose.

CHAIRPERSON FROINES: Well, Joe's just done formaldehyde. And so by process of elimination --

PANEL MEMBER BYUS: If you think.

CHAIRPERSON FROINES: And then I would -- since Roger's not here, let's appoint Roger to be the exposure person.

PANEL MEMBER BLANC: Good.

CHAIRPERSON FROINES: There's very little democracy in this. But I did ask for volunteers first.

PANEL MEMBER BYUS: Sure.

CHAIRPERSON FROINES: So Tobi, Craig, and Roger.

DPR ASSISTANT DIRECTOR JONES: Okay. All right. Thank you.

CHAIRPERSON FROINES: I should say that I talked with Shankar Prasad today. And I don't know whether this is confidential and I'm breaking a confidence, but there is movement on replacing Peter Witschi. And so we may have another panel member in the foreseeable future.

So that's good. That will be -- because that's -- that position is the position of a pathologist. So it would add some more toxicology expertise to the panel.

Did you have a sense of when -- the other document -- I don't remember. There was a second chemical listed that was going to be later. Was that chlorpiriphos or --

DPR ASSISTANT DIRECTOR JONES: No, that was athidithion.

CHAIRPERSON FROINES: Do you have any dates?

DPR ASSISTANT DIRECTOR JONES: No, I'm sorry, I don't. But it is -- in terms of our processing of the Director's assessment and working with OEHHA and ARB, it's on a similar track. So I would say it would come in behind sulfurofluoride. It would come in behind sulfurofluoride.

CHAIRPERSON FROINES: Okay. So I think that's it for now. We'll take up the risk prioritization document in June -- in July. And then we'll try and talk with Helliker and Terry Tamminen, and then we'll go from there.

Thanks, Tobi.

DPR ASSISTANT DIRECTOR JONES: Thank you.

CHAIRPERSON FROINES: Sorry to keep you all day.

DPR ASSISTANT DIRECTOR JONES: That's okay.

CHAIRPERSON FROINES: Finally, who is the ETS person, who's lucky to have Stan having dropped off --

MR. KRIEGER: Good afternoon, Dr. Froines and members of the Panel. My name is Robert Krieger. I am lead staff for the ETS party exposure assessment.

Today I'll just be giving you a brief update on the status of where we are in our ETS report.

As you know, in December 2003 we released a public version of a report for a 90-day comment period which ended March 29th. We also had a public workshop on the report on March 15th, which some of you were in attendance.

To date we have received 25 comment letters, 14 of which are health related, 8 are exposure related, and 9 comment letters are supportive of our report and our program as well.

Currently both ARB and OEHHA staff are in the process of summarizing and responding to these public comments. Our next test will be to prepare a Part C of the report, which addresses the comments, as well as update Parts A and B of the report where appropriate.

We plan to take the revised Part A, Part B, and Part C available to the Scientific Review Panel for formal review in time for a meeting in September if one can be arranged at that time.

And that's basically our update on ETS.

CHAIRPERSON FROINES: So you're planning for the panel to take it up in September?

MR. KRIEGER: Yes, the formal review of the whole revised Parts A, B, and C in September.

CHAIRPERSON FROINES: And the panel will receive the comments and your response to comments.

MR. KRIEGER: Oh, that will be in August. They won't be in September at the meeting. But you'll get plenty of time to review those, report and comments before the meeting.

CHAIRPERSON FROINES: This is going to be a lot of material that people are going to be looking at. So the earlier, the better I think for all of us.

I think that -- you know, you saw today that we had at least two people who just came back from long trips. We had Roger, who was teaching. And so given the fact that this is a group of people who meet relatively infrequently but have very, very busy schedules, the sooner that everybody gets a complete package I think the better.

Paul.

PANEL MEMBER BLANC: That's true. We're so important.

(Laughter.)

PANEL MEMBER BYUS: That's why we get paid so much.

(Laughter.)

CHAIRPERSON FROINES: I haven't heard the Governor was going to plan a new bond so we can get a higher pay.

So it looks like we're about to do it in September.

MR. KRIEGER: Yes.

CHAIRPERSON FROINES: And you finished your monitoring for -- you finished the exposure piece?

MR. KRIEGER: Yes, the monitoring's complete. It's in our current version right now.

CHAIRPERSON FROINES: Okay. Thanks.

MR. KRIEGER: Thank you.

PANEL MEMBER BLANC: I'd like to make a motion that we adjourn.

CHAIRPERSON FROINES: One other item -- just one other item is that the diesel suit will be heard as far as we know at the end of June.

Right, Jim? What's the date?

PANEL MEMBER HAMMOND: We need a closed session for this.

CHAIRPERSON FROINES: No, this is information.

No, we don't need -- why don't we just not take

this up.

MR. BEHRMANN: Actually if you were just going to speak about dates, that would not necessitate a closed session. There will be a one-day trial toward the end of June. And in that case there are some exchanging briefs at this time.

CHAIRPERSON FROINES: That's sufficient.

MR. BEHRMANN: I could ask Kirk at the next meeting to give a more detailed update, and that could be done in a closed session then.

CHAIRPERSON FROINES: Well, next meeting is -- it's theoretically past tense, so that --

PANEL MEMBER BLANC: Well, it would be a better update then.

(Laughter.)

CHAIRPERSON FROINES: Okay, Paul. Make a motion.

PANEL MEMBER BLANC: I move that we adjourn.

PANEL MEMBER BYUS: Second.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: Meeting is officially adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 4:10 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 28th day of May, 2004.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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