MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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A P P E A R A N C E S

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Cort Anastasio, Ph.D.

Jesús A. Araujo, M.D., Ph.D.

Alan R. Buckpitt, Ph.D.

Stanton A. Glantz, Ph.D.

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, Scientific Review Panel

Mr. Peter Mathews, SRP Support Administration

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. John Budroe, Chief, Air Toxicology Risk Assessment Section

Dr. Kenneth Kloc, Toxicologist (Specialist)

Dr. John Faust, Chief, Air, Community and Environmental Research

I N D E X

P R O C E E D I N G S

CHAIRPERSON KLEINMAN: Good morning. I'm Michael Kleinman. I'm the Chair of the Scientific Review Panel, and I'd like to welcome everybody to this meeting.

The panel goals for the meeting are going to be to cover one agenda item, which is the panel's review of the inhalation cancer Unit Risk Factor for Perchloroethylene. This factor was developed using the risk assessment methodologies for developing URFs under the Air Toxics Hot Spots Program.

The document has undergone public review and comment over the course of the year. There were four sets of public comments which will be discussed as part of the proceedings.

The lead Panel members for this chemical are Drs. Alan Buckpitt and Stanton Glantz. Dr. Glantz has provided comments to OEHHA already, and some changes have already been made to the document in response to those comments.

Today we'll hear a presentation from OEHHA staff on the perchloroethylene document, including responses for the public comments, then we'll discuss and provide feedback through OEHHA on the document. The materials for the meeting have already been provided.

The SRP members are available on the website for the public.

As a reminder, please speak very clearly into your microphones, and this will help the court reporter, as well as to make clear to everyone else who is speaking.

You know, the meeting will allow the OEHHA to first present the work on how they've developed the risk factor, and then the leads will provide their comments, then each of the Panel members will have an opportunity to provide additional comments, and then there will be a general discussion, and we'll take any additional comments or suggestions for the staff.

So before we actually begin, I'd like to have a roll call of the panel members here just for the record.

Dr. Katharine Hammond?

PANEL MEMBER HAMMOND: Here.

CHAIRPERSON KLEINMAN: Cort Anastasio?

PANEL MEMBER ANASTASIO: Here.

CHAIRPERSON KLEINMAN: Jesús Araujo?

PANEL MEMBER ARAUJO: Here.

CHAIRPERSON KLEINMAN: Alan Buckpitt?

PANEL MEMBER BUCKPITT: Here.

CHAIRPERSON KLEINMAN: Stanton Glantz?

PANEL MEMBER GLANTZ: Here.

CHAIRPERSON KLEINMAN: And three of our members are not available for the meeting, but we do have a quorum and we can proceed. So at this point I'd like to move to the OEHHA presentation.

MR. BUDROE: Good morning, Chair Kleinman, Panel members.

For today's presentation we will be doing a presentation on the hot spots inhalation cancer Unit Risk Factor for perchloroethylene document. And the presentation will be done by one of our staff members, Dr. Ken Kloc. Dr. Kloc.

DR. KLOC: Thanks, John.

(Thereupon an overhead presentation was presented as follows:)

DR. KLOC: So today we'd like to briefly go over the methodology that we used to do our perchloroethylene Unit Risk Factor update.

The update is based on some new scientific information that's become available since our last development of a perchloroethylene Unit Risk Factor, and the current -- the update is based on our latest cancer risk assessment methodology which was completed in 2009 and which we'll be referring to as the "Cancer TSD."

And then once we finalize our new value for perchloroethylene, we'll be adding a short summary of the development of -- the technical development aspects to Appendix B of the Cancer TSD.

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And briefly just to show you where this analysis fits in the overall risk assessment process, it's part of -- that's up there on the slide, is the classic four elements of the risk assessment process, and our update fits into the Dose-Response Analysis portion.

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DR. KLOC: On slide 4 we have a picture, a pictorial representation of the structure of perchloroethylene. It's primarily used as a chemical intermediate, a solvent, and a cleaning agent. It's relatively volatile, and the Air Resources Board estimated that in 2010 approximately 3800 tons per year of perchloroethylene were emitted into the air of California.

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DR. KLOC: Perchloroethylene was listed as a air toxic contaminant, or toxic air contaminant in California in 1991, and OEHHA's previous potency analysis was carried out shortly after that in 1992.

It was based on a national toxicology program inhalation bioassay that was done in 1986, and at the time the value was based on an extrapolation from mouse liver tumor data.

And also in the 1992 value we used a simple pharmocokinetic model to estimate the internal metabolized doses. And the 1992 value came out to be about 6 times 10 to the minus 6 risk per microgram per meter cubed of exposure.

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DR. KLOC: For epidemiological studies, there have been numerous studies published on perchloroethylene exposure, primarily in occupational settings. And we've reviewed them several times, these studies, and none of them actually have exposure assessments that are suitable for doing a quantitative assessment; so that means that we then move to animal studies to develop data for the dose-response assessment.

However, the epidemiological studies suggest that PCE exposure increases at least three types of cancers in humans: Bladder cancer, non-Hodgkin's lymphoma and multiple myeloma.

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DR. KLOC: The carcinogenic action of

perchloroethylene is generally believed to be due to its metabolites, and that's a parent compound.

And PCE is generally metabolized in two biological pathways. The first is oxidation, generally carried out by the cytochrome p450 system where you have PCE being oxidized by cytochrome p450 enzymes and forming several highly reactive intermediates, which eventually react to -- either with biological molecules or to form soluble additional metabolites which are less reactive.

Some of the reactive metabolites are up on the slide. PCE epoxide, trichloroacetyl chloride, and oxalyl chloride. And then some of the less reactive further downstream metabolites are trichloroacetic acid, and then you have oxalic acid, carbon dioxide, and carbon monoxide. And it's possible that some dichloroacetic acid is formed, but its unclear whether or not it forms in this pathway.

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DR. KLOC: The second major metabolic pathway for a PCE is the glutathione-conjugation pathway. And that's mediated by glutathione as transferase -- the first step of this pathway is mediated by glutathione as transferase enzymes.

And then several other enzymes participate in

the ultimate degradation and elimination via a mercapturate. However, there's some other enzymes within mammalian systems that can intervene and actually create chemically reactive and potentially biologically damaging molecules. And some of those -- some of the enzymes are beta lyase, again, cytochrome p450, and flavin mono-oxygenase 3.

The two major reactive metabolites that can cause damage are dichlorothioketenes and unsaturated sulfoxides of the glutathione pathway.

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DR. KLOC: On this next slide it's just essentially -- it's just a repeat of some of the information on those previous diagnosis listing some of the potentially genotoxic and tumorigenic metabolites.

On the left side of the table are the metabolites for the oxidative pathway, and on the right side are some of the metabolites for the glutathione-conjugation pathway.

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DR. KLOC: So our update was based on several new studies. One of the studies was a lifetime inhalation exposure study in mice and rats, which was carried out by the Japanese -- or the Japan Industrial Safety and Health Association in 1993. It's quite

similar in its procedures and reporting to the 1986 National Toxicology Program study, and it did have a few additional -- it had a few advantages in that it used a few additional low-dose groups in the testing and that -- actually, the Japanese strain of Fischer 344 rats used in this study have a relatively low rate of one of the tumor types that have been known to be elevated, which is mononuclear cell leukemia.

The American strain of the Fischer rat has a relatively high rate of mononuclear cell leukemia.

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DR. KLOC: Another new study used in the update was a physiologically based pharmacokinetic model, or PBPK model, which was published by Chiu and Ginsberg in 2011. And that model used a Bayesian Markov Chain Monte Carlo method to obtain most likely values for key metabolic parameters in the two main modes of metabolism of PCE.

The Bayesian method also allows a calibration of the PBPK model, using a wide range of data which is available from both rodent and human studies. And this was in vivo data from a wide range of studies.

And an advantage of this 2011 PBPK model is that -- over the previous models, is that it included a separate glutathione-conjugation pathway, and it's the

first model to have done that.

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DR. KLOC: This is sort of a complicated diagram, but it shows a pictorial representation of the Chiu and Ginsberg PBPK model.

On the left it shows the various compartments that were modeled for the parent compound, which is PCE. So if you look closely, you can see the various tissues and organ systems that were modeled.

And on the right it shows a smaller subset of compartments that were modeled for some of the oxidative metabolism components.

And then in the lower right is some of the compartments modeled for conjugative metabolism.

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DR. KLOC: Now, one of the, I suppose, innovations of this latest PBPK model is that it included a Bayesian analysis additional to just traditional PBPK modeling.

The Bayesian analysis is basically a statistical method to use the available data to calculate the most probable values for the important PBPK parameters. So it's essentially a sophisticated calibration process, if you will.

In order to do this calibration process, the

model had to incorporate several routes of exposure and elimination, such as inhalation, oral, intra-venous, and exhalation and urinary elimination.

And then once you do the Bayesian analysis, you come up with the most likely values based on all the prior data that you had available. And then you can use those most likely values, which in this case are the rate constants for the enzymatic transformations. And you can use that to run the PBPK model in sort of the traditional mode, which is just you plug in your parameters and you estimate doses.

And so that's the way -- actually, that's the way U.S. EPA did it when they did their reevaluation of PCE, and that's the approach that OEHHA took.

However, the one thing that we did do in order to simplify matters is since we were only interested in calculating internal doses based on inhalation exposure, we were able to extract the inhalation-only portion of the PBPK model.

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DR. KLOC: And this diagram is showing -- the diagram of the inhalation-only extract of the PBPK modes is shown on this slide. Let's see. If you sort of memorize that very quickly, I'll go back and show you the original model.

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DR. KLOC: So this is basically showing you a diagram of the left-hand side -- I'm going the wrong way -- of the original model. So if you look at the left-hand side there, you'll see most of the compartments are in place.

--oOo--

DR. KLOC: Most of the compartments are also included in the extract that we used.

So basically we used the same blood and air-flow compartments as Chiu and Ginsberg. It included the wash-in/wash-out effect for the respiratory tract, which was part of the original model.

We included the first oxidation stuff in liver, kidney, and lung. We included the first glutathione-conjugation stuff in liver and kidney, and this is what was done in the original model; and then we used the posterior modes which were determined by the Bayesian analysis by Chiu and Ginsberg. So we used those values that they determined with their sophisticated calibration process in order to run our model. And we were able to reproduce the Chiu and Ginsberg inhalation results in an adequate manner,

meaning to a good level of significant figures.

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DR. KLOC: So this table here is a table that's based on values reported by Chiu and Ginsberg. And it also happens to be the values that we obtained with our model extract. You know, the simplified form which is for inhalation only.

I just want to -- it's sort of a dense slide. I just want to make a couple of points about it. If you look at the middle of the slide, we present internal dose-metric estimates for PCE oxidation as a percent of the amount inhaled. And so in the middle there you'll see PCE oxidation for mouse, rat, and humans. And you'll notice that mice oxidize a lot more of their intake compared to humans. So mice do about 10 to 20 percent of oxidation and humans are about 1 percent of oxidation of the amount of PCE that they inhale.

In the lower portion of this table, the dose metric is PCE conjugation, and the order of metabolism is reversed in this case. So, for example, the mice do very little -- according to the best estimates of the model, mice do very little PCE conjugation of the amount that they inhale. However, humans can do up to about 9 percent, according to the model estimates

In the lower right-hand cell of this table, I have highlighted what's called "the prediction range." For an example, that 1 ppm. And if you'll notice, the prediction range for humans for PCE conjugation is relatively wide.

And this is one of the issues with the model in that it was not able to decipher. In other words, it found relatively high-probability values for a low as well as a high estimate for conjugation, even when taking into consideration all the in vivo data in the calibration process.

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DR. KLOC: So in the next slide I just wanted to show you some of the dose-response data from the two rodent bioassays. This is the earlier National Toxicology Program study which was done in 1986. And in that study, that was done in both mice and rats.

And in mice it found elevated liver tumors, hepatocellular adenoma or carcinoma. And in rats it found elevated levels of mononuclear cell leukemia, kidney tumors, brain tumors, and testicular tumors.

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DR. KLOC: On the next side this is the Japanese study, which is the new study that we're incorporating. And in a slightly different strain of

mice, it also found liver tumors. In addition, it found hemangiomas and hemangiosarcomas, as well as an increase in harderian gland adenomas.

And in rats, like the NTP 1986 study, it found mononuclear cell leukemia.

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DR. KLOC: So our Cancer Modeling Approach, what we decided to use. We assumed that PCE acts primarily through its genotoxic metabolites to form cancers, and we deemed the NTP 1986 data and the Japanese 1993 data to be adequate and appropriate for use in quantitative dose-response assessment.

We also used our extract of the Chiu and Ginsberg PBPK model to estimate internal metabolized doses due to inhalation-only exposures.

And the dose metric we chose was the sum of the first step of PCE metabolism of both the oxidative pathway and the glutathione conjugation pathway.

Using the dose-response data from the bioassays, we calculated both single and multi-tumor risks, and we considered uncertainty in some of the data in coming up with our final "best estimate."

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DR. KLOC: Here's some of the details of the actual Dose-Response Analysis. We used the later

version of U.S. EPA's Benchmark Dose Software. We used the multi-stage cancer model and the assumption of low-dose linearity, which is one of the typical methods that we use according to our 2009 cancer guidelines.

Benchmark risk was calculated at 5 percent. We calculated the benchmark dose at the lower percentile. 95th percentile was benchmark dose. And we also used the Benchmark Dose Software to do multi-tumor summation in cases where animals had multiple tumors at different -- in different tissues. I'm sorry. I misstated. In the case where animals had tumors in multiple sites.

And, finally, we did a cross-species adjustment of the benchmark dose using the standard three-quarter-power body-weight scaling process or procedure.

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DR. KLOC: So this table shows -- it's a little bit large. I just wanted to show you -- give you a feeling for the number of calculations that we did and the number of potential Unit Risk Factors that we came up with for our further considerations.

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DR. KLOC: On the next slide I take some of the data that was in that original table just for

comparison purposes. So here these are the two cases in which we did a combined-site risk. In other words, we took tumors that were observed in animals in multiple tissues and used the Benchmark Dose Software to do a summation of risks.

So in the Japanese study the male mouse had tumors in multiple tissues. And we did a summation, and our combined site number was 4E to the minus 6.

And the summation is a -- it's a statistical procedure, but if you just don't worry too much about precision, you can just actually add up those numbers, just do a simple sum and get pretty close to that combined site value. And the advantage of thinking of it in those term is that you can see which tumors dominate the ultimate combined risk.

So in this case liver tumors are pretty close to the combined site risk, and the harderian gland and the hemangiosarcomas don't add too much.

The other study in which we did a combined site risk was the NTP 1986 study, which was one of the original studies that we used in the older value. And so we added up mononuclear cell leukemia, the testicular tumors, the kidney tumors, and the brain gliomas and came up with -- that's the highest -- that's the largest risk value that we calculated out of

all the various risk values that we calculated.

And that's dominated by mononuclear cell leukemia and the testicular tumors. If you add those up, they come up to be about almost 1.60 to the minus 5.

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DR. KLOC: On this next slide I show a comparison of the values between the Japanese study and the NTP studies for the two tumor types that were seen in both studies. And it shows that the values between both studies are really quite consistent.

So, for example, the liver tumors in the males and the females for both Japanese and NTP studies are really quite close, with the males being somewhat more sensitive than the females.

And in the lower part of this table there's a comparison between the two studies for the mononuclear cell leukemia. And in this particular case the NTP study was about -- very roughly about two times higher in terms of the risk estimates that we got. And, again, the female rats are less sensitive than the male rats for this particular effect.

PANEL MEMBER ANASTASIO: Can I interrupt for a second?

DR. KLOC: Sure.

PANEL MEMBER ANASTASIO: I'm a novice to the cancer stuff. Can you explain the Unit Risk Factors to me, especially the units and how you would use that then to understand the risk for populations.

DR. KLOC: Okay. So the Unit Risk Factor is a -- it's a value which is -- when you use animal data to develop it, basically you take the original bioassay dose-response data. So the animals are exposed to a certain inhalation exposure, you know, micrograms per meter cube or parts per million; and then you see what the increment of cancer is in the various dose groups is.

Then you use the multiple-stage cancer model to develop basically a nonlinear regression analysis to get a slope factor at low doses. And once you get that slope factor, you use a few other assumptions to be sort of health protective when converting from species, from, say, rats to humans; and you come up with an estimate for a slope factor in humans.

And the slope factor essentially says for each lifetime exposure to, you know, a part per million, how much additional risk will a population receive from that?

And in our case the humans we used are additional -- it's incremental risk in the population

per microgram per meter cube of external exposure to the substance.

PANEL MEMBER ANASTASIO: Just to make sure I understand, so if you had an exposure of, say, 1 microgram per year lifetime and the Unit Risk Factor is 1 times 10 to minus 6, you would expect 1 case in a million of extra cancers because of that?

DR. KLOC: Exactly.

PANEL MEMBER ANASTASIO: So the higher the URF, the more dangerous, the more potent something is as a carcinogen?

DR. KLOC: Yes.

PANEL MEMBER ANASTASIO: Thank you.

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DR. KLOC: So some of the considerations that we went through in looking at these various values we developed in finally choosing our final URF.

So we judge the mouse liver tumors and the rat mononuclear cell tumors to be -- the data from those tumors to be more certain. For one reason, we had a good qualitative and quantitative agreement in the two primary studies, and then we also had some qualitative support for mouse liver tumors from an additional study that I didn't mention yet. It was a National Cancer Institute oral study that was done way back in 1997 that

observed increases in mouse liver tumors.

Another consideration, we felt it was -- the NTP study in rats found some tumors that weren't found in the Japanese study -- the testicular, the brain tumors, and the kidney tumors.

We thought that -- we sort of deemed those to be less certain data, but we thought they were important to include in the study, mainly because the strain of rats was slightly different. I mean, it's a substrain of rats, the American substrain, and so that's genetically slightly different than the Japanese substrain. So we thought that it was -- that both of these studies in rats gave us non-redundant information to incorporate into this analysis.

However, like I said, we did deem these results to be somewhat less certain. For example, with the testicular tumors, there's a high historical background rate in this animal model. And in the control group for the NTP study the background rate was 71 percent.

Nonetheless -- I mean, the statistical tests show that there was a statistically significant increase upon various dose categories.

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DR. KLOC: Other considerations. The other

consideration was that male rodents were consistently more sensitive than the females, so we chose to focus our attention on the male rodent values. And for those, the Unit Risk Factors that we calculated were within a relatively narrow range, 4E to the minus 6, to 1.6E to the minus 5, which is about a factor of 4.

So taking into consideration all the various somewhat vague uncertainties, we decided that it might be good to choose some sort of a middle value and to de-emphasize some of the less certain data. But we chose the geometric mean of both the male mouse and rat Unit Risk Factors from both studies as the proposed final value that we would come up with.

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DR. KLOC: I think this is the last slide. We'll just show you the four numbers that went into the final calculation. So it will be the Japanese multi-site value, the NTP liver value for male mouse. And for male rat, the Japanese MCL value and the NTP multiple-site value.

Ultimately, our Unit Risk Factor was about 6 times 10 to the minus 6 per micrograms per meter cube. And if you remember to the very beginning slides, that's actually pretty much the same number as it was in the 1992 version.

PANEL MEMBER ANASTASIO: Sorry to interrupt. What was the current EPA value?

DR. KLOC: It's 23 times less potent. I don't remember the exact number, but 23 times less.

So that's the presentation to this point. And at this point I will ask the Chair if they would like to continue or take a break.

The rest of the presentation, by the way, is going to be covering the main comments from public commentators.

DR. GLANTZ: I think it would be useful to explain the differences between the way you did it and the way EPA did it to account for that difference, because the commenters jumped all over that, as you recall.

So why don't you go through, you know, the differences between -- you know, the decisions you made versus the decisions that they made that led to that difference. It's pretty direct, actually, but I think it's worth explaining and getting it on the record.

CHAIRPERSON KLEINMAN: All right. Perhaps in the context of this, to go over -- you know, since the commenters had done it; you responded to that, so why don't we just continue with the discussion at that point.

DR. GLANTZ: Rather than doing it in the context of the comments, it would just be quicker and clearer for them to just explain it. And then we can deal with it in the context or the comments, rather than conflating the two. Because it is an important point of judgment in the document. And it's not that complicated, actually, so...

DR. KLOC: All right. I'll take a crack at it, even though I don't have any slides. And my colleagues should jump in if I miss anything.

So anyways, I would say that the main difference, which leads to about a factor of 10 or 11, that we're a little bit more health-protective by a factor of 10 or 11, has to do with the fact that we used a total metabolized dose which incorporates that glutathione-conjugation pathway.

U.S. EPA apparently in their 2008 draft used the same dose metric. But then in their 2012 draft they backed off of that and went to an oxidation-only dose metric.

In our document, we basically do a calculation in which we show that the difference between those two dose metrics will give you approximately a factor of 11 additional conservatism or health protectiveness; meaning if you utilized the total metabolized dose with

glutathione conjugation in it, it becomes 11 times more potent in your final answer. So that's the 11 times.

And then there's another factor of 2 or so that our number is more health protective or more conservative, if you will. And that probably comes into play because we used the NTP data in addition to the Japanese data.

If you notice in the -- if I remember this correctly, the MCL data in the Japanese study gave a factor which is about two times less than the MCL data in the NTP study, two times less potent, and so that could come into play.

And then the other thing was that U.S. EPA didn't do multi-site summation and we used the multi-site summation procedure, which gives you a higher potency factor in general because you're summing up tumor types.

Some other potential sources of that additional, you know, two, two and a half level of health protectiveness would be -- well, in the NTP study we summed up several tumor types that I think -- U.S. EPA did the calculation for those tumor types, but they ultimately decided not to consider them; so they didn't consider testicular tumors.

I don't believe they considered kidney tumors;

although actually in our calculation the kidney tumors are a relatively minor factor because they didn't add in very much to the final answer. But the testicular tumors did add in about 50 percent to that high value.

On the other hand -- so what we did, we took sort of a median value of the various numbers we chose, so we came down a bit from our most -- the most stringent potency factor that was calculated amongst all the values that we calculated.

DR. GLANTZ: So I'm coming at this from the point of view of the modeling. I'm not a toxicologist but -- I mean, I think what they did was better than what the EPA did because it was more comprehensive in terms of the data set that was used because it's considered total internal dose for both pathways, and it seems to me irrational to just ignore the larger of the two pathways.

And I think that it's also looking at trying to get at all of the effects together. So, I mean, I think it's a much more defendable approach than what EPA did. I think it was very odd that when you have something that you know is bringing -- a chemical is being metabolized into something with toxic results that you would take the pathway that's producing most of the internal exposure and just ignore it, which is what EPA

did.

And so I, at least as I understand all of this -- and I met with the staff about the comments I had sent them before the meeting and we talked about this, and I really think that this is a far superior, more defendable scientific analysis than what's in the EPA report.

I don't even think it's even a matter of being health conservative or not. I think it's just better because it's making use of more information and everything that we know about the multiple pathways; so...

PANEL MEMBER ANASTASIO: So on that note it does seem you want to take into account the GSH conjugation, but it seems that the estimate for that is extremely uncertain, and so how do you constrain that?

DR. KLOC: Yeah. Let me -- yeah. I can go back and address it. You know, one of the things about the Chiu and Ginsberg model in that area of what I call uncertainty -- and, actually, at that point I probably should have pointed out is that we're not sure if it's uncertainty. It actually could be actual biological variation that's being represented there in that very wide spread numbers.

And Chiu and Ginsberg spent a lot of time

actually trying to figure out how much of that spread was due to uncertainty versus actual biological variation, and they were unable to, unfortunately, even with various quantitative calculations that they did.

So it's one of these unfortunate decision points in which you, even though you do very sophisticated analysis and have quite a bit of data in front of you, you still have this sort of an irreducible unknown that you have to make your decision based on.

PANEL MEMBER BUCKPITT: I'll have some comments that I've written, but part of that uncertainty, I think, goes back to some of the work that was done where they're showing huge range in the rates of metabolism. And in looking at the primary literature in that area, I think some of that literature, particularly in the low side, is badly flawed.

So I think OEHHA has really taken a good approach to this thing. I think they're right on the money.

PANEL MEMBER HAMMOND: I was just going to comment that I do think it's also important, the variability, as you talked about that, and certainly the bluebook risk assessment. They talk about there being 10,000-fold variability for some of these factors. I don't know if there's any better data someplace on that,

but I think it's not inconceivable. It certainly makes sense that that could be true variability.

DR. KLOC: Right. So for the glutathione-conjugation pathway, the first step is mediated by glutathione S-transferase. And so it's know in human populations some of the various genotypes of this enzyme are actually absent, so those members of the population won't -- they do not have any of that enzyme to carry out that particular portion of the pathway; so that could lead to some pretty large variation if you have some efficient metabolizers and zero metabolizers.

The problem is that one of the unknowns with the data is that people have not figured which isoforms of GST are most important in this particular pathway. They just know that GST in general does it.

PANEL MEMBER ANASTASIO: If I could summarize for myself, the higher the fraction of internal dose that gets conjugated by GSH, the higher concentration of toxic metabolites you have; is that correct?

DR. KLOC: Generally, that's -- yes. That's sort of the assumption that people generally make. There's a few more enzymatic steps that have to occur before you get to your ultimate toxicant. But in the analysis that we've done and that other people have done, they assume that if you do the first step that

increases the probability that you're going to go through the second, third steps of enzymatic processing to get to that ultimate toxicant.

PANEL MEMBER ANASTASIO: And you were using this estimate on slide 15 -- the 9.4 percent of the intake is conjugated GSH? That's the OEHHA use in the model?

DR. KLOC: Right.

PANEL MEMBER ANASTASIO: Okay. And Alan, you're suggesting or saying that based on the literature the higher value is actually more likely to be correct?

PANEL MEMBER BUCKPITT: I think the value that they used is certainly within the reasonable range, and I think their data does suggest that.

Some of the publications that they had to base their analysis on showed either no activity at all or very low activity in the human. But if you look at the analytical methods employed with that, they were either quite insensitive or they were just plain wrong. They had such high background levels that you'd never see anything. So I think they've rightly set a number on this that's correct.

PANEL MEMBER ANASTASIO: I think I understand now. Thank you very much.

DR. KLOC: You're welcome.

CHAIRPERSON KLEINMAN: And the reactive compounds that are the real toxicants, their biological half life is going to be rather small so that the chance of detecting them, you know, during the process becomes very difficult; so -- and you really can't do much other than identify the initial process, and then you really have to rely on the toxicokinetic modeling to end up with the potential dose of the carcinogens. It does seem to make sense.

I think it would probably be useful to have Dr. Glantz and Dr. Buckpitt, you know, provide their comments on where we've been so far, and then move on to the responses to the other comments.

Alan, do you want to start?

DR. GLANTZ: Why don't we let Alan go with first. I've more or less said what I have to say, actually, but I have a couple more minor points.

PANEL MEMBER BUCKPITT: Okay. And, again, this would be a reiteration of some of the things that I've said. And it's relatively short, so we're not going to be here for a long time.

I will say that I thought this document was quite well written, particularly with Stan's improvements. That you evaluated the literature, not just enumerated the literature. You looked at some of

the factors associated with your risk assessment. And I think you did a great job of being succinct and clear.

I think that this committee does need to really think about and discuss the business of the 20-fold or 23-fold difference between the EPA and OEHHA's level and determine whether that is justified.

So let me go through from my take on your document what I thought the two issues were. And we just discussed this.

One is the use of the total metabolism in doing the dose metrics. And I'll go through in more detail about the glutathione-conjugation pathway but, again, going through the literature. There's very good evidence, I think, that you selected properly.

And then the other issue that's key is the use of multiple site of tumors and the use of the mononuclear cell leukemia. And there's a lot of pushback from the DoD and the California Chamber of Commerce on those issues.

So let's go through the discussion on the differences and rates of formation of the glutathione conjugates. There are only a few studies out there that actually use perchloroethylene. One was the DeKant publication in 1998, and they show that there's no detectable rate of metabolism or PCE in humans.

Well, if you look at their method, they were doing HPLC with UV detection; they were using 260 nanometers. That's pretty doggone insensitive. So you'd have to have a pound of glutathione conjugate generated in those incubations to really even see something.

I was surprised that they didn't use lower wavelengths on that; but, nevertheless, I think that's probably -- for yesterday's standard that was probably adequate, but we know that there are glutathione conjugates formed from that.

So then you're left with a couple of papers from Larry Lash and Trevor Green on trichlorethylene. Trichlorethylene is essentially perchloroethylene minus chlorine. So you can say, Well, the two compounds aren't the same, but they're close enough so that the glutathione pathway is going to be pretty similar.

Green's paper said, Well, you know, there's not much activity. In fact, I think he reported that there's no activity in the human. But if you really take a close look at the paper, he was using carbon 14 labeled material. He had so much contamination from the potential glutathione conjugate that he would have had to have seen a ton of metabolic activity to actually see it. His incubations were contaminated with about

50 percent of the trichlorethylene glutathione conjugate. So in my mind those studies are really not very helpful.

The other thing is that he used only cytosolic fractions when he did those analysis. If you look back at some of the data on hexachlorobutadiene and some of the other chlorinated compounds, there's an equal, if not greater, amount of glutathione conjugation actually generated in microsomal incubations. There are microsomal glutathione transferases.

The last manuscript reports values that are what? 5,000 fold higher than what were reported by Green. And I'm not certain where you came up with your numbers, the 5750 on page 18, but you can sort that out later; but clearly very high rates of metabolism.

And Larry Lash's publications have been criticized for the method that he used. And essentially what he did was he took these glutathione conjugates that did not absorb very well in the UV, and he derivatized them with fluorodinitrobenzene. Essentially went from an old method that Don Reed had published on doing glutathione analysis.

That method has been criticized quite a bit for the fact that if you're not very careful and cap the supplied glutathione, you get a lot of variability in

the assay. Well, you don't have to worry about it in the case of looking at these conjugates because they're already capped.

Fluorodinitrobenzene has been used as a derivatizing agent for means for 30 years, 40 years. It's a pretty stable reaction, and done properly, will give you pretty good numbers. So I think you're right on the money in that regard.

If you look -- and there have been some studies of rat versus human excretion of the N-acetyl trichlorovinyl cysteine derivative, so this would be the mercapturic acid from perchloroethylene exposure.

You can see levels in the human exposed to -- and it's dose responsive. It's not what the rat is. If you step back and say, all right, let's calculate how much conjugate is produced per body weight. But it's certainly not the 25,000-fold difference that you see in the two publications looking at trichlorethylene metabolism.

So, again, I think this shows that certainly the human can make these glutathione conjugates, and part of that is excreted as the mercapturic acid.

What we don't know -- if you look at the metabolic pathways, what we don't know is how much of that gets siphoned off to generate the reactive

metabolite, essentially the thioketene from beta-lyase metabolism.

So that's a data essentially whole that we have no way of plugging, but certainly we should use the conjugative pathways, as well as the oxidative pathways, in doing these analysis.

So that really is the summation of the glutathione pathway. I think it's very well justified, and I think the pushback from your DoD and others is not well-founded.

The other thing that you could think about doing -- and I'm not sure this is really going to clarify anything, but if you look at -- there have been AMES assays on the PCE epoxide, on the trichloroacetyl chloride, on your glutathione and cysteine conjugates with and without beta-lyase. If you look at the glutathione part of that pathway, they generate some really nasty metabolites.

So you could go through and make a list and say, well, you know, this dichloroketene is really a potent mutagen. It doesn't translate to being a potent carcinogen, but, you know, it should be a concern. I'm not sure you want to go there, but certainly if somebody said, Well, you know, your use of the glutathione pathway is not well justified, I think you could use

that as one of the arguments that those metabolites are important.

And then the other issue -- and it's minor in comparison -- was the use of multiple tumor sites and the use of the MCL. And, again, that's a directive that you folks have to live with; so I think that's a nonissue at this point.

I had a few typos. Other than that, I thought it was a nice clean document.

CHAIRPERSON KLEINMAN: Thank you.

Stan.

DR. GLANTZ: Well, I sort of made my main points earlier. But I think this issue about the one factor where there is a lot of uncertainly in a bimodality in the distribution, which is concerning, but I think -- as I understand it, the higher mode is the more probable mode; right?

DR. KLOC: That's correct.

DR. GLANTZ: Do you remember by how much?

DR. KLOC: You know, I don't remember what the log likelihood units values were. If I can just hazard a guess, I would say it was 1300 log units.

DR. GLANTZ: Versus what?

DR. KLOC: Well, you know, the Chiu and Ginsberg analysis, it was a partial Bayesian analysis,

so they only determined the modes. They didn't actually determine the entire distributions.

DR. GLANTZ: Oh, okay.

DR. KLOC: So I'm not clear as to whether or not you can actually get a probability value out of just knowing where the modes are located.

DR. GLANTZ: Okay. But I think it's -- the fact that it's the more likely mode, the higher peak, is important. And, again, if you go back and look at the cancer risk guidelines, it says in there that when you have this kind of uncertainty you should go with the higher number.

So I think -- and based on the earlier discussion, which was -- you know, there's a lot of variability, in-a-person variability, and the sort of general principle of going with the susceptible sub groups; and I think that's a reasonable approach to take.

And the one other thing in the changes that were made in the document to put the models in, which I'm glad you liked. It made it a lot clearer to me. I think the one point that didn't come through is when you put that slide up showing the predictions of the Chiu and Ginsberg model and the predictions of the OEHHA model to the number of digits that were in that table,

they were the same. So I think that could be made a little clearer in the document. Because, you know, when I met with the staff, I said, "Well, where's the difference? It's like there isn't any."

So the reduced model performs very, very well. And the important thing, I think, to understand about the reduced model is they didn't get rid of anything that is related to the inhalation pathway. All they took out was the other pathways, but all the kinetics for perchloroethylene that were related to inhalation were present in the simplified model. And I think that's why it came out so good, is because those other factors just aren't -- they're not being considered.

So, I mean, I also agree that -- I think it was well done. I thought that the -- I mean, I read all of the public responses and response to comments, and I thought the responses were quite well done; and the comments were actually pretty thin in terms of the substance of them.

So that's what I have to say.

CHAIRPERSON KLEINMAN: This might be a good time for the rest of the panel to have any other comments, and then we can move on to the responses to the public comments.

Kathy, do you want to start?

PANEL MEMBER HAMMOND: I thought the document was well written and made good sense, as I read it. And I certainly agreed with the inclusion, for instance, of MCL and the multiple sites and the different metabolic pathways. I think that those are really important. And jumping ahead to the comments -- and the comments seemed to be kind of, Why don't you have U.S. EPA numbers? And I guess California's been better than the U.S. EPA for a long time, and this is just one more instance.

PANEL MEMBER ANASTASIO: Yeah. Just one general comment based on my comments before.

I think it would be helpful for a reader to understand the difference between what you did and what EPA did. You talk about that, but often you talk about just one side of it. You just, you know, EPA did this.

It would be helpful -- for example, on page 9, as an example, you talk about what EPA did. You know, they just use oxidative metabolism. It would be helpful, I think, in that same paragraph to say, But we did this for this reason. Because that is the big contrast, you know, the EPA number from OEHHA number.

So I think whenever you bring up the EPA number, you should indicate what did you do differently and why. And, again, that's all in there, but it's helpful as a reader if it's in the same place.

CHAIRPERSON KLEINMAN: Jesús.

PANEL MEMBER ARAUJO: Yeah. I think that the document is very well written and very clear. I agree with all the comments. I just have a question for my own clarification.

So we've been discussing about the different approaches of the EPA versus us, or you and I'm reading here that it says -- so the EPA did take the Chiu and Ginsberg model to calculate the positive factors. And in some place also it mentions the dose metrics, but it didn't really take it for a calculation of the concentrations? I mean, what is it what it took or what is it what it didn't, as compared to what you're taking?

And if we go to the Table 1 that you presented, you know, they have, like, a different -- the model, they have different concentrations and the prediction range, that table, Table number 1.

So is there a comparison that you could do, let's say, on that table? What you -- the EPA did versus if you were to be doing this, how would that look? Because that already looks pretty good, you know, coming from the model of Chiu and Ginsberg. Pretty much of the prediction ranges and includes the values that are included in the table.

So the EPA didn't take anything of this model

when they made their decisions?

DR. KLOC: For the inhalation risk factor that they calculated, they used the center numbers, which refer to PCE oxidation, percent of intake oxidized. Those are the values they used.

And actually, even though I hadn't mentioned it, we independently were able to calculate U.S. EPA's input values; so their application of this model we were able to reproduce.

DR. KLOC: So the difference between what EPA used, which was just the values for PCE oxidation and what we did, was we also added in the values for PCE conjugation to create a total metabolism.

Did I answer your question?

PANEL MEMBER ARAUJO: Yeah. But that's where I get confused in how you present it. In the eyes of the EPA -- on page 7 -- so you're saying the EPA used the Chiu and Ginsberg model to estimate a trial dose metrics in its recent PCE cancer-positive transferase, and then you go on to the various things. It uses a Bayesian Chain Monte Carlo, et cetera, et cetera, et cetera, and you refer to the table.

So it's not really clear to me. On one hand you're saying they're using this model, and in some other places you're saying that they're using only a

part of this model.

DR. KLOC: Okay. So maybe just --

PANEL MEMBER ARAUJO: Maybe it's my own confusion. I don't know if that looks clear to the other members of the panel. And if it did, maybe I need to be paying more attention.

DR. KLOC: I think I see your point. You know, it is a little confusing because both OEHHA and U.S. EPA use basically the same model. It's a little more complicated because we've extracted a certain part, so we have this more streamlined version of the model that we're using. So it makes -- the presentation is a little -- maybe a little bit difficult to follow in that sense.

Is that what you're getting at?

PANEL MEMBER ARAUJO: Yes. But part of it would be the presentation. The other could be like -- aside from theoretical considerations that -- to be in more comprehensive and inclusive is better than not. And I don't know if there is any possibility of showing it and demonstrating it, you know.

And when I see this table, for example, I'm going to say, Did the EPA do this table and this table is already included in the prediction ranges and all the values that are, like, both in pathways? I'm saying,

How much better can it be, you know?

And it is true there's a large variability, but as part of the large variability they're able to predict it.

So the model is critical. You know, I mean, they're actually able to really predict other values, so how much better in being more inclusive, you know?

DR. KLOC: I think we do have a section in the document where we actually calculate what the difference in the final value would be if you used either oxidation only or the total metabolized dose. So we actually -- we show that it would be about a factor of 11.

PANEL MEMBER ARAUJO: But that's an estimate, and can you prove it? I mean, whether the predicted values correspond to what actually was measured and the one -- this model was actually more accurate than the model that they used?

What I'm saying is can we go beyond the theoretical consideration and actually use any data that would support, you know, one or the other?

DR. KLOC: I would say that the Chiu and Ginsberg model, because it's basically calibrated and incorporates utilizing that Bayesian statistical method, it incorporates all the useable in vivo data that was available up to 2011; so it's probably the best estimate

that you could possibly come up with.

And in fact -- we didn't go into this. In the U.S. EPA -- Chiu and Ginsberg actually developed this model, I believe, in conjunction with the work that the U.S. EPA was doing at the time in order to develop their number; and the National Research Council made the recommendation at the time that this model be developed in the way that Chiu and Ginsberg did it.

So it does represent sort of the state of the art in terms of our capability to estimate the internal doses due to inhalation exposures.

PANEL MEMBER BUCKPITT: I wonder if it would help if you had a section of your report that essentially said these are the levels; this is the Unit Risk Factor listed by the EPA; this is what ours is, and the differences are related to A, B, and C. Would that help clarify the difference?

PANEL MEMBER ARAUJO: What you're saying is presentation; right? Just on working on a more clearer presentation?

PANEL MEMBER BUCKPITT: Exactly. In other words, if you had a question about why their numbers were so much different from the EPA, would it be worth putting in a paragraph in your report saying, All right. This is what the numbers were, and these are why they're

different.

It's sprinkled throughout your document, but maybe focusing in one place.

DR. GLANTZ: Well, no. Because that is one of the big issues that came up in the public comments. And you're right, it is in there. It's just sort of scattered.

And so I think just putting a paragraph or two with a heading just explaining why they're there, but basically the things that you said in the presentation why they're different -- how they're different, why they're different, and why what you're doing is better. And just put it all in one -- I mean, you can leave it sprinkled, too, but I would just add a heading that says, you know, why we use this, where the differences are coming from, and why what we did makes more sense.

I don't think it's a substantive change to the document, but I think it would make it better in terms of clarity. Again, because that was like the main substantive issue that was raised in the comments.

CHAIRPERSON KLEINMAN: Katharine.

PANEL MEMBER HAMMOND: As a non-toxicologist, I have a couple of questions.

Based on what Dr. Buckpitt said -- and I'm looking at this lower right-hand cell on the PCE

internal dose metrics and that range. I noticed in the footnote you comment that it's a bimodal distribution. And correct me if I've got this wrong, but I'm wondering if Dr. Buckpitt is telling us that it's bimodal but the low end of that bimodal is really where we have poor-quality data. And that would make sense to me, then, that you've tended to use a value that's near the high end, the 10.

And perhaps rather than having all of that, it might be better -- I know that sense of that huge range that is upsetting to a lot of people, but the huge range is there because there's poor-quality data dragging it down at the low end.

And so maybe there should be an evaluation of those data, as he suggested, and then you exclude those data because it's poor quality, rather than putting it into the table.

So that's one comment and suggestion. I have a second one after that. And, again, not my area.

DR. KLOC: One of the difficulties -- that's a good idea, but one of the difficulties in implementing it is that the -- so the data that Dr. Buckpitt was speaking of is in vitro data; correct?

DR. HAMMOND: Uh-huh.

DR. KLOC: So that prediction range that was

calculated by Chiu and Ginsberg is based on all the in vivo data. So in their paper they calculate this prediction range based on in vivo data, then they proceed to look at the in vitro data to see whether or not there's consistency. So it would be difficult to discount the prediction range by just looking at the in vitro data.

PANEL MEMBER HAMMOND: And then I guess the other thing about the -- it's the in vivo data that you're saying is reflected here. In vivo would be including people who have no -- I don't know how to say this right, but none of this conjugation route; is that correct? So it's actually real.

I mean, in other words, you would expect there to be a zero at the end of this because they don't have the glutathione conjugate.

DR. KLOC: There's a probability. The thing is that humans have several isoforms of glutathione as transferase. Only a few -- only, I believe, two of them can have members of the population that have zero.

And so if PCE is metabolized by several of the isoforms, there might be some overlap and some redundancy in the pathway. But then again, no one knows if it's a specific isoform that's primarily responsible. And if it's a specific isoform form that can have a null

genotype, then you'll see this huge potential variation.

PANEL MEMBER HAMMOND: Okay. That makes sense then. But at the same time it makes sense there may be this range; it may be real, so we leave it there. But we certainly know that a large portion of the population is at that high end, and so we want to include that in the risk assessment.

Again, my second question is from a non-toxicologist. It seems to me -- and I may be misinterpreting it -- that it's as if all the metabolites are equally toxic. It's an implicit underlying assumption here whether they're through the oxidation route or the conjugation route. Is that correct? And is it that we just don't know or -- it seems like we're just saying as long as it's metabolized now it's bad.

DR. KLOC: Right.

DR. HAMMOND: Is that correct?

DR. KLOC: That is an assumption. It's unavoidably simplistic.

PANEL MEMBER HAMMOND: But it's because that's the limit of our knowledge?

DR. KLOC: Correct.

PANEL MEMBER HAMMOND: Okay.

CHAIRPERSON KLEINMAN: One of the things based

-- you know, working off of what Kathy said, given that there is this range of sensitivities within the human population, it is part of our goal to protect the more sensitive members of the population, and therefore taking the upper mode or the more sensitive mode does make sense in terms of, you know, our public health mission as well.

It might be useful, though, to actually document -- and I think there's a fair amount of data out there on, you know, what percents of the population have different isoforms of GST. And just to put that in to show, you know, that this is a major part of the diversity of the human population, which fits into -- this is empirical, measured data; and you'd expect to have that kind of uncertainty, perhaps.

PANEL MEMBER BUCKPITT: Equally important to your enzyme activities, of course, is the supply of the co-substrate, and that can vary a lot between individuals, depending upon how well fed they are and whether they're alcohol abusers, and the rest of it.

PANEL MEMBER ARAUJO: Yeah. But just to wrap up on this issue that I first mentioned, I agree with Dr. Glantz's comment and that your presentation was excellent. And it was very clear, and it contains the elements that are already in the other report. And

it's a matter of now just going back to the report, actually look at your presentation, and see how you can instill like the same clarity, you know, perhaps with the same -- the flow of how you present it. You know, in some of the places you can put in some things and it will make it a little bit more clear for the reader. One little comment.

And in relation to this cause, maybe in the beginning and how you start, like how they -- you saw, how they talk toxicokinetics. So you have like two paragraphs, then you go to the PCE metabolites and you list them. Then you have a long paragraph in here where it talks about some metabolites that could or could not be, and so many species or the other. That sounds a little bit confusing. And then you come up with something incredibly clear, which is when you refer to the figures and then you talk about the oxidative pathways and the GSH pathways. So I would suggest to move that up front. And, actually, even just present the pathways maybe from the beginning.

And once the reader starts, like, having some idea about the different species, then you can talk about the specific metabolites and whether some of those metabolites already have been demonstrated or not to be in part of these pathways in the different species.

So the second comment that I would like to make is like a -- so we're really talking about like major pathways that are involved here, and with the GST; so we have to consider all the NRF2 pathways, or NRF2 or phase 2 responses, and with the cytochrome p450. So we're talking about like a hydrocarbon receptor pathways and phase 1 responses.

And I don't see reports on, you know, perchloroethylene and NFR2 or perchloroethylene and HR. Is it something that came up, or do you recall when you were investigating this, or there was really nothing?

DR. KLOC: The only thing that comes to mind at this point is that -- there was one study I came across which indicated that you can -- that PCE exposure can induce metabolism in rats over a longer term of exposure. And I don't remember if it -- oh. And it's the conjugation pathway, actually. So the conjugation pathway can be induced on long-term exposure to rats. So whether that involves a nuclear signaling pathway I can't comment on at this point.

PANEL MEMBER ARAUJO: Okay. And you mentioned towards the end of the document the PPR alpha pathways, and there are people who have been involved with tumorigenesis but have -- there are also many regulators of lipids and lipid metabolism and major regulator of

mitochondria alpha oxidation or beta oxidation.

I'm saying that he referred to the PPR alpha pathways, which are major regulators. It's a major regulator of the lipid metabolism. But you don't really say much of that in the report. Maybe because there is not much in there. Is that the case, or you just obviate it and...

DR. KLOC: In our review we relied at that point on some pretty extensive reviews that U.S. EPA did for -- when they did their Unit Risk Factors for trichloroacetic acid, and I believe it was -- well, maybe it was when they did their own perchloroethylene number. But yes, we didn't do a extensive original analysis on that point.

CHAIRPERSON KLEINMAN: I think this would be a good time to go through the responses to the public comments because that may open up some additional discussion points.

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DR. KLOC: All right. So we received public comment from four organizations: the Center for Environmental Oversight, U.S. Department of Defense, California Chamber of Commerce, and the Halogenated Solvents Industry Alliance. A total of 44 individual and compound comments were received and were addressed

in our written response.

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DR. KLOC: Several of the criticisms were shared by the commentators. And since there were so many for this presentation, we thought that it perhaps might be just best to try to group them and give you a general feel for how we addressed the general issues.

So there is basically eight -- we identified what we thought to be eight major issues. And I'll go through them very quickly and then go through them with a little bit more detail.

So critical comments related to us not following U.S. EPA methods, criticisms with our use of PBPK inhalation model, criticisms with use of the NTP study data. Also, commentators were critical of our use of rat MCL data.

--oOo--

DR. KLOC: Criticism was voiced of the total metabolized dose and the use of multiple tumor types in doing our calculation. And then the use of the geometric mean in our final deliberations. And then, finally, many commentators felt like we needed to do an extensive uncertainty analysis.

--oOo--

DR. KLOC: So bear with me. I'll be mostly

reading here through the eight issues.

So the first issue was we did not follow U.S. EPA guidelines and we should adopt the U.S. EPA potency value.

So our response was that OEHHA has independent responsibility under California law to develop potency values for protecting the health of Californians. Our potency updates is based on our 2009 cancer guidelines, the Cancer TSD methodology. And the cancer TSD was reviewed and approved by this panel.

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DR. KLOC: We also clarified that we agree with several or some of U.S. EPA methods and, therefore, some of the portions of our cancer guidelines are quite consistent with the U.S. EPA guidance. However, U.S. EPA methodologies is not exactly the same as U.S. EPA, and where it differs we tend to be more health-protective.

And OEHHA, finally, used currently available scientific information and developed our estimate that we believe is consistent with our guidelines, considered uncertainties in the data and, finally, it is what we believe to be health-protective.

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DR. KLOC: The second issue was that the PBPK

model was not validated and it's unclear whether it reproduces the Chiu and Ginsberg model results. We clarified for the commentators that our model extract uses relevant inhalation equations and modeling parameter values from the original Chiu and Ginsberg paper. And that includes the posterior modes, i.e., the most likely values for the key model parameters, which were determined by Chiu and Ginsberg through their Bayesian MCMC simulation.

Chiu and Ginsberg equations and input parameters and model results were peer-reviewed and validated. Our use of the inhalation-only components of this model is not a reanalysis of the data.

--oOo--

DR. KLOC: And we also mentioned that in Table 1 of our draft we presented dose-metric estimates that were reported by both Chiu and Ginsberg and also obtained by our inhalation-only model at the level of significance presented in the table.

Based on the concordance of the estimates, we deemed the inhalation-only model to be adequately reproducing the original model results.

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DR. KLOC: Issue number 3 was that OEHHA should not use the National Toxicology Program 1986

data.

And our response was that different strains and substrains of rats and mice which were used in the actual two studies, and generally in the carcinogenic testing programs, displayed genetic and phenotypic variation as a result of mechanisms such as genetic drift.

The two rodent cancer models, the Japanese and the NTP, showed variability with respect to types of tumor elevated and the strength of the dose-response relationships. It is unknown whether or not this is due to genetic variation, but the observation suggests that the data from each study provides non-redundant information that's useful to our analysis.

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DR. KLOC: Issue number 4 is that we should justify better or not use rat MCL data mainly because it's not -- the criticism was that it was not a relevant tumor type in humans and that Fischer 344 rats have a high background rate of MCL.

And in our response we note that our 2009 cancer guidelines do not require us to have tumor concordance between rodents and humans in order to use data for dose-response analysis.

Our draft also discussed evidence that --

notwithstanding that general principle, our draft also discussed evidence that rat MCL corresponds to at least one form of human leukemia, which is Large Granular Lymphocyte Leukemia. And that arises from a lymphocyte or a monocyte lineage, and the cell or origin appears to reside or undergo transformation in the spleen.

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DR. KLOC: We also noted that the U.S. EPA and the National Research Council said that in their analysis of perchloroethylene, which occurred around 2010/2011 -- they stated: "discounting a rodent neoplasm simply because it has no human counterpart is not a scientifically defensible position. Strict site concordance is not a requirement for relevance in extrapolation of hazard potential."

So U.S. EPA and NRC agree with OEHHA on this issue.

--oOo--

DR. KLOC: Finally, regarding the statistical issues, the Japanese study had a relatively low control group rate of MCL, which is only about 20 to 22 percent. And this was actually at the high end of the historical background rate, which ranges between 6 and 22 percent for the rat substrain used. So in this case a false positive result is quite unlikely.

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DR. KLOC: The fifth issue was that we should check -- justify better our dose metric or we should not use the GSH conjugation pathway because of the large uncertainty.

And our response was that the precise mechanisms by which PCE causes increased tumor formation are not known. However, oxidation and conjugation of PCE in rodents and humans produce several potentially genotoxic and/or tumorigenic metabolites. Some of these are stable enough to circulate widely throughout the organism. Also, PCE metabolism showed saturation effects in the rodent studies. Thus the metabolized dose is a reasonable choice for the dose metric.

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DR. KLOC: And, additionally, those metrics used by U.S. EPA, while they avoid the use of the GSH-conjugation pathway, may be less accurate and are less health-protective than using a total metabolism dose metric.

The PBPK results for the GSH conjugation could actually be due to biological variation within the population, as opposed to modeling uncertainty. And as we had already mentioned in the discussion, some humans are devoid of one or more GST isoforms, which may

contribute to a large range of PCE conjugation levels. And also there is some evidence that long-term PCE exposure may induce GST metabolism.

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DR. KLOC: And continuing on, on this issue, there's an additional issue here. There's still substantial uncertainty regarding the formation of the reactive alpha, beta-unsaturated sulfoxides that happened through the GSH-conjugation pathway. And this actually may be more important in humans than in rodents. At least some of the initial papers on this subject indicate such.

So including the GST-pathway in a total dose-metric versus using an oxidation-only dose metric would increase the PCE cancer potency factor by a factor of approximately 11-fold.

And because population variability and uncertainty -- sorry. Let me restate that. Population uncertainty in toxicokinetic uncertainty is properly addressed by making appropriate health-protective assumptions in the cancer potency assessment. And that's consistent with our 2009 cancer risk guidelines.

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DR. KLOC: Finally on this issue, because it was a big issue, we included significant additional

discussion in the document on both the uncertainty of variation aspects, as well as the total metabolism dose-metric.

Issue number 6.

DR. GLANTZ: To that point, I think if you make the editorial changes to the document -- and, again, they're not substantive; they're editorial -- that we were talking about earlier, I think that will further solidify the response to this comment.

DR. KLOC: Thank you.

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Issue number 6 was that we should not use tumor types other than liver tumors in mice.

Our response was that the use of data from multiple tumor types is based on our cancer guidelines, 2009. And a quote from that is: "...for chemicals that induce tumors at multiple sites, the single-site approach may underestimate true carcinogenic potential."

And in our guidelines we give the example that the overall assessment of cancer from cigarette smoking was estimated from all the sites at which the agent induced the tumors, which included lung, bladder, leukemia, and others.

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DR. KLOC: In addition, our draft included

some sections justifying the use of rat mononuclear cell leukemia, as well as renal tumors.

And again we restate that we do not require interspecies tumor concordance. And we generally, based on our guidelines, generally use all tumor types that appear to be statistically elevated in the exposed groups.

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DR. KLOC: Issue number 7. We should justify or not use a geometric mean of multiple potency estimates. Instead, we should choose a value from a single tumor type.

Our response was that our guidelines do suggest as a default option the typical method of identifying the single study that represents the best estimate of potency. However, it does not prohibit using alternative methods, for example, in this case, the geometric mean for deriving potencies.

DR. GLANTZ: Yeah. One other point on that is using that -- using a geometric actually lowered the estimate, so I don't see what they're complaining about. I mean, I think if you used the best study you would have had a higher potency.

So of all the comments, that was the one that befuddled me the most.

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DR. KLOC: And in addition, both the Japanese, as well as the National Toxicology Program studies, were deemed to provide acceptable and non-redundant dose-response information suitable for a quantitative estimate of cancer potency. But because some of the higher potency estimates appeared to be more uncertain for various reasons, OEHHA chose the mid-range of the availability values as a best estimate of the overall cancer potency of PCE. But this was still a value that the office judged to be adequate to protect public health.

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DR. KLOC: And the final issue. No uncertainty analysis was presented in the document, and we need to provide a comprehensive uncertainty analysis.

In response, we state that we had discussed various uncertainties throughout the first draft and that we added to this in the revised document, covering several of the more important aspects affecting the potency factor derivation.

In addition, we noted that Chiu and Ginsberg provided a detailed quantitative uncertainty analysis in their PBPK modeling paper. And U.S. EPA, in their own derivation of the PC number, provided a range of PCE

potency estimates obtained by using various other dose metrics.

OEHHA considered and referenced all of this information in deriving our potency estimate.

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Finally, we believe that it is neither necessary nor desirable to carry out a comprehensive uncertainty analysis in all cases.

And the National Academy of Sciences has stated on this issue that: "If an uncertainty analysis will not substantially influence outcomes of importance to the decision maker, resources should not be expended on the detailed uncertainty analysis..."

So that is basically our set of general responses to what we believe to be the major categories of comment.

CHAIRPERSON KLEINMAN: Any other comments?

I just had one. And it goes back to their critique of the comparison between the inhalation-only model that you used versus the full model. And it seems like -- and I think you actually did some comparison. I think you mentioned that there was a comparison, and you did come up and you were able to come very close to the original value.

And it seemed to me that when you look at the

total model, the parameters you left out, dermal and ingestion, which would complicate the mathematics in the programming, if you included the dermal, which is really the -- you know, it would have been a relevant route, you would have done nothing but increase the amount of material coming in and that would have given you, you know, an even greater discrepancy compared to the EPA value.

So I think that, you know, there really is good justification for what you did. I think it's conservative, and it really deals with the major amount of exposure.

Any others? Kathy.

PANEL MEMBER HAMMOND: Following up on that, I thought about this and then decided not to say it, but since you brought it up, there have been studies that have looked -- for instance, putting people in respirators and chambers exposed to solvents that have demonstrated there's significant dermal uptake from, you know, air borne levels and not, you know, just putting a liquid on the skin.

So it's actually -- one could really make the argument it's not an insignificant exposure that has been omitted from this. So, again, if there is any error there, it's being insufficiently protected. In

other words, you have underestimated the true exposure by not including the dermal component because air borne concentrations can lead to dermal uptake. And that was removed from the model; right?

DR. KLOC: So, for example, let's say that we used the complete model. We would have put in zero for all the pathways. We would have just zeroed out the pathways. The equations would be there, but they would be set to zero.

PANEL MEMBER HAMMOND: I guess what I'm saying is that they shouldn't be set to zero. There are data from various Scandinavian studies that show dermal uptake. You put someone in a chamber with air borne solvents exposures but with respirators they're not breathing -- there is no inhalation. The true value of inhalation is zero. You can demonstrate there's a dermal uptake from air borne.

DR. KLOC: Right. I think it's covered when you do a risk assessment in the exposure portion of the assessment.

So what we did was we calculated a dose response for an internal -- for an equivalent internal dose. And so in the exposure assessment if you added -- if you assume that the individual is inhaling chemical and also getting some internal dose due to dermal

exposure, and if you summed up those two doses, you could use this -- our slope factor -- I mean our Unit Risk Factor to calculate the risk, which would incorporate an addition of that dermal absorption.

Now, the potential uncertainty there is whether or not metabolism from a dermal intake is equivalent to a metabolism from an inhalation intake. And it's a good question.

PANEL MEMBER HAMMOND: Well, I think the liver may not be but the kidney would be, and some of it -- yeah. It gets on that complex side.

DR. KLOC: But perhaps our other programs which develop risk factors for other pathways of exposure might have relevant factors that could be used in that case. So perhaps an oral intake factor could be used in place of a specific dermal risk factor. I'm sorry. I meant to say an oral risk factor, an orally relevant risk factor could be used for dermal in place of having knowledge about what the actual dermal Unit Risk Factor would be.

Do my colleagues have any clarifications or additions?

CHAIRPERSON KLEINMAN: And just one other point. You mentioned that, you know, if you take into account the conjugation pathways you probably explain

about 11 -- you know, a 11-fold part of the discrepancy. So is the other 2.3 primarily from including the MCL, or is it -- you know, are there other factors?

DR. KLOC: We haven't done an explicit analysis of that additional 2 or 2.3. I could guess at a few potential sources. I think, perhaps, just using the NTP study data, because some of the NTP study data indicated some more potent values, and also the summation of tumors in those two cases, that's probably where most of it comes from.

CHAIRPERSON KLEINMAN: I think that the panel is very supportive of using the multiple-tumor approach as far as the conjugation pathway; so I don't think, you know there's any critique, really, in the methodology. I think what Stan is saying in terms of clarifying, you know, some of these points by editorial changes would be very helpful.

DR. GLANTZ: So having said all of that, I'd like to make a motion to approve the document, subject to these editorial changes. I didn't hear any substantive criticism at all, and I felt like everybody felt like you did a good job with the public comments.

So I think there will be a little bit of rewriting to clarify the points that the panel made, but what I'd like to move is that we approve the document

and then delegate -- as the panel has done many times, delegate to the Chair, you know, to look at it one last time. And then if the Chair needs to consult with other panel members, we can, but that way we'll be able to just move things forward.

PANEL MEMBER BUCKPITT: I'd like to second that.

CHAIRPERSON KLEINMAN: All right. Well, we have a motion. Any discussion on that? Any critique? Then can we have a vote?

Kathy?

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER ANASTASIO: Yes.

PANEL MEMBER ARAUJO: Yes.

PANEL MEMBER BUCKPITT: Yes.

DR. GLANTZ: Yes.

CHAIRPERSON KLEINMAN: Unanimous.

DR. GLANTZ: I wish every report that came before us was as easy.

CHAIRPERSON KLEINMAN: All right. So just to wrap up then, the panel has, you know, voted approval of the document with the additional changes to be made. The Chair will review those to make sure they were consistent with the panel's comments, and we will get that information back and turn that around as quickly as

possible.

So I think on that basis we have fulfilled our statutory obligation in this matter. And if there are no other suggestions, then I think I'll ask for a motion to adjourn.

PANEL MEMBER ANASTASIO: Move to adjourn.

PANEL MEMBER HAMMOND: Second.

CHAIRPERSON KLEINMAN: All in favor?

(Ayes.)

CHAIRPERSON KLEINMAN: Any opposed?

All right. Then I therefore declare this meeting adjourned. Thank you.

DR. KLOC: Thank you.

(Thereupon the Air Resources Board Scientific Review Panel adjourned at 12:00 p.m.)

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REPORTER'S CERTIFICATE

I, Jacqueline Toliver, a Certified Shorthand Reporter for the State of California, do hereby certify:

That I am a disinterested person herein; that the foregoing Air Resources Board Scientific Review Panel on Toxic Air Contaminants hearing was reported in shorthand by me, a duly qualified Certified Shorthand Reporter, and thereafter transcribed into typewritten form by means of computer-aided transcription.

I further certify that I am not of counsel or attorney for any of the parties to said hearing or in any way interested in the outcome of said hearing.

IN WITNESS WHEREOF, I have hereunto set my hand this 11th day of July 2016.

JACQUELINE TOLIVER, CSR
Certified Shorthand Reporter
License No. 4808