TELECONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ON TOXIC AIR CONTAMINANTS

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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FRIDAY, FEBRUARY 6, 2015

9:25 A.M.

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A P P E A R A N C E S

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Jesús A. Araujo, M.D., Ph.D.

Paul Blanc, M.D.(via teleconference)

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S. Katharine Hammond, Ph.D.(via teleconference)

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

Dr. Daryn Dodge, Acting Chief, Air, Epidemiology and Risk Assessment

I N D E X

P R O C E E D I N G S

CHAIRPERSON KLEINMAN: Good morning. I'm Mike Kleinman. I'm the Chair of the Scientific Review Panel, and I want to welcome everybody to this meeting. Starting a little bit late, but unfortunately that's technical life in this country.

We have around our table Drs. Jesús Araujo, Cort Anastasio, Beate Ritz, Alan Buckpitt and Sarjeet Gill. And for the record, I would like the people on the phone to just tell us who you are, so if you'd go ahead and do that, please.

PANEL MEMBER GLANTZ: Well, at UCSF we have Kathy Hammond, Paul Blanc, and Stan Glantz.

PANEL MEMBER HAMMOND: And could you introduce yourself, please.

Come over here so they can hear your.

And also a visitor.

MS. ASHLEY-SUTHERLAND: Kate Ashley-Sutherland.

PANEL MEMBER HAMMOND: She's from OEHHA she says. You guys must know her.

CHAIRPERSON KLEINMAN: Okay. Thank you.

The goal for this meeting today is going to be to review two REL documents. And the first one will be toluene diisocyanate reference exposure levels, and that's SRP draft dated November 2014. Following that, we'll

discuss the methylene diphenyl diisocyanate reference exposure levels.

The reference exposure levels were developed using risk assessment methodologies for developing RELs under the Air Toxics Hot Spots Program that OEHHA has developed -- or -- OEHHA we has developed. They've produced acute 1-hour, 8-hour repeated exposure, and chronic RELs for both compounds. The documents have undergone public review, and OEHHA has responded to the comments to that public review.

Today, we're going to discuss the RELs for the two compounds. We'll hear a presentation from OEHHA about the derivation of the RELs, and then a discussion of the responses to the public comments, following which the Panel members will have an opportunity to raise any other questions that they might have.

The leads for the discussion for the Panel will be Drs. Buckpitt and Gill. So I think we should begin with the presentation on TDI.

(Thereupon an overhead presentation was presented as follows.)

DR. BUDROE: Okay. Good morning, Dr. Kleinman, members of the Scientific Review Panel. My name is Dr. John Budroe. I'm Chief of the OEHHA Air Toxicology Risk Assessment Section. And I'd like to present Dr. Daryn

Dodge. He'll be presenting -- doing a presentation on the non-cancer reference exposure level documents for toluene diisocyanate and methylene diphenyl diisocyanate.

Dr. Dodge.

DR. DODGE: Thank you, Dr. Budroe.

Okay. I'm going to go onto slide number 2, toluene diisocyanate. I'll just refer to it as TDI.

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DR. DODGE: TDI is used in flexible polyurethane foams, adhesives, and coatings. It's a high volume chemical. It's production in each year is over a billion pounds of product. It's volatile with a vapor pressure of 0.023 millimeters mercury at room temperature. It has two highly reactive NCO groups, or isocyanate groups, that when inhaled react with the lung tissue and macromolecules in lung-lining fluid. It is also known as one of the most potent low molecular weight sensitizers.

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DR. DODGE: Slide 3. Acute exposure in animals and humans, you see sensory irritation; eye, nose, throat irritation; respiratory tract irritation and tissue damage in animals, and this is dose dependent. In workers, you can see airways hyperresponsiveness at very high levels. With chronic exposure, it's a sensitizer via the inhalation route, as well as the dermal route, and it's

known as a occupational asthmagen.

Before extensive controls were put in facilities that manufactured TDI, 20, 30, 40, years ago, you often saw sensitizing rates in the range of 5 to 10 percent of the worker population exposed.

With chronic or other chronic endpoints include bronchitis, rhinitis, and conjunctivitis. And you also see an accelerated decline in lung function as measured often by FEV1 or forced expiratory volume in one second. And this is in the absence of asthma.

The 8-hour and chronic RELs, I'll go over in a little bit, are based on this endpoint. Our current chronic REL is also based on this as well as the U.S. EPA RFD, which is similar -- or RfC, which is similar to our chronic REL.

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DR. DODGE: We'll talk about the acute reference exposure level derivation first. One of the earliest human studies was from Germany. We translated this from German to English. This was an acute exposure study lasting 20 minutes in which a group of human -- normal human subjects were exposed from about 10 parts per billion up to hundreds of parts per billion. At 10 and 20 parts per billion didn't see any sensory irritation, but at 50 parts per billion and above they did.

Later studies in Germany, among -- there was several publications produced. And this was -- it appears to be based on the same group of 30 or so subjects, half of which were non-sensitized asthmatic subjects. What they found was there was a response in some of the asthmatic subjects at 10 parts per billion and above. The measure they used was a 100 percent increase in airway resistance at or above this level. And at 10 parts per billion, they saw 1 out of 15 asthmatic subjects respond to a greater than or equal to 100 percent increase in airway resistance. And this was followed up by 20 parts per billion, which they saw another subject have this same endpoint.

Next slide.

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DR. DODGE: So far our acute REL derivation, the point of departure is 10 parts per billion or 71 micrograms per cubic meter. This is a LOAEL -- LOAEL. This is a lowest observable adverse effect level.

Now the exposures in the subjects were one hour, which is the time that the acute REL is based on, so there was no time adjustment. A default uncertainty factor of a full 10 was used though for the LOAEL to NOAEL uncertainty factor. And this is because we feel that the asthmatic response is a severe effect.

Intraspecies toxicokinetic uncertainty factor was 1. This is because the subgroup examined here was a sensitive subgroup of asthmatics. Intraspecies toxicodynamic uncertainty factor is root 10 or 3. And this is to -- this is because we believe that children could be at increased risk, or especially asthmatic children.

Accumulative uncertainty factor is 30. So dividing the point of departure of 71 by 30 gets us 2 -- a rounded 2 micrograms per cubic meter.

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DR. DODGE: Onto the next slide. This is for the 8-hour and chronic RELs. Both the 8-hour and chronic RELs are based on the same study by Diem et al., 1982. And this is based on decreased lung function found in TDI workers. This particular study was a prospective study. So the workers were followed from the beginning of their employment at a new facility that manufactured TDI, and it went on for five years.

What they found was the group that was exposed to an average of 1.9 parts per billion, they found an accelerated decrease in lung function as measured by FEV1. The NOAEL group was 0.9 parts per billion. The sensitizing incidence over the five-year period was 12 out of 277 workers or 0.9 percent per year. For the 8-hour

time adjustment for the 8-hour REL, we simply took a 5-day over 7-day adjustment, or made a 5-day over 7-day adjustment. This is because the 8-hour REL is for 7 days per week, and the workers were exposed for 5 days per week.

The chronic time adjustment included a 10 cubic meter over 20 cubic meter adjustment. This is in recognition that the workers working for an 8-hour -- active 8-hour period are going to breathe approximately half the air they're going to breathe in a day -- in a full day, which is 20 cubic meters.

For both the 8-hour and chronic REL derivation, we used a subchronic uncertainty factor of root 10. This is because it's a five-year study. Normally, we use a UF of 1 if the study exposure duration is 12 percent of a life span or greater, and this was less than that.

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DR. DODGE: Go onto the next slide, slide number 7. For the intraspecies toxicokinetic uncertainty factor, we used a full 10. And this is because of the toxicogenomic variability we saw between exposed workers and workers that were also exposed -- it was due to the -- the sensitized work -- the group of sensitized workers compared to workers that were exposed but didn't become sensitized. We saw a 10-fold difference in the

toxicogenomic variability, which I'll get into in the next slide.

For the toxicodynamic, it was 10, and this is for the high sensitizing potential, as wall as toxicogenomic variability and increased sensitivity in asthmatic children.

The cumulative uncertainty factor is 300 for both these RELs resulting in a 0.015 and 0.008 micrograms per cubic meter for the 8-hour and chronic RELs respectively.

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DR. DODGE: Now, I want to go briefly into the toxicogenomic data. Some gene variances -- some gene variants are associated with increased sensitivity for diisocyanate-induced asthma in workers. In particular, let's look at the third line down. We see an odds ratio, or OR value, of 10.36. And for this particular gene variant on epoxide hydrolase, what they're seeing is a 10-fold greater OR in the workers -- the group of workers that had acquired diisocyanate-induced asthma. And this is compared to a group of workers that were also exposed to TDI or other diisocyanates, but did not become sensitized.

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DR. DODGE: Next slide, slide number 9. This is the proposed TDI RELs, a summary of them.

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DR. DODGE: Now, at this point, I'll ask the Chair if he would like me to go on with the comments or responses or take some questions now?

CHAIRPERSON KLEINMAN: Why don't we go ahead with the comments and responses and then we'll open it up to the Panel for their comments.

DR. DODGE: Okay.

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DR. DODGE: We received comments from the American Chemistry Council as well as the Polyurethane Foam Association. Go on to slide number 11 for the first comment.

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DR. DODGE: And this comment, a Darcey et al., 2002 study investigating community complaints regarding emissions from a TDI facility has study limitations. OEHHA should include Wilder et al., 2011 study that showed no community effects or emissions from TDI facilities.

So our response. OEHHA revised the section and included Wilder et al. In particular, we say possible exposure of the general population to TDI via emissions from a facility that used TDI to manufacture polyurethane foam has been reported. This is the Darcey et al. the earlier study.

However, a follow-up report at 5 TDI manufacturing facilities in the same State show 1 part per trillion or no current TDI exposures to nearby residents.

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DR. DODGE: Next comment, slide 12. This comment, OEHHA suggests free TDI may be emitted or extracted from foam products. OEHHA needs to include studies by Hugo et al., Vangronsveld et al., and CARB, which is the California Air Resources Board, that show no exposures occur from polyurethane products.

And our response. We revised the section in question and included the suggested references. In particular, our revised sections note studies did not find emissions of detectable levels of free TDI from Consumer products that were made with TDI. So none of these 3 studies found off-gassing from the products.

However, we go on to say, toluene based extraction resulted in microgram per gram levels of free TDI extracted from foam. This is -- in particular, this is from the Vangronsveld study. The authors concluded that the TDI extracted from foam may have been due to decomposition of parts of the foam structure by the solvents, a process that is unlikely to occur under typical household uses.

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DR. DODGE: Next slide, number 13. This comment, OEHHA incorrectly attributes accidental exposure of children to MDI when xylene was almost certainly the chemical children were exposed to. This is because of the, number 1, extreme volatility difference; number 2, the low MDI content, which was 0.1 percent in xylene; and number 3 is irrelevant, because it does not reflect use of any TDI-based products.

Now, what this comment is referring to is a study from South Korea, where workers were laying down this material onto a track. It appeared to have been sprayed and aerosolized. Wind direction changed and start blowing it to classrooms -- nearby classrooms. The students started experiencing sensory irritation and some asthma-like effects.

Our response was that OEHHA revised the paragraphs in question, and note the author's Jan et al., 2008 assumed all the to symptomology was due to MDI, even though xylene also caused acute eye and respiratory problems or symptoms. Thus, some of the -- some proportion of the eye and/or respiratory effects could have been caused by xylene exposure.

However, we also add volatility differences may not matter, because the tract was sprayed and the solvent mixture appears to have been aerosolized.

Number 2, low MDI content is -- can you hear me okay?

Okay. Low MDI content counterbalanced by high difference in toxicity. For example, our xylene acute REL is 22 milligrams per cubic meter and our proposed TDI REL is 0.002 milligrams per cubic meter. And lastly, MDI is qualitatively similar to TDI, and we believe it's relevant for this study.

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DR. DODGE: Next comment, slide 14. OEHHA inappropriately supports that the TDI released from foam explains, A, the wheezing by children using non-feather bedding, and B, the higher indents of asthma among firstborn children compared to their younger siblings.

We extensively revised this section. And briefly, we note that some studies found greater dust mite allergen in synthetic pillows and emphasize that no off-gassing of free TDI has been found.

And also that the Karmus and Botezan study was removed from the summary because this study, in particular, does not have a discussion of the association between new polyurethane products and the effects in firstborn children.

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DR. DODGE: Okay. Go onto slide 15. Next

comment, childhood asthma is a Th2-driven process, while TDI-induced asthma is a Th1-driven process. Thus, if the Th2 pathway predominates in early life, while the Th1 pathway is less well developed, children will be less sensitive not more sensitive to the development of diisocyanate asthma, because it is primarily a Th1-driven pathway in humans.

Our response. OEHHA revised and expanded the discussion of immune response in atopic asthma and TDI-induced asthma. Research shows that both asthmatic states are more complex than simply saying one is Th1 driven and the other is Th2 driven. Elements of both Th1 and Th2 pathways can be seen in both atopic asthma and TDI asthma.

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DR. DODGE: To continue further onto the next slide. We also added that regardless of differences in T cell profiles, the clinical manifestations and pathophysiological changes observed in TDI-induced asthma are remarkably similar in some aspects to those of atopic asthma, including airway hyperreactivity, the presence of eosinophilic lung infiltrates and mucus hypersecretion in airways.

Finally, we stated that differences in T cell profiles in childhood atopic asthma and diisocyanate

induced-asthma does not inform us regarding the response of immune systems in infants and children to TDI exposure. So we can't assume children will be less sensitive to development of TDI-induced asthma compared to adult workers.

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DR. DODGE: Next slide, number 17. Comment, use of the full default LOAEL-to-NOAEL UF of 10 for the acute REL based on 1 in 15 asthmatics responding to TDI exposure is too high. Number one, the severity of this temporary effect is subjective and overly conservative. Two, the response frequency of 7 percent at 10 parts per billion TDI is clearly approaching the NOAEL. Number 3, a UF of 3 provides a more objective yet still health responsive basis for a LOAEL to NOAEL uncertainty factor.

Our response. Number 1, we consider an asthmatic response a severe adverse effect. Number two, a second person responded to 20 parts per billion exposure. And number 3, one-third of the group experienced sensory irritation and chest tightness during exposures. Thus, we do not consider a 10-fold uncertainty factor to be overly conservative.

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DR. DODGE: Slide 18, next comment. A toxicodynamic uncertainty factor of 3 is more appropriate

to protect children with asthma, because, one, asthma in children is primarily Th2 driven; number 2, most diisocyanate asthma is due to overexposure incidences well above 20 parts per billion.

And our response is that it is inappropriate for OEHHA to assume that children will be less sensitive to the effects of TDI than adults. OEHHA views asthma as a disease that disproportionately impacts children. The potential to either induce or worsen asthma are considerations in assigning the value of the intraspecies UF.

Also, it is unclear how important high exposures are from inducing asthma, although they do appear to have a fact -- it is a factor. Some workers may be sensitized by long-term low level exposures, while others could be sensitized by mixed low level and brief high exposures.

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DR. DODGE: Next slide, number 19. The comment. OEHHA should explain specifically why it did not consider other studies -- and they're referring to Ott et al., 2000 here -- either alone or in combination with Diem et al. as the basis for its 8-hour and chronic RELs.

The Ott et al. study was summarized in text and table of our REL summary. In it Ott concluded that work exposures up to 5 parts per billion time weighted average

found little correlation between TDI exposure in either FEC -- FVC or FEV1 decrements.

Specifically, our response is that Diem et al. established a NOAEL and LOAEL of 0.9 and 1.9 parts per billion respectively for accelerated lung function decrement. It is a well-conducted study with an established NOAEL and LOAEL lower than the Ott et al. study conclusion.

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DR. DODGE: Next slide, number 20. Comment. Longer term studies, again Ott et al., 2000, indicate that a sub -- that a subchronic uncertainty factor of 3 is not justified. No lung function decrements found in Ott et al. study -- the mean exposure duration was 9.3 years -- and the longer duration of TDI exposure, the lower the risk of developing TDI-induced asthma.

Our response. Ott et al. conclusion was a 5 part per billion or less where no lung function decrements were observed. This is what we call a free-standing NOAEL, because researchers did not establish a LOAEL. There was a sensitizing incidence in this study of 0.7 percent per year.

To go on with our response. The Diem study found a NOAEL and LOAEL below 5 parts per billion for lung function decrements in a 5-year study. Default subchronic

uncertainty factor used because the study duration was less than 12 percent of a human lifespan. Incidence and severity of this lesion may increase with exposures longer than five years. Therefore, we think the uncertainty factor is justified.

And also to add, the mean latency to sensitization in study by Malo et al., 1992, was 7.3 years. So we feel that the subchronic uncertainty factor can also be used to protect individuals who become sensitized with lower level exposure over a longer period of time.

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DR. DODGE: Next slide, number 21. Comment. OEHHA inappropriately uses a time-adjusted exposure for the 8-hour REL based on the chronic REL, using the supposition that TDI may cause respiratory sensitization with only intermittent low level exposures.

Now, originally, our 8-hour REL was the same as our chronic REL, so they had both the same number. In our response, we find some merit in this particular comment. OEHHA has revised the time-adjusted exposure of the 8-hour REL from 0.001 to 0.002 parts per billion due to a duration-dependent component for pulmonary effects.

For example, the acute concentration times time studies, specifically by Pauluhn, in rodents found that

both exposure duration and concentration were equally important. So it's the dose that counts. Some recovery occurs with 6-hour daily exposures, which is close to what a 8-hour daily exposure would be for our 8-hour REL, versus an 18-hour daily exposure in an MDI -- in MDI rodent studies. And I'll get into this a little bit later with MDI.

The C times T studies in TDI-sensitized subjects observed that bronchial responsiveness was neither exclusive concentration nor duration dependent.

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DR. DODGE: So next slide, number 22. In this comment, 10 cubic meters over 20 cubic meter adjustment factor not needed for extrapolation for the chronic REL. Acute studies in rodents show no sensory irritation or inflammation below 23 parts per billion, which suggests some sort of threshold.

Our response. It's unclear in humans that pulmonary function changes based on 8-hour worker exposures will also be protective for continuous chronic exposure. So we used the standard default of 20 over -- I'm sorry, 10 or 20 cubic meters. Also, acute studies may not be particularly relevant for chronic exposures and developing a chronic REL.

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DR. DODGE: Next slide, number 23. In this comment, a 10-fold intraspecies toxicokinetic, or TK, uncertainty factor for the 8-hour and chronic RELs is inappropriate. Diem et al. study already includes potentially sensitive workers, so no TK UF is needed.

Our response is that the general population is likely more genetically varied than a worker population, so we feel that the 10-fold uncertainty factor is justified.

Also, it's there to account for the up to 10-fold greater susceptibility based on mean odds ratio values to diisocyanate-induced asthma in workers with specific gene variance associated with metabolizing enzymes, including glutathione S-transferase, epoxide hydrolase and N-acetyltransferase.

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DR. DODGE: Next slide, number 24. In this comment, an intraspecies toxicodynamic uncertainty factor of 10 is not supported by scientific evidence, indicating children are less sensitive to TDI-induced lung function decrements. Children are less sensitive, because TDI asthma is primarily a Th-driven process.

Our response is that we applied a intraspecies TD UF equal to 10 to account for, number one, pharmacodynamic variability among humans, including infants and children;

number 2, increased odds of developing isocyanate-induced asthma was associated with a number of genes related to toxicodynamic variability, including genes involved in immune regulation, inflammatory regulation in antioxidant defense; and third, no evidence that children are less sensitive to TDI-induced sensitization or pulmonary lung function decrements.

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DR. DODGE: Okay. That concludes the presentation for TDI.

CHAIRPERSON KLEINMAN: Okay. Thank you. What I'd like to do now is give our Panel leads the opportunity to give their comments, and then we'll go around the table for comments from the rest of the Panel.

So, Dr. Buckpitt, would you begin?

PANEL MEMBER BUCKPITT: Certainly.

I found both reports very well written, doing a very good job of covering the literature on the health effects. I'd spent some time poking through the literature to determine that your report was quite thorough. You had looked at all the major studies in this area. You discussed both the key long-term studies in humans, which is what you use to set your RELs, as well as animals.

I think appropriately you use the human studies

because there were good data in that area to establish your reference exposure levels. The endpoint chosen for the assessments was airway reactivity, while the level set for chronic exposure were based on the long-term epidemiologic studies relating to decrements in lung function to TDI exposures. Again, I felt that these were appropriate.

The TDI document did a good job of indicating whether the studies had corrected for decrements in FEV1 with age, smoking history, and sex, et cetera. So the corrections had been done.

You did a very good job essentially evaluating the literature references. Where they had difficulties, you pointed those out in your report. I thought that was quite well done. An example of that, when measurements of TDI were reported with less reliable methods, the report noted that as a deficiency. There was a really good discussion over the mixture between 2,4-TDI and 2,6, and how that influences the analytical chemistry associated with the methods commonly used to measure the levels of these diisocyanates.

Studies used to set the acute REL were small, 25 total split between 15 asthmatics and 10 non, but the exposures were quite well defined. Measurements of airway resistance likely an excellent endpoint. The uncertainty

factors make sense to me. The acute REL of 0.3 parts per billion is consistent with protecting children.

While this issue was challenged by ACC, and they made a valid point regarding the release of TDI from polyurethane foam products, you did go back and correct your report. And I thought those were appropriate corrections.

I found the studies on genotype variance quite interesting. I think you used those appropriately to set your uncertainty factors. I will say I'm mystified by the fact that epoxide hydrolase, which has, to my knowledge, no obvious role in the metabolism of this compound is such an important gene variant.

So the suggestions. I think if we look out there, I found several really pretty good papers looking at the molecular mechanisms. And I mentioned this to you last time, Daryn, that while they're not really important in setting the RELs, you've used the important literature for that. I think it would be nice to include a section in your report that goes over some of the mechanisms where TDI quite clearly reacts with glutathione, probably non-enzymatically. And that then becomes a shuttle chemical, if you will, to get TDI into the cell, that you get carbamylation of human serum albumin from that think. And that, I think, arguably could be a mechanism by which

this is producing an asthmatic response.

So I think if you incorporated some of that as you did in the MDI document. You had more material there than in the TDI. I think there's plenty of material out there that would be useful for that.

So I'd simply suggest that as an addition to your report. The review document mentions the reactivity with nucleophiles, but expansion of this is warranted. And I think maybe expanding your figure 2, which is your metabolism figure, to include conjugation with glutathione, would be certainly appropriate. The data are quite strong, both in -- certainly in animals. And those conjugates have been isolated and quite well characterized with physical methods.

Let's see, the GWAS studies, again quite interesting. I am unable to determine why they had such an effect with the microsomal epoxide hydrolase, again because it does not participate in the metabolism of that. I suppose the only way of sorting through that is the probability that that also affects other gene variants or gene expression levels of their enzymes.

I would find it helpful if you included, either in an appendix or up front, a list of abbreviations. The common things you don't have to deal with, but there were quite a few things RADS, RAW, RAST. If you're like me and

you read over it, and then you say, gee, what was that again? Then you've got to go back up a couple paragraphs to figure out what that was. So if you can include a table, again an appendix would be great. I think it would be very helpful in terms of reading the report.

I found a couple of instances, and they're probably already corrected at this point, where the title simply said toluene and it really should be toluene diisocyanate.

On page four, the document describes studies on TDI disposition in animals, but this was using carbon 14 labeled material. And all it really followed was the carbon 14, so that they couldn't tell whether it was a metabolite or the parent compound. And I think making that clearer probably would be appropriate.

The only other -- so the one question that I had on some of your tables, so page 23 Table 3, page 27 tables 5 and 6, were the numbers presented in those tables corrected for the normal decline in FEV1? And if so, just simply footnote that in the table so that it's clear.

DR. DODGE: Okay.

PANEL MEMBER BUCKPITT: And then I've got a couple of garbage things, right, that I'll turnover to you. But overall, I thought you did a great job putting that together.

DR. DODGE: Thank you.

PANEL MEMBER GILL: I have actually very limited comments compared to what Alan has already mentioned. Overall, I agree in the sense that document is actually very well written. The literature is very good.

I think the one you're referring is to the Poulsen 2014 article, which is not in -- cited, because it continues further with regard to glutathione metabolism and how it first, you know, metabolizes with the glutathione and then transcarbamoylation to serum albumin, which probably leads to asthmatic incidence. It would be nice to include that in the literature review as a background for mechanistic evaluations.

DR. DODGE: I'm sorry, which article was that?

PANEL MEMBER GILL: It's Poulsen something, 2014, correct?

He has the reference, I think.

PANEL MEMBER BUCKPITT: I have it in the material that I'll give you.

DR. DODGE: Okay.

PANEL MEMBER GILL: That is an article which talks about how glutathione could be involved in this.

Also, the link between the genotype is also quite useful information. I worked with epoxide hydrolase for maybe 10, 15 years. And I -- he asked -- Alan asked what

is the mechanism? It actually has got nothing related to metabolism when I look at it. But when he was talking about it, then it came to my mind actually, because epoxide hydrolase is involved in actually metabolism of a lot of lipids.

And there is no data in this particular literature as to what the lipid composition of the lung changes. If that's a case, then it is possible that epoxide hydrolase, which leads to metabolism of lipids, which are related to asthmatic incidence. So therefore, it's not actually a causal relationship, but it could be a link that means those who are normally susceptible, in any case already, will become more susceptible to TDI, because there is a link between increased metabolism of lipids in the lung, of which epoxide hydrolase is involved, that that could be involved in asthmatics. So if you want to include that into a genotype, you may want to incorporate a section on mechanistically what there could be involved.

But as I indicated, that's a possible -- is what epoxide hydrolase displays, but I don't know whether there's a causal link between TDI and that particular incidence, because it may be just one population is more susceptible than to the other. That's what I think.

I have just one other comment, in the sense that -- two other comments. One is the comment that the

ACC made in terms of the default NOAEL To LOAEL of the factor of 10 you used answered in the factor. I agree with what you did, because -- but you use the language that ACC used in the comment in itself is, I think, an -- suggests that if you use the word -- it's clearly approaching NOAEL. If you see that, that means it is not NOAEL. And so your conclusion is correct, because I think the way the language is is very legalistic, and the approach you responded is appropriate in that case.

And finally, I want -- I asked -- David had asked me whether there's any issue that I wanted to talk about. One of the comments that I would like to bring up - this is regarding both of the isocyanates - is the issue of impurities.

I did not see any -- any of the literature. I went back to the documents and the papers, what percentage of diamines are present in the mixtures? And it's never listed anywhere, because diamines is a precursor to the synthesis of this. And the way the synthesis is done is fractional distillation, which will never give a purity.

The reason I'm asking is because diamines itself can be quite reactive compounds. Isocyanate is very reactive and when a compound is very reactive, it just gets sequestered. But as we see the metabolism, the metabolism compound -- the key metabolite is a diamine

which is also a precursor. So is it a precursor or is it a metabolite?

I think it would be nice for you guys to see whether there is any impurities, and impurities are always of concern sometimes. And I would at least try to see whether you can pinpoint in both cases the amount of impurities that are present.

If there are one percent, I would not be concerned. If there are 10 percent, I would be a bit more concerned. And so I think you need to look at that as such. I don't think it affects the overall scope of the document. I think that the literature is fine, and I think it would be just nice to see if there is any issue that could get involved in that case, and that are involved in both isocyanates.

DR. DODGE: Yes, I can do that and look that up.

CHAIRPERSON KLEINMAN: Thank you. I'd like to open it up to Panel discussion now. And I think we'll start with the Panel members that are on the phone. So what I'd like you to do is identify yourself and speak into your microphones and we'll take comments off the phone first.

PANEL MEMBER BLANC: Paul Blanc here in San Francisco. Can everyone hear me?

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER BLANC: Great. So I'd like to talk through a basic conceptual issue that I'm grappling with in these two documents. And I -- the way I view it is this might be a very good opportunity for OEHHA to come up with a logical approach on how to deal with an air toxic contaminant, which is capable of sensitizing individuals and then once they are sensitized, they have a response to --

CHAIRPERSON KLEINMAN: Paul, can you hear us? I think we lost that line.

Should we re-dial it?

(Thereupon a discussion occurred off the record.)

(Off record: 10:14 AM)

(On record: 10:14 AM)

CHAIRPERSON KLEINMAN: We're going to have to wait until they call back in on the line.

PANEL MEMBER BLANC: Hello. It's Paul Blanc again. I'm so sorry. We were unplugged.

CHAIRPERSON KLEINMAN: Okay. Paul, thank you. Would you like to continue, please?

PANEL MEMBER BLANC: Yes. So as I was saying, I think there is some confusion between three scenarios. One, a person who is non-asthmatic, who is exposed to TDI and has an irritant response, which could include bronchospasm and temporary increase in non-specific airway

hyperreactivity; an asthmatic who is not sensitized to isocyanate, who is exposed to isocyanate and has a non-specific bronchospastic response; and third, someone who has been sensitized to isocyanate and has an anamnestic response and -- due to prior sensitization, and therefore has specifically bronchospasm in follow up to exposure to toluene diisocyanate. So those are three different scenarios.

And the interpretation of the Baur and Vogelmeier work was that that supported a scenario where persons with non-specific airway hyperreactivity, that is asthma, but without sensitization, were more responsive to TDI than people without airway hyperresponsiveness.

I am not sure I was convinced by that, because there seem to be a lot of negative literature beyond that one study of normal people and asthmatics not sensitized who were exposed to toluene diisocyanate and what their airway response was or wasn't.

There's a second issue, which is entirely separate, which has to do with what level of exposure is associated with induction of specific sensitization. That's a very complicated question. It's been very hard to study, and it's been very hard for regulatory agencies, who are concerned with workplace exposure, to develop standards that protect against sensitization.

But here's the big difference. When OSHA thinks about toluene diisocyanate, they actually don't care at all about workers who have been sensitized. And their standard is not designed to protect people who have been sensitized.

Whereas, the population bases reference exposure limits that are developed by OEHHA or recommended by OEHHA are designed to protect the population at wide, including those people who are pre-sensitized. They're more than susceptible.

Now, there are two elements. There is the element which you appropriately dealt with, which was susceptibility for sensitization, which was the basis of your genetic information. And then there's a separate question, which is sensitivity to exposure once you're sensitized.

There wasn't -- there wasn't a, I don't think, clear thinking, or clearly stated thinking, about exposure that induces sensitization. Now, it might be that you would come to the same ultimate reference exposure limits. But what is clear to me is that your intraspecies variability has to take into account two things. One, you did, which was 10-fold susceptibility to sensitization, but then once sensitized, there's probably 1,000-fold or greater difference in how people respond to TDI if they're

sensitized or not sensitized.

But reading your document it's as if you didn't think about or take that into account at all there, and then got, I think, overly hung up on the childhood issue because of previous precedent that we've dealt with with childhood asthma and what that means.

But I don't -- you haven't convinced me that an asthmatic -- a non-sensitized TDI asthmatic is more responsive to TDI than the effects of TDI than a regular person. I don't think the one event described by Baur in the weight of the evidence is -- it's not convincing, I think, or at least it has to be dealt with more for what it is.

I think what you've done is you've taken the sort of cookie-cutter approach to standard development and applied it to something which is, I grant you, very challenging, but it would be great if we could come up with a different kind of template for this sort of problem, because there are going to be other things for which the main human health effect is sensitization. And so it would be good to deal with this in, what would seem to me to be, a more logical way than I see here.

And I think one of the reasons why this may seem to be coming up late in the game for you, because you've invested a lot of time and energy, is there really has --

doesn't seem to have been a much -- a medical side input that you've gotten. And, you know, there are some world experts, not just in California, but in other places in the United States on the specific subject of isocyanate-induced asthma.

And I think you should take a step back and maybe have a close read of this from someone like Carrie Redlich at Yale, who you only cite two publications of her as an author at all, and yet she's published widely on this subject. So I'm a little surprised at that.

And I think I'll stop my comments there for now. Rather -- I don't -- really don't want to get into the weeds and talk about, you know -- you know, on a lower level. I'd like first to have a back and forth on this sort of more fundamental challenge, I think, which is not easy, I acknowledge that.

CHAIRPERSON KLEINMAN: Thank you, Paul.

Are there other comments?

PANEL MEMBER HAMMOND: This is Kathy Hammond. And thank you. This is really a very challenging area, I think, and complex. And I think Paul has some good insights in this and I second a lot of that.

So just a few other things. One is that in the worker study, particularly for something like this, the survivor effect is really important. For something like

this, you are quite likely to have people who are more sensitive leaving the workforce, because -- and so some of the longitudinal studies, you know, you find two years later they have only half as many people at the workplace, but they don't know what happened to them. And so trying to say what the incidence of different things are or what the effects are is very difficult when you haven't followed those other people.

And I know this is very challenging for this, but I do think that here when we know that there is this range of sensitivity and people do have to leave the workplace often, and they might do it without knowing, you know, just what's going on. So it's important to worry about that bias that can be in the study -- those studies. It's cited, I think, in one or two of the studies, but it really needs to be discussed as a whole topic.

Then, secondly, I didn't think -- you know, I was going back. As I read it through, I don't think there's a section that's really on the measured exposures. It's mentioned occasionally through there, but I think you might want to try to talk about what the exposures are, in fact, that have been measured, which may not be much in the environment, but you know -- because this is really supposed to be for outdoor concentrations, so we should probably have something on that. And there maybe just not

be enough information.

And then a very small thing that just to check, it's about 1,000-fold, you -- on page 8 just above 5.1.3, you talk about TDI reactions -- I mean, asthmatic reaction to TDI of 2 to 20 ppm, and I think that might be ppb.

DR. DODGE: Yes, that's correct.

PANEL MEMBER HAMMOND: That seems really high. I didn't look up the original paper.

DR. DODGE: That's correct. That was -- that was a typo that we need to correct.

PANEL MEMBER BLANC: Paul Blanc. You know, what Kathy is doing reminded me about one thing, which is the -- the study which is the basis of your chronic REL and your subacute REL -- no, your chronic REL. In the slide presentation it was said that this was the lung function loss in people without asthma, but a substantive subset of the workers became sensitized. So I don't know if you have access to the actual data, but it would seem to me that it was likely not normally distributed in terms of the response. If you had some people who were sensitized, they had a big drop in lung function, and the people who weren't sensitized I'm not sure they had an accelerated drop in lung function. So is your outcome really a loss in lung function or is it simply that you had a loss in lung function, because that's a marker for

the subset that are getting sensitized?

I mean, it would be -- this returns to what I was trying to say, which is the endpoint is not an average of accelerated loss in lung function of 200 people. It's the 20 people who've become sensitized who are losing a lot of lung function that you -- that's the effect that you've found a trigger for. And that's the study in which it's divided dichotomously between above and below a certain level.

But the issue, if you could do it, is you'd want to benchmark what is the exposure level which is likely to induce sensitization. And I suppose you could then work backwards from that and then put it in an uncertainty factor for the people who really were sensitized, which would be 1,000-fold, or something like that, not 10 and not 100.

Because isn't the regular -- isn't our guiding principle that we use a default uncertainty factor, but if we actually know something about variability, we use the real number?

PANEL MEMBER GLANTZ: So this is Stan. These are -- this is all not my area of expertise, but I think -- since I think Paul has raised -- and Kathy has agreed, have raised a couple of kind of fundamental questions, it would be -- I'd appreciate hearing what

OEHHA and other Panel have to say about those specific issues now, rather than having everybody comment and then have me try to remember what everybody said. But I think that would be more productive, if that's okay with everybody else?

CHAIRPERSON KLEINMAN: I think that's a good strategy. So why don't we take some time for the Panel members to respond, you know, give their thoughts on this topic.

PANEL MEMBER GLANTZ: Okay. But we are having kind of a hard time hearing you, and the phone is turned up all the way, so please be louder.

CHAIRPERSON KLEINMAN: Okay. We'll start with Dr. Araujo.

PANEL MEMBER ARAUJO: Could you rephrase again what is what you want to comment about?

CHAIRPERSON KLEINMAN: What Stan was saying was Paul had raised some issues about the populations that might be affected more greatly by TDI exposure, and that there could be three or four different types of scenarios. And there isn't very much specific information on what populations and the general public are actually falling into the more sensitive class.

We have some information from occupational exposures, and even that is pretty sketchy, but we don't

know very much about the sensitivity characteristics of the general population, but there are some additional literature that might be able to cast a light on this. And Paul was recommending that some of that should be summarized into the document.

PANEL MEMBER GILL: Can I get into a comment first actually before. Paul, can you hear me?

PANEL MEMBER BLANC: Yes, I can. Thanks.

PANEL MEMBER GILL: So if you look at the three scenarios you have described, and the major issue that will accomplish scenario 3, where people are pre-sensitized to isocyanate. And so in those cases, you would see people becoming asthmatic much more greatly than compared to the other -- at least even compared to the second scenario you've described, where people are sensitized to non-isocyanate, but other sensitizing agents.

So in terms of developing rules and regulations, do you think that's an appropriate parameter to use for developing regulations where one part -- or a couple of individuals are pre-sensitized to isocyanate?

PANEL MEMBER BLANC: Well, it's not a trivial question, because it's not a rare event. It's true that we typically, for carcinogenesis, use a one in a million cutoff. I think that -- I don't -- I don't have an

obvious answer to it, but I would say that if the question is what is the range of variability of response in the human population to exposure to isocyanate, we know very well that there's a subset of people, and maybe a small subset, but we've created them, that will respond at a level that's 1,000 times lower than what the legal standard is.

And that hasn't been a problem for OSHA, because that's -- they don't -- that's not in their mandate. But unfortunately -- or fortunately, we have to think about that. And I wouldn't simply defer to what the EPA did on this subject, because I'm not convinced that they took it into account. Although, it would be interesting to see what they're test was, you know, in justifying that, the federal EPA.

And as I said, I think the scenario number 2, I'm not convinced by the data that were presented that a person with non-specific airway hyperreactivity who is not sensitized to isocyanate is necessarily more responsive than someone else.

In fact, there's a fairly short list of substances in which we're pretty sure that asthmatics respond differentially to non-asthmatics. Sulfur dioxide is one of the few. Chlorine, there's some data for it. Ozone, in fact, does not operate in that way, so it is not

impossible to show that ozone preferentially induces airway -- increased airway resistance in people with non-specific airway hyperresponsiveness.

Although, there is a subset of people when exposed to ozone who are more responsive than others, but it's not on the basis of preexisting airway hyperresponsiveness.

So now if you knew that something did that, that's important, because about 12 percent of the population has non-specific airway hyperresponsiveness, about half of whom have something that resembles clinical asthma, and half of whom don't, but still that have twitchy airways.

So I think that one way or another the document and OEHHA have to come to grips with what their policy is about this, and what they're trying to do in their adjustment factors, for one thing, their uncertainty factors or not uncertainty, the human variability factor, the intraspecies variability, because on the face of it, we -- this is one chemical for which we know something about the intraspecies variability, and it's quite large.

PANEL MEMBER GILL: Thanks.

PANEL MEMBER BLANC: So just to come back to what I said before, to my mind, there would be more logic in coming up with a starting point that might be higher than

what you've gotten with a presumption that Baur established that asthmatics nonspecifically respond to isocyanate, but on the down -- on the other end, being more realistic about how big the human variability is, taking into account that a subset of people are sensitized.

Now, that subset of people are going to be adults not children. So I think this is one particular case in which you could make the argument that we're actually not thinking about childhood vulnerability, in terms of the legislative mandate for that.

By the way, since, you know, maybe TDI use has gone down, so you could say that the people who were out there who were sensitized may be older. You know, it could be an aging population issue, but I think that's, you know, probably not -- there's not a way to say that with data. It's not a data driven statement.

CHAIRPERSON KLEINMAN: Okay. If you can hold on a moment, Peter has said that the technical staff --

PANEL MEMBER GLANTZ: Can you talk louder, please?

CHAIRPERSON KLEINMAN: Yeah. We're going to try to --

PANEL MEMBER GLANTZ: Get closer to the microphone?

CHAIRPERSON KLEINMAN: Yeah. Can you hear me now?

PANEL MEMBER GLANTZ: Barely.

CHAIRPERSON KLEINMAN: Okay. We're going to hang this -- hang up the call and we're going to try to reconnect. Peter said that technical staff can do it if you call back in about five minutes. Can you do that?

PANEL MEMBER GLANTZ: Okay. So should we take a five minute break?

CHAIRPERSON KLEINMAN: Yes, take a five minute break.

PANEL MEMBER GLANTZ: Okay. Bye.

CHAIRPERSON KLEINMAN: Sorry.

(Off record: 10:36 AM)

(Thereupon a recess was taken.)

(On record: 10:42 AM)

CHAIRPERSON KLEINMAN: Okay. Thank you. Hopefully, you can hear us better now.

PANEL MEMBER GLANTZ: You said thank you. We can hear you. That's very exciting.

CHAIRPERSON KLEINMAN: Okay. Then with that, we will reconvene. And Paul, I believe you were --

PANEL MEMBER GLANTZ: I think Paul ran off to the little boy's room.

CHAIRPERSON KLEINMAN: Oh, okay.

PANEL MEMBER GLANTZ: That doesn't need to be in the record.

CHAIRPERSON KLEINMAN: Now, we're having a little technical problem on our end, because your sound isn't coming through very clearly.

Can we goose up the --

PANEL MEMBER HAMMOND: Can you hear me?

PANEL MEMBER GLANTZ: Well, I'm -- can you hear me now?

CHAIRPERSON KLEINMAN: Yeah, that's getting better.

PANEL MEMBER GLANTZ: Okay I'm talking, so you're -- are you fine?

CHAIRPERSON KLEINMAN: Yeah, we can hear you.

PANEL MEMBER GLANTZ: Okay. Well, I guess we ought to maybe -- Kathy raised a couple of different points than Paul did. Maybe we could hear what people think about that while we're waiting for Paul to get back.

CHAIRPERSON KLEINMAN: All right. So we were starting with Dr. Araujo. So let's start there.

PANEL MEMBER ARAUJO: Can you hear me know?

PANEL MEMBER GLANTZ: Yes.

PANEL MEMBER ARAUJO: Okay. I think this is a really, you know, very complex situation that you're raising. And I don't want to elaborate too much on it,

because honestly I don't really feel that I have a major, major contribution to this.

But perhaps, at one point, it would be -- if we ask ourselves do we know or is it -- is there data about, and how significant is this problem in the case of the isocyanate-induced health effects or asthma in particular? Do we know the percentage of people or the number of people that is affected. By that, I mean, either sensitized or pre-sensitized and subjects could be more sensitive to the effects induced by that?

If it is a very, very small number, so maybe this is something that could be discussed in the -- and it shouldn't really influence like regulatory decisions, but it could influence, like the knowledge or things that perhaps physicians need to know, or the moment of, you know, having patients or subjects that are sensitized to it. So maybe they do need to have like an awareness, and that they cannot be exposed or working in places where the levels could be above a certain number, you know.

If, on the other hand, the problem is more significant, I mean, it affects a larger, more significant number of people, and I don't want to say a number in particular. So maybe that should indeed end up in something that affects a regulatory decision. But I just don't have the -- you know, enough knowledge to guide or

advise one way or another.

CHAIRPERSON KLEINMAN: Thank you.

Cort.

PANEL MEMBER ANASTASIO: This is well outside my expertise, so I'm going to defer to the other Panel members.

CHAIRPERSON KLEINMAN: Beate.

PANEL MEMBER RITZ: So actually one thing that is more general that came to my mind when I was reading this was this issue of whether TDI is or isn't off-gassing from consumer products, because that would then really probably be an issue, for example, for the sensitized workers, but maybe also for children and very small children.

And I know we had the slide here where language was changed to emphasize that several studies did not find any off-gassing. But I'm just wondering whether those really were studies that considered all possible situations, such as newer pillows, newer foam versus older et cetera. It just, you know, was -- it seemed very specific. It didn't seem like there was a more general broad concern for consumer product contamination. And that's what would worry me because that would then increase the population exposure throughout, if that's the case.

DR. DODGE: One study, in particular - I think it

was the Vangronsveld study - did look at new products -- new polyurethane products. And I'm not sure if Hugo et al. did. It's certainly -- I think this issue could be looked at more extensively than just a few studies though.

CHAIRPERSON KLEINMAN: Yeah. Another issue along those lines that wasn't really addressed was that thermal degradation of polyurethane foams does give rise to release of large amounts of TDI and MDI, but not in the vapor phase. It's in particulate phase as ultrafine particles.

And that could be another complete source of exposure to firefighters, first responders, people in the community that are exposed to smoke from burning furniture and car seats, anything where polyurethane foams are used. So there could be events that could cause relatively high exposures and might even be sensitizing doses that we have no information on, but we could speculate that these could occur.

DR. DODGE: Yeah. In fact, there is a study of another diisocyanate in which they theorized that that exactly happened. It was heated and the diisocyanate was released in that fashion.

PANEL MEMBER GLANTZ: So Paul is back, so we can go back to talking about his point.

PANEL MEMBER BLANC: Sorry.

CHAIRPERSON KLEINMAN: Okay. So --

PANEL MEMBER RITZ: Can I actually ask you?

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER RITZ: Is that just extreme heats or does that include heats we have on a normal summer day in California? So we're talking fire, not heat?

CHAIRPERSON KLEINMAN: Well, there were laboratory experiments where they heated this stuff under various conditions. And I did not see numbers below say 200 degrees, but I have not looked in depth for other things at more environmental temperatures. But it makes sense that you would have some thermal degradation even at high ambient temperatures.

PANEL MEMBER HAMMOND: It would seem to me that's really important to ask.

CHAIRPERSON KLEINMAN: Thank you, Kathy.

PANEL MEMBER HAMMOND: Yeah, I think it's very important to discuss that, because those are other issues. But can OEHHA and can CARB deal with consumer product degradation? I guess if you have fires, that becomes community exposure. Has anyone measured community exposures around fires?

I mean, again, I think that there's not much in the document, very, very little about measured exposures -- measured community exposures in air. And it

may not exist -- the data may not exist, but at least it should be reviewed. I'd like to know if it's comprehensively looked at, and definitely a fire would be source of that such exposure. Has anyone outside the lab looked at what those exposures are, like in the real world?

DR. MARTY: Kathy, this is Melanie Marty from OEHHA. We did look to see what types of measurements had been made for ambient air. We did not look at any measurements that had been made during a structural fire, for example. So we could look for that. I don't know that that scenario is under any regulatory purview of CARB.

So just a reminder, these numbers that we generate go to the Air Board and they use the information in their regulatory processes. And then also the primary use of these numbers is for emissions from stationary sources in California.

CHAIRPERSON KLEINMAN: This is Mike. In response to that, what I think -- or at least my point was that I'm trying to come up with, relevant to what Paul said about there being different sensitivities and scenarios, are there ways that people in the general public could be exposed to something that could sensitize them?

And I think this is a possible scenario, which

even though we don't have evidence, it would perhaps make us think that this is -- you know, should be treated much more conservatively than otherwise.

DR. MARTY: Okay. This is Melanie again. So just a couple things. We do have actually in our guideline document, which we used to develop these numbers, that we recognize there are cases where we will not be able to protect people from idiosyncratic responses. So we have discussed this issue, and in particular with the isocyanate, since they are such potent sensitizers and you do have case reports of people responding at remarkably low concentrations.

So having said that, we do recognize the three cases Paul is talking about. We may not have been very clear in the document that we recognized that. And so I think we could add certainly more text discussion around that.

The second issue is we -- in order to generate a number, we need enough data that gives us a dose response. And, you know, Paul, I think you pointed out yourself, people have tried to figure out a concentration that would protect everybody from sensitization. And it's probably a really, really hard thing to do, because we're also different in sensitization, is the response is a very individual response.

So we realize we could not do a dose response analysis for sensitization itself, so we took the available information we had on dose response related to respiratory parameters and used that as the basis of our reference exposure level.

So on the acute REL side, that's where we're using responses of asthmatics.

PANEL MEMBER BLANC: Paul, here. You're using response of one asthmatic in the Baur study. And yet, other studies have not shown that asthmatics are sensitive, so -- are more responsive than non-asthmatics or do you believe that you do have other data that indicates that?

I'm not a -- I'm not a lead on this document, so I didn't necessarily hone in on every -- hone in on every -- the nuance of every study. It also seems to me that if you actually had the data -- raw data from the study that you used for the chronic REL, in fact, maybe you could maybe model what the dose response for sensitization was because they -- they're the ones that reported a 0.7 percent sensitization rate per year among their population. And they had how many years of follow up? Nine years? Is that the one with nine years or...?

PANEL MEMBER HAMMOND: And it may well be underestimated by --

CHAIRPERSON KLEINMAN: Right, right. But in any event, I know that in the past OEHHA has gone the extra mile and gone to an investigator and gotten the data so that they could do that kind of modeling. Has that been something you've considered for that study, given how central it is to your -- to your estimation?

DR. DODGE: Dr. Blanc, this is Daryn. Regarding the Diem et al. study, they did take into account the 12 individuals that had become sensitized, and it was not a factor in the reduction of pulmonary function -- accelerated decrease in pulmonary function.

PANEL MEMBER BLANC: What do you mean they took into account? Can you just tell us what they -- they re-ran the model excluding them?

DR. DODGE: Yes. Whether they excluded them or included them, it was not a factor in the higher dose group.

PANEL MEMBER BLANC: And how did they -- how did they define sensitization? Because as you probably know by now, having delved into the morass of this literature, in fact, IgE is not a reliable measure, and one of the big challenges, and have been linked, isocyanate as not a good measure. So there's no good immunologic measure of sensitization.

DR. DODGE: Correct, but they might have used the

gold standard of actually --

PANEL MEMBER BLANC: It is not a gold standard.

DR. DODGE: -- exposing the individuals to TDI itself to see what kind of result --

PANEL MEMBER BLANC: I doubt very, very highly that they would do inhalation challenges. I would be extremely skeptical if that's how they defined it. But it should be obvious from the article, right?

DR. DODGE: Well, if it's not in -- if it's not currently in the document, I will put it in there how they defined sensitized workers.

PANEL MEMBER BLANC: But coming back to the more fundamental question, do you think that the data could be had from them, the raw data?

DR. DODGE: There is another study I refer to alongside Diem that's in the document. It gives a little more information. It appears to be sort of the industry study. It's got more information, but it's not a really good breakdown of every individual in the results of every individual.

I looked at that, and, you know, it's very difficult to figure out from that study, well, is the -- for example, the sensitized individuals, which group did they fall into? It appears that some of some them may have been actually in the low dose NOAEL group or the

NOAEL that was used for accelerated decrease in lung function.

So I could --

PANEL MEMBER HAMMOND: Well, I mean, that's actually kind of -- I think that's a little bit of a problem. I mean, so the dichotomy is set based on the lung function, and then -- and they say three of the workers were in the low -- three of the 12 sensitized workers were in the low exposure group.

DR. DODGE: That appears to be true, yeah.

PANEL MEMBER HAMMOND: So they're not people who have been unaffected by the exposure? That's not -- you know, it's a LOAEL for the lung function, but we know that sensitization is -- the response for sensitized individuals, at least, the LOAEL for that is going to be much lower.

DR. DODGE: That's correct.

PANEL MEMBER BLANC: It says actually here, at least in your summary, that the way the defined sensitization -- you're saying that the -- that the --

PANEL MEMBER GLANTZ: What page are you on?

PANEL MEMBER BLANC: I'm on page 23.

You're saying that the parallel study or analysis of the same data set was Hans Weill's study analysis from 1981? Is that the same -- so it's the same co --

PANEL MEMBER HAMMOND: It's the same numbers.
PANEL MEMBER BLANC: Is it the same cohort, is that what you mean? You have the Diem study from 1982. And it's the same number, so it's -- the Weill study is the same cohort although published a year before?
DR. DODGE: That's correct. It was looking at the same group of people, the Weill study appears to be sort of an industry-generated study. It wasn't -- and the actual published report was the Diem et al. study.
PANEL MEMBER BLANC: Oh, I see, so Weill was not published. It was an internal report of some kind?
DR. DODGE: Well, it wasn't peer reviewed like the Diem et al. study was.
PANEL MEMBER BLANC: Okay. So I think, by the way, as an side, you should indicate that it was nonpeer-reviewed study, but -- if that's the case. But --
DR. MARTY: Paul, it's a NIOSH technical report, Weill.
PANEL MEMBER BLANC: I see. Okay. Well, then that's harder -- then it's not an industry study.
DR. MARTY: Yeah, it's not an industry study.
PANEL MEMBER BLANC: Okay. So, in any event, they say they define sensitization based on people who were clinically asthmatic at the workplace basically, if they developed recurrent respiratory signs of symptoms

upon repeated exposure to low concentrations of TDI.

So in fact, that's not sensitization. That's people who are clinically have developed asthma.

CHAIRPERSON KLEINMAN: Okay. Any further comments?

Dr. Buckpitt.

PANEL MEMBER BUCKPITT: Paul, I understand --

PANEL MEMBER GLANTZ: This is Stan.

Again, I'm kind of an observer to this discussion trying to -- and so where have we ended up? I mean, what does OEHHA propose to do in response to these issues Paul is raising?

CHAIRPERSON KLEINMAN: Before we get a response from OEHHA, I'd like to give the other Panel members a chance to chime in.

So Dr. Buckpitt.

PANEL MEMBER HAMMOND: Did you finish your comment? You didn't give your comments yet?

PANEL MEMBER GLANTZ: I don't really have any.

PANEL MEMBER BUCKPITT: Paul, I understand your -- the points. And I think your points are well made. I wonder if there's a fairly recent study -- now, this is in rats. So it's the Brown, Norway, and Wistar rats, but they're looking at exactly the point that you bring up. And they both skin sensitizes and inhalation

sensitizes these animals to TDI to determine whether there was a threshold in essentially making those animals more susceptible.

And I wonder if -- it's not going to be a perfect study, but I think they do show that there's really a threshold for those responses. And I wonder if that could help us out in terms of being comfortable with where these RELs have been set? That's the Jürgen Pauluhn study, and toxicology. Let's see, it's 319, 10 through 22 of 2014.

PANEL MEMBER BLANC: Well, there is one approach that we've used in the past, which is a sort of mind experiment, where we say, okay, here's a REL we got to using a kind of standard approach, but were we to have done A, B, C, we would have come out essentially the same way. And perhaps I would feel comfortable if I saw that in the document.

It would be like I say, okay, so this is what we do, because this is how we do, but were we to have taken the dose that sensitizes, taken a benchmark approach or a NOAEL approach that gets us with a safety factor for the sensitization in rats, and then we put in a 10-fold factor for genetic variability in humans, which increases the risk of sensitization, and then we put 1,000-fold factor in for the response of people to isocyanate if they've been sensitized, then we would come out with 0.008 parts

per billion just the same. That would make me feel more comfortable, or if you were very close, or in the ballpark.

DR. MARTY: We could take a look at that. Although, I'm not sure I, you know, would put exactly the uncertainty factors that you just mentioned. We can look at that and see where it would come out using the animal data and our typical default assumptions about extrapolation from animals to people, and then extrapolation from sensitive two sensitive individuals.

But at some point, we have to recognize it's not possible to predict everyone in the population. And there are case reports that they -- I'm sure you're aware of -- of responses to very, very low concentrations of the isocyanates in sensitized individuals.

PANEL MEMBER BLANC: Well, first of all, these -- I would differ a little bit. These are not one-off case reports in the Journal of Medical Case Reports. These are -- some of them are a series of people that have had controlled human exposure to -- actually to define whether or not they are isocyanate sensitized. For example, a series from, you know, Malo in Quebec, which I think are some of the papers you cite with Vandenplas probably. So it's -- it's, you know, smaller than a house, but it's bigger than a bread box, I think.

And I think you -- maybe you could then have an estimate of what you think the rate of people that are sensitized in the California population are. And, if that number is less than one in a million, you know, then you could say, well, in the same way that we regulate -- we do risk estimates for carcinogens getting it down to one in a million excess incidents, or whatever your standard is.

Then you could say, since there's only one in a million people in California who are sensitized to isocyanate, we don't -- you know, we take this as being a completely idiosyncratic. In essence, below the level which we normally attempt to modify risk.

PANEL MEMBER HAMMOND: Although, I think making that up, you might want to take into account Mike's comments about how high might have been the exposures during fires.

PANEL MEMBER BLANC: Or whatever your -- whatever your --

PANEL MEMBER HAMMOND: That might lead to sensitization.

PANEL MEMBER BLANC: Well, you say what's the prevalence of sensitization based on all these things or the likely prevalence. I mean, I think at least you need -- at least you need to say it, because people can't read into the document those presumptions. It's

like -- it's kind of the equivalent of what would be the limitations section of a paper, you know. It's hard to see your acknowledgement of some of the -- some of these presumptions and limitations.

DR. MARTY: Well, I think we can look at what data are available to make an estimate of the number of individuals sensitized to TDI. I don't think -- or isocyanates in general. I don't think that that's going to be very simple to do or are very, you know, quantitatively robust, I guess.

PANEL MEMBER BLANC: Well, for example, there's some data from Ontario from Susan Tarlo's group on what the number of people who have received compensation for isocyanate.

PANEL MEMBER HAMMOND: For workplace?

PANEL MEMBER BLANC: From workplace. Well, those people are an N of people in the population of the Province of Ontario. Similarly, Quebec, any worker with suspected isocyanate asthma in Quebec is sent for challenge testing. It's one of the few places. So the data on the number of cases that they've seen over X years, assuming that some of them haven't died, is the number of sensitized people in the Province of Quebec. So you can get some sense. Is it 1 in 1,000,000? Is it 1 in 100,000?

DR. MARTY: We could get a sense. I don't know how much that's going to inform the choice of uncertainty factors. We're applying to develop a reference exposure level. We still would not have dose response data on reaction of sent -- of isocyanate-sensitized individuals to variance concentration.

PANEL MEMBER BLANC: Oh, yeah. That's not -- that's kind of not what I meant. I meant more your policy points. Because clearly, the issue of whether it's idiosyncratic or cannot be addressed by standard, you'd have a different sense if it is 1 per 1,000,000 versus 1 per 1,000. And I'm not arguing it's 1 per 1,000 are sensitized, but -- that's correct, isn't it? I mean, that would have different policy implications?

DR. MARTY: It could. We haven't sat down and pounded out any kind of policy using numbers.

PANEL MEMBER BLANC: Is the --

DR. MARTY: But again, the other thing to think about too is at the reference exposure level we're setting, our -- is that going to be a number that impacts people sensitized or not, and is it going to be a number that protects from sensitization, which is, you know, something that NIOSH is -- or OSHA is not doing, but, you know, we would like to do.

PANEL MEMBER BLANC: No, OSHA -- no, let me

correct again. OSHA does protect against sensitization. That's what their standard is. It doesn't protect sensitized people. Theoretically, that's what it does. So, you know, who knows how they came up with it, but that's the rationale. You know, I don't know. I'd be curious what -- Jesús, are you still there at the table?

PANEL MEMBER ARAUJO: Yes.

PANEL MEMBER BLANC: So putting on your physician hat, what's your take on all this?

PANEL MEMBER ARAUJO: I am with you. This was exactly my comment that the -- not knowing much about the particulars of these problems, it seems to me that it all relates to how you express the prevalence of this. So if this is something that is extremely small, so maybe we can just treat it as you're saying. Maybe it's something that's idiosyncratic or something that doesn't really require that regulation for those people. But if it is something that is -- that involves a more significant number of people, then we should do something. I don't think we know that. I think that everything will be more like speculations.

By the way, I will have another comment about use of the -- not a sensitization, but in relation to the susceptibility. But that will come when I have -- I don't want to divert, but it's something that I will connect to

this. There could be another -- suffice to say for now, there could be another group of people that could be susceptible. We just don't know. We don't -- may not have enough knowledge about it.

DR. DODGE: Dr. Blanc, this is Daryn again. One of the factors we tried to take into consider in trying to grapple with this whole issue of workers that -- or people that may have become sensitized is what kind of data -- what kind of data are out there -- I'm getting an echo effect -- what data is out there in which there is a controlled human study of somebody that had been sensitized to diisocyanates?

The lowest concentration I could find in a study in which a worker that was sensitized, and then had an asthmatic reaction was a study by Suojalehto, 2011, in which a concentration of 0.05 parts per billion resulted in what they considered an asthmatic reaction. And he had -- this person had become sensitized probably due to MDI or methylene diphenyl diisocyanate.

So our -- so the question is, is our RELs, our 8-hour and chronic RELs how do they compare to this lowest number that I -- that we could find? And right now, they appear to be lower than that number or right around that number, at least for these two compounds.

So when we --

PANEL MEMBER BLANC: You know, I agree that I think the numbers that you got to are public health protective. So that -- and I know that there have been times when our discussion has circled around whether a number is appropriately public health protective, but I'm not sure that you got to it in a way that is logical and supportable enough. So that's one reason why just pragmatically I suggested perhaps doing an alternate calculation just seeing that you're in the ballpark.

I do think in terms of human control studies, the controlled studies, I'm going to return to the chamber studies -- the exposure chambers. In North America, it's only in -- in Quebec, basically at this point, and in Italy, which may be where the study you referred to, and Vandenplas has in Belgium, but they have a protocol when they test somebody with isocyanate, and they start with an exceedingly low number, and then they go up. And then they have a cutoff for what they say is a positive response.

In those reports, I think they can tell you what their -- there's a reason why they start as low as they start, and they have a certain percentage of people who respond, and they stop when they get to when they respond.

So that might be some reasonable guidance for what is -- what is, in fact, a threshold for bronchospasm

in someone who has been sensitized. Not all of these -- it turns out some of these people don't have isocyanate asthma, so it becomes a negative study. But I think those data, for your purposes, are actually pretty useful. And I can understand why you didn't go that route, because it wouldn't be something you would typically look at in this kind of risk assessment, but -- in a generic risk assessment. But in this particular chemical, I think it's -- it could be very informative. I can't promise you, but I think that there's something there for you.

And I do think if there's -- I don't know what the mechanism could be for OEHHA to bring in a respiratory physician or consultation for this particular challenge that you face, but I think you could get a lot of -- a lot of help quickly that way that might be extremely useful, not just for this chemical, but there may be others down the pipe where it's going to be not an unrelated set of questions.

And just in terms of how the word idiosyncratic is used or not used. I would tend, in a medical sense, not to use the word idiosyncratic for someone who's sensitized to a known sensitizing agent. Idiosyncratic tends to be more I don't know why they responded this way or they had an out-of-the-box response. But I grant you, there's overlap, and some of it's just personal usage.

DR. MARTY: So, Paul, while you were talking, I think another approach we can take to inform the uncertainty factor, particularly for the acute reference exposure level, which is the one that's based on an asthmatic response, is to look at whatever data are available on measured responses in sensitized individuals and then see where those concentrations are that trigger the response in relation to the acute reference exposure level, and then drop it down if it seems like that number is too high.

PANEL MEMBER BLANC: Yeah, it would be useful to see that. And I think with the other study, if it truly was a NIOSH study, it seems to me NIOSH has the raw data. In fact, they have to give you the raw data, unless they say we lost it. And maybe they've actually done this analysis, but never have gone anywhere with it, in terms of what's -- what's -- now, I'm talking about sensitization and what's the dose response for sensitization.

DR. MARTY: We can ask Weill.

PANEL MEMBER HAMMOND: And you could ask them how they define sensitized.

PANEL MEMBER BLANC: These are clinically sensitized.

PANEL MEMBER HAMMOND: So that's a clear

definition to you.

PANEL MEMBER BLANC: Well, it's a very, very --

PANEL MEMBER HAMMOND: A high threshold?

PANEL MEMBER BLANC: -- high threshold, right? These are people who -- sensitized means you're actually clinically sick with asthma. It doesn't mean that you have antibodies. So it means that you've become sensitized.

PANEL MEMBER HAMMOND: So you might think that more people are sensitized.

PANEL MEMBER BLANC: Much more than that.

PANEL MEMBER HAMMOND: And they might 0.9 percent per year getting sensitized.

PANEL MEMBER BLANC: Right, getting clinically sick.

PANEL MEMBER HAMMOND: In the new factory that has much lower TDI concentration.

PANEL MEMBER BLANC: Right.

PANEL MEMBER HAMMOND: Whatever the level is doing.

PANEL MEMBER BLANC: You know there's a couple other minor things. You discussed -- and I understand, Melanie, the point about fixed sites and much more relevant I think to your next -- to your next exposure, MDI, and will be even more relevant to HDI, if you were

doing one on that.

You know, it's not so much the factories producing this stuff, it's where it's used in the field or was used in the field. So that's -- that's not really captured, I think, very well in the description of scenarios for exposure of -- it's not simply big factories that are producing TDI or producing products with TDI, it's people who are, particularly in the foam world, you know, people who are using -- using -- generating polyurethane out there in the field. So I think there needs -- and maybe it's a lot smaller than I think it is, but I think it needs to be alluded to.

And I have a technical question also. In terms of the pre-polymer, how would that figure into this REL? If I measured -- technically, if I were to measure isocyanates would the pre-polymer come out -- be detected as TDI as three molecules of TDI, despite a sampling and analysis?

DR. DODGE: This is Daryn again. If the pre-polymer is in aerosol form, as it likely is, and the TDI is more of a -- in the vapor form, it may be missed depending on the type of equipment being used to try and measure them.

PANEL MEMBER BLANC: Right, but would you actually then when you did your -- let's say you had the

right sampler, so you were capturing both aerosol and vapor, and then I do a GC -- you know, LC analysis, will I measure separately TDI and TDI pre-polymer, or will the TDI pre-polymer all be converted to TDI? Does your REL include TDI as TDI and pre-polymer?

DR. DODGE: You know, I don't have -- I can't recall finding much information regarding TDI in regards to your question. However, there is quite a bit of information out there on HDI, hexamethylene diisocyanate, because it often -- you often find the vapor HDI in a mixture of pre-polymers that are aerosols. And for that compound, they do measure those separately, the vapor form and the aerosol form, with the assumption HDI is the air -- is the vapor and the pre-polymers are all in aerosol form.

PANEL MEMBER BLANC: And so your view would be that the pre-polymers are not biologically active?

DR. DODGE: Oh, they definitely are. However, they could deposit in different areas of the lung compared to the vapor.

PANEL MEMBER BLANC: So maybe I'm not asking the question in the right way. And I'm looking across the table at Kathy. I think she could ask the question in the right way that I'm asking about what your standard covers. Does it cover TDI as TDI and pre-polymer or only TDI, if

it's in the form of TDI --

DR. DODGE: For this --

PANEL MEMBER BLANC: Does your proposed -- as your proposed REL?

DR. DODGE: The proposed REL is based on TDI, the monomer.

PANEL MEMBER HAMMOND: Not the pre-polymer.

DR. DODGE: No. However --

PANEL MEMBER HAMMOND: But you just said there is a biologic response to a pre-polymer.

DR. DODGE: Oh, yes. Yes. People become sensitized to pre-polymers, not necessarily TDI, but all other pre-polymers of like MDI and HDI. I'm not as familiar with the pre-polymer and how often it's used for TDI.

PANEL MEMBER BLANC: But you have a -- you thought enough of it to make it part of figure number one.

DR. DODGE: The information I have is from occupational studies in which there are manufacturing TDI.

PANEL MEMBER BLANC: I think someone else has to re-ask my question, because I think I'm just not asking it the right way.

PANEL MEMBER HAMMOND: Well, you know, I kind of -- I'm guessing that what I'm hearing from you is just some of the difficulties of knowing what's out there. But

I had -- maybe I misread this, but when I was reading this, I thought you were saying some place that people were talking about and were, in fact, using the pre-polymer, thinking it was less dangerous, less biologically active.

DR. DODGE: Oh, no, that's not the case. It's less --

PANEL MEMBER HAMMOND: Okay. I misread that then. Sorry.

DR. DODGE: Well, it's not a vapor, so it's not going to vaporize, and so it's not going to be as much of a threat to workers via the inhalation route.

PANEL MEMBER HAMMOND: I think that sometimes one has to -- that may or may not be true. And I think aerosols can also pose risks to workers. And so before I would make such a statement, I'd want to make sure that that was true, you know.

DR. DODGE: It is true. If it's -- if the aerosol is being sprayed or heated, you will get exposure via the inhalation route.

PANEL MEMBER HAMMOND: Correct. Right. Right. Exactly

PANEL MEMBER BLANC: Which it almost always is sprayed.

PANEL MEMBER HAMMOND: And so I guess there are

multiple components to Paul's question. See if I can tease them apart. If we think we have -- let's just treat them as two different chemicals, TDI and the pre-polymer. And you're saying that they both have biologic effects. And am I hearing that the pre-polymer might be even more biologically active, is that correct?

DR. DODGE: From what information is out there, if you're going to do a comparison of potency for the effects, generally, the monomer is going to be more toxic than the pre-polymers.

PANEL MEMBER HAMMOND: Okay. So the other -- I mean, so one issue is pretend these are -- I mean, they are two different chemicals. Treating them as two chemicals for just a moment, one would want to say when you're looking at health effects, you'd want to see to the decree to which you can separate them, their health effects in the particular study.

And the other piece is -- that Paul is referring to is the degree to which we're measuring one or the other -- the TDI itself as the monomer or the pre-polymer. And so one of the questions, is there multiple chemical methods for measuring concentrations in the various studies, the Marcali reagent, which is with respect for photometric, which was thought to underestimate, I think there was a mention of a liquid chromatographic method.

And I didn't actually systematically go through and try to figure out, you know, which ones use which. And what -- and I don't know, and I don't know if you know or have known, you know, which of these methods responds and in which ways to the monomer and to the pre-polymer?

There's a lot in what I just said. Am I clear or do I need to restate it?

DR. DODGE: I think so. The issue here is that all of the studies we had looked to the monomer, TDI. I don't have a good feel about how much of the pre-polymer is used out there and what the exposure is unfortunately.

So we had to rely on the TDI studies, nearly all of which, as far as I know, use the monomer TDI. A lot of the -- a lot of the occupational studies, they were manufacturing TDI, the monomer, so that's what they were looking at.

PANEL MEMBER BLANC: Well, let's say --

DR. MARTY: So this is Melanie. Just to throw in another consideration, we're looking at chemicals that are listed under the Air Toxics Hot Spots Program and the monomers are listed not -- not the oligomers.

PANEL MEMBER BLANC: So I may -- if I were in the South Coast Air Quality Management District, and I came up and I did really good levels, and I found that there was an acute level of 2.9 -- 0.29 parts per billion TDI and

another 1 part per billion TDI pre-polymer, I would be okay, right, because I'm under the reference exposure level for TDI?

DR. MARTY: You know, I don't think we can get into the risk management arguments at this phase. And, you know, your hypothetical I'm not even sure is something that the South Coast AQMD would be able to measure. Most of the time these are applied to results of modeling from emissions from specific facilities.

PANEL MEMBER BLANC: Right.

CHAIRPERSON KLEINMAN: But I think where we are is that we don't have good strategies for measuring and -- well, not for measuring, but for developing risk approaches for multiple chemicals in many instances, and this is yet another one.

I think what I'd like to do, because some of these issues are becoming more specific to the diisocyanates, in general, I'd like to go through the MDI. And then we can have, you know, a specific discussion of the MDI, and then see if we can't bring some of this altogether.

So if we could continue with the OEHHA presentation on MDI, I think we can get back on track with that.

PANEL MEMBER ARAUJO: May I -- I thought that

those were just the comments about the specific questions or -- of -- that Paul raised and also Stan, but I do have some additional comments about the MDI that I would like to mention.

CHAIRPERSON KLEINMAN: MDI or TDI?

TDI or MDI?

PANEL MEMBER ARAUJO: Well, it's probably both, but it's more in relation to the MDI than the TDI.

CHAIRPERSON KLEINMAN: Okay. So we're going to start with the MDI now, and then we'll have a chance to go --

PANEL MEMBER ARAUJO: No, no. I'm sorry. I'm sorry. I'm saying TDI. I'm sorry, yes.

So the comments that I wanted to make is in relation to also some observations from both, Alan Buckpitt and Sarjeet Gill, where they praise overall the document, but they did have some observations on the findings and your reporting that the -- some genotypic variance for the epoxide hydrolase and show increases susceptibility.

I have to add that is not only on the epoxy hydrolase, and they also talk about the GST and they also talk about the superoxide dismutase. So I went back to the figure -- and by the way, this also connects in with the MDI somehow, but I think they both cover the evidence,

and that is at least publishes more in relation with the TDI.

So I went back to the figure where you show the chemistry, and -- of the TDI, and also on all the text that you wrote about the metabolism, and I couldn't really figure out and how is that antioxidant genes that are being involved, that somehow altered the toxicity of the TDI and could connect with it.

So in other words, and -- is there oxidative stress like a component of the toxicity or it is somehow involved in the metabolism or catabolism of the -- in TDI?

So it's not apparent. The chemistry doesn't show it. So I started doing some literature researches, and to see what could be these connections between the TDI and the epoxy hydrolase?

And it turns out that there is a paper, and I'm going to give you the reference later, but it's a paper by Kim et al. from 2010, K-i-m, that -- where they noticed that patients that had been exposed to TDI had decreased levels of ferritin. Later on, they also showed on the same paper that there was decreased levels of transferrin in the blood.

They ended in some cell culture, where they exposed the epithelial cells into these compounds. And it turns out that they demonstrated the same. The TDI

resulted in decreased expression of the ferritin. And specifically, the ferritin light chain. The ferritin has two chains, the light chain and the heavy chain. And the light chain was increased. And I don't know if also in the cell culture they also noticed this with the transferrin.

So they hypothesized that maybe this was in relation to a transcription factor which is an NrF2. They mentioned an expression of some antioxidant genes that related by NrF2, such as heme oxygenase-1, where they've done quite a bit of work, and it was decreased. But it also decreased the levels of cellular level antioxidant genes.

In general, when you have oxidative stress, there is a regulation of the antioxidant. So NrF2 is actually translocated to the nucleus, and it eats the expression of the heme oxygenase-1 and these other antioxidant genes. But in this case, the TDI leads to the opposite. It is to decrease expression of that.

So they continue, and in the same paper they show that there is some phosphorylation changes of the MAP kinase that regulate on the activation of NrF2, and they stop there.

So it seems that somehow this compound leads to some changes, some intercellular signal changes that leads

to a decreased translocation of NrF2 from the cytoplasm to the nucleus and to a decreased expression of the antioxidant genes. And all this can result in increased oxidative trees.

So it may be that the increased oxidative stress is not due to the chemistry of the compound, but due to some regulatory changes or these regulatory changes on the antioxidant genes.

So then I went to another paper that you didn't reference in your document and -- which is by Brown. And they talk about biomarkers of this compound. And they mention about biomarkers of oxidative stresses. Unfortunately, I haven't had access to the full document, so I only saw the abstract and the abstract this is just as much as they say, so I don't know what other biomarkers that they are relating.

If this is the case, so the group of people that could be potentially susceptible for these compounds is bigger, or maybe it could be again in relation to all people that have some susceptibility to handling of the ROS and oxidative stress.

And last point, they could be -- you had some questions about whether why are you increasing -- or why are you taking into consideration increases in activity for the children, if the children has more of a Th2-driven

process, while the TDI induced in asthma is more like a Th1.

Well, it turns out that the oxidative stress that is involved in the triggering or enhancing of asthma is a Th2 process, which is what is most prevalent in the children. So here you -- I think that you explain it -- you address it very well in your document. You gave enough reasons why their comment was not really that appropriate, and -- but this is an additional argument, where -- and in addition to, I think that at the end this is not really just a pure Th1 or Th2, it's probably mixed, and you have components of both.

CHAIRPERSON KLEINMAN: Are there other comments before we move on to MDI?

PANEL MEMBER RITZ: I'd just like to emphasize that, yes, if there is a lot of oxidative stress, then we need to also look at neurotoxicity, especially since we're saying that there are some possible acute affects that are being noticed by workers, right?

And I saw that there was a 2014 paper by Hughes that questions neurotoxicity in diisocyanates. So I think for the future we should probably look out for that.

CHAIRPERSON KLEINMAN: Okay. So shall we go on with the MDI now, please?

--o0o--

DR. DODGE: Okay. Methylene diphenyl diisocyanate I'll refer to as MDI.

Here, we're discussing two forms of the compound, MDI and polymeric MDI, or I'll refer to as PMDI. These are both used mainly in rigid polyurethane foams.

Now, the ones that are worked with mostly in developing polyurethane foams is PMDI. What this is is a 50 -- generally, about a 50 percent mixture of monomeric MDI and pre-polymers of MDI, mostly the trimer. Then you'll have a couple -- you know, small percentages of the higher oligomers.

MDI has replaced TDI in a number of processes, in particular, because it has a lower vapor pressure, so it's thought that workers will be exposed less by the inhalation route using this compound. So exposure is going to occur primarily during spraying applications or heating.

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DR. DODGE: The toxicity of MDI is qualitatively similar to TDI. You see acute irritation of lungs, upper respiratory tract. Symptoms, headaches, sore throat, cough, chest tightness. In animal studies, you see respiratory epithelial damage and pulmonary edema. If exposures are high enough, you see reactive airways dysfunction in humans, occupational workers.

With chronic exposure, like TDI, you can become sensitized. Like TDI, you have occupational asthma following a latency period. With MDI you see hypersensitive pneumonitis. Though this is fairly rare, it occurs more often than TDI. And some have theorized that the reason this is more common in MDI is because it is more lipophilic than TDI, and generally MDI is found partially as a vapor, partially as an aerosol. And the aerosol form can find its way deeper into the lung, into the pulmonary region.

--o0o--

DR. DODGE: Next slide, so we're on slide 27 now. This is the -- start the derivation here of the acute REL. There wasn't human studies available that could really -- we could use to determine acute RELs, so we're basing it on a rodent study. Quite a bit of work has been done by Pauluhn. And this is what we base our acute REL on, a study in rats, where the critical effect is an increase in total protein an bronchoalveolar lavage fluid.

The exposures were 6 hours. Increased protein was found in the lung lavage fluid at 3 hours post-exposure. Often peaked at 1 day post-exposure, and decreased dramatically by 3 and 7 days post-exposure.

In this study, there was no NOAEL. The lowest concentration used, 0.7 milligrams per cubic meter, was a

LOAEL. We attempted to do some benchmark dose or benchmark concentration modeling with this data using continuous models supplied by U.S. EPA. Could not get a good line or acceptable line fit to the data. It's -- these continuous models generally are pretty finicky, so we had to rely on a NOAEL/LOAEL approach.

--o0o--

DR. DODGE: Onto the next slide. So our point of departure is 0.7 milligrams per cubic meter. We applied a 6-hour to 1-hour time adjustment, because the acute REL is based on a 1-hour exposure. We used Haber's Law where CN times T equals K, where N is one. And this is based on another study by Pauluhn in which he found concentration in time are equally important in the effects that are found in the lung -- in the rodent model he used.

We then applied a human equivalency concentration adjustment. This is a U.S. EPA HEC formula for short. And the -- we multiplied the HEC, which is 1.2 -- 1.7 times the time-adjusted point of departure.

Now, the way this HEC -- or concentration adjustment is done, it's the RGDR, the regional gas distribution or deposition ratio. This is the minute volume in the animal over the surface area of the animal. This is the pulmonary region specifically, and this is divided by the minute volume in human divided by the

pulmonary surface area. This resulting ratio is 1.7.

I also did the RDDR, which is the regional deposited dose ratio. This is with the assumption that it could be an aerosol. It basically came out to the same ratio, because the aerosol particles generated -- apparently it doesn't have -- it isn't a factor -- or it doesn't result in a different ratio with animal and human.

--o0o--

DR. DODGE: On to the next slide, the uncertainty factors applied. A LOAEL to NOAEL uncertainty factor of root 10 is used. This is because the effect is a mild effect. Pauluhn found that the most sensitive indicator of changes in the lung was the change or increase in total protein in lavage fluid.

He found lactate dehydrogenase levels, LDH levels, increase at roughly a 30-fold or greater concentrations. And usually this is an indication of cell injury or cell lysis. So we decided to use a root 10 for this particular uncertainty factor.

Interspecies uncertainty factors. A toxicokinetic value of 2 is used. This is for any residual -- it's a default factor that we used for any residual differences in the toxicokinetic result from the HEC approach that we just talked about, or it counts for that.

The toxicodynamic is a root 10. And this is another default that we use when we don't have any information to inform us on the differences between animal and humans regarding the toxicodynamic interspecies.

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DR. DODGE: Next slide, number 30. Our total intraspecies uncertainty factor is 30. And the breakdown is toxicokinetic UF of root 10. This is because the relative pulmonary minute volume to surface area ratio is 3-fold greater in infants compared to adults.

The toxicodynamic is a full 10 to address the toxicodynamic diversity in human population including sensitive populations.

The resulting cumulative uncertainty factor is 600. So we take the adjusted point of departure of 7.2 milligrams per cubic meter and divide it by 600, and we get a proposed acute REL of 12 micrograms per cubic meter.

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DR. DODGE: Now I'd like to discuss the 8-hour REL derivation. This is based on a study in polymeric MDI. It's a 2-year rodent study. The critical effect is increased incidence of bronchiolo-alveolar hyperplasia, and to a lesser extent pulmonary fibrosis. The study I used was from Feron et al. which was a reexamination of the original material from Reuzel et al.

The reason Feron looked at it again is because he had access to the histopath slides of two chronic studies that were done with MDI or PMDI. Okay. This one was PMDI. The other one he looked at was animals were exposed exclusively to MDI.

So he had pathologists -- the same pathologists looked at both sets of slides, so he could get a more consistent finding across the two studies. This study, the exposure was 6 hours per day 5 days per week, which is pretty close to what we're looking at for an 8-hour REL. So this is why we used it for this -- for the 8-hour REL.

The other study -- the other chronic study was 18 hours per day 5 days per week. And we thought what was more appropriate for a chronic REL, which is -- it was closer to a continuous type exposure. So based on this particular study, we have the data down here for hyperplasia. The NOAEL was the lowest dose of 0.19 milligrams per cubic meter, and the LOAEL was the next highest.

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DR. DODGE: Go onto the next slide. We did a benchmark concentration approach to find our point of departure rather than rely on a NOAEL/LOAEL approach. Our point of departure is the BMCL05, which is 0.118 milligrams per cubic meter. The multi-stage model was the

best of a number of models, in terms of fitting a line to the data. And this is shown below in the same -- in the same slide here.

The BMCL05 is the 95th percent -- 95th lower confidence limit on the five percent response rate for this particular endpoint.

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DR. DODGE: So our point of departure is 0.118. We do a time adjustment of 6 hours over 24 hours, times 5 days over 7 days, times 20 over 10 cubic meters. So the 6 over 24, 5 over 7 gets us to a continuous type exposure. Then we adjust it by 20 over 10. Again, this is using the common assumption that a worker during his 8 hours of work will breathe half the air -- half the total air he'll breathe in a day -- in a full day. So that's 10 cubic meters.

We applied -- I applied a HEC adjustment. In this case, it was an RDDR, which is a regional deposited dose ratio, because PMDI is primarily an aerosol. It turned out it didn't really matter, because whether I did an RGDR or RDDR it was approximately the same value, because the aerosol droplets were of a size that it -- it seemed to, you know, mimic in a vapor, or at least deposit in the same region using the U.S. EPA HEC model.

Anyway, the HEC value was 2.26, and I multiplied

this by the time-adjusted point of departure to get a 0.01 -- 0.0951 milligrams per cubic meter.

The uncertainty factors applied. Toxicokinetic, again, is a 2 and the toxicodynamic is a root 10, essentially for the same reasons that these same uncertainty factors were applied in the acute REL.

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DR. DODGE: Going on to the next slide. The intraspecies toxicokinetic and toxicodynamic uncertainty factors are 10 each. Again, this is for the same reason as the TDI 8-hour and chronic RELs. The 10 is for the toxico genomic variation. That's for the TK and for the TD, or toxicodynamic. The 10 is for individual variation sensitizing potential and increased sensitivity in asthmatic children, as well as toxicogenomic variation.

The cumulative uncertainty factor is 600. So when the adjusted point of departure is divided by 600, the result is a REL of -- or proposed REL of 0.16 micrograms per cubic meter.

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DR. DODGE: Next slide talk about the chronic REL derivation now. This was a study in MDI. And this is the other study that Feron on looked at sid by side with the other chronic study that we just -- that I just discussed. In this particular study, the exposure for 18 hours per

day, five days per week, closer to what we would like to see for sort of a chronic REL development or continuous type 24-hour per day exposure.

The critical effect here though is increased incidence in severity of interstitial fibrosis. This was seen at the lowest dose of 0.23 milligrams per cubic meter. And if you look at the data set below, the response at the lowest dose was quite high, in terms of incidence compared to the control.

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DR. DODGE: Next slide. We were able to use a benchmark concentration. We were able to fit a line to the data, even though there is a large difference between the zero and the low dose. We had -- we used a BMCL10 in this case, because the data was not sensitive enough to find the BMCL05, or a 5 percent response rate. So our point of departure here is the 95th lower confidence limit on the 10 percent response rate for interstitial fibrosis.

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DR. DODGE: Next slide. The time adjustment for the BMCL10, being used as the point of departure, was 18 over 24 hours times 5 days over 7 days.

Now, for this chemical, this particular study, it was found that the generated form of this MDI was partially in a gaseous formal and partially in a aerosol

form, or that's what the animals were exposed to, at least at the lower doses.

So I split the difference here, and I assume that half was gas, half was aerosol. So that's how I estimated the HEC here, which was 3.41.

The interspecies uncertainty factors, just like for the 8-hour REL was 2 and root 10. These are defaults.

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DR. DODGE: And again, the intraspecies toxicokinetic and toxicodynamic uncertainty factors are 10 each. The resulting cumulative uncertainty factor is 600, which when divided by the adjusted point of departure results in a proposed REL of 0.08 micrograms per cubic meter.

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DR. DODGE: And here is a summary of the proposed RELs, acute is 12, 8-hour is 16, and the chronic is 0.08 micrograms per cubic meter.

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DR. DODGE: Now, if the Chair would like, I could go on with the comments and responses.

CHAIRPERSON KLEINMAN: Well, I'd like to give the Panel a chance to comment. I just want one point of clarification on the acute, and the 8-hour RELs. Those are based on the polymer. Whereas, the --

DR. DODGE: Correct.

CHAIRPERSON KLEINMAN: And then the other is based on MDI directly, is that correct?

DR. DODGE: Correct.

CHAIRPERSON KLEINMAN: Okay. And I just wanted to ask whether the uncertainty factors used for the polymer form were adjusted in any way to account for differences in toxicity or potency of the polymer versus the monomer?

DR. DODGE: Um-hmm. That's another thing Feron looked at in his 2001 study. He actually thought the -- you know, the one is a chronic study that looked at MDI and the other one looking at PDM were remarkably similar considering, you know, that the exposure duration differences and the concentrations used. And remarkably similar in the sense that where these compounds seem to have their major effect in the lung. So he felt okay in making the comparisons he did.

PANEL MEMBER GILL: I have a question in the sense that the uncertainty factors you have, for example, the 8-hour REL is -- and the chronic, you're coming to the same cumulative uncertainty factor of 600. Whereas, there is -- if you look at the effects that are at the lowest -- at the LOAEL level for the chronic study, there are significant effects at the lowest level that you have seen

compared to the 8-hour study.

So my question is how confident are you of the cumulative data taking the uncertainty factors based on the substantial difference, which are the LOAEL levels?

DR. DODGE: Well, first off, I'd like to say that in his comparison Feron thought -- proposed that the reason there seemed to be a greater effect in the study that exposed the rats to 18 hours per day was because the animals just didn't have enough time to recover with that long of an exposure. So he thought that was probably the main reason there seemed to be an increased potency at least with this MDI two-year study. More that than a difference between PMDI and MDI.

Does that make sense?

PANEL MEMBER GILL: Not really. Well, that's an explanation he has.

PANEL MEMBER HAMMOND: Although if that's true, if when you make your time adjustment, you know, in a chronic exposure, there's no time to recover.

DR. DODGE: Yes, that's correct. That's one reason we applied the time adjustment.

PANEL MEMBER HAMMOND: I thought the time adjustment is kind of -- whereas, you're trying to get to the same concentration, time to time duration total. But if there's recovery that's important, then the rate of

exposure is important as well, and it's important to have a place for recovery time.

CHAIRPERSON KLEINMAN: Are there -- let's throw this open to the Panel leads to, you know --

PANEL MEMBER GILL: Let's finish the comments, first.

CHAIRPERSON KLEINMAN: You want to go through the --

PANEL MEMBER GILL: There aren't many.

CHAIRPERSON KLEINMAN: All right. So at that suggestion, let's go ahead with the response to the public comments, and then we'll get our comments in.

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DR. DODGE: Okay. We received comments from the American Chemistry Council.

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DR. DODGE: And comment number 1, page 41 -- or slide 41. His first comment. Genotypic variation in MDI metabolic enzymes is not a relevant consideration for development of RELs for MDI. The formation of glutathione adduct with MDI is not enzyme mediated. Genetic polymorphism is not expected to affect adduct formation.

Our response. Researchers point out that MDI can react directly with GSH, and that GSTs, or glutathione S-transferases, can help facilitate the reaction of GSH

with MDI. GSTs are critical in the protection of cells from reactive oxygen species, which are generated by diisocyanates.

Also, the genomic data indicate that variation in GST enzyme activities are modifiers of susceptibility to diisocyanate-induced asthma.

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DR. DODGE: Next comment. The formation on associations between genes and isocyanate-induced risk are limited and not consistent. And there are contradicting reports in the literature for the importance of N-acetyltransferase reactions.

Our response. Several researchers have observed that genetic variants of antioxidant defense genes for GSTs and NATs are associated with increased susceptibility to diisocyanate-induced asthma. However, there are some contradictions in the literature and we added language noting this.

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DR. DODGE: Next slide. In this comment, MDI causes portal of entry effects and available data have been unable to show that metabolism contributes, in any significant way, to the immune response effects caused by MDI.

And our response here. A number of researchers

believe diisocyanates may react with proteins possibly via GSH conjugates to form protein conjugates. The protein conjugates may be immunogenic, and the formation of hapten complexes may give rise to immunological reactions.

Work by Wisnewski et al. indicates that GSH can act as a shuttle for MDI. Once MDI-GSH is absorbed, MDI-albumin conjugates are generated via GSH mediated transcarbamoylation, which exhibit distinct changes in confirmation and charge.

These MDI-albumin conjugates are specifically recognized by serum IgG of work -- MDI workers with diisocyanate-induced asthma, suggesting one possible pathway for MDI to -- in promoting immune responses.

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DR. DODGE: The next slide. Their comment is even the highest levels of respirable MDI aerosol are a factor of 2,400 below the 4-hour acute LC50 in animals.

And our response is that the adverse effects the RELs are based on are respiratory irritation, inflammation, and/or lesions to respiratory tissue, not lethal concentrations.

Our proposed RELs range from 0.08 to 6 micrograms per cubic meter which is well within the levels generated during workplace operations.

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DR. DODGE: Next comment. Researchers have shown that after removal from further exposure, the majority of individuals with diisocyanate-related asthma show improvement or totally recover. So at the suggestion of the commenter, we added more language than we had in the document about the potential for recovery following sensitization to diisocyanates.

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DR. DODGE: Next comment. OEHHA failed to review the recent publication on neurotoxicity, Hughes et al., 2014, which reviews the Reidy and Bolter study and points out numerous limitations in this paper that links -- for links between neurological effects and MDI exposure.

In response, we had already noted in the MDI REL document that there were limitations in the Reidy and Bolter study. We included a summary of findings by Hugh et al. -- Hughes et al. in the REL document pointing out some additional limitations in the Reidy and Bolter study.

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DR. DODGE: Next comment. For the acute 8-hour and chronic RELs, the use of a 3- or 10-fold interspecies toxicokinetic uncertainty factor for metabolic variability is inappropriate because MDI is a direct acting irritant on lung tissue.

Our response is that if a default interspecies

toxicokinetic UF is applied when there is little or know data on TK interspecies differences, whether or not the chemical is a direct or indirectly acting agent on respiratory epithelial tissue. This is consistent with our default uncertainty factor approach used in deriving RELs.

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DR. DODGE: Next comment. For the acute 8-hour and chronic RELs, an interspecies toxicodynamic uncertainty factor of 10 is not appropriate, because genotypic variations in metabolic enzymes are not relevant to TD -- or to MDI, and because children should be less sensitive, not more sensitive to the sensitizing effects of diisocyanates.

Our response is that a number of gene variants, including glutathione S-transferase enzymes have been reported to be associated with increased sensitivity to the disease in workers, which suggests that diisocyanate-induced asthma represents a complex disease phenotype determined by multiple genes. Mean OR, or odds ratio, values were up to 10.

Also, it is unknown how children will react to MDI exposure early in life, when the immune system is still developing.

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DR. DODGE: And to go on with our response here on the next slide. Further, OEHHA considers asthma to be a disease that disproportionately impacts children. Thus, whether MDI induces asthma or triggers existing asthma in children, we would use a higher toxicodynamic uncertainty factor to protect children as we have for other RELs.

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DR. DODGE: The next comment. The 8-hour REL was derived by OEHHA using a time-adjusted exposure concentration, 10 over 20 cubic meters, calculated in a manner inconsistent with OEHHA guidance and practice. OEHHA is mixing rodent and human exposure approaches in a less than transparent manner to reduce the standard time adjustment factor.

And in our response, our noncancer guidelines show that it is appropriate to use a 20 over 10 conversion factor -- conversion for 8-hour RELs based on a chronic exposure study.

For example, we have used this conversion for acrolein and acetaldehyde 8-hour RELs that are based on rat studies with exposure of 6 hours per day 5 days per week. And as noted in our acetaldehyde REL, the time adjustment for 8-hour REL used is 6 over 24 hours times 20 over 10 cubic meters, rather than a 6 over 8 hour, because we assume that the 8 hours includes the active waking

period when an adult inhales 10 cubic meters of air, i.e. half the daily total intake of 20 cubic meters.

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DR. DODGE: Next slide. For the 8-hour and chronic RELs, OEHHA should transparently indicate that it's selection of a five percent benchmark response, or BMR, is a policy decision that results in a 3-fold lower BMCL than was calculated by U.S. EPA, which used a 10 percent BMR to derive a REL-like value, or RfC, for MDI with the same data set.

And our response is that OEHHA presents our use of the 5 percent benchmark response, or BMR, in our non-cancer guidelines, and cites supporting documentation showing why 5 percent BMR appears to be equivalent to a NOAEL in a well designed and conducted animal study.

A response range of 1 to 5 percent approximates the lower limit of adverse effect detection likely to occur in a human Epi study. And in large laboratory animal studies, the detectable response rate is typically in the 5 to 10 percent range.

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DR. DODGE: And that concludes that part of the presentation.

CHAIRPERSON KLEINMAN: Okay. Thank you. I'd like to throw this over to the leads. We'll start with

Dr. Gill.

PANEL MEMBER GILL: Well, since we had such an extensive discussion earlier, and those are all still relevant here, I'm going to just focus on a few issues actually, because we'll come back to the issues which we were previously discussing.

Now, the first one, just simple things. One, on page three, I think you got the structure of the MDI wrong. If I'm not mistaken, there's no isocyanate groups down there. It should have isocyanate moieties. So on page three.

DR. DODGE: I see the problem. Thanks.

PANEL MEMBER GILL: Okay. You need that -- so okay.

And also, similar to my comments in the earlier part of impurities, I would like to see some section talking about impurities, because I'm still concerned of the diamines, because of the synthesis pathways. And the diamines could be -- since, as I indicated earlier, these are highly reactive isocyanates, so the diamines could be an issue. So you need to know approximate impurities of those particular issues.

And as Blanc pointed out, if there is a sensitization to diamines, which is under his stage -- category 2 type of things, then I think you may want to

look on that particular issue.

The other one I'd like to bring up that I do not see any discussion on particulate sizes that are involved in this. It is -- it would be useful to indicate whether they're all in vapor phase, which they are not. The question is how much -- what size the particulates are because on where the deposition in the lung would be, I think it would change -- if there is any data that's available, I think it is appropriate to bring this into this particular component.

Then there are two other things that are -- which I think would be useful to do is, one, is in the whole document, anyone actually with TDI, I did not mention that. I do not see any discussion on adduct formation, because isocyanates do form adducts in -- a significant amount of adduct formation, and they see some of this as spontaneous.

While this may not be carcinogenic, it may have some epigenetic effects. So I would like to see some discussion, whether there are any of this -- I know there's literature for other isocyanates in the literature on adduct formation, so it may be appropriate to discuss some of that in some form in the document to -- I don't know whether it has adduct implications, but clearly it may have, in the longer term, some consequences.

The other one is in sensitization. In this particular case I think there is some data on skin sensitization, which I did not see much discussion on skin sensitization. Is there?

DR. DODGE: That's correct. The exposures are, you know, emissions from a facility, and the compound doesn't last long out in nature before it breaks down. It seems to me that the exposures are really going to be only inhalation to the community. There's going to be not enough of a buildup on any surfaces that would cause one to think that dermal route, at least outside of worker exposure studies, where they come in contact with it, would be an important route.

PANEL MEMBER GILL: True, but there are -- in terms of the form applicators, okay, not in manufacturing, but in form applicators, you would see some potential exposure through the skin route, which could lead to a sensitization, which could lead then to make those individuals much more sensitive to asthmatic --

DR. DODGE: Right, I see your point, yeah.

PANEL MEMBER GILL: So I'm talking about those who were actually not in a facility, but in terms of those who actually use it. So that exposure of sensitization, it's not there, as far as I can see. And I think it would be useful to, at least discuss as a possible route of

exposure, not necessarily in terms of development of REL, but in terms of the overall document as such.

DR. DODGE: Okay.

PANEL MEMBER GILL: Then I will just -- overall, I am actually -- to me, the studies were appropriate, because you don't have human data. You rely essentially on rodent studies. And I think that is actually appropriate.

And I just would like to also talk about your comments to the reviewers, the outside comments, which I think were -- I will just talk about the first two responses, which is on slides 41 and 42, saying that glutathione is not involved in MDI metabolism is actually probably incorrect. And knowing how isocyanates are metabolized and your response is appropriate.

And definitely based on the data that is in TDI, I do not see why these should not apply also to MDI. The same criteria would hold, because the genotypes are likely. And if you look at Jesús's, then also the response that the T helper cells 2 versus was T helper cells 1 cause allergic response versus non-allergic response, and so therefore children are also susceptible -- are sensitive is also appropriate in this particular case. So I think those comments that you made are -- in response to the outside reviews are actually

valid.

There are a couple of studies which you have missed, and I've actually noted them. I will give it to you. One of them is also I think a more general discussion by Wisnewski recent article I think last year or so, so -- but those are minor issues. That's all I have.

CHAIRPERSON KLEINMAN: Thank you.

Dr. Buckpitt.

PANEL MEMBER BUCKPITT: Okay. I don't have a lot to add to that. I agree with your assessments. I'd be a little tougher on the ACC in terms of their comment with glutathione transferase. It's correct that MDI will react non-enzymatically, but most of those reactions are catalyzed by glutathione transferases, even very reactive things like N-acetyl-para-benzoquinone. Some of that reaction is catalyzed enzymatically. So it's not just the soft electrophiles that --

PANEL MEMBER GILL: It's just the rate increases.

PANEL MEMBER BUCKPITT: It's the rate.

PANEL MEMBER GILL: Rate issue. So you're correct what to do, but --

PANEL MEMBER BUCKPITT: So they are way off base. Just tell them that it's not all non-enzymatic.

As with the TDI, I would make more of an issue of

the conjugation of the glutathione and the use of that as the transport. So you had some in your document. I'd certain put it in my figure, because that may be a significant mechanism for essentially conversion of the MDI, and I think bears on the genetic variance that you talk about later.

And then finally, Table 3. If we look at that, there's no indication of how these data were binned. In other words, what constitutes mild fibrosis? And were those sirius red staining, was it hydroxyproline levels, how were those determined? So you might put that in your -- as a footnote to --

DR. DODGE: Okay. This is in reference to the two chronic studies?

PANEL MEMBER BUCKPITT: Yeah.

DR. DODGE: Okay.

PANEL MEMBER BUCKPITT: So Table 3, and I think Table 4 as well. Just indicate what criteria were used to bin those data. And then I had some minor comments that I'll just simply pass to you.

DR. DODGE: Okay. Thank you.

CHAIRPERSON KLEINMAN: Okay. I understand that Dr. Ritz has to leave in about 15 minutes, so I'd like to give her an opportunity to comment.

PANEL MEMBER RITZ: So for the -- there wasn't

much epidemiology. It was mostly case studies. So I don't have much. But what I also saw in the other document was that Table 9 of this one, where you're referencing all of the odds ratios, it's really not very clear what they represent. Are they interactions, or are they subgroup odds ratios, and also what the genetic model is that they're assuming here. There's probably a little bit of information you could add just to make it easier to read, and also to reword maybe the heading of the table so that it's easier.

DR. DODGE: Okay.

PANEL MEMBER RITZ: Otherwise, I don't think I have anything else in this one. Oh, yes. When you're stating the reference levels, you're often jumping between scales. Just make sure that you always reference the ppm or ppb, as well as the microgram and milligram, because I think for the reader that makes it just much easier.

CHAIRPERSON KLEINMAN: Thank you.

Dr. Anastasio, I think you have to leave earlier as well, so if you'd comment.

PANEL MEMBER ANASTASIO: Sure, I'd be happy to.

One comment was on page 34, you're talking about the gas versus particle partitioning of MDI. And you -- let me go back to that page. You're calculating what fraction of the MDI is in the vapor phase. From this

paragraph, it sounds like you're only considering the vapor phase for the toxicity, but later you actually talk about both the vapor and the particle phase toxicity. So my suggestion is on the paragraph on the top of page 34, indicate that even though you're separating particle from vapor, you're going to consider the toxicity of both later. You're not discounting the particle phase.

DR. DODGE: No, I'm not.

PANEL MEMBER ANASTASIO: Yeah. From the text, initially I thought you were going to only consider the vapor phase. Does that make sense?

DR. DODGE: Right, no, no.

PANEL MEMBER ANASTASIO: So I think if you just clarify that both are toxic and that you're just looking at the partitioning here on the top of 34.

DR. DODGE: Okay.

PANEL MEMBER ANASTASIO: I had two other kind of bigger picture, maybe not so easily definable questions. And both actually were raised by Paul. One is the question of analysis. You know, you talk in the MDI document how certain analytical methods cannot see the polymeric forms of MDI. And I think that's a big issue. I understand Melanie's point that, you know, the toxic compound as defined in the regulation is the MDI monomer, but it does seem a big oversight, if we can't also

include, you know, the amounts of the polymeric form. And then -- so I don't know if there's an answer to that, but I guess I would encourage OEHHA somehow to include other forms of the monomer in the overall concentration that is -- that is part of the REL.

DR. DODGE: I believe we can go after both in our regulation. We'll take another look at that again, but I'm -- that's why I included both.

PANEL MEMBER ANASTASIO: Okay. Yeah, that would be great.

The other point I had was raised initially in the TDI document, how you're saying essentially there's cross-sensitization. Certain individuals can be sensitized with TDI, but then show that sensitivity with another diisocyanate. And so the bigger picture issue I'd like to raise is it would be nice to have some total diisocyanate regulation. Now I know this is not your responsibility, but I'd like to at least raise the issue that, you know, rather than having -- well, sorry, not rather, but in addition to having RELs or individual diisocyanates, it would be great to have some reference level for total diisocyanates.

DR. DODGE: Yeah. Some researchers have attempted to do that, how many NCO groups are there in the total mass.

PANEL MEMBER ANASTASIO: Right.

DR. DODGE: And some -- and especially with HDI, hexamethylene diisocyanate, they -- some researchers have looked at that more carefully. And they found some differences in toxicity, so that may not hold -- that kind of relationship may not hold real well in all cases.

PANEL MEMBER ANASTASIO: Okay.

CHAIRPERSON KLEINMAN: Thank you.

Dr. Araujo.

PANEL MEMBER ARAUJO: Okay. So I have some comments, and where I do agree with Sarjeet in suggestions of -- and do give more consideration to the chemistry and to the formation of the adducts. And that should have been mentioned also in the previous one, and not because we -- and also if you put it in one, I think you should be putting it also in the other.

And let me raise a question here, because several papers show the majority of these effects based on the TDI, and then because we're assuming that the isocyanates or the MDI will have a similar chemistry, so we ended -- so they ended up like assigning papers that were based on a TDI like for the MDI toxicity. Is it something that is appropriate?

And if it is, shouldn't we have a disclaimer where we are making these assumptions or where there is a

paper where it says that the isocyanate chemistry or toxicity is probably common to the various types, such as the MDI, TDI, and the others? Because otherwise, it just look like it's an extrapolation.

One of the comments that it says and that we shouldn't really be involved in the GSTs. Maybe it's because the papers are really referring more to the TDI than the MDI or not.

PANEL MEMBER BUCKPITT: (Shakes head.)

PANEL MEMBER ARAUJO: These are directed to the MDI.

PANEL MEMBER BUCKPITT: There's very good evidence of MDI -- there's very good evidence with MDI. I think there was a 2013 paper in ChemBio Interactions. And those adducts have been well characterized.

PANEL MEMBER ARAUJO: Good. So if the references can be just -- either references can be compound specific for the different documents, it could be better. If they cannot compound specific or in one of the documents we ended up like using references for the other, I think that a disclaimer should be done about the similarity or the extrapolation or the common chemistry. What do you think?

PANEL MEMBER GILL: I think it's best if you keep the specific compound involved, in particular cases, if you can. If you cannot, then I think you must have a

disclaimer because it's -- otherwise it's unfair saying that this chemical chemistry applies to the other. We cannot generalize it. We have to be more specific to a particular compound. And in most cases, it can be done. So I don't think that's a problem.

For most of the data that is presented, as I can see, has been specific to MDI and the other one specific to TDI. Now, that's why, for example, the data which they used in terms of the REL and all that, because it's applicable only to MDI. There's no equivalent data that is -- so you cannot transfer in that case. So I think in most cases, the data is sufficient to --

PANEL MEMBER ARAUJO: So that's good. Especially, if we can do that with the metabolism and the GSTs and the formation of adducts.

I'm finding some difficulties to make a dose distinctions, like let's say with genotypic and variance. And they -- you put a table in the previous document, and with the various studies, where they are cited, right, and you put the references.

You're not saying anything here. And you're just mentioning one sentence, and where you are justifying the genotype in a number of instances including GST, NET, and epoxide hydrolase to justify one of the factors that you're using, but you're not referencing that.

And one of the problems that I see using the references is that I went back to that table. And under those studies, and in particular the main study or one of the studies, you know, it's like -- you're publishing a -- in a Journal of Allergy, it is just difficult. I mean, it's pretty much like a review of studies. The majority of the studies are actually based on the TDI. They talk -- it's -- they mention MDI twice. And when they reference it, they reference -- they reference to isocyanate. So it's not clear to me when they're talking about TDI, when they're talking about MDI, when they could even do an extrapolation.

So it seems to me that you will need to go to the references -- to the original references and reference them properly, and not when you are really referring to the TDI and when you're referring to the MDI, or, if -- again, if an extrapolation is made, you should say it.

And I would say also that in addition of in adding the comments on the adduct formation and importance of the GST metabolism, so these could be an opportunity in the previous case of including the comments about inter-cellular signaling, Rf2, HO1, antioxidant genes and oxidative stress, I don't know, and I haven't found, similar references with MDI.

However, some of the comments in there I think

they are probably an extrapolation like from the TDI. And if it is extrapolations, it could be likely that oxidative stress could be used, but I haven't seen any reference that supports that.

And what else?

Oh, okay. And please instruct me on this. I just couldn't -- so you showed us two studies, so the Hoymann et al. from 1988 and the Feron et al. from 2001, as your leading studies for the -- as base for the chronic RELs.

When I look at the data that you show in the document for the Hoffman et al., I was impressed by the incidence of some of the findings, like interstitial fibrosis in just the controls when the exposure is 0, and the differences in between the two different studies. The reason why you're choosing a LOAEL of 0.23 is because Hoymann uses 0.23 and he finds toxicity at that concentration.

However, if you look at the controls again, it is very high. Unfortunately, I don't have access to that study. It is in a proceedings book or something like that, so I couldn't really have access to the document of the study of Hoymann et al. to see what is the control group made of.

If the control group is just -- this is not the

work -- this is not a model of pulmonary fibrosis, were you expecting already to see some degree of pulmonary fibrosis on top of which you are evaluating the effect of the MDI, this makes me think that this is particularly high. So I don't know what was going on in that study, and I wonder whether we're really -- whether we're just -- they ended up, like I was saying, an unusually increased level of toxicity that it could have been seen if the study did really -- didn't show some increased sensitivity.

I don't know if I'm explaining myself well. Let's go to Table 6, for example, okay? Look at the Reuzel 8-hour study. The interstitial fibrosis at exposure consideration 0, which is a control, is 2 out of 59 animals. So that's pretty low. The interstitial fibrosis is the control -- controls of the Hoymann is 10 out of 80.

So, in general, animals don't really get interstitial fibrosis with short exposures of just receiving nothing, right? So I think that you want to say something, Alan. Please do.

PANEL MEMBER BUCKPITT: That may be the assay used to detect fibrosis. So if it's a sirius red staining, you may see that on the controls where you really don't have a fibrotic lesion. So I think it's

important again that you look at what the criteria were for saying that you had a fibrotic lesion in those lungs. But I agree, those numbers are quite high in the controls.

PANEL MEMBER ARAUJO: So they could be misquoting that.

PANEL MEMBER BUCKPITT: Exactly.

PANEL MEMBER ARAUJO: And if they're misquoting that in the controls, they could be misquoting that also in the -- in the others.

PANEL MEMBER BUCKPITT: (Nods head.)

PANEL MEMBER ARAUJO: So how reliable could that study be?

PANEL MEMBER BUCKPITT: Again, that's why you have to go back and see what the criteria were.

PANEL MEMBER ARAUJO: Why did you choose that study?

DR. DODGE: The Hoymann study?

PANEL MEMBER ARAUJO: (Nods head.)

DR. DODGE: Because it was 18 hours per day exposure, which is closer to what we're looking at for a continuous type exposure with the chronic REL.

PANEL MEMBER ARAUJO: Did you -- I assume that you really went through the paper, because you extracted all the data and tabulated and all that. And should you revise or go back again and see how trustable it could be

or maybe like -- I don't know if you get some advice of some specialist in the area. By no means, am I, you know, a pulmonary pathologist, but if this is not a reliable study and it shows just an unusually high of something that it shouldn't have happened, I don't think we should be using that study for regulations.

DR. DODGE: I can go back and look. I don't recall exactly what Feron said about it when he looked at those slides, you know, alongside the other Reuzel slides.

PANEL MEMBER ARAUJO: So just make sure that you have somebody who really is knowledgeable in this, and attests that this is a solid study that can be used for this purpose. Otherwise, I think that is is --

DR. DODGE: I'll have to take a look. I assume that he thought they were justifiable to use, you know, to make comparisons when he did his 2001 study. Again, I don't recall what he says.

PANEL MEMBER ARAUJO: Okay.

CHAIRPERSON KLEINMAN: I think when you look at Table 6 there is a little bit of comfort in the fact that there is, with increasing dose, also an increasing degree of severity of the lesions. So even if they have a high baseline for whatever assay they were using, there is a real dose response relationship here. So there is some comfort to that.

Jesús, do you have any other comments?

PANEL MEMBER ARAUJO: No. Yeah, that's it. Thanks.

CHAIRPERSON KLEINMAN: Okay. I'd like to give our colleagues on the phone a chance. Are you there?

PANEL MEMBER GLANTZ: Yes. Hello.

PANEL MEMBER HAMMOND: Sorry, we were muted.

CHAIRPERSON KLEINMAN: Thank you.

PANEL MEMBER HAMMOND: What was the question? What do we have to say?

I just have a few comments. I notice that the document says that the MDI emissions from facilities declined 80 percent from whatever it was, 2008 to 2010. Were some factories shut down or something, do we know? How does that estimate change, just curious?

DR. DODGE: Which page are you referring to?

PANEL MEMBER HAMMOND: I'm on page four just above metabolism, the sentence just before that. And in two years it looks like it declined 80 percent. I was just curious why, how?

DR. DODGE: Yeah, that is a good point. That I'll have to correct because of recent information we got --

PANEL MEMBER HAMMOND: Oh, okay.

DR. DODGE: -- which suggests that not all

facilities are being -- have to report their emissions every year. In fact, like every --

PANEL MEMBER HAMMOND: Oh, okay. Yeah, so maybe we should get that a little clearer.

DR. DODGE: Yeah, I'm glad you pointed that out. That does need to be fixed.

PANEL MEMBER HAMMOND: And if -- I think there should be something about what measurements have been made in the community. And if there are none, it needs to be said.

DR. DODGE: Okay.

PANEL MEMBER GLANTZ: Well, this is Stan. Again, this is not the stuff I usually have a lot to say about, so I've enjoyed listening to the conversation.

I guess the one thing I would just put in the record on both this one and the first report is that subject to the issues that Paul Blanc raised that you're going to explore further, I think that the application of the uncertainty factors was certainly consistent with the policies that we've developed over the years, and that's something I do know about.

And so I think that the way that OEHHA handled the criticism of the use of the uncertainty factors was appropriate.

Again, I think if on further investigation the

issues that Paul raised lead you to be able to move beyond the defaults, then obviously you should do that. So that's all I have to contribute.

Paul had to leave for a few minutes, so he's not here. So that's everyone at UCSF.

CHAIRPERSON KLEINMAN: Very good. So we have some very specific comments. And what I'd like to ask the Panel members to do is for things like changes to the text or additional references to put those in writing and get those back to OEHHA within the next week or so, so that they can take those into account in their revision of the document.

And if you have -- you know, if there are no other specific changes that we want to discuss here at the meeting, you know, I think we have basically had a very good discussion of, you know, some of the issues raised here. And I think there are some overarching issues that really could be considered perhaps in the next version of the reference documents -- not the reference, but the guidelines, how to deal specifically with sensitizing agents, and perhaps a little bit more information on some of the issues.

You do mention thermal degradation with respect to MDI, but none of that was in the TDI document. And I think it does represent some source of exposure, both to

workers and to the general public. So I think at least making that comment or putting it out there could be helpful.

DR. DODGE: Okay. So, Dr. Kleinman, I'll be relying strongly on the transcripts that come. If the Panel members want to send me additional information that maybe wasn't covered as well or they want additional -- something else for me to work on, you can probably have them send me something, but otherwise I'll be concentrating on the transcripts and what was said today to answer questions.

CHAIRPERSON KLEINMAN: Right, but Dr. Gill had mentioned he had some references, and I think --

DR. DODGE: Correct, yes.

CHAIRPERSON KLEINMAN: -- Jesús also had. So those are the sorts of things that I think would be helpful for you.

All right. Well, the State law asks OEHHA to seek our advice and recommended changes, and I believe we've satisfied that obligation. So I think we can successfully say we've considered this, and we've -- you now have some information to work with.

I believe that we have some information now on what are some of the next items that will be coming down the pike for the Panel to be reviewing. So we'll have a

2015 update. So I wasn't -- are you going to --

DR. BUDROE: Yes, Dr. Kleinman. I certainly will. The four documents that we expect to bring before the Panel in 2015 will be of -- the first one will be carbonyl sulfide acute 8-hour and chronic REL document. The second one will be ethylene glycol monobutyl ether, and that will be a REL document. There will be a REL document for toluene. And then finally, there will be a cancer potency factor document for tert-butyl acetate.

And I've been reminded that we will be bringing this document back before the Panel.

CHAIRPERSON KLEINMAN: Very good. I don't believe we've got a date set for the next meeting. I guess that will be decided on later.

So I wanted to give the Panel an opportunity if there are other matters that should be brought up at the moment?

We do have an opportunity to discuss either administrative issues or anything else related to our documents?

PANEL MEMBER BLANC: This is Paul Blanc here.

Just in terms of prioritization, which has been something we've talked on and off about for years, where do we stand on that? There's been various attempts to prioritize, particularly problem-ridden toxic substances.

And I know that there are some other efforts at the CalEPA level at least to develop priority lists. And are we synchronized in that way?

DR. MARTY: Hi, Paul. This is Melanie. So at one point several years ago, the ARB was working on a methodology to prioritize chemicals as candidate toxic air contaminants. They dropped that project, and it's, as far as I know, on the back-burner somewhere. So I can't really tell you what's going on with that. That's really a question for the Air Board.

So okay that would be for chemicals that are not yet toxic air contaminants. So that's one area of prioritization that the Panel, at one point, had been involved in, and that program -- or that process isn't moving anywhere.

Then another thing that we have been doing is through this process of trying to get more reference exposure levels to apply for risk assessment and more cancer slope factors, so there's a couple of things that happened. We communicate with the air districts do they have a facility that's emitting something that they need either a reference exposure level for to deal with it or a slope factor to estimate risk?

So that's one thing that we do routinely. We work with the Air Board also asking the same questions.

So there are -- there's a long list of chemicals listed under the Hot Spots Program that have no numbers, so they are not dealt with in risk assessment.

PANEL MEMBER BLANC: And is there a point at which you'd want some structured input from the SRP in terms of what our take might be if we had our druthers on prioritization among those?

DR. MARTY: Well, we haven't talked about looking at that. So that's something that the, you know, Panel can discuss and we'll discuss with ARB and the districts. If we want to figure out a way to, you know, have some special meeting on that and how would you approach that, and -- so that is something that could happen.

PANEL MEMBER GLANTZ: Yeah. Well, this is Stan. I mean as one of the people who's pushed the prioritization question on and off forever, I think it would be good to put that on the agenda for the next meeting to sort of review what the prioritization is. I mean, the previous times this has come up the discussions did lead to some changes in prioritization. And because preparing these documents takes so long and takes so much resources, I think, you know, having some input to make sure that the most important things are being addressed first would be a good idea.

So I think, you know, we should just -- whenever

we have the next meeting, hopefully to finish off these two RELs we talked about today, to have that be something that's on the agenda and where we get something to look at in advance of the meeting would be a good idea.

DR. MARTY: Okay. And Stan, you just reminded me of another piece that the Panel looked at, and that was when we -- it was 2001, we prioritized the toxic air contaminants under the SB 25 process.

PANEL MEMBER GLANTZ: Right.

DR. MARTY: And so I think you were actually the lead on that document, so we --

PANEL MEMBER GLANTZ: Yeah, I was. And, you know, if there's a need, that's one of the things I kind of ended up leading a lot of. And if you need any input, I'm happy to -- you know, in terms of getting ready for the Panel, I'm happy to work with you guys on that.

DR. MARTY: Okay. Sounds good.

PANEL MEMBER GLANTZ: But as you recall, I mean, every time we've done this, the priorities did get shifted around some. So again, because there is such a lot of work that goes into these things, we want to make sure that the most important things are being looked at first.

DR. MARTY: Okay. So I think an easy thing would be to say what we've prioritized for the last decade or so and how and what the input was. And then --

PANEL MEMBER GLANTZ: Yeah, and also to look at what's on the list --

DR. MARTY: Right.

PANEL MEMBER GLANTZ: -- you know, to -- and take a look at that, and, you know, see if we have any suggestions for shuffling things around on that.

PANEL MEMBER BLANC: And then similarly -- Melanie, this wouldn't be for you, but for the -- for Peter and the Panel, is I'd like to have somebody come back to us from the Pesticide group and tell us what their planning on bringing to us, because there's been radio silence from the Department of Pesticide Regulation for several years.

So I think that would be something our Chair would need to work with staff to -- but not with OEHHA, because it's not OEHHA's -- it would be only indirectly OEHHA.

CHAIRPERSON KLEINMAN: This is Mike --

PANEL MEMBER BLANC: OEHHA, you don't have anything that's in development from the Pesticide people that you're commenting on currently, do you?

DR. MARTY: Sorry. Not currently under the TAC Program. We have documents we comment on, but they're not related -- they're pesticides that are not undergoing review as TACs. So we have not seen a TAC document from

the DPR in awhile.

PANEL MEMBER BLANC: Yeah. So I think that's always been --

PANEL MEMBER HAMMOND: They need a little prodding.

PANEL MEMBER BLANC: And since John isn't -- John Froines isn't here to say it, so I figure I've got to bring it up.

And then finally, I think in light of our conversation today, you know, it's been a long time since we've had a meeting that was focused on scientific understanding with a regulatory or risk assessment bent to it. And I do think that the challenges that came up today with sensitizers and how they fit into the general paradigm of risk assessments, if we were ever to have a content theme-based session where we brought in outside expertise, I think that would be helpful to the Panel on a -- and I think it would be helpful to OEHHA as well. I know that takes a lot of advanced planning, but I'm not saying we should do that this spring or this summer.

CHAIRPERSON KLEINMAN: Stan, I think that's a great idea organizing a workshop around a specific topic like that could be very beneficial.

On the pesticide issue, I'll work with Jim and Peter and see if we can't get an update on what Pesticide

management is considering for the near future. And --

PANEL MEMBER BLANC: Well, I'd like to move that we adjourn. Paul Blanc here.

CHAIRPERSON KLEINMAN: That was my next word.

PANEL MEMBER BLANC: Is there a second?

PANEL MEMBER BUCKPITT: Second.

(Ayes.)

CHAIRPERSON KLEINMAN: I don't even think we need a vote. I declare us adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 12:53 p.m.)

C E R T I F I C A T E O F R E P O R T E R

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, 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;

That the said proceedings was taken before me, in shorthand writing, and was thereafter transcribed, under my direction, by computer-assisted transcription.

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 17th day of February, 2015.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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