TELECONFERENCE MEETING
STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL
ON TOXIC AIR CONTAMINANTS

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
CONFERENCE ROOM 550, 5TH FLOOR CONFERENCE
1001 I STREET
SACRAMENTO, CALIFORNIA

UNIVERSITY OF CALIFORNIA, BERKELEY
UNIVERSITY HALL, ROOM 757, 7TH FLOOR
ENVIRONMENTAL SCIENCES DIVISION, SCHOOL OF PUBLIC HEALTH
2199 ADDISON STREET
BERKELEY, CALIFORNIA

UNIVERSITY OF CALIFORNIA, DAVIS
DEPARTMENT OF MOLECULAR BIOSCIENCES
ROOM 1001 VM3B, 1ST FLOOR
SCHOOL OF VETERINARY MEDICINE
ONE SHIELDS DRIVE
DAVIS, CALIFORNIA

UNIVERSITY OF CALIFORNIA, IRVINE
DEPARTMENT OF MEDICINE, SUITE 100
100 THEORY
IRVINE, CALIFORNIA

UNIVERSITY OF CALIFORNIA, LOS ANGELES
COEH LIBRARY, ROOM 46-060
FIELDING SCHOOL OF PUBLIC HEALTH
650 CHARLES E. YOUNG DRIVE SOUTH
LOS ANGELES, CALIFORNIA

UNIVERSITY OF CALIFORNIA, RIVERSIDE
BIOLOGICAL SCIENCES, ROOM 3117
EUCALYPTUS DRIVE
RIVERSIDE, CALIFORNIA

THURSDAY, AUGUST 20, 2015
10:12 A.M.

JAMES F. PETERS, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

A P P E A R A N C E S

PANEL MEMBERS:

Michael T. Kleinman, Ph.D., Chairperson(via teleconference)

Cort Anastasio, Ph.D.(via teleconference)

Jesús A. Araujo, M.D., Ph.D.(via teleconference)

Alan R. Buckpitt, Ph.D.(via teleconference)

Sarjeet S. Gill, Ph.D.(via teleconference)

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

Beate R. Ritz, M.D., Ph.D.(via teleconference)

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, Scientific Review Panel

Mr. Peter Mathews, SRP Support Administration

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Melanie Marty, Assistant Deputy Director, Division of Scientific Affairs

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

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

Dr. David Siegel, Chief, Air, Community and Environmental Research Branch

I N D E X

PAGE

1. Review of “Toluene Diisocyanate Reference Exposure Levels” – SRP Draft (May 2015) and “Methylene Diphenyl Diisocyanate Reference Exposure Levels” – SRP Draft (May 2015)

From its previous meeting in February 2015, the Panel will continue reviewing the proposed reference exposure levels (RELs) for toluene diisocyanate (TDI) and methylene diphenyl diisocyanate (MDI). These two documents summarize the toxicity and the derivation of the proposed acute, 8-hour, and chronic RELs. RELs are airborne concentrations of a chemical that are not anticipated to result in adverse noncancer health effects for specified exposure durations in the general population, including sensitive subpopulations.

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b)(2)). In response to this statutory requirement, OEHHA adopted in 2008 a Technical Support Document that describes the derivation of acute, 8 hour and chronic noncancer RELs. This guideline has been used to develop the RELs for both TDI and MDI. After the Panel’s review the two documents will be finalized and will be added to Appendix D of the Technical Support Document. 3

2. Consideration of administrative matters. 71

Adjournment 73

Reporter's Certificate 74

P R O C E E D I N G S

CHAIRPERSON KLEINMAN: Very good. I'd like to officially call this meeting to order. And we'll get started.

This morning, we have two items that we are going to be reviewing. And those are the draft documents for toluene diisocyanate reference exposure levels, and second is the methylene diphenyl diisocyanate reference exposure levels.

And the lead discussants for those documents were Sarjeet and Alan Buckpitt -- Sarjeet Gill and Alan Buckpitt. I think before we actually go into the -- those topics, we should go around and each member provide their information. As Peter mentioned before, each Panel Member should state their name, their location, and affiliation. And let's start with the people present in Sacramento. Can we go around the table there, please.

DR. DODGE: Okay. Daryn Dodge with OEHHA.

DR. SIEGEL: David Siegel with OEHHA.

DR. BUDROE: John Budroe, OEHHA.

DR. MARTY: Melanie Marty OEHHA.

MS. SAKARW: My name is Yuko Sakarw from DTSC.

MS. McCarthy: Sherri McCarthy with American Chemistry Council.

MR. WONG: Pat Wong, ARB.

PANEL LIAISON BEHRMANN: Jim Behrmann with ARB.
MR. MATHEWS: Peter Mathews, Air Resources Board.
CHAIRPERSON KLEINMAN: Thank you. And now the Panel Members. Alan Buckpitt are you on?
PANEL MEMBER BUCKPITT: Good morning. Al Buckpitt Vet Med 3B, UC Davis. And this is Cort Anastasio in the same location at UC Davis.
MS. WONG: Ms. Jeanne Wong, DTSC.
CHAIRPERSON KLEINMAN: Okay. Sarjeet.
PANEL MEMBER GILL: Yes. Sarjeet Gill at UC Riverside. Good morning.
CHAIRPERSON KLEINMAN: Morning.
Beate, are you there?
PANEL MEMBER RITZ: Yes. Beate Ritz at UCLA in the COEH Library on the fourth floor of the Fielding School of Public Health.
CHAIRPERSON KLEINMAN: And is Jesús there as well?
PANEL MEMBER ARAUJO: Yes, Jesús Araujo in the same location at UCLA.
CHAIRPERSON KLEINMAN: And Kathy Hammond?
PANEL MEMBER HAMMOND: Kathy Hammond at UC Berkeley. And I'm in room 757, University Hall. And I'm joined with two people. Do you want their names also?
CHAIRPERSON KLEINMAN: Yes.

CAL/EPA DEPUTY SECRETARY SOLOMON: Hi. This is Gina Solomon with CalEPA here in University Hall with Kathy Hammond.

MR. YANG: This is Jianming Yang from OEHHA.

CHAIRPERSON KLEINMAN: Did I miss anybody?

Okay. Hearing none. I'd like to go to the first order of business, and that is our review of the toluene diisocyanate reference exposure level draft document. And, Alan, I believe you were the first lead on that document, so I'll turn this over to you.

PANEL MEMBER BUCKPITT: Did we want to hear from OEHHA? They sent some slides. Did we want to go through those first?

DR. MARTY: Yes, we do.

CHAIRPERSON KLEINMAN: I think that would be a good idea, yeah.

DR. BUDROE: Okay. I'd like to introduce Dr. Daryn Dodge from our Air Toxicology and Risk Assessment Section. My name is John Budroe the Section Chief of the section. And he'll be presenting primarily the revisions to the documents in response to the Scientific Review Panel comments on the document.

DR. DODGE: Okay. This is Daryn Dodge in Sacramento. So I have the slides in front me, and when I go on to the next slide, I'll note that. The slide

numbers are in the bottom right-hand corner.

(Thereupon an overhead presentation was presented as follows.)

DR. DODGE: Okay. What we'll -- that was pretty much slide 1. Let's go on to slide 2.

--o0o--

DR. DODGE: Preceding SRP meeting, which was on February -- in February in 2015, earlier this year. We presented the draft RELs for toluene diisocyanate. Now I'll go over TDI first and then MDI following.

So for TDI, we presented acute, 8-hour, and Chronic RELs. The numbers are shown in the slides. These have not changed since the meeting. The basis of these RELs have not changed as well. The acute REL is based on 10 to 20 parts per billion LOAEL. This was a chamber study, in which non-sensitized asthmatic subjects were exposed to TDI resulting in a few of them having an increase in airway resistance.

The 8-hour and chronic RELs are based on an occupational exposure study, in which there was an accelerated -- accelerated lung function decline measured with -- as FEV1 or forced expiratory volume in one second.

Go on to slide number 3.

--o0o--

MR. MATHEWS: Hello, Mike?

CHAIRPERSON KLEINMAN: Yes.

MR. MATHEWS: Could you ask all the Panel members to put their end on mute unless they're contributing to the meeting, because we're getting echoes coming back through electrically.

CHAIRPERSON KLEINMAN: Okay. I agree with that. So if you're not speaking at the moment, put your phones on mute, or your microphones on mute. And just remember to unmute them when you are going to make a contribution. Thank you.

MR. MATHEWS: Thanks, Mike.

DR. DODGE: Okay. This is Daryn again in Sacramento.

Slide number 3, TDI is used in flexible polyurethane foams, adhesives, and coatings. Global production capacity of TDI exceeds a million tons per year. TDI is volatile with a vapor pressure of 0.023 millimeters mercury at around room temperature.

Now, I did add a few sentences in there from studies in which they measured environmental or occupational levels of vapor versus aerosol form of TDI. And, in general, we're talking about vapor being about 95 percent with the remainder being in aerosol form. TDI, along with other diisocyanates are known as one of the most potent low molecular weight sensitizers.

Okay. Let's go on to slide 4.

--o0o--

DR. DODGE: The main revision to the document, which we spent a lot of time with at the last SRP meeting, I'm just going to state it as a general comment, was basically we needed to -- we were asked to state more clearly what adverse effects we are trying to prevent with these RELs?

So with a number of the following slides, I'll be trying to present the more clearly stated reasons, or how we were trying to prevent these -- the effects with these RELs.

--o0o--

DR. DODGE: Let's go on to Slide 5. Okay. For the acute REL, who are we trying to protect? So we attempted to lay this out more clearly, starting with the acute adverse affects.

Number 1, it's sensory irritation and respiratory inflammation. Number 2, asthmatic episodes in non-sensitized asthmatics. Number 3 is we want to prevent -- or try to protect people from being sensitized and a resulting induction of TDI asthma with infrequent acute exposures. And number 4, we would like to protect individuals from an asthmatic reaction in which they have already been previously been sensitized by some other

source.

Slide number 6, next slide.

--o0o--

DR. DODGE: So I'll be going over these acute adverse effects one by one starting with sensory/pulmonary irritation in normal subjects.

PANEL MEMBER HAMMOND: Excuse me. This is Kathy at Berkeley. Do you want to -- for us to weight for questions or would you like us to ask questions as we go along?

DR. DODGE: This is Daryn in Sacramento. I'm fine if you want to interject a question or a comment.

PANEL MEMBER HAMMOND: Okay. On the who are we protecting question, my understanding, and when I read the document, was that you were specifically not trying to do numbers 3 and 4, because I thought we don't have data enough for number 3. And number 4, the calculations where there were too few people to fit into that category, that the probability of that -- those people being near a hot spot was extremely low. That was how I read the document. Did I misread that?

DR. DODGE: Well, we'll get into that a little later.

PANEL MEMBER HAMMOND: Okay.

DR. DODGE: Those two points.

PANEL MEMBER HAMMOND: All right. I can wait. I can wait.

DR. DODGE: Okay. So I'll return to slide number 6 here. In normal subjects, the evidence shows that, you know, there's an early German study in which a 30-minute exposure to 20 parts per billion was NOAEL, and at 50 parts per billion was a LOAEL. And this was for sensory irritation, mainly eye irritation.

In a later German study, there's some evidence that 20 parts per billion for two hours resulted in similar sensory irritation. And a final study here, exposure to 5 parts per billion for 6 hours followed by 20 parts per billion for 20 minutes. This essentially reflected the occupational 8-hour standard of about 5 parts per billion threshold. Twenty parts per billion being the short-term exposure threshold for occupational exposure.

In this study, there was some borderline effects. A decrease in specific airway conductance, a decrease in a maximal expiratory flow at 25 percent forced vital capacity. There was an increase in bronchoalveolar lavage albumin level, which I found really quite interesting, because in animal studies with TDI an increase in protein level in bronchoalveolar lavage fluid is one of the most sensitive indicators of change. And this is indicative of

a functional impairment at the blood air barrier.

There was also borderline effect of increased bronchial lavage fluid levels of macroglobulin.

--o0o--

DR. DODGE: Slide number 7. So asthmatic episodes in non-sensitized asthmatics. This is what the acute REL is based on. A specific comment from the SRP was to state -- was to more clearly present the data for increased sensitivity of asthmatics compared to normal subjects. Now, this is referring to a series of studies published by Baur and colleagues.

So there's five points. The first two points here on this slide, and the remaining three on the next slide, which we try to lay out why we believe this endpoint can be used as the point of departure for the acute REL.

So number 1, in asthmatics, Baur and colleagues, they found a significant pulmonary function decrement measured as a 100 percent or greater increase in airway resistance. This occurred in 2 of 15 non-sensitized asthmatic subjects exposed. They also exposed a group of normal people without asthma. And there was no change in airway resistance in these normals.

Point number two, there was a measured increase in airway resistance between 50 and 100 percent in 5

additional asthmatic subjects in this study.

Going on to slide number 8.

Point number 3, there's a higher sensitivity of the responding asthmatics relative to other asthmatics in the study to nonspecific challenge with acetylcholine.

Now, what I mean by this, is before the asthmatic subjects were actually exposed in a chamber to TDI, there was an -- there was a measure of how responsive they were to nonspecific challenge with acetylcholine. Three of these 15 asthmatic subjects responded at the lowest level of ACH, which was less than 0.1 milligrams. The others were above this level.

Two of these 3 so-called sensitive nonspecific asthmatics were the ones that responded to TDI with a significant increase in airway resistance.

Point number 4, Baur and colleagues, they had a higher total inhalation dose measured as concentration times time, or exposure duration, used -- compared to most other studies exposing non-sensitized asthmatics to TDI. Now, this is in response to a specific comment at the last meeting in which there was three or so other studies out there, in which they exposed non-sensitized asthmatics to TDI, and they got no response.

Well, this is possibly because Baur and associates exposed their asthmatic subjects to a higher

concentration, and a higher -- for a total exposure duration that was higher than these other studies. And this could be the reason why the other studies saw no response and Baur and colleagues did.

The final point I'd like to make is that subjective symptoms of chest tightness, rhinitis, cough, labored breathing, throat irritation and/or headache was experienced by roughly a third of the asthmatic subjects exposed to TDI. So taking all this together, all this evidence, we believe there is greater sensitivity to TDI and some asthmatic individuals compared to healthy adults, as well as other asthmatic individuals who may not be as sensitive. Thus, we believe this is adequate in which to base the acute REL on.

--o0o--

DR. DODGE: Okay. Going on to slide 9.

Now, evidence for the acute REL protecting against sensitization and induction of TDI in asthma. Now, evidence that infrequent acute exposure at the REL should not result in sensitization is here in four bullet points.

I revised the document fairly extensively to support these points, and I'll just go over each briefly. Occupational exposure on the order of months to years leads to sensitization and occupational asthma. Now, for

the acute REL, we are really only talking about exposures maybe a few times or several times per year. We're not talking about consistent daily exposures.

Second point, there is no evidence that infrequent exposures, as low as the proposed REL, will result in sensitization. The third point here, animal studies indicate that the threshold for pulmonary irritation and sensitization are interrelated. In other words, if you protect the animal from pulmonary irritation, you are likely also protecting the animal from sensitization. So we extend this to human exposure as well.

The final point is that the acute REL is three-fold lower than the NOEL of 0.9 parts per billion used as the point of departure for the 8-hour and chronic RELs. This NOAEL for the occupational exposure is based on an accelerated decrease in pulmonary function, which is likely related to chronic inflammatory lesion or event.

So if we are below this NOAEL with the acute REL, we should be protecting individuals from inflammation as well as sensitization.

Okay. So going on to slide 10.

--o0o--

DR. DODGE: Now, can we protect sensitized individuals with this acute REL? And this is response to

specific comments from the SRP is what is the potential for exposure in individuals already sensitized, and will the acute REL protect these individuals?

So, number 1, OEHHA estimates that roughly 12 to 43 individuals per million may be sensitized to any particular diisocyanate, including TDI. And the basis for this -- basis for this is two studies, one in Quebec, in which there was an estimate made of a number of workers in the diisocyanate industry and how many of those reported being coming down with TDI or diisocyanate asthma.

The other was the estimate of number of individuals or workers in a diisocyanate industry in California or as actually the U.S. as a whole, and estimate that during their working lifetime roughly 5 percent of these workers will become sensitized and come down with diisocyanate asthma.

So it's a rough estimate, but we're talking only 10 to 40 or 12 to 43 individuals per million in a population. So this is presented as kind of a risk estimate.

The other point I wanted to make here in number 2 is that in chamber studies to confirm diisocyanate asthma, they usually start at 5 parts per million. And if they get no response, then they move up step-wise to 10 and 20 parts per billion. Usually, it's 30-minute exposures or

less.

So our RELs are well below 5 parts per billion. However, there are a few studies out there in which individuals -- workers were exposed to 1 part per billion TDI, and resulting in a pulmonary -- decrease in pulmonary function.

Now -- and the lowest measured in the literature was for MDI, in which translated to parts per billion was 0.05 parts per billion resulted in a sensitized worker becoming -- coming down with a decrease in pulmonary function.

--o0o--

DR. DODGE: So going on to the next slide, number 11. So can we protect sensitized individuals?

Well, our conclusion is that the acute REL is lower than the exposures used to test for sensitization. You know, it's 0.3 parts per billion. And the studies -- or the exposures used to test for sensitization usually starts at five parts per billion and move up step-wise. So a lot of -- a lot of workers are not going to respond at the lowest level, but maybe at subsequent levels of 10 and 20, so our RELs are well below this.

Our RELs cannot be designed to protect all hypersensitive individuals. And we state this in our REL guidance. So, you know, obviously, there are some workers

that do respond at very low levels before -- below the acute REL. But, you know, we state up front that we cannot -- these RELs are not designed to protect all hypersensitive individuals.

Bullet point 3 here is that the likelihood of risk of a sensitized individual being exposed to TDI emissions is very low. We're talking perhaps 10 to 40 in a million. So taken together, we feel that the acute REL is acceptable for the purposes of the Hot Spots Program.

Okay. Let's move on to slide 12.

--o0o--

DR. DODGE: The 8-hour and chronic RELs, the adverse effects we want to prevent with these RELs.

Number 1 is the accelerated lung function decrements not related to TDI induced asthma. And this is the basis of the 8-hour and chronic RELs. Number 2, sensitization and induction of TDI asthma. Number 3, can it prevent asthmatic reaction in individuals previously sensitized to TDI?

Okay. Let's go on to slide 13.

--o0o--

DR. DODGE: So the 8-hour and chronic RELs are based on a study by Diem et al. It's a five-year prospective study, one of the best out there. They measured an accelerate lung function decline in 8-hour

time-weighted average. The NOAEL being 0.9 parts per billion, the LOAEL 1.9 parts per billion.

Okay. They also stratified workers by time spent below or above 20 parts per billion. So those workers exposed for a total time of 0.19 months or less to 20 parts per billion or more over the five-year period, they saw no lung function decline.

Those workers that spent over 0.9 -- 0.19 months to 20 parts per billion or more, there was a lung function decline. So this was sort of a way to get at the question of short-term high level exposures. This relationship was not as strong as the time-weighted average, but it was still a -- significant.

Let's -- slide number 14.

--o0o--

DR. DODGE: Now, the presentation of the workers that were sensitized or sensitive was -- in this study was presented in a separate document, a NIOSH report by Weill et al. And there -- and they conclude that -- or it includes a study of the 12 sensitive workers.

Now, I did change the document to note that they are -- they were indicated as being sensitive, not sensitized. This is in response to a comment that came in from the SRP at the first meeting. They're sensitive because they did have a decrease in pulmonary function, or

they reported that they did, when they were -- the workers, when they were exposed to TDI but, they hadn't gone in to be, you know, exposed in a chamber to really assess whether this is true or not.

Weill at al. stratified the jobs by exposure. High exposure jobs were -- had 6.8 parts per billion. That was sort of -- that's a time-weighted average, 8-hour, moderate was 3.2, and low exposure jobs were time-weighted average of 1.6 parts per billion.

So based on these job categories, 10 of these sensitive workers were in the high or moderate exposure groups, or jobs, 2 of the sensitive workers were in low exposure jobs. However, 6 of these 12 workers were exposed to major spills, in which there is high levels of TDI. And it was unclear which particular job these workers were in and what the exposure levels were. So that could have an impact on whether the workers became sensitive or not.

Now, I included in the document some additional information here, in that 6 of these sensitive workers -- 6 of the 12 went on to become part of a larger chamber exposure study to determine if they were actually had TDI induced asthma. Two of these 6 workers were determined to have TDI-induced asthma. And it was inconclusive about the other four.

--o0o--

DR. DODGE: Slide number 15. Okay. The support here for the 8-hour and chronic RELs protecting against sensitization and resulting asthma.

Number 1, the acute, subacute, and subchronic animal studies indicate that there's a threshold for pulmonary irritation/inflammation and sensitization are interrelated, and they fit the C times T model, or the concentration times time or exposure duration model.

So the idea here is that if you protect the animal from pulmonary irritation or inflammation, you also are protecting them against becoming sensitized.

Point number 2. It's known from occupational studies that reducing exposure reduces the prevalence of occupational asthma. So if you can get the exposures low enough in the areas of our 8-hour and chronic RELs, you should be able to prevent occupational asthma.

Now, there is a caveat here. This is point number 3. A recent study, and this was added as a -- as -- in a comment from SRP this particular study, by Gui et al. 2014, the caveat that this study is that it shows a low prevalence of symptoms even in a state-of-the-art facility with very low exposures. So we're talking levels of 0.5 to 5 parts per billion during peak hours, generally well below 5 parts per billion.

So even in this -- in these -- in this paper that called this facility a state-of-the-art, because it's -- it was a new facility for manufacturing TDI or TDI products, they were getting a prevalence of pulmonary symptoms in a few of the workers. However, our RELs are considerably below the 0.5 to 5 parts per billion peak levels that occurred in this facility.

Going on to slide 16.

--o0o--

DR. DODGE: Now our support that the 8-hour and chronic REL is protecting against sensitization in asthma. The specific comment here from the SRP is that uncertainty factors used to derive RELs appear appropriate, but need to more -- be clearly stated to present evidence for the REL derivations. And this was in reference to our toxicogenomic data, in which I had gone over at the previous SRP meeting, in which we applied a 10-fold uncertainty factor for the toxicokinetic, and a 10-fold for the toxicodynamic, based on the toxicogenomic data, resulting in a full 100-fold increase or interspecies uncertainty factor.

Now, I really didn't have anything more to add here in response to this comment, other than that -- this recent study by Gui et al. seems to suggest that even in their -- what they called their state-of-the-art facility

with low TDI exposures, they're still getting some prevalence of pulmonary symptoms in a few workers. And this could possibly be because there's just a wide variation in response in the human population to TDI.

And that in order for us to attempt to predict -- or protect these individuals, we should use the full 100 -- 100-fold uncertainty factor -- interspecies uncertainty factor.

--o0o--

DR. DODGE: Slide number 17 now, can we protect sensitized individuals?

Now, this is essentially the same information I gave for the acute REL. Our estimate -- our -- essentially, our risk estimate that there's only 10 to 40 individuals per million may be sensitized in a population. The levels used to confirm diisocyanate asthma in chambers are generally 5 parts per billion, but can be down to 1. Our lowest -- the lowest published level that resulted in a response was 0.05 parts per billion. This was actually for MDI. Our proposed 8-hour and chronic RELs are well below this level.

--o0o--

DR. DODGE: So slide number 18, can we protect sensitized individuals?

Well, our conclusion is that our RELs in all

likelihood protect sensitized individuals. The RELs are much lower than the levels used to determine diisocyanate asthma. However, we note that the RELs cannot be designed to protect all hypersensitive individuals. Again, this is in our REL guidance.

And the likelihood that a sensitized individual will be exposed to TDI emissions is very low. We're talking 10 to 40 in a million. Thus, we believe the RELs will be -- are acceptable for the purposes of the Hot Spots Program for these particular effects from TDI.

--o0o--

DR. DODGE: Slide 19. These are the other changes to the document in response to comments from the SRP. We added a list of acronyms at the front of the document. We added a study that measured emissions of TDI facility stacks -- from facility stacks, and a non-occupational exposure study resulting in asthma symptoms. And this was due to a comment that came in asking for more information on environmental exposures and emissions to the environment. And if we didn't find any, please state that up front.

So there's actually very little information out there, and I did put that in there. But I did find these two studies and put a short summary of each in there. We added study summaries on thermal degradation of

polyurethane and with the estimated TDI emissions.

We added summaries of mechanistic studies that were recommended for inclusion. We added a summary of a TDI -- a recent TDI challenge study by Raulf-Heimsoth, 2013, that was recommended for inclusion.

--o0o--

DR. DODGE: Slide 20. We added a section on quantitative analysis methods for airborne TDI. We added a summary of a TDI occupational study, by Gui et al. I already mentioned this earlier in another slide that was recommended for inclusion.

We added a summary of a consumer product exposure study, in which emissions and solvent extraction of TDI from polyurethane foam was measured. We added more detail to the study summarized in the toxicogenomic section, and also stated more clearly what specific diisocyanate the workers were exposed to in these toxicogenomic studies.

--o0o--

DR. DODGE: Slide 21. I moved the information on TDI pre-polymers into its own section to more clearly present this information. This new section summarizes the toxicological studies of TDI pre-polymers. Actually, there's very little data on the toxicology to these -- of these TDI pre-polymers, insufficient to determine REL values.

Most exposures are to the TDI monomers, the 2,4 and 2,6 monomers. Thus our hot spots TDI RELs are really specific for only the TDI monomers, and not the pre-polymers at this time.

So that concludes the TDI document changes. I'd like to ask the Chairman, at this time, if we should have comments or if I should go on to the methylene diphenyl diisocyanate document?

CHAIRPERSON KLEINMAN: I think it would be good to give people a chance to comment on the changes that you've made. And let's -- I'd like -- yeah, let's let Alan and Sarjeet sort of lead the discussion on that. And so I'll leave -- yeah, are there additional comments or -- you know, relevant to the presentation or the changes in the document?

PANEL MEMBER BUCKPITT: I did review the revised document. As you know, I felt like the first document was very well put together, but the RELs were well justified. I had asked for some additions to the document in terms of mechanisms, some additional references to be added, and that was done and done well.

I think the section on the report pertaining to release was strengthened again by further additions to the new literature. I've had a few minor grammatical things that I'll send to you later. But otherwise, I thought the

document really was quite well done. I think it was well done to begin with, but I think the changes that were made added to the clarity. And I certainly agree with all of the essentially RELs that were set and the justifications for those in the document.

I had some additional comments related to the PFA and the ACC panels, but we can wait on those, if you'd like.

CHAIRPERSON KLEINMAN: Sarjeet, do you have any additional comments?

PANEL MEMBER GILL: Yeah. Actually, I turned off for a while and I'm back on the phone.

I had actually very limited comment on this section. But I have to say overall the revisions that were done were much clearer and clearly contributed -- it makes the document much easier to read.

I think the best part, in my opinion, were the explanations that follow each of the REL derivations at the front and I think that is good.

But a couple of points. I think when you introduce data from different literature, there is a tendency to include analysis of the papers in your summary. And I would -- an example I'll give is -- and I'm referring to -- actually page 11 of the revised document where the revisions are actually -- so I have to

find which one, because I was reading the document which had the revisions in it with the underlines. And it's on page 11.

And basically, for example, if you read, for example, that -- this paragraph is, "Cell culture of A549 cells...", and you on and write a sentence. And you -- then you conclude this study suggests TDI down regulates expression in airway cell epithelial density. I think it's always important to actually use some qualification, in this case, because when people are using cell cultures and then you're referring to airway epithelial, I think going from one to the other is not necessarily a valid judgment to do. So you should change some minor things. And I can send you the information like on a separate basis. Okay. That is one.

And then the next one also the same thing is, for example, when you talk about protein kinase NF2 signaling, then you conclude at the end phrase, which you suggest which may contribute to the development of airway inflammation TDI-induced asthma. I think when they're using -- again, they're using a cell line and then using an inflammation in vivo, I think that is a very causal relationship which will be difficult to actually make in some cases.

So be cautious in how you do that. And I'll send

you information on this separately. They're only for minor changes.

I don't have any specific changes, except as Alan has pointed out, it's in response to the reviews from ACC and the PFA regarding some of those comments, and -- when we go into a discussion of that.

That's all I have on this particular case.

CHAIRPERSON KLEINMAN: Thank you.

Kathy, did the subsequent discussion clarify the issues that you were concerned with?

PANEL MEMBER HAMMOND: They helped quite a bit. I still have a little reservation about the protection of sensitized individuals, because I felt the presentation also said, and I agree the same as the document, that the REL -- that sensitized people are too few, and that, you know, that there are so few people, that the likelihood of there being near a hot spot is very low. And that since RELs are specifically not supposed to protect every last person, and it's not the mandate to protect hypersensitized people. I agree that the discussion when the RELs are okay, but I do not think it should be characterized as protecting sensitized people. And I think there is a distinction.

So for instance, I would not want someone who is sensitized to think that the REL was sufficient so that

they could actually move next to a facility -- next to a hot spot. You know, so I just think it's how it's characterized. And now I haven't gone back to -- I don't remember seeing in the document that characterization that it protected sensitized people. And I'd have to go back and reread it for that, but it was just in the slide that I had seen that.

I thought -- I think in the document the statement was just made that the number of sensitized people would be very small, so the probability of their being near a hot spot was infinitesimally small and therefore we don't have to do to it.

So as long as the document doesn't specifically say we're protecting sensitized people, but rather that the public health of the State is sufficiently protected, I would feel okay with that.

Does that make any sense or am I being clear?

DR. DODGE: That makes sense. This is Daryn in Sacramento. Thank you, Kathy.

PANEL MEMBER HAMMOND: Okay. And then this second thing I have is very little. It's just a tiny thing. But there's a reference on page 13 to the OSHA permissible exposure limit of 20 ppb, and it says but no 8-hour time-weighted exposure limits. What's unclear to the reader is that that 20 ppb -- then you say what is

that? It's a ceiling. I looked it up. Okay. So we should say that, you know, that that 20 ppb is a ceiling level, if we're going to reference the OSHA PEL, we have to say it's a ceiling PEL, which is a level that should never be reached, even for a few seconds, kind of thing.So that's what the OSHA PEL is.

DR. DODGE: Okay.

PANEL MEMBER HAMMOND: And actually, you know, what's implicit in that, which is interesting, is the belief by OSHA that this is not a concentration times time, but rather a threshold that just reaching it can cause reaction of -- which kind of goes against some of this presentation. But I think that the OSHA PEL is older. And I, myself, have some skepticism about the concentration times time, but I think -- I think the document is really good. I think you've done a lot of improvements and I want to thank you all for that.

But I would just say that please put the designation of the OSHA PEL as a ceiling.

Other than that, I think -- I'm okay.

CHAIRPERSON KLEINMAN: Yeah. I think that's a very valid point the marking it as a ceiling level. And that shouldn't be a problem to add to the revised document.

Daryn, does that make sense to you?

DR. DODGE: Yeah. This is Daryn. Yes, it does. Thank you.

CHAIRPERSON KLEINMAN: Beate, do have any comments on this?

PANEL MEMBER RITZ: Yes. I think it's a really well put together document, and I enjoyed reading the worker health studies. They're very clear. And the information I was looking for was there.

But then as an epidemiologist, I love to go to tables and just, you know, kind of get an overview of what's out there from the table. And I struggled a little bit with Table 14. And I think that could be improved, if possible beyond what's there. It's -- so what I'm missing is that in a table in every -- for every study, you mention how many workers there are, because for some you do, for others you don't. And also what the mean age or the age range of those workers were. Because if you're talking about lung function and decline of lung function -- if we're talking about workers in the age range of 20 to 25, that's very different from workers 60 to 65. So I would like to know what kind of worker they actually had and see that in this table.

And I also would like to know what the reference group was, because one of the important studies that is cited here, I think it was the Ott study, had 4 percent of

the people being low exposed or unexposed from -- in an epi sense, you know, that's -- that doesn't give you any power to see anything. So if there's a threshold or even if there is a dose response, your exposure range may be too low or the number of unexposed too low to really see any differences. So it would be important to know how -- you know, what the exposure -- the unexposed group how big that really was.

And finally, there are several mentions in this table where the annual loss is described as not existent, but it's unclear to me whether that was a P value that was not less than 0.05 or whether -- and that might be because the group of workers tested was too small or the FEV change is too small to be estimated with the number of workers, which is likely, or whether that really means there is no effect estimate difference. So if that could be made clear by saying no statistically significant change or something else, I would really like that better. That's pretty much it.

CHAIRPERSON KLEINMAN: Thank you. Daryn, do you have a response?

DR. DODGE: Oh, no, I -- yeah, this is Daryn. Yeah, I can work with that, and I'll -- I can improve the tables as Beate suggests.

CHAIRPERSON KLEINMAN: Okay. Thank you.

Jesús, do you have a comment?

PANEL MEMBER ARAUJO: I agree with the previous comments that this version is very much improved as compared with the previous one. And I don't really have any particular observations.

CHAIRPERSON KLEINMAN: Thank you. I had just a few minor grammatical or typographical type things, which I don't think we have to go into. I did have -- well, I think it's just a -- possibly a typographical error, and I'll point it out in the written comment, but it doesn't change anything in terms of the sense of it.

I think overall the Panel comments, I think, are all quite clear. And I think there should be no problem in incorporating those. Daryn seems to agree with that, so why don't we move on to MDI.

PANEL MEMBER ANASTASIO: Hey, Mike, this is Cort at UC Davis.

CHAIRPERSON KLEINMAN: Oh, I'm sorry, Cort.

PANEL MEMBER ANASTASIO: Yeah, I just have a few comments.

CHAIRPERSON KLEINMAN: Yeah.

PANEL MEMBER ANASTASIO: First, I agree with the other comments that the draft is quite good. I think it's a nice piece of work. I just have a few small comments. I'm going from the version that has track changes. So on

page three, I think the list of acronyms is great. For someone who's not toxicologist, this really helped me, and I would recommend that this be a standard feature of future RELs.

Similarly, I think it would be helpful to have line numbers on the SRP draft. I know when I'm making comments, the small typographic errors and things like that that I sent to Dave, it would be really helpful just to be able to say line whatever and not have to count it out myself. So if you guys could have line items, that would be great.

On page five, the last paragraph, third line down, it says, "The anticipated rapid degradation of emitted TDI in the atmosphere...". That's true. You know, the lifetime is on the order of a day, but I would make it clear that the products could be as toxic as TDI, or at least make some indication that, you know, TDI disappears, but it's unclear what the toxicity in the products are.

For example, in the atmosphere, I think that you'd probably get mostly hydroxylated diisocyanates. And they may be as toxic as the parent compound. So even though it's TDI has disappeared, it doesn't mean the toxicity has disappeared. So I'd make that clear.

And then the last one I had is on page 21. This

is in Table 2, the at the bottom, the Raulf-Heimsoth paper. Under pulmonary sensory findings you have no FEV1 decreased greater than 20 percent and no increase in eosinophils, but that seems to contradict the text on the previous page, where there was a decrease in FEV1 and there was an increase in eosinophils. So just ask you to check those to make sure that it's actually not the opposite of that.

PANEL MEMBER GILL: This is Sarjeet here. I think there are no FEV1 decreases actually should be on the Vandenplas study compared to the other one, is that correct, Daryn?

DR. DODGE: I'm sorry, what was that again?

PANEL MEMBER GILL: The one that Mike was referring, the one referring to the no FEV1 decrease which is greater than critical set, I think that is in the wrong row. It is -- it should be in the one above, the Vandenplas study.

DR. MARTY: We will check.

DR. DODGE: Yeah.

PANEL MEMBER GILL: Check it, because I -- this was when I read two months ago, I highlighted it and moved it to the row above. And check and see whether that should be the other one, because that would rectify the correction that was made just now.

PANEL MEMBER ANASTASIO: This is Cort. I mean that may be true for the Vandenplas study, but it appears that the Raulf-Heimsoth study showed an FEV1 decrease, as well as an increase in eosinophils. So for that particular study, the new study, I would just make sure you character it from that.

DR. DODGE: Yeah. I'm going to have to fix that entry into Table 2 clearly. Yeah. Okay.

PANEL MEMBER ANASTASIO: Yeah, those were my comments. Thank you.

DR. DODGE: All right. Thank you, Cort.

PANEL MEMBER GILL: Mike.

CHAIRPERSON KLEINMAN: Yeah.

PANEL MEMBER GILL: Mike, this is Sarjeet Gill.

CHAIRPERSON KLEINMAN: Yeah.

PANEL MEMBER GILL: I had one other comment which comes also with the NPI study, and that is regarding water vapor -- that water is -- vapor would not destroy the isocyanates. That I think is probably not correct from a chemistry point of view. If you put isocyanates with water probably will definitely be very reactive. So I think that sentences both with TDI and MDI should be changed a bit, because it also contradicts some other statements further -- later in the document.

I have this information more with MDI, but I

think it also shows in TDI. I will refer to it a bit more specifically with MDI, so you can correct that with the TDI document. It's the same thing, because I think it conflicts in both cases.

PANEL MEMBER ANASTASIO: This is Cort at UC Davis. I was reading a few of the papers that were cited in the TDI document. And I thought there was fairly good evidence that TDI does not react depreciably with water vapor. I agree in liquid water, it undergoes hydrolysis, but I think the water vapor reaction might be slow enough that it doesn't matter in the atmosphere, specifically for TDI.

DR. DODGE: Yeah. I think the point that I -- this is Daryn in Sacramento. I think the point I wanted to make with that was that -- and maybe it didn't come out real clear is that other atmospheric processes break down TDI faster than the water vapor in the air. But when TDI is directly injected into liquid water, yeah, there is going to be -- it is going to breakdown. But in terms of atmospheric processes, it's -- atmospheric water doesn't appear to be -- or water vapor doesn't appear to be a real big player in breaking it down.

PANEL MEMBER GILL: Okay. Okay. Well, I think you should maybe put a couple of sentences -- comments then I think it would be a little bit easier, but in any

case, that's fine.

DR. DODGE: Okay.

CHAIRPERSON KLEINMAN: If there are no -- are there any further comments?

If not, why don't we move ahead with the MDI discussion.

DR. MARTY: Mike, this is Melanie. I'm wondering if you guys want to state your approval of the TDI document before we move on to MDI, or do you want to wait? It's your call.

CHAIRPERSON KLEINMAN: We could discuss that now. I think with the comments, you know, provided today, and, you know -- you know, those -- you know, and with the agreement that those are going to be incorporated into the revised document, I'd like to ask the Panel to indicate their approval.

PANEL MEMBER ANASTASIO: Mike, can I interrupt for a second?

CHAIRPERSON KLEINMAN: Yes

PANEL MEMBER ANASTASIO: But I wonder this would be a good time to talk about the PFA and ACC comments before we approve it.

MR. MATHEWS: Can you identify yourself?

PANEL MEMBER ANASTASIO: Sorry. This is Cort at UC Davis. We should have some comments about the

comments.

CHAIRPERSON KLEINMAN: Okay. So on the -- do we want to -- why don't we do that then. Daryn, do you have -- you know, do you want to just summarize the responses to the comments?

DR. DODGE: Well, I can briefly state that these comments came in a little shortly before our -- the scheduled SRP meeting that was canceled. These comments were essentially the same ones that came in during the public review period. So I had -- really, I had already responded to those comments. There was a few new things in there, but relatively few. I mean, that's sort of an overall summary.

PANEL MEMBER BUCKPITT: Mike, this is Al Buckpitt. I went through the comments from both the PFA and the ACC panels to essentially make sure that the report had dealt with those comments, and that the -- just to make sure that the comments didn't have merit. And, in general, I found that the report dealt quite well with the comments.

You know, we could take the first one from the PFA panel, they said that TDI reacts with atmospheric water. Well, really, the papers cited indicated that the reactions were carried out in water, not in a humid atmosphere. And I think the report is indeed clear in

that case.

And I can go through the rest of these things or I could send them to you, but there are no issues that I thought were brought up by either ACC or the PFA panel that I felt were not dealt with adequately in the report. So we can be more specific if you'd like or I can simply send these along for the record. But I did take some time to look at the comments from both panels to make sure that we were on -- that we considered them and were on solid ground.

CHAIRPERSON KLEINMAN: Thank you, Alan.

Cort, does that discussion, you know, satisfy you that we've, you know, dealt with the comments appropriately?

PANEL MEMBER ANASTASIO: Yes. That works for me. You know, a lot of the comments were about uncertainty factors. And I had a difficult time evaluating them. So I certainly trust Alan and Daryn's judgment on those.

CHAIRPERSON KLEINMAN: Okay.

PANEL MEMBER GILL: Mike, this is Sarjeet.

DR. SIEGEL: And we responded to those. This is Dave Siegel. We did respond to all those comments.

PANEL MEMBER ANASTASIO: Yes.

PANEL MEMBER GILL: Mike, this is Sarjeet Gill.

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER GILL: I agree with Alan in the sense that the responses which OEHHA has done to the -- both the ACC and PFA comments is actually appropriate, and I do not see any ill concern in any of the responses as such.

CHAIRPERSON KLEINMAN: Thank you. Yeah, I had looked at them before the last meeting, and my recollection was that I didn't have any issues with the way the comments were responded to, so -- then having said that, I'd like to --

PANEL MEMBER BUCKPITT: Mike, this is Al Buckpitt. Can I jump in for one?

CHAIRPERSON KLEINMAN: Yeah.

PANEL MEMBER BUCKPITT: I'm a slow reader. I'm slow in a lot of things, but we had a comment from ACC on the acute toxicity in children. And the report clearly states that OEHHA was unable to locate any studies demonstrating exposures to children. The chemical similarity of MDI and TDI support the discussion of the January -- I'm sorry, of the Jan et al. study in the TDI report. The ACC raises the issue of symptoms being related to the exposure of xylene. And this is probably a good point maybe worth mentioning in the report.

So that was the only variance that I found that -- and if you look at, there have been studies

showing that some of the solvents including xylene alter peak expiratory flow in children with asthma. And I cite there the Delfino study. And I'll send this along. It's in the Journal of Exposure Analytical Environmental Epidemiology. It's an old paper. So that's the only significant comment that I had. Sorry.

CHAIRPERSON KLEINMAN: Thank you.

Daryn, do you have any response on that?

DR. MARTY: Yeah, this is Melanie. So when we're looking at the section on page 21 in the not strike out, sorry, Acute Toxicity to Infants and Children, we do say that some proportion of the eye and respiratory effects could have been caused by xylene exposure. So we did agree with the ACC that it was a mixed exposure.

PANEL MEMBER BUCKPITT: Right. And I think that's the right thing to do, Melanie. So I'm perfectly satisfied with that.

PANEL MEMBER ARAUJO: This is Jesús Araujo. However, their comment is not only that a portion of the symptoms could have been due to the size and exposure, but they argue that it was mainly due to size and exposure, and not to the isocyanate, so -- and they make a, you know, fairly certain arguments or why is it that they think it is this way.

So what would be your comments? Do you feel

confident that we -- in the way how it is presented is that this is -- the symptoms were mostly due to the isocyanate exposures and maybe a proportion -- a portion of those symptoms were due to the xylene, as opposed to what they're saying, which is exactly the opposite, or try to have like a position that it goes in the middle, where that since this was a mixed exposure, it was difficult to determine what portion of the symptoms were to due one and what portion of the symptoms were due to the other.

DR. MARTY: Well, do you think that our discussion on page 21 is not adequate. You know, the question you're asking is pretty darn hard -- I mean, you can't attribute 60 percent to this, 40 percent to that. So I think what we did was say, okay, we can't really tribute a specific proportion of the response to xylene versus isocyanate.

PANEL MEMBER ARAUJO: What I'm saying is that in the way how it reads is that you presented -- or the impression that it gives to the reader is that most of the symptoms are due to the isocyanate exposure, and then you disclaim at the end, well, but you're not sure whether a portion of these are due to the other.

They presented exactly the opposite. So it's sort of like how do you present it. If you try to -- you try to -- you try to make a case more for that symptom and

then you make your disclosure that you're not sure, or you do exactly the opposite, which is what they're doing, as opposed to just saying up front you just don't know what is due to what. So you're having all these symptoms and it could be for either one.

But in the way how it reads, it really -- it is presented as stated it's most likely due to the -- or at least the impression that I receive. I don't know. If that is not the impression that other Panel members and -- felt, so maybe just, you know, ignore my comment.

DR. SIEGEL: No, we can go back and --

DR. MARTY: So, Jesús, I think what we do say is the authors attributed the effects mostly to MDI. And then we caveat it by saying, the authors assume the symptomatology was due to MDI, even though xylenes are also known to cause acute eye and respiratory symptoms. Thus, some proportion of the eye and respiratory effects could have been caused by the xylene exposure. So, you know, we presented what the author's thought and then we caveat it with the issue of multiple exposures.

DR. DODGE: Yeah. This is Daryn in Sacramento. That is correct.

CHAIRPERSON KLEINMAN: And I think the other point that's important is that in that paragraph it stated that it's unclear if children were more prone to the acute

effects than adults. So the RELs are not necessarily stating that there is acute, you know -- an additional sensitivity for children, which I think is, you know, germane to this point, that, you know, in this particular case you couldn't differentiate all of the effects or assign all the effects to the isocyanate or to xylene or a combination.

DR. MARTY: So, Mike, we do have a section 9.4 where we are indicating we believe that the isocyanates should be added to the list of toxic air contaminants that may disproportionately impact infants and children under Senate Bill 25. And this is -- it's primarily focusing on asthma as a disease that disproportionately impacts children, and the potential of TDI to induce or exacerbate asthma. So we do actually make that recommendation in this document.

It's a different -- slightly different issue than what you're talk -- what you're bringing up with regard to this particular paper.

DR. SIEGEL: We do cite Jan.

DR. DODGE: This is Daryn in Sacramento. The -- what I was trying to say is that Jan et al. only looked at children. They did not -- I'm sure there was some teachers, adults, exposed as well, but they didn't look at those. They were concentrating on the children,

so we don't know what happened in adults that were exposed. That's -- that was the point I was going to -- I was trying to get across with the Jan et al. paper.

PANEL MEMBER ARAUJO: This is Jesús from -- at UCLA. Yeah, I think that it's an important point, and to -- really to make sure we do agree, because it is exactly the point of the American Chemistry Council in that they're arguing that there should not be really any increase in sensitivity attributed to the children. And I think that there is a fundamental biology aspect that where they are basing this on.

And the way how the document is presented is that the isocyanate is induced in like a Th2 response, and that the children tend to have like a higher Th to responses than the adults. And this is why we're arguing that the children -- that this should be really -- weighed heavier in children than in adults.

But they are arguing that this is not the case. They're arguing that the isocyanate is more -- the asthma induced by isocyanate is more like a Th1 response, and therefore -- and that it should be calculated the opposite of what we're arguing in -- or we're presenting in the document.

From what I read, I don't really understand their claim, I have to say, because I think from the bulk of the

literature that I've read that it is mostly like a Th2. And there is some animal data where they talk about a Th1, a large Th2, but I don't really see the data that they're using to say that this is mostly like a Th1 response.

But if what they're saying is true, I think that they have a point. What if your feeling -- you know, you have read the literature a lot more than me, especially on this issue whether the isocyanates are inducing responses that are either Th1 or Th2.

DR. DODGE: This is Daryn in Sacramento. We did respond to this pretty extensively during the public comment period. Essentially, you know, it's a mixed response, Th1, Th2, and for TDI asthma. It's not only specifically a Th1 type of response. Of course, atopic asthma adult -- or the childhood asthma onset that's mostly Th2, but that also can be mixed, depending on certain things that can happen.

And I tried to present that in the document. But in response to the comments, the public comments, I went into it much more extensively.

DR. MARTY: The other issue here too is -- this is Melanie -- is that in the Hot Spots Program, we laid out reasons why -- in a document in 2001, why we would be concerned about a toxic air contaminant disproportionately impacting children. And one of the reasons is not just

induction of asthma, it's also exacerbation of asthma, because children especially 0 to 4 have higher prevalence rates than older children and adults. They're hospitalized more often.

So just the ability of TDI to exacerbate existing asthma is a reason to list it as a toxic air contaminant that disproportionately impacts kids, no matter what argument you want to make about whether it induces asthma in children. And like Daryn said, we had pretty extensive responses to that issue in the response to comments.

CHAIRPERSON KLEINMAN: This is Mike. Just looking at that paragraph, the last part of the paragraph on page 82, the way it's phrased to me says that because children have a higher prevalence of asthma, they will have -- and rapid development of lung during infancy, which, you know, is important, but they will have a higher -- you know, there will be more children with asthma, you know, proportional to the adult population that might be exposed.

So whether they're more sensitive than the adults is part of the issue, but the other issue is that there's a higher likelihood of being exposed, which I think is the way -- you know, from the way this sentence is phrased I think that was one of the driving factors.

So I don't think we're saying that, as Melanie

said, that we are saying that there's more causation of new asthma, but because of the increased prevalence in the children population, they will have a higher likelihood of being exposed, and therefore that makes them a sensitive subgroup, because they're already susceptible. Is that --

DR. MARTY: Yeah, they have a higher likelihood of responding. So, you know, it fits with what we've been doing since 2001. If we have a chemical that exacerbates asthma, we view it as disproportionately impacting children, because asthma disproportionately impacts children, so -- and in this case, we have some reason to believe that you could have induction of asthma in children, despite the ACC's arguments that they think that it's Th1 not Th2. We didn't actually buy that argument, if you look at our responses to comments, which you guys did look at, but it was in the first meeting in February.

PANEL MEMBER GILL: Mike, this is Sarjeet here. This regarding Th1 and Th2 responses, it is not as clear cut as actually the document already -- and I think I looked at it, and it talked about in terms of differences between obese children and children, there's a slightly different response in Th2, Th1 responses.

And if anyone is familiar with immunology, there's is no so clear-cut definition of Th1, Th2 response to any particular agent, you see. So I'm not surprised

that you would see a response from one versus the other, and it's not as clear cut as the ACC puts it. That would be very surprising.

And secondly, if you look at slide 35, I think OEHHA has already made some comments regarding why they view that they still put that particular data in there, because I assume the exposure occurred after the track was sprayed, and so that exposure was not occurring while the spraying was applied.

So if that's the case, then I think it becomes less of an issue compared to that, you know, just on the track, which is MDI itself. Am I correct, Daryn.

DR. DODGE: Yeah, I think you're correct. Yeah.

PANEL MEMBER GILL: That's how I read your response on 35 when you also talk about differences in toxicity. And although they're similar -- although the toxicity is -- clearly toxicity is lower, and so therefore you consider that still a significant study to include it in the document. And I think having that study in the document is good. And the way you qualified it in the way that the authors assume all symptomology, that's not what you are saying. I think that's a valid statement.

And then you used some proportion. Although, I would change the word "some" to "a" proportion of the eye and respiratory effects could have been caused by xylene,

because some you tend to quantify it as if you're going to stay. You will not quantify what response there is. That's all.

DR. DODGE: Okay.

CHAIRPERSON KLEINMAN: This is Mike. Does anyone else on the Panel want to comment on the comments or response to the comments, or is anybody, at this point, uncomfortable with the adequacy of the responses that OEHHA made?

Okay. Hearing none.

PANEL MEMBER GILL: I'm --

CHAIRPERSON KLEINMAN: Yep, go ahead.

PANEL MEMBER GILL: I'm fine. Sarjeet Gill.

CHAIRPERSON KLEINMAN: Okay. Thank you.

If no one is uncomfortable, you know, or if no one feels that we've not dealt with the comments appropriately, then let's return to the question of add -- with all of the caveats and comments that were made today, are we prepared to say that the Panel approves the REL and the -- you know, the document for the REL?

PANEL MEMBER BUCKPITT: Yeah, maybe Mike -- this is Al Buckpitt -- I could make a motion to approve the document with the minor changes that have been discussed this morning.

CHAIRPERSON KLEINMAN: Thank you.

Do we have a second?

PANEL MEMBER GILL: Second, Sarjeet Gill.

CHAIRPERSON KLEINMAN: Excellent. I guess we'll have to do this as a roll call vote, since I can't do a show of hands.

So, Alan?

PANEL MEMBER BUCKPITT: I'm raising my hand. This is Buckpitt, yes.

(Laughter.)

CHAIRPERSON KLEINMAN: Sarjeet?

PANEL MEMBER GILL: Yes.

CHAIRPERSON KLEINMAN: Kathy?

PANEL MEMBER HAMMOND: Yes.

CHAIRPERSON KLEINMAN: Beate?

PANEL MEMBER RITZ: Yes.

CHAIRPERSON KLEINMAN: Jesús?

PANEL MEMBER ARAUJO: Yes.

CHAIRPERSON KLEINMAN: Cort?

PANEL MEMBER ANASTASIO: Yes.

CHAIRPERSON KLEINMAN: And I vote yes as well.

So I believe we have the unanimous approval.

Excellent. Thank you very much.

So shall we move on to the MDI document?

DR. DODGE: Okay. This is Daryn in Sacramento. I'll go on with methylene diphenyl diisocyanate, or MDI

starting on slide 22.

Okay. At the preceding SRP meeting in February, we presented the draft RELs for MDI. Now, these numbers have not changed since the first meeting, and the basis for the RELs have not changed.

Unlike TDI, MDI -- the MID RELs rely on animal data. And this is because none of the human information was adequate enough to base a REL on, only a best supporting.

The acute REL was based on a LOAEL finding of increased total protein in bronchoalveolar lavage fluid in rats. The 8-hour REL is based on a benchmark dose analysis for polymeric MDI. The finding was a bronchiolo-alveolar hyperplasia in rats. And the chronic REL was based on a separate chronic exposure study in monomeric MDI, in which interstitial fibrosis was seen at the lowest concentration.

Going on to slide 23, methylene diphenyl diisocyanate, or MDI. It's -- this one is semi-volatile. MDI and polymeric MDI, which I'll refer to as PMDI, are used mainly in rigid polyurethane foams. MDI and PMDI have essentially the same toxicological potencies and endpoints. So the RELs are going to be relevant to both.

And the basis for this conclusion is the chronic -- in particular, it's the chronic -- the two

chronic animal exposure studies, one with MDI and one with PMDI.

Slide 24. So just like for TDI, the general comment, SRP comment, was to state more clearly the adverse effects we are trying to prevent in a potentially exposed population. So overall, the information is going to be much the same here, or the presentation is much the same.

Slide 25. Now, since we're relying on animal studies, I'm not going to go over the information on the pulmonary inflammatory effects. I'm going to try and combine both here to keep things moving. Go straight to sensitization and induction of MDI asthma and the evidence we have that our RELs should not result in sensitization.

So in the MDI studies, the animal studies, we have acute, subacute, and subchronic studies that indicate the threshold for pulmonary irritation/inflammation and sensitization are interrelated and fit the C times T model.

This is largely based on a number of studies by Pauluhn, in which you stay below the threshold resulting in pulmonary inflammation. You're also going to protect the animal from being sensitized.

Point number 2 is that it's known that from occupational studies, human occupational studies, that

reducing exposure will reduce the prevalence of occupational asthma, and that we get the RELs low enough, we should not see any occupational asthma, or very little.

And the third point is that the toxicogenomic data suggests a large variation in response in the human population. This is why, again, we use the 100-fold intraspecies uncertainty factor.

Slide 26. Can we predict -- protect sensitized individuals or can we protect public health, I should say, from individuals that have already been sensitized, you know -- you know, protect them from these RELs?

So the SRP comments were essentially the same as for TDI, what is the potential for exposure in individuals already sensitized, and will they protect individuals or, I should probably interject that we're going to say public health?

Again, it's -- the rough estimate is the same, 10 to 23 -- I'm sorry, 10 to 40 or 12 to 43 individuals per million may be sensitized to any particular diisocyanate. And this induce MDI, TDI, and other related polyisocyanates.

Most chamber studies for MDI also start at 5 parts per billion and move up to 10 and 20 if there's no response at 5. This is to confirm diisocyanate asthma. Again, with MDI, there's a few studies, where we have

exposures as low as 1 part per billion, resulting in a sensitized individual responding. And the lowest reported is 0.05 parts per billion, in which a sensitized individual had an asthmatic response. So this lowest reported in the literature is below our acute REL or MDI.

So going on to slide 27, the conclusions. Can we protect from sensitization? It's the same as for TDI. RELs are lower than exposures used to confirm diisocyanate asthma, at least the 8-hour and chronic lower -- you know, they're lower than the lowest reported concentration eliciting a response. Again, our RELs cannot be designed to protect all hypersensitive individuals, as written in our REL guidance.

The risks. The likelihood of risk of a sensitized individual being exposed to MDI emissions are very low. Hence, our -- we expect our MDI RELs to be acceptable for the purposes of our Hot Spots Program.

At slide 28, these are the other changes to the document in response to comments from the last SRP meeting. We also added a list of acronyms at the front of the document. We included more details on sampling and analysis techniques for both vapor and aerosol phase, since you'll have exposure to both with MDI.

We added a NIOSH non-occupational exposure study based on the comment for more environmental exposure

studies and more environmental release studies.

We added study summaries on thermal degradation of products made with TDI -- I'm sorry, MDI, highlighting those studies that had estimated MDI emissions resulting from thermal degradation.

We added summaries of mechanistic studies that were recommended for inclusion. We also added summaries of DNA adducts studies. We did this for TDI as well.

Slide 29. We included more detail for studies summarized in the toxicogenomic section and more clearly stated what diisocyanate the workers were exposed to for each toxicogenomic study. And we also added a study by Choi that was in the TDI document, but not in the MDI document.

Slide 30, other changes to the document. This is in response to an SRP comment to explain the high background level of pulmonary fibrosis in rats from the Hoymann et al. chronic study versus the Reuzel et al. chronic study. If you recall, Hoymann et al., the control rats had quite a bit higher level of fibrosis compared to Reuzel -- the Reuzel study, which was -- the background level was fairly low.

So I looked into this and found a couple of references, which looked at the aging rat pulmonary pathology. And what they found is that in aging rats,

they do develop pulmonary fibrosis, and it could vary depending on the strain of the rat.

Now, in the two chronic studies on MDI, Hoymann and Reuzel, they both use Wistar rats in their studies. However, they were from different colonies. So even within different colonies of the same strain, there appears to be differences in fibrosis or the level of fibrosis in the lung as the animals get very old.

And support for this is -- can be shown that, you know, even though we're talking about two different colonies of Wistar rats here, the Hoymann rats did not live as long. They had a greater -- they had a greater amount of spontaneous tumors occurring earlier compared to Reuzel.

So even though we're talking about the same strain, there was differences here in regard to spontaneous tumors, so why can't there be differences in the level of fibrosis in the lung?

Okay. And that's what I have for MDI.

Any comments?

CHAIRPERSON KLEINMAN: Sarjeet, you were one of the leads on this.

PANEL MEMBER GILL: Yeah, that -- just like the TDI document, it was -- the changes that were made made the document much easier to read. So once again the

acronyms are quite useful. There are some still missing. For example, MBDL should be added, because -- and there's a section I have to actually refer it back to again, so that would be useful to add.

DR. DODGE: What acronym was that? I'm sorry, Sarjeet. This is Daryn. What acronym was that.

PANEL MEMBER GILL: BMDL.

DR. DODGE: Oh. Okay. Benchmark dose. All right.

PANEL MEMBER GILL: Those limits Yeah, because that's in one of the graphs. That's why I think we missed it, because of the double level. I think you should add it, besides the purpose.

The other question I have is do you have any studies looking at dermal exposure to MDI?

DR. DODGE: Yes, there are a number of studies out there looking at dermal exposure, yeah.

PANEL MEMBER GILL: Okay. Because on page seven you -- I think you should provide the citation for the statement, "Occupational occurs through inhalation of vapors and aerosols and through dermal contact with compounds containing MDI". It would be -- this is a statement you make. It would be nice to have references after that citation, that particular fact itself.

DR. DODGE: Okay.

PANEL MEMBER GILL: Okay. And on page 9, you make a statement, "As described above, MDI reacts with GSH in lung fluid that can then be absorbed into the bloodstream". It's this later phrase, "...that can then be absorbed into the blood stream". I went through the paper. I did not see any evidence that it a GSH conjugate is the one that goes in.

If that's the case, then I think you should just change the phrase to give some uncertainty, rather than saying that, "can", you can use that, "could", or some other phrase that you -- so that it could be a bit more -- unless you have strong evidence that it is transported as a conjugate, which I doubt, but then I think it would be best to add some word of -- instead of "can", I would change it to "could". Okay.

DR. DODGE: Okay.

PANEL MEMBER GILL: And the other one is in terms of you indicated on page 9 also that MDI is a absorbed as an MDI-albumin conjugate, which goes through transcarbamoylation, and that's the Wisnewski study, if I'm not mistaken.

There's also some indication that that's not the only protein that is conjugated with MDI, at least not with TDI. I could find with MDI. It also goes with hemoglobin. And so I think you should check on it. If

that's the case, you should just add a reference that it's also MDI hemoglobin, and MDI conjugate -- albumin conjugates.

DR. DODGE: Okay.

PANEL MEMBER GILL: Just check on that.

DR. DODGE: All right.

PANEL MEMBER GILL: On page 11, this is something I referred to earlier in TDI, but I did not have the exact page number. This is on page 11 of the corrected version, not the track changes version. And this is on page 11. Let me look at it. Just hold on.

On page 11 in the first paragraph, last sentence, where you -- the last phrase you basically say, "... which may contribute to the development of airway inflammation of TDI-induced asthma". This is the outcome on the paper itself, but I think this is a conclusion which I would not agree with, in the sense it was mostly done with cells. And then you're trying to do it -- this in vivo.

I would split the sentence that -- you can leave that confusion, but split that into a separate sentence. So would you say the last phrase, which I think is a bit speculative. You could just change it to, "...NrF2 signaling pathway have been shown to conjugate to inflammation". That is true. And I don't know whether it's to airway inflammation, because NrF2 signaling does

contribute to inflammation. So just after that sentence two separate conclusions, but I'll leave it as that.

Then on page 13, you deleted the study by Vangronsveld in 2013, but you added the study by Hoffmann and Schupp in 2009, am I correct?

DR. DODGE: I'm still trying to get to that page.

DR. SIEGEL: Which study was that deleted?

PANEL MEMBER GILL: Vangronsveld. If you look at the tracked indices, you'll see that.

DR. DODGE: So this was on page 30.

PANEL MEMBER GILL: Page 30 of the final draft. By the track indices, I know what page it is.

DR. DODGE: Yeah, I'm looking at what I had changed.

PANEL MEMBER GILL: But I don't know why -- what is the rationale for the deletion, because I think both studies could be actually done -- left in there.

DR. DODGE: Okay. Could that have been -- could that have been because it was only referring to TDI, this study?

PANEL MEMBER GILL: Well, this -- I put that in, but I -- let me see what it says.

DR. DODGE: I was trying to look at my previous -- or my strike-out version.

DR. SIEGEL: Here it is. Here.

PANEL MEMBER GILL: On page 31. That's on --
DR. SIEGEL: Here it is, yeah.
PANEL MEMBER GILL: That was TDI, I believe.
DR. DODGE: Yeah, I think I struck it out because it was only talking about TDI, and I found a paper -- a related paper that looked at MDI.
PANEL MEMBER GILL: Okay. Okay. So that's fine. That's the rationale you had for that.
DR. DODGE: Yeah, I think that was it, yeah.
PANEL MEMBER GILL: Okay. On page 47, there is a sentence, the last paragraph, the first sentence.
DR. SIEGEL: Is this of the strike-out, which --
PANEL MEMBER GILL: Showing supporting data.
DR. SIEGEL: Which document?
DR. MARTY: It's the accepted changes.
DR. SIEGEL: Accepted. Okay. Strong, what?
DR. DODGE: What section is it?
PANEL MEMBER GILL: Section 8, page 47.
DR. SIEGEL: Here. It starts -- the paragraph starts with, "Strong"?
PANEL MEMBER GILL: Paragraph starting with "Strong supporting data...". That first sentence I had to read it three times to understand what you were saying. I know what you're saying now, but if I read it I think it would be a bit difficult. It's a run-on sentence, and you

may want to rewrite it.

DR. DODGE: Yeah, you're right. Okay. That is a -- that should be cleaned up.

PANEL MEMBER GILL: Because, I mean, it -- all the facts are correct, but it's just a run-on sentence.

DR. DODGE: Um-hmm.

PANEL MEMBER GILL: And a similar thing happens on page 48. Let me see where on page 48. It starts with, "The pulmonary irritation-sensitization threshold...". Yeah, that same sentence, first paragraph -- second paragraph sentence.

DR. DODGE: Yeah.

PANEL MEMBER GILL: It is also a very long run-on sentence. Just split it up. So I would split it up after "animal models", and put a period and say, "This assumes the peptides and proteins...". Then it seems fine.

DR. DODGE: Okay.

PANEL MEMBER GILL: And on page 48, I think you had said that it is PMDI, I think it is TDI somewhere, under the Feron study.

DR. DODGE: The wrong diisocyanate.

PANEL MEMBER GILL: Yeah.

DR. DODGE: Okay.

PANEL MEMBER GILL: I assume it is MDI instead of PMDI that study. Sorry, on page 51. Sorry. On page 51

the second paragraph. Got it?

DR. DODGE: Yeah.

PANEL MEMBER GILL: Well, that's all I have actually. And the other comments that I had were regarding to the ACC and PFA. That's all I have, Mike.

CHAIRPERSON KLEINMAN: Okay. Thank you. Alan, do you have any comments?

PANEL MEMBER BUCKPITT: I can't add a lot to that, Mike. I've got a few minor things that I'll pass on to Daryn, you know, typos and that sort of thing, but otherwise I thought again the document initially was well written. I think the changes that have been added really are great. So I don't have a lot to discuss here.

I do have some things -- the responses to the American Chemical Council, but we can, or we can go through that later.

CHAIRPERSON KLEINMAN: Okay. Thank you. Going around the rest of the Panel. Kathy, do you have any comments?

PANEL MEMBER HAMMOND: No, thank you.

CHAIRPERSON KLEINMAN: Beate?

PANEL MEMBER RITZ: This is Beate. As an epidemiologist, I was just fascinated by the comparison between the TDI and MDI reference levels being so different when you base it on humans versus animal

studies, it seems. So we are an order of magnitude higher here basing it on animal studies, which I'm a little surprised by, but that's just me. And I understand there aren't enough human studies to base this on. It just surprised me a bit.

CHAIRPERSON KLEINMAN: Thank you, Beate.

Jesús.

PANEL MEMBER ARAUJO: Yes. Jesús at UCLA.

I also think that this document it was improved. And I have a relatively small comment in terms -- in relation to an addition that it was added to the document. They included a reference from -- the study from Kim et al. in 2010. And with a, you know, pretty long-hand description of the findings.

But I think that there is a portion that it may be misinterpreted, but maybe just go and mention exactly what is -- that is in the -- okay, yeah. So it's in page 10. At the bottom of page 10, that they say or it says, "Finally, Kim et al. (2010) investigated the transcription factor Nrf2. The expression of several antioxidant proteins is regulated by Nrf2 by binding the antioxidant response element (ARE) in the promoter of target genes". This is correct.

They continue, "TDI did not change the total level of Nrf2, but suppress the binding of Nrf2 to ARE

region of HO-1 promoter". And then it continues the paragraph. "TDI also suppressed nuclear translocation of Nrf1 through suppression of phosphorylation of mitogen-activated protein kinase...".

The way how we it reads is as if somehow TDI blocks that binding of the thing in the nucleus to the promoter region of HO-1. That's exactly what it's saying. And I know why they put it this way, because this is exactly also how what's written in the publication, but the publication presented more data that when you read it altogether, it was clear that the reason why there was decreased binding is because of what they're arguing after. There was no decrease in the total levels of the protein Nrf2 in the cells, because the decrease in the translocation -- in the decrease of translocation of the Nrf2 from the cell to the nucleus. Therefore, there was an increase of the Nrf2 in the cell and a decreases nucleus.

So when they did and as assay issues to measure on the binding of the Nrf2 to the heme oxygenaseone in the cells, that binding was decreased. But the reason why it was decreased is because it was less protein in the nucleus. So obviously, there is going to be less binding, but now because it is a specific binding of the region, which is the way how it is read.

So I would just suggest to change this and say maybe alter the sequence of how they present this fact. TDI did not change the total level of Nrf2 period. It suppressed nuclear translocation of Nrf2 through suppression of phosphorylation mitogen-activated protein kinases, therefore, suppressing the binding of Nrf2 to the ARE region of HO-1 promoter. That is one suggestion.

Another suggestion, if you don't like it this way, would be to just omit the whole sentence where it says but it did suppress the binding Nrf2 to the ARE region of the HO-1 promoter.

DR. DODGE: Okay.

PANEL MEMBER ARAUJO: And I think that this is really, you know, the only comment that leaded to a change in the document.

CHAIRPERSON KLEINMAN: Yeah. This is Mike. I think the first way you phrased it is better, because I think the -- it is important to, you know, point out that if you block translocation of the Nrf2 into the nucleus, you're going to reduce the antioxidant response. So, yeah, I like the first way you phrased it.

PANEL MEMBER ARAUJO: Okay.

CHAIRPERSON KLEINMAN: Thank you. Any other comments, Jesús?

PANEL MEMBER ARAUJO: No. No other comments.

CHAIRPERSON KLEINMAN: Okay. Cort, do you have any comments?

PANEL MEMBER GILL: Mike, Sarjeet here. But whatever it is make sure, because the last phrase is actually -- it does not support the in vitro versus in vivo studies. So that's why I suggested make that a separate phrase -- phase a separate sentence, as I indicated earlier.

CHAIRPERSON KLEINMAN: Okay. Thank you.

Cort, do you have any comments?

PANEL MEMBER ANASTASIO: No, I have no comments. I thought it was a good report.

CHAIRPERSON KLEINMAN: Great. I have just a minor point of clarification. I just wanted to double check that on page 48, paragraph 3, talking about sensitization of individuals to MDI or PMDI. The sentence reads, "Once sensitization has occurred, exposure to even exceedingly low concentrations of TDI below threshold limit values..., et cetera, et cetera. Is this specifically saying that the people were, you know, sensitized to the MDI or PMDI, but later were more sensitive to TDI? Is that what that literature reference is driving at or was this supposed to be sensitive to MDI?

DR. DODGE: Oh, yeah, I think I meant to -- you know, I pasted this in an didn't change all the TDIs to

MDIs is basically what happened here, I think.

CHAIRPERSON KLEINMAN: Okay.

DR. DODGE: I used the same paragraph sentence in both documents, and I didn't fix the TDI to change it to MDI.

CHAIRPERSON KLEINMAN: Okay. That's what I thought, but I just wanted to check that. I really -- you know, I think I agree with the comment -- the other comments that have been made. I think the document is in very good shape.

Shall we move on to responses to the external comments?

DR. SIEGEL: These are -- This is Dave Siegel. Again, these are the same comments that we responded to earlier. I just wanted to point that out, that we feel they're the same comments.

CHAIRPERSON KLEINMAN: And so --

PANEL MEMBER BUCKPITT: This is Al Buckpitt, and I believe, Dave, that you and Daryn have answered those comments appropriately.

DR. SIEGEL: Thank you.

CHAIRPERSON KLEINMAN: Sarjeet, you agree?

PANEL MEMBER GILL: Yeah, I agree. Actually, I will send in my written document to Daryn, and I guess, just like Alan has said, they are actually mostly

addressed. And I see no real necessity to address it further. That's it.

CHAIRPERSON KLEINMAN: Thank you. Are there any further comments or questions from the Panel members?

If not, Sarjeet, would you like to pose a motion to approve the MDI document?

PANEL MEMBER GILL: I will do that. So I propose that we approve the document as is written with the minor modifications suggested today.

PANEL MEMBER BUCKPITT: I'd like to second that. This is Al Buckpitt.

CHAIRPERSON KLEINMAN: Thank you. Again, we'll just go around the phone circle here.

So Alan, your vote?

PANEL MEMBER BUCKPITT: Yes, approve.

CHAIRPERSON KLEINMAN: Sarjeet?

PANEL MEMBER GILL: Yes, approve.

CHAIRPERSON KLEINMAN: Kathy?

PANEL MEMBER HAMMOND: Yes, approve.

CHAIRPERSON KLEINMAN: Beate?

PANEL MEMBER RITZ: Yes, approve.

CHAIRPERSON KLEINMAN: Jesús?

PANEL MEMBER ARAUJO: Yes, approve.

CHAIRPERSON KLEINMAN: Cort?

PANEL MEMBER ANASTASIO: Yes.

CHAIRPERSON KLEINMAN: And I approve. So we have unanimous approval for both documents now.

And so that, I believe, concludes the first point on our agenda. And again, I wanted to just thank OEHHA and the staff for doing, you know, an excellent job of taking all the comments into account, all the SRP suggestions. And I think the final documents are very strong and well justified. So I think that's it.

DR. DODGE: Mike, this is Daryn in Sacramento.

CHAIRPERSON KLEINMAN: Yes.

DR. DODGE: I'd like to thank the Panel for reviewing these documents. Now, the changes that has been requested should I go ahead and fix those and have you have final approval from you regarding these latest changes?

CHAIRPERSON KLEINMAN: What I'd like is for the final changes to be sent both to me and to Alan and Sarjeet, since they were the leads on the discussion. And then unless there's some further question about it, I think we're ready to move those forward.

PANEL MEMBER GILL: Daryn, this is Sarjeet here. I will send you my comments later today, so you can see those in the written format. It may be easier to analyze than what I'm saying on the phone. And if you can then -- if Mike agrees, then you can send it to the track changes

and then we can send it back to Mike for final approval.

PANEL MEMBER BUCKPITT: I'll do the same, Daryn. I'll probably do that through Peter Mathews, because I have his email address.

CHAIRPERSON KLEINMAN: Yeah, I think that, you know, just as a matter of record, it's probably best to send all those official documentations through Peter, so that there is an official record of everything, you know, for the Committee. So thank you, Alan. That's a good suggestion.

I wanted to just mention that in terms of consideration of administrative matters, I wanted to thank everyone for their help and support while my wife and I went through a rather unpleasant episode. But I just wanted to mention that she's recovered very nicely and we're back on track. And hopefully, I will not be the cause of further disruption to our scheduling. But again, thank you very much to all of you for the support, kind words, and helping this process forward.

DR. MARTY: And than you, Mike. Happy that she's doing well.

CHAIRPERSON KLEINMAN: Thank you.

PANEL MEMBER BUCKPITT: Same here, Mike.

PANEL MEMBER GILL: Same here.

CHAIRPERSON KLEINMAN: I appreciate that. Thank

you.

We have plans to schedule our next meeting in December. And I believe, at that time, there will be some appropriate mention of the contributions that George Alexeeff has made to, you know, the science of risk assessment and risk analysis and to toxicology in general. I was really sorry to hear of his passing and his contributions are going to be very much missed. And we'll be able to at the December meeting discuss that in more appropriate detail.

I don't have any other administrative issues that we need to bring up at the meeting, but let me ask around the Panel, are there any other issues that we need to discuss?

PANEL MEMBER ARAUJO: No, just to confirm the date in December. Is that December 18th?

MR. MATHEWS: This is Peter Mathews. That's correct, Friday, December 18. It will start in the morning. We haven't determined the time yet.

PANEL MEMBER ARAUJO: Okay.

MR. MATHEWS: But in all fairness, it will be a morning/afternoon session.

CHAIRPERSON KLEINMAN: Okay. And the agenda will be sent out in advance and posted as usual as soon as everything is straightened out.

Peter, are there other administrative details that we need to discuss today?

MR. MATHEWS: No, I think we're possibly done.

CHAIRPERSON KLEINMAN: Excellent. I want to thank everybody for their contributions, especially Alan and Sarjeet for taking lead roles on these discussions. And Daryn, Melanie, David, I think the documents are very well done, and I'm very happy with the way everything is turning out.

So based on that, can I have a motion to adjourn?

PANEL MEMBER GILL: Sarjeet. So moved.

CHAIRPERSON KLEINMAN: Second?

PANEL MEMBER BUCKPITT: Second. Buckpitt.

CHAIRPERSON KLEINMAN: Okay. I declare this meeting is adjourned then.

Thank you. 12:17 PM

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 12:17 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 31st day of August, 2015.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
License No. 10063