MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ELIHU HARRIS STATE BUILDING

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FRIDAY, JULY 8, 2005

9:30 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, CHAIRPERSON

Dr. Roger Atkinson

Dr. Craig Byus

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Lynton Baker, Staff Air Pollution Specialist

Mr. Jim Behrmann

Mr. Peter Mathews

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Ms. Mary-Ann Warmerdam, Director

Ms. Tobi L. Jones, Assistant Director

Dr. Roger Cochran

Mr. Joseph Frank, Supervisor, Exposure Assessment & Mitigation

Dr. Wynetta S. Kollman

Dr. Lori Lim, Staff Toxicologist

Mr. Randall Segawa, Senior Environmental Research Scientist

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PROCEEDINGS

CHAIRPERSON FROINES: This is to formally open the meeting of the Scientific Review Panel on July 8th, 2005.

We are short two panel members who are unable to attend, Gary Friedman and Paul Blanc. But there is a quorum, and so we will proceed.

Dr. Plopper is in attendance, Dr. Landolph, Dr. Atkinson, Dr. Hammond, Dr. Glantz and Dr. Byus and myself.

And so we'll proceed with the discussion of sulfuryl fluoride and proceed from here.

So, Tobie, welcome.

So that for the record this is -- well, why don't you introduce yourself for the record.

DPR ASSISTANT DIRECTOR JONES: Is this adequate?

I'm Tobie Jones, Assistant Director at DPR. And I'm pleased to be here today to provide you some opening comments on our presentation on our sulfuryl fluoride risk assessment.

First and foremost, I want to thank Drs. Byus and Atkinson for working very closely with our staff, providing some excellent comments on improving our draft assessment, and also helping us in preparing making sure that the presentation today is clear for all of the panel.

In the course of that review Dr. Atkinson

identified the possibility that sulfuryl fluoride is a possible greenhouse gas. And we acknowledge that possibility. And we also acknowledge the desirability of having better data on the fate of this molecule in the air.

The administration and the collective Cal EPA family has prioritized efforts to curb the greenhouse gas emissions. And we at DPR look forward to playing a role in that effort and examining our role in the recent Governor's executive order pertaining to greenhouse gas emission reductions.

DPR's had a policy of completing risk assessments on all of the fumigants registered as pesticides in California. Fumigants by their nature can lead to exposures. And they represent about a quarter of the pounds of pesticides applied in California. And of course the fumigants have varying degrees of hazards.

Our presentation of sulfuryl fluoride today represents our efforts to continue to move forward on our policy to fully assess the risks from fumigants and put appropriate controls in place.

I'd like to bring to your attention some changes in the use of sulfuryl fluoride to further illustrate our need to complete the assessment. While we were in the midst of preparing this assessment, a new use of sulfuryl

fluoride was introduced as a commodity fumigant. And the use that we'll be discussing today is focused on the use that was in place prior to this, which is solely as a structural fumigant. The use as a commodity fumigant is to treat commodities after harvest.

With this new use, we have exercised our authority to ask for additional monitoring data from the registrant. When we receive this monitoring data, we will amend this assessment to cover the new exposures, including bystander, worker and dietary risks.

Because of the manner in which structural fumigants are regulated in California, DPR cannot impose restrictions on the use by county-based permits, as we do with agricultural pesticides. Rather we have to promulgate regulations on mitigation measures. And we need your external peer review in order to advance and move forward on those regulations. So we look forward to the completion of this process.

As we've seen with other pesticides that have come through the toxic air contaminant process such as methyl parathion, uses and regional distributions continue to change. And for that reason we elected to move forward on the risk assessment we're presenting today rather than wait until acquiring additional data on this new use.

PANEL MEMBER BYUS: I have a question.

I just became really aware of this recently. I mean I thought we were talking about all uses of sulfuryl fewer fluoride in the state, and apparently that is not the case. I mean just to make sure everybody's clear on what you're saying here.

As I understand it, it's all the -- it's being used now to fumigate food commodities like nuts and raisins and grains. And so it's actually -- they're fumigating all of the food products. Correct me if I'm wrong.

DPR ASSISTANT DIRECTOR JONES: That's right, or some -- I'll say some food products.

PANEL MEMBER BYUS: Some of them. But primarily raisins, nuts and grains, as well the grain structures -- the silo fumigation of the structure itself.

And so we run -- and so this document really doesn't deal with that aspect of exposure, correct?

DPR ASSISTANT DIRECTOR JONES: That is correct. And that's why I wanted to explain to you up front our thinking in moving this assessment forward and recognizing that this other new use -- and, Craig, I think -- we don't know the extent to which that new use will take place, because in part it is replacing or it will replace over time uses of methyl bromide, which is being phased out. So this will be a developing use.

And we -- as I indicated, we do want additional data from that use that we will use in amending this assessment to address the new uses. And it will address the food use, as you --

PANEL MEMBER BYUS: So it would be basically exposing the silos and the various commodities at different exposure scenarios. And bystanders and those people that live near these place -- which are more or less permanent fixtures, are they not?

DPR ASSISTANT DIRECTOR JONES: Yes.

PANEL MEMBER BYUS: I mean I would imagine they're not moving them all around, like doing different houses for termites. So I mean there would be a whole different exposure scenario for the bystanders, for people living in the area, that could be significantly different than what we're reporting here in this document for Vikane?

DPR ASSISTANT DIRECTOR JONES: That is correct.

PANEL MEMBER BYUS: So primarily here -- so even though it says -- in a sense it's sulfuryl fluoride (Vikane) and it's -- so sulfuryl fluoride obviously we're dealing with the toxicity, is common. But the exposure aspect is just for Vikane; is that correct?

DPR ASSISTANT DIRECTOR JONES: That is correct.

PANEL MEMBER BYUS: Just so -- I mean I just want

everybody to realize that. I sort of just became aware of it myself.

So thank you.

DPR ASSISTANT DIRECTOR JONES: Okay.

CHAIRPERSON FROINES: Does -- I used sulfuryl fluoride in my house when I bought it, so that I'm an experienced sulfuryl fluoride person.

PANEL MEMBER GLANTZ: That explains your behavior.

CHAIRPERSON FROINES: I knew somebody would say that.

(Laughter.)

CHAIRPERSON FROINES: I am the living example of the brain vacuole, right.

(Laughter.)

CHAIRPERSON FROINES: You see, you can't --

PANEL MEMBER GLANTZ: That's a joke, for the record.

PANEL MEMBER BYUS: For the record.

PANEL MEMBER GLANTZ: Not clearly, but --

CHAIRPERSON FROINES: Yeah, there are doubts among the panel about whether it's accurate or not.

PANEL MEMBER HAMMOND: Are we going to take a vote?

CHAIRPERSON FROINES: Now, can I ask my question?

Can I interrupt you guys to get to the point?

(Laughter.)

CHAIRPERSON FROINES: That raises I think significant exposure questions that we'll have to deal with over time, I would assume, because it sounds like, as opposed to a home use, that there will potentially be greater amounts in use. Whether that translates to exposure is another question. Is that correct?

DPR ASSISTANT DIRECTOR JONES: I don't know whether I could address the question of greater amounts. But it will -- the new uses pose different exposure scenarios. And it's for that reason that we have asked the registrant -- and U.S. EPA also has asked the registrant to develop additional monitoring data for this use. And I believe timing-wise the registrant will be developing that data over the next probably a year to a year -- 18 months, and then we will use that data in expanding this risk assessment. So it will --

PANEL MEMBER BYUS: So it adds to the baseline level of fluoride that people have in them from eating these things. It now goes up, how much it goes up from the residue.

PANEL MEMBER HAMMOND: Does it get absorbed by the food?

PANEL MEMBER BYUS: Yes, as far as --

PANEL MEMBER HAMMOND: It does?

DPR ASSISTANT DIRECTOR JONES: Yes.

PANEL MEMBER HAMMOND: Oh, it does?

DPR ASSISTANT DIRECTOR JONES: Yes.

PANEL MEMBER BYUS: Oh, yeah. It's in. -- and now will be in your food. And it raises your fluoride baseline level by some amount that's unclear.

DPR ASSISTANT DIRECTOR JONES: And I think if you're interested in that element on a current basis, there's a very extensive discussion of its contribution in food as the result of EPA's setting a tolerance for that. And there's very extensive federal register notice on the tolerance petition when this was proposed.

So if -- and I could provide that reference to you, John, if you'd like --

CHAIRPERSON FROINES: Sure.

DPR ASSISTANT DIRECTOR JONES: -- for the committee if you want to read more about that.

CHAIRPERSON FROINES: I think the fluoride issue's going to get hotter, you know, because there's this new evidence osteosarcoma that seems to be emerging. And so fluoride in and of itself I think is going to be a topic of some interest over time. So I think it will come back to us in one form or another.

The other issue I would raise in terms of

thinking about monitoring is the issue of spikes versus integrated determination of exposure. I think that in some of these cases we have very high short-term duration exposures. But then if you take the average of the distribution, it turns out to be much different than the spike would indicate. And so how we addressed short-term high exposure or high concentrations versus the various averaging approaches we might take is an issue. I think that is something that we need to think about over time. And I think we'd be happy to talk with you further. And Kathy's smiling because she knows that she'd be the assigned helper.

(Laughter.)

CHAIRPERSON FROINES: So let's go ahead. I don't mean to hold you up.

DPR ASSISTANT DIRECTOR JONES: Just a couple -- just one last point.

We provided OEHHA's final findings to the panel earlier this week. And I recognized -- in the course of working through that I recognized the valuable role that Eleanor Fanning formerly played with this Committee in helping with the coordination of providing all of the documents to you. So I apologize for any confusion that we may have created providing you draft findings -- preliminary draft findings, but you do have the final

findings from OEHHA.

I'd like to now turn it over to DPR staff.

CHAIRPERSON FROINES: There was a question I had about that, because there were some -- there was a list of nine topics that I read the responses to. But then there was an -- it seemed like there was an OEHHA attachment that I didn't see the response to. And I didn't know whether that was me not finding it effectively or whether it was -- whether there was an issue.

And maybe we should just go ahead and worry about that as we get into it.

DPR ASSISTANT DIRECTOR JONES: I think that --

CHAIRPERSON FROINES: There was this long attachment from OEHHA that was an earlier discussion, and so may have been incorporated and that's where I may have -- so it may have been me.

DPR ASSISTANT DIRECTOR JONES: Okay. I think at this point turning it over to our staff. Dr. Wynetta Kollman will be discussing the environmental fate, dr. Roger Cochran will be discussing the exposure assessment, and Dr. Lori Lim will be discussing the health assessment.

So I think, unless you have any further questions of me, I will step back and turn it over to DPR staff.

PANEL MEMBER ATKINSON: So what's the -- do you have any idea of the expected use of sulfuryl fluoride for

commodity fumigation in California?

DPR ASSISTANT DIRECTOR JONES: Not specifically. I think --

PANEL MEMBER ATKINSON: Is it going to be larger than used for house fumigations or not?

DPR ASSISTANT DIRECTOR JONES: I don't know. I perhaps can consult with the registrant, who is sitting in the audience, and see whether they have that. But I think one thing to consider is, in entering the commodity fumigation market, sulfuryl fluoride then competes with other compounds that can be used for some commodity fumigation. And then also in some of the other fumigations pertaining to facilities -- large facilities. Some organizations as a result of the phaseout of methyl bromide have looked at other non-chemical treatments, like heat treatment, that depending on the facility may be used.

So I think trying to kind of predict the amount and the comparison of this new use to the structural use is a bit premature. But it's where our use supporting data will be a very important way to be able -- for us to be able to track that.

CHAIRPERSON FROINES: There are going to be interesting issues. You know, toxicology's done at 70 degrees, because they want to keep the animals happy. But

in homes in L.A. and silos you may get much higher temperatures. And so that's going to have potential significance in terms of -- potential exposure -- pardon me -- for the two potentials. But I think that the temperature is a variable that we haven't thought much about, because our toxicology is in one framework and the actual exposure may be in a different context.

So as we get into this there are some interesting issues I think.

Is that fair, Kathy, what I just said?

PANEL MEMBER HAMMOND: Sure.

CHAIRPERSON FROINES: Thank you.

DPR ASSISTANT DIRECTOR JONES: Okay. Thank you.

CHAIRPERSON FROINES: You see the danger of raising the commodity issue at the beginning.

DPR ASSISTANT DIRECTOR JONES: Well, I think for the reason -- craig discussed that -- I wanted to make the panel aware of that up front.

CHAIRPERSON FROINES: No, I think it's a very important issue.

Thank you.

Will you keep us informed on the greenhouse gas question too. Because I don't think the panel on any chemical to date has -- that's not been an issue, whether it be ARB or DPR. And so that's a new issue coming down

the road.

Welcome.

(Thereupon an overhead presentation was Presented as follows.)

DR. KOLLMAN: I'm going to briefly describe --

CHAIRPERSON FROINES: Can you introduce yourselves for the record.

Thank you.

DR. KOLLMAN: I'm Wynetta S. Kollman.

I'm going to briefly describe the physical and chemical properties of sulfuryl fluoride, its application and use patterns in California, and its fate in the environment.

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DR. KOLLMAN: Sulfuryl fluoride is a colorless, reporter odorless gas belonging to the chemical family of inorganic acid halides. The chemical name, trade name, CAS registry number, and the molecular formula and weight are listed in this slide.

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DR. KOLLMAN: Sulfuryl fluoride is non-corrosive to metals, stable to light, and stable up to 400 degrees C when dry. It is soluble in water without hydrolysis and is also soluble in common organic solvents such as ethanol, toluene, and carbon tetrachloride.

This slide lists additional physical and chemical properties.

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DR. KOLLMAN: Vikane is an insecticide, rodenticide used for the fumigation of sealed structures, such as dwellings, buildings, barns, vehicles, fumigation chambers, rail cars, and surface ships in port and their contents, such as construction materials, furnishings, and household effects.

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DR. KOLLMAN: Full pesticide use reporting in California was implemented by DPR in 1990. All agricultural use must be reported monthly to the county agricultural Commissioners. The county agricultural commissioners forward these data to DPR, who annually compiles and makes available a pesticide use report.

For nonagricultural applications detailed information such as meridian township range and section is not provided.

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DR. KOLLMAN: This slide is a graphical representation of total pounds of sulfuryl fluoride used in California from 1993 to 2002. Total use ranged from 1,502,091 pounds in 1993 to 3,042,882 pounds in 2002.

The average annual use for this reporting period

was 2,211,097 pounds.

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DR. KOLLMAN: Sulfuryl fluoride is used in all California counties. This slide shows use by county from 1999 through 2002 for counties with annual use over 60,000 pounds.

--o0o--

DR. KOLLMAN: Use of sulfuryl fluoride occurs throughout the year. This slide shows monthly use for 1999 to 2002.

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DR. KOLLMAN: Data addressing the fate of sulfuryl fluoride in soil and biota are not available. That data was not required for federal re-registration due to sulfuryl fluoride's chemical properties and its registration for strictly indoor uses.

Following application in aeration of treated structures, sulfuryl fluoride is dissipated into the atmosphere in a gaseous state. There would be little likelihood that residues would leach to groundwater.

--o0o--

DR. KOLLMAN: Sulfuryl fluoride enters the atmosphere in the gas phase. Once present it may be transformed and then removed through reaction with atmospheric radicals. A search of the open scientific

literature produced no citations relevant to the fate of sulfuryl fluoride in the atmosphere or if it absorbs light as wave lengths greater than 290.

The uptake of sulfuryl fluoride into cloud water with subsequent hydrolysis is unlikely since it is soluble in water without hydrolysis.

PANEL MEMBER ATKINSON: Have you done calculations on that. Has anybody in your department proceeded on that? I mean that's presumably the most likely atmospheric loss process, is uptake into cloud water and then hydrolysis.

Do you have any further insights into that?

DR. KOLLMAN: No, I don't.

CHAIRPERSON FROINES: Roger, why would hydrolysis be unlikely? It would seem likely to me.

PANEL MEMBER ATKINSON: Well, apparently it doesn't hydrolyze. But, yeah, the obvious thing you'd write down is sulfuryl fluoride plus two waters gives 2HF and SO3, which then goes to sulfuric acid. But --

PANEL MEMBER HAMMOND: Well, I'm not sure if -- the question is: Which is unlike, the uptake into the water -- into the cloud water or the hydrolysis?

PANEL MEMBER ATKINSON: Well, it's not -- the two are not really -- you can't really separate them. I mean the uptake into the water is clearly not very much. But

if hydrolysis does occur, then it essentially just moves the equilibrium and the thing will go through.

PANEL MEMBER HAMMOND: Right.

CHAIRPERSON FROINES: But if you have -- if you have a thermodynamic issue, that if you are getting hydrolysis, then more is going to be taken up.

PANEL MEMBER ATKINSON: Yeah.

PANEL MEMBER HAMMOND: Well, and I thought that it -- it doesn't have a low solubility in water I mean in the first place. So --

PANEL MEMBER ATKINSON: Yeah. But it's Henry's Law Constant is so low that the -- you can calculate that the washout ratio or washout time or wet deposition time is just thousands of years. But --

PANEL MEMBER HAMMOND: Is there any data on --

PANEL MEMBER ATKINSON: -- if it hydrolyzes -- if it was to hydrolyze in cloud water, that would be a possibility.

PANEL MEMBER HAMMOND: So on what basis do you say that it's unlikely?

DR. KOLLMAN: Although it's soluble in water, it doesn't hydrolyze.

PANEL MEMBER HAMMOND: Do we know that it doesn't hydrolyze?

DR. KOLLMAN: Yes, we do.

PANEL MEMBER HAMMOND: Oh, people have done experiments --

DR. KOLLMAN: Yes.

PANEL MEMBER ATKINSON: But it hydrolyze at higher pH's right?

DR. KOLLMAN: That's correct.

PANEL MEMBER ATKINSON: So you'd need to do a -- need to look up a sort of -- pH's of typical cloud water in different parts of the world. I have no idea. I assume it would be slightly acidic, but that's not necessarily the case.

CHAIRPERSON FROINES: And then you would end up with HF.

PANEL MEMBER ATKINSON: Yeah. Well, that's not a problem. I mean all the HFC -- CFC's -- sorry -- HCFC's and HFC's lead to HF by exactly the same route ultimately, and you get lots of it. That's not a problem.

CHAIRPERSON FROINES: But why do you say that?

PANEL MEMBER ATKINSON: Oh, there's so much HF in the earth's crust that another few hundred thousand tons coming down in rainwater isn't a problem. They went through this --

CHAIRPERSON FROINES: Unless it's a person who happens to be sitting underneath those thousands of tons --

PANEL MEMBER ATKINSON: Well, you don't get it all at once.

CHAIRPERSON FROINES: No, I know.

(Laughter.)

CHAIRPERSON FROINES: I know. It's a tough situation.

PANEL MEMBER ATKINSON: But, you know, that is probably the most likely -- at least offhand it would appear the most likely loss process. But if that doesn't happen, then you really are probably faced with a greenhouse gas.

Somebody should be looking into what does happen to this compound. Either you need -- in my view, either the companies should be urged to look into it or some agencies do it.

PANEL MEMBER BYUS: I mean so if it -- assuming that it were a greenhouse gas at this level of use, how significant is that? I mean if you make an assumption --

PANEL MEMBER ATKINSON: It depends upon its ultimate atmospheric lifetime and it's absorption intensities. There are other chemicals --

PANEL MEMBER BYUS: Well, a worst-case scenario, what would it be?

PANEL MEMBER ATKINSON: I don't know.

PANEL MEMBER BYUS: Okay.

PANEL MEMBER ATKINSON: I mean they're worried about other things like the -- I think there's some other sulfur fluoride compounds that were in -- it was reported in science a few years ago that have only, you know, thousand tons a year usage. But they build up -- could potentially build up over decades or centuries.

CHAIRPERSON FROINES: So the issue of the hydrolysis is undoubtedly pH dependent?

PANEL MEMBER ATKINSON: Yeah, undoubtedly. Well, that's already stated in the report. It does hydrolyze apparently at higher pH's.

CHAIRPERSON FROINES: Higher pH being?

PANEL MEMBER ATKINSON: Somewhere up around 10, if I remember.

PANEL MEMBER PLOPPER: What about 7.4?

PANEL MEMBER ATKINSON: I don't know.

CHAIRPERSON FROINES: Well, that's what I was getting at.

PANEL MEMBER ATKINSON: There doesn't seem to be any data.

CHAIRPERSON FROINES: Well, but there is the presumption in the document that there is -- sulfuryl fluoride does release fluoride.

So would you consider that a hydrolysis --

PANEL MEMBER ATKINSON: Yeah, I would assume it

would be.

PANEL MEMBER PLOPPER: Well, that's what it says in here.

CHAIRPERSON FROINES: Well, let's go ahead.

DR. KOLLMAN: Well, this is the final slide.

Are there any questions?

PANEL MEMBER ATKINSON: We're essentially faced with no knowledge whatsoever of the ultimate environmental fate of this compound.

PANEL MEMBER PLOPPER: So if it doesn't hydrolyze in a cloud, why does it hydrolyze in the respiratory system? I don't know if it's the same thing, but it's -- that's a super-saturated environment.

I'm not a chemist. I'm asking this because I don't know.

PANEL MEMBER BYUS: We know it's not that acid. We know it's not pH10.

PANEL MEMBER LANDOLPH: No, I think there's a lot of basic questions that just haven't been answered. I mean there may be some enzymatic hydrolysis. There's just -- it's a field which is ripe for investigation. I'm kind of bothered that such a widely used chemical has such a posity of data in the database on the toxicology and chemistry of it around physiological pH. I think there should be some recommendations to the state that this

matter be pursued.

CHAIRPERSON FROINES: Well, I think that -- I mean I think this discussion is raising a clear contradiction. On the one hand we have the statement that hydrolysis is unlikely. But in the document we have multiple statements that hydrolysis occurs readily and that there are significant questions about whether the fluoride ion is in fact the toxicologic main issue. So there's a -- there's an issue that's cloudy at this point.

Pardon my pun.

PANEL MEMBER LANDOLPH: Yeah. I mean I agree with that. As I was reading this document, I have to express some skepticism -- and it's just my scientific nose speaking -- that all this toxicity's due to fluoride ion. I think there's something else going on. There's not much discussion about the fluorosulfate ion. There's not any, you know, toxicological discussion of the whole molecule itself and what it might do.

I was a little bothered by the pulmonary edema that seems to keep surfacing. And I wonder exactly what's causing that, whether it's the whole molecule or an enzymatic byproduct of that molecule. So there's just an enormous amount we don't know about this compound.

PANEL MEMBER PLOPPER: It could also just be the sulfuric acid and hydrogen sulfide.

PANEL MEMBER GLANTZ: Could you talk louder.

PANEL MEMBER PLOPPER: Oh, sorry.

It could be the -- I mean SO2 becomes -- is a toxic compound on its own. Because that's the byproduct, right?

PANEL MEMBER HAMMOND: But it doesn't cause pulmonary edema.

PANEL MEMBER PLOPPER: Pardon?

PANEL MEMBER HAMMOND: But it doesn't cause pulmonary edema.

PANEL MEMBER PLOPPER: It sure does.

PANEL MEMBER HAMMOND: Does it? SO2?

PANEL MEMBER PLOPPER: Well, it depends on --

PANEL MEMBER HAMMOND: Oh, at very high levels.

PANEL MEMBER PLOPPER: Huh?

PANEL MEMBER HAMMOND: At very high levels.

PANEL MEMBER PLOPPER: Well, if this -- all this is going to convert to fluoride, then that means there's going to be a lot of sulfate around. I'm not a chemist, but that's my basic interpretation. And parts per million will cause edema. It's very short term, but it's there. It's very toxic, it's very -- it's the same type of pathology pattern. So --

CHAIRPERSON FROINES: So I don't know if we're going to get to this, but presumably if the fluorides are

coming off, that's a hydrolysis process. And so you're going to end up with sulfate. Wouldn't you?

PANEL MEMBER ATKINSON: Yes.

CHAIRPERSON FROINES: So --

PANEL MEMBER PLOPPER: Doesn't that become H2SO4? I mean -- again, I'm not a chemist, so I'm just -- but I know that's bad stuff.

PANEL MEMBER LANDOLPH: And the fluorosulface ion before that.

CHAIRPERSON FROINES: Is there any -- well, you may not be the right person, but let's ask anyway. Has anybody looked at the sulfate concentrations in vivo in animal studies?

DR. KOLLMAN: That's out of my field.

CHAIRPERSON FROINES: Yeah, we'll get to that.

DPR STAFF TOXICOLOGIST LIM: Sulfate -- pharmacokinetic study.

CHAIRPERSON FROINES: I'm sorry. Will you talk -- well, we can ask you questions.

Thank you very much. You've raised a lot of interesting questions.

So then at least at this point we can say that the data that DPR's been operating with is not sufficient.

PANEL MEMBER ATKINSON: Right.

CHAIRPERSON FROINES: At least I get three

nodding heads on this side. They're ignoring the issue.

Randy, are you next?

DR. COCHRAN: My name's Roger Cochran. I'm with the Worker Health and Safety Branch at the Department of Pesticide Regulation.

(Thereupon an overhead presentation was Presented as follows.)

DR. COCHRAN: All previous toxic air contaminant candidates had ambient air levels to which entire communities were exposed. But because of the limited size of the application sites and the limited amount of sulfuryl fluoride, as Vikane, is applied on a given day, the likelihood of community-wide exposure is almost nonexistent. Only application site exposures are likely, with the chemical gone in two to three days, except for residents of the treated homes. Thus, we're assuming that acute exposure is the only potential issue for bystanders.

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DR. COCHRAN: So what is Vikane used for in California? The primary registered use is as a structural fumigant. Mostly this consists of residences, apartment buildings and other commercial buildings.

"Fumigation commodity" refers to non-food, non-feed commodities such as pallets, dunnage, furniture, burlap bags, et cetera, like beds and mattresses.

"Fumigation other" refers to unspecified reported use of fumigant.

Regulatory pest control includes any pest control work performed by public employees or contractors in the control of regulated pests.

Vertebrate pest control includes any pest -- vertebrate pest control performed by public agencies or work under the supervision of the state or county agricultural commissioner.

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DR. COCHRAN: Where in California is sulfuryl fluoride used?

Most building fumigations takes place in the areas where you have most of the buildings located. In this case, Los Angeles County. The Deputy Agricultural Commissioner of Los Angeles County, who deals with structural fumigations in that county, said that there were approximately 120 structures fumigated each day last year, at an average cost of $2,000 per fumigation. He said that the vast majority of the structures fumigated were involved in real estate transactions. And because the real estate market seems to be as active this year as last, they expect about the same number of fumigations in the county this year.

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DR. COCHRAN: Is sulfuryl fluoride used at only certain times during the year? No.

CHAIRPERSON FROINES: Can I just interrupt with a comment?

DR. COCHRAN: Yes.

CHAIRPERSON FROINES: I have -- in my house have done termite -- no, I'm being serious here -- termite eradication three or four times in the last 10, 15 years. And so that there is a time when the real estate transaction occurring and somebody's buying a house and doing the terminate. But I actually think there's a fair amount of people like me who tent their houses because they have termite problems.

So I think that seeing it as strictly a real estate issue may -- it may not be an accurate estimate of the number of termite eradications that actually go on. And I stay that not with some expertise; it's just as a homeowner who's had to deal with termites. So it's an interesting --

DR. COCHRAN: Could I ask how many times you've had your home fumigated?

CHAIRPERSON FROINES: Probably four times. I bought it, once, and then I fumigated -- I'm about to do it again. So say in the time I've owned it, five times. And I think that that's not uncommon in southern

California, because you never get rid of them. You know, they just come back and come back and you -- it's a constant battle.

DR. COCHRAN: If you're aware of any studies that show that this occurs, we'd be happy to incorporate it into the document.

CHAIRPERSON FROINES: No, I -- it was by no means a criticism. It was just I noticed that I -- I noticed that you focus on the real estate. And my experience was a little bit different than that. And I think that that's probably not inaccurate. Although I certainly -- I don't think there's any numbers, because there's no reason why anybody would be -- would people be reporting those?

DR. COCHRAN: Whether it occurs repeatedly?

There's a number of different alternatives too that are less expensive to use. There's ways of treating different types of infestations with less expense and whatever. It's just -- at this point in time it's an assumption that we've made. And, as I said, if you have data that would indicate otherwise, we'd be happy to incorporate it.

CHAIRPERSON FROINES: It's completely subjective.

PANEL MEMBER BYUS: I have one brief question about the ship fumigation. It struck me -- I mean do you know much about that? Because I mean ships are huge, and

I would imagine the amount of fumigant would be quite large. And it would probably be done at the same place every time. And sort of how -- so that exposure scenario could be considerably different than a house. And --

DR. COCHRAN: The exposure scenario on a ship is going to be different. Essentially what they do now when they fumigate a cargo hold is they cause all of the -- they anchor the ship offshore. And -- it's not tied up at the dock. And then the crew is evacuated from the ship.

PANEL MEMBER BYUS: Good.

(Laughter.)

DR. COCHRAN: And then the holds are fumigated. And until the level of the fumigant is down to a level that's acceptable, which is on the label, then the crew is not allow back on.

PANEL MEMBER BYUS: How do they vent -- I mean they don't actually tent a ship, do they?

DR. COCHRAN: They do tarp the holds.

PANEL MEMBER BYUS: They do? Really? Okay.

DR. COCHRAN: Yeah. What you're trying to do is -- you're not going to keep it in there. And as I'll show you later with a picture of a tent on a house, it's not airtight. But it does tend to retard the material from escaping so that it lasts a little bit longer and performs the function it's intended to do.

PANEL MEMBER BYUS: Okay.

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER PLOPPER: Can I ask a question about this slide?

DR. COCHRAN: Yes.

PANEL MEMBER PLOPPER: Is this all of the use or is this just the use associated with Vikane?

DR. COCHRAN: This is the use associated with Vikane.

PANEL MEMBER PLOPPER: Okay. So this is not all the use then?

DR. COCHRAN: No. I'm talking strictly in my presentation about the exposure from Vikane, that particular formulation. We don't have the data yet for the other formulation, that is --

PANEL MEMBER ATKINSON: This is fumigation of houses --

DR. COCHRAN: This is fumigation -- structural fumigation is what you're looking at for that particular slide.

PANEL MEMBER PLOPPER: Just structural fumigation?

DR. COCHRAN: Right. Because about 97 percent of the Vikane use is for structural fumigation.

PANEL MEMBER ATKINSON: And the other 3 percent?

DR. COCHRAN: If you go back to the other slide, it shows the other stuff in there? You can see it's minuscule.

Next slide.

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DR. COCHRAN: There are essentially three phases of structural fumigation. There's an application phase, in which the sulfuryl fluoride is piped into a tarped structure and maintained for 20 hours. This is followed by the aeration phase, in which the sulfuryl fluoride is vented.

There are essentially two methods utilized for venting the structure. One is the Stack plan, which involves 12 hours of active ventilation through an exhaust stack of unspecified diameter and height with a tarpolin in place, except for a small opening on the side opposite the exhaust fan so that fresher air can flow into the structure.

The other form of aeration is the tarpolin removal and aeration plan or TRAP plan. TRAP involves tarpolin removal after only ten minutes of active ventilation through a plastic duct, which is usually secured at the roofline, followed by approximately sixty minutes of active aeration. The home is then closed until the following morning, at which time it is tested to see

if there's any remaining sulfuryl fluoride.

Once the sulfuryl fluoride concentration in the home drops below five parts per million, the contractor can certify that the home is cleared. And the last phase then is the post-clearance phase.

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DR. COCHRAN: So what does the treated structure look like?

The structures are enclosed in tarps. And then the sulfuryl fluoride, as I said, is introduced. And -- let me see. I think this structure is going to be ventilated with the Stack plan. And this is the stack here. The chimney is actually here in the back of the structure. But this is the stack that's going to be used for ventilating it.

PANEL MEMBER ATKINSON: So which is most used, the Stack or TRAP method?

DR. COCHRAN: We're trying to get people to go to the Stack method. But from the industry point of view, the faster that they can turn it over, the more homes they can fumigate. And so they're going to want to try to do it with the TRAP method.

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DR. COCHRAN: This is the picture of a sampling station that's used by the Air Resources Board. It's

similar to the sampling stations referred to in the exposure assessment document. Basically it consists of a stand, a sampling tube -- if you hit it a couple of times. There's the charcoal tube at the top. And then there's the pump at the bottom. And the air pump draws the ambient air through the sampling tube at a fixed rate, usually about three to six liters per hour.

Can I have the next slide.

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DR. COCHRAN: The air contaminated with sulfuryl fluoride is drawn through a tube containing active charcoal. This is what the sample tube basically looks like, with an 800 milligram activated charcoal front that -- stuff is coming through this, which is glass wool. This is the 800 milligrams of charcoal in the front portion. This is a separator frit. And this is 200 milligrams of the activated charcoal in the back portion, and it's kept in place by this frit. So that the air is flowing through the tube in this particular direction.

Now, if all of the sulfuryl fluoride is trapped in the front charcoal, then one can be reasonably certain that all of the available sulfuryl fluoride in the air that's drawn through the tube has been collected. However, if you find sulfuryl fluoride in the rear portion, we have what is called breakthrough. And the

certainty that we would have that all sulfuryl fluoride has been collected is gone.

It's possible of course to add the amount of sulfuryl fluoride from the back portion to the amount in the front portion. But you don't know if you captured everything.

The total volume of air can be calculated multiplying the flow rate times the time of operation. To estimate the time-weighted air concentration, the amount of sulfuryl fluoride extracted from the charcoal is divided by the volume of air that was pumped through the tube.

There's another technical issue that needs to be considered in this monitoring. And that's in sample collection, which concerns the efficiency of the extraction procedure. When one extracts sulfuryl fluoride from the charcoal, how can you be sure that all of the sulfuryl fluoride adhered to the charcoal has been extracted and measured?

The technique used to determine recoveries involves reference samples called field spikes. A known amount of sulfuryl fluoride is introduced into the sample tube under field conditions and then extracted and analyzed to see if the known amount is actually measured. If the measured amount is less than the known amount, then

we look at what -- we have what is called the percent recovery.

Can I have the next slide.

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DR. COCHRAN: Monitoring studies were conducted in order to measure the concentration of sulfuryl fluoride in the application site air outside of fumigated structures. The original Air Resources Board monitoring study, which was done in 2002, was not acceptable because there was breakthrough in more than 80 percent of the sample tubes. Instead we relied on the monitoring studies that were conducted by Dow Agrosciences under Good Laboratory Practices procedures.

Next slide.

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DR. COCHRAN: This slide shows a diagram of a structure that was treated with sulfuryl fluoride. The numbered circles around the structure depict the monitoring stations that were set up at various distances from 5 to 50 feet from the structure. Nearby structures are indicated by the other boxes in the diagram.

Aeration was accomplished in this instance using the Stack method. Now, this structure was fumigated five times to give us five repetitions of the fumigation procedure, plus the outgassing, et cetera. The duration

of each sampling period varied between one and eight hours, depending upon the phase of the fumigation.

For purposes of this exposure assessment, time-weighted averages for the highest sulfuryl fluoride concentrations detected among the 24 sampling stations during a given sampling period within a replicate were used in estimating the bystander exposure. Airs samples collected were corrected for background and an analytical recovery of 83 percent.

We had no data on potential differences between outdoor and indoor sulfuryl fluoride air concentrations for bystanders. Consequently we assumed that bystanders would be potentially exposed to the measured application site air concentrations during all stages of the fumigation procedures. Thus, acute bystander exposures during the application phase were calculated using the upper bound of sulfuryl fluoride concentrations and then exposure duration of 12 and 24 hours, respectively.

As we assumed it would be unlikely a bystander would be exposed to more than one fumigation per year, annual exposures were based on one exposure per year. And because that one exposure may be the upper bound sulfuryl fluoride concentration, the annual exposures were estimated using this 95th percentile of the 24-hour exposure duration.

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CHAIRPERSON FROINES: Recognizing that the ARB data was problematic because of the breakthrough, when you -- you still had that data. Now, I don't know how serious the breakthrough was. But were the numbers that you saw from the Dow study, were they in any way comparable to the ARB studies? Or was the ARB studies had so much breakthrough, that you couldn't use it at all?

DR. COCHRAN: The ARB study had about 80 percent breakthrough, so you can't use it. But they have given us subsequently a study from two other buildings that were fumigated. We just haven't had a chance yet to analyze that data. So we will be able to give you an answer to that and give you the comparison, but to see if the numbers are approximately the same.

CHAIRPERSON FROINES: That would be very interesting, I think.

PANEL MEMBER HAMMOND: In the difference between the ARB study and the Dow study, did they sample for different time periods or different flow rates?

DR. COCHRAN: I don't remember offhand what that is, as to why there was the breakthrough. It can be because your flow rate is different. It can be because the air concentrations --

PANEL MEMBER HAMMOND: Well, that's what I'm

asking. That's what I'm asking.

DR. COCHRAN: Yeah, it can be because of the air concentration is greater. In other words, if the structure is fumigated with a higher concentration --

PANEL MEMBER HAMMOND: That's exactly why I'm asking the question. Because if the sampling times and flow rates were comparable, then that means that the breakthrough was due to the concentrations. And that's very important information.

So I think even though there's a problem with breakthrough, you don't throw that data away. Those data indicate minimal levels of concentrations. They don't tell you the true concentration, but they're minimal levels. And I think it's very important to understand -- you know, to add that data to your set of data even though you know that --

CHAIRPERSON FROINES: Yeah, that was precisely my question.

PANEL MEMBER LANDOLPH: Yeah, I agree that. They're lower bounds, and you shouldn't throw them away.

CHAIRPERSON FROINES: Lynn, do you want to comment? Is that --

PANEL MEMBER HAMMOND: And since there's so little data on all of this, it's very important to not lose any of it.

CHAIRPERSON FROINES: Tobie, is that okay, if Lynn --

ARB AIR POLLUTION SPECIALIST BAKER: Lynn Baker with the Air Resources Board. I can try to help answer your question, Dr. Hammond.

The monitoring study that we conducted in 2002 was at a higher flow rate than had been used by Dow in their studies.

PANEL MEMBER HAMMOND: What was it?

ARB AIR POLLUTION SPECIALIST BAKER: It was I think a liter a minute through tubes that were much smaller. They were 400 milligrams in the front section, 200 milligrams in the back section at a liter a minute; where the Dow studies had been done at a fraction of that.

PANEL MEMBER HAMMOND: Do you know what they were?

ARB AIR POLLUTION SPECIALIST BAKER: I know they were less than a half a liter a minute. I can't remember exactly.

But also the structures that Dow had monitored had an -- oh, three to six liters an hour by Dow, where we had used a liter a minute. So it's a substantial difference.

Also, though, the application rate of the structures that Dow had monitored had an application rate

of 16 ounces of sulfuryl fluoride per thousand cubic feet. The house that we monitored in 2002 application rate of 51 ounces per thousand cubic feet. So about a three times higher application rate.

PANEL MEMBER HAMMOND: So that would imply that the actual concentration was higher in the ARB study as well.

ARB AIR POLLUTION SPECIALIST BAKER: I would expect that it would have been higher, yes.

PANEL MEMBER HAMMOND: Right. So it is important not to lose that data.

ARB AIR POLLUTION SPECIALIST BAKER: Our data was invalidated because we found very little because the -- there was so much breakthrough, as Roger mentioned, that -- 80 percent of the samples had breakthrough. And we found as high as -- I can tell you here exactly. We found as high as four and a half micrograms per cubic meter, which was a fraction of what Dow found in their samples.

PANEL MEMBER HAMMOND: You mean the total -- the concentration?

ARB AIR POLLUTION SPECIALIST BAKER: The concentration -- the concentration in the samples that were collected around the perimeter of the house were much lower. And we saw a breakthrough, as he said, in 80

percent of the samples.

Now, I don't know if you want me to expand on this, but I can very briefly. Because of that problem, DPR requested us to do additional work. So we did more method development work and did additional studies, as Dr. Cochran mentioned, last summer, and we've just recently given those final reports to DPR. But in those studies, instead of a liter a minute, we used a tenth of a liter a minute.

PANEL MEMBER HAMMOND: Which was about -- that's what Dow used.

ARB AIR POLLUTION SPECIALIST BAKER: Actually I take that back. We used a twentieth. We used 50 cc's per minute.

PANEL MEMBER HAMMOND: And the Dow rates were 50 to a 100 cc's per minute?

ARB AIR POLLUTION SPECIALIST BAKER: Yeah. And we used the larger tube. We used the 800 milligram, 200 milligram. And during the venting period, when you would expect to see the highest concentration, we had backup tubes to ensure that we --

PANEL MEMBER HAMMOND: Behind the whole time?

ARB AIR POLLUTION SPECIALIST BAKER: Yes, two tubes in series to ensure we wouldn't see any breakthrough.

PANEL MEMBER HAMMOND: And You did not have breakthrough?

ARB AIR POLLUTION SPECIALIST BAKER: No, we did not have breakthrough.

PANEL MEMBER HAMMOND: And are those concentrations included in this report though?

DR. COCHRAN: No, no.

ARB AIR POLLUTION SPECIALIST BAKER: No.

DR. COCHRAN: We just got the study. So --

ARB AIR POLLUTION SPECIALIST BAKER: You know, if -- now or later if you want, I can summarize -- I don't want to take --

CHAIRPERSON FROINES: I'll call Joe. But this is clearly a very important issue. It does not, however, impact our determination of the report in terms of the TAC character of it. Although obviously it could affect MOE's. But it may have more implications for management issues than for risk assessment.

So we should probably go on.

PANEL MEMBER GLANTZ: Can I just ask one question?

CHAIRPERSON FROINES: Well, wait. Joe was ahead of you.

PANEL MEMBER GLANTZ: Oh, I'm sorry.

PANEL MEMBER LANDOLPH: You may have this data.

You've got a plethora of data here I'm trying to understand.

Do you have curves showing -- if the concentration is X in a house being treated, do you have concentric circles showing what the concentration would be at various times, so we could get a feel for how this would impact neighboring houses, approximate to a structure?

ARB AIR POLLUTION SPECIALIST BAKER: We do not have the concentrations inside the house during the treatment. But we do -- we did collect -- while the house was treated with the tarp and then during tarp removal and following tarp removal we had concentric rings of samplers, north, south, east, west, at different distances, from 5 feet out to 80 feet, to address both very adjacent concentrations as well as the neighboring house.

PANEL MEMBER LANDOLPH: And what are peak concentrations that you might register in, say, a neighboring structure? Approximate to one that's being fumigated.

ARB AIR POLLUTION SPECIALIST BAKER: While it's being vented?

PANEL MEMBER LANDOLPH: While it's being fumigated and while it's being vented. Do you have those

numbers?

ARB AIR POLLUTION SPECIALIST BAKER: While it was being fumigated, there is some leakage. But their concentrations were on the order of a thousand micrograms per cubic meter around the perimeter of the house. Now, I don't believe -- and I can -- I wasn't prepared to bring my report with me. It's over on the chair. But I don't believe that we measured it out at 40 or 80 feet while the structure was tarped. We did during the venting period and following the venting period.

And then DPR also requested us -- after the aeration was all done and the home had been cleared for reentry, after the applicator had gone in and determined that the concentration was below 5 ppm, they asked us to collect two 24-hour samples inside the house for sulfuryl fluoride and chloropicrin, to look at those levels.

PANEL MEMBER LANDOLPH: And what maximum values did you get?

ARB AIR POLLUTION SPECIALIST BAKER: Inside the house?

PANEL MEMBER LANDOLPH: Um-hmm, the adjacent house.

ARB AIR POLLUTION SPECIALIST BAKER: Oh, we didn't measure the adjacent house. Inside the treated house. Following aeration we measured a 24-hour

concentration of 2400 micrograms per cubic meter. And that was -- so that would be about -- hold on -- would be about 600 parts per billion. So about six-tenths of a ppm, which was below the 5 ppm limit.

And we also measured about 83 micrograms per cubic meter for 24 hours for chloropicrin. But that's off the subject.

CHAIRPERSON FROINES: Stan, did you have a question?

PANEL MEMBER GLANTZ: Yeah. The application rate that were used in the house you monitored and the one Dow monitored were wildly different. And -- I mean what is the more -- what is typical use?

ARB AIR POLLUTION SPECIALIST BAKER: Typical for termites is more on the order of the level that Dow treated.

PANEL MEMBER GLANTZ: Did you just use these very high rates to try to get an upper bound or --

ARB AIR POLLUTION SPECIALIST BAKER: DPR specially requested that we look for a home that was being treated for powder post beetle where they use a higher application rate.

PANEL MEMBER HAMMOND: So it was a real-world sampling; it wasn't a test --

ARB AIR POLLUTION SPECIALIST BAKER: Oh, yes.

Oh, no, it was a real-world sampling, one in -- a home in the Loomis area, which is out east of Sacramento, and then in Grass Valley. Large homes. So not only a higher application rate because of the powder post beetle, but they were larger homes. So more material.

PANEL MEMBER GLANTZ: And then of the use, the -- I mean how typical is that? I mean is it mostly 95 percent termites and of 5 percent that or is there --

ARB AIR POLLUTION SPECIALIST BAKER: Something like -- a vast majority of treatments are for termites. We had trouble finding powder post beetle treatments. But they do exist. But I don't know if it's a tenth.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: This is Randy Segawa with the Department of Pesticide Regulation.

Yeah, the great majority of the applications are for termites down in southern California. Powder post beetle is mainly a problem in northern California. But even in northern California the percentage of those applications are quite small.

CHAIRPERSON FROINES: Randy, I have a question that is it a little bit of an off -- it's my impression that chloropicrin is generally used now with sulfuryl fluoride, that you generally don't find one without the other. Is that correct? And if that's correct, what are

the relative proportions?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: That is correct, that chloropicrin is used as a warning agent for all structural fumigations. However, that's not the case for the new food uses of it. But for structural fumigation it's always included as a warning agent. The relative amounts are very low. That is, chloropicrin is probably on the order of 1 percent or so.

CHAIRPERSON FROINES: Oh.

ARB AIR POLLUTION SPECIALIST BAKER: I can tell you, for example, Dr. Froines, the Grass Valley home that we monitored where we measured the highest sulfuryl fluoride concentrations, that home had a treatment rate for sulfuryl fluoride of 40 ounces sulfuryl fluoride per thousand cubic feet, for a total of 202 pounds of sulfuryl fluoride. They used 6 ounces of chloropicrin.

CHAIRPERSON FROINES: Why is it -- I've had the impression that -- and this reflects my lack of knowledge -- that the percent of chloropicrin has been rising. Is that faulty?

DR. COCHRAN: No, it's not faulty. Roger Cochran again.

No, it's not faulty. They're looking at using chloropicrin to replace methyl bromide for some fumigations as well. So they're in the process of --

we're in the process of evaluating chloropicrin as a fumigant itself.

CHAIRPERSON FROINES: Yeah.

Joe.

PANEL MEMBER LANDOLPH: I would find --

CHAIRPERSON FROINES: And then we can -- go ahead.

PANEL MEMBER LANDOLPH: I would personally find it useful to have a short section capturing the discussion, the data on the ambient levels of the sulfuryl fluoride in adjacent houses and all that, because I think that's an issue we should just have a good grip on before the documents is finalized.

ARB AIR POLLUTION SPECIALIST BAKER: Dr. Landolph, we don't have any data on concentrations in adjacent houses. We have these concentric rings that are out in the direction of the adjacent homes, but no concentrations in those adjacent homes.

PANEL MEMBER LANDOLPH: Okay. And that data I think would be useful too as a surrogate.

CHAIRPERSON FROINES: There is information in the document on that already.

Thanks, Lynn.

ARB AIR POLLUTION SPECIALIST BAKER: Okay.

CHAIRPERSON FROINES: That was useful. This is

clearly a changing issue, which is going to have lots of implications over time.

DR. COCHRAN: Okay. The data derived from the ambient air sampling during a sulfuryl fluoride structural fumigation at the rate that was just indicated. The time we had averaged representing the sulfuryl fluoride air concentration detected among the 24 sampling devices is plotted here.

Okay. So what we used is the 95th percentile -- or 95 percent confidence limit on each of these various measurements from the five different samples -- or five replicates that you had.

Could I have the next please.

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DR. COCHRAN: The absorbed dose through the inhalation route is calculated using the two formulas shown on the screen. The terms are defined below. The 18 percent absorption retention factor comes from the data derived in an inhalation pharmacokinetic study in rats. This study will be discussed Dr. Lim in her presentation, which is to follow.

Can I have the next.

--o0o--

DR. COCHRAN: Now, this is derived from chemical-specific ambient air monitoring data from

Maxwell, California. The structural fumigations that were provided by Dow Agrosciences. The study investigators corrected the samples for background and an analytical recovery of 83 percent, and the estimates apply to both genders within a given age group.

The acute 12-hour absorbed daily dose was estimated to be the daily sulfuryl fluoride exposure that may occur during the first 12 hours of the application phase, calculated using the 95th percentile of sulfuryl fluoride concentration.

Exposure was assumed to occur during both indoor and outdoor activities. And we're not differentiating between the air concentrations indoors or outdoors.

The acute 24-hour absorbed daily dosage was estimated to be that sulfuryl fluoride that may occur during the entire application phase up to 24 hours a day.

The annual absorbed daily dosage is the estimated daily dosage that results from bystander exposure during outdoor activities amortized for one year. And this is from the 24-hour ADD divided by 365 days.

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DR. COCHRAN: But because the Dow-monitored study was performed at the industry's standard application rate, a factor of ten-fold was added to the air concentrations reported to approximate the exposure that could occur at

the maximum rate that is legal on the label.

The maximum label rate may be used to control structural pests other than termites, as you heard, like powder post beetles. So as a consequence, when we're talking about the exposures, we're looking at what the label allows, and we're assuming that there is a linear relationship between the amount used and the amount of exposure that there will be.

PANEL MEMBER GLANTZ: Are the differences that you have with age just reflecting differences in breathing rates?

DR. COCHRAN: Breathing rates and body weights.

PANEL MEMBER GLANTZ: Okay. Good.

DR. COCHRAN: We have a standard assumption on that. And there's a memorandum of understanding between Worker Health and Safety and Medical Toxicology as to what those standard measurements are, so that we're all on the same page.

Can I have the next slide.

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DR. COCHRAN: The highest sulfuryl fluoride air concentration's detected during Stack aeration were used to calculate the 95th percentile and average sulfuryl fluoride air concentrations to which bystanders may be exposed during the aeration procedure.

As opposed to application phase, the highest air concentrations of sulfuryl fluoride during aeration occurred at 1 hour, and at 4 hours.

The acute one-hour ADD absorbed dose is the daily sulfuryl fluoride exposure during the first hour of aeration using the Stack method. A one-hour exposure duration in default breathing rates and body weights were used to get the absorbed dose.

The acute four-hour absorbed daily dosage is that which occurs during the first four hours of aeration using the Stack method.

And these were the two highest exposures that we saw. And, again, the annual ADD is estimated based on the four-hour exposure multiplied by one day divided by 365 days.

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DR. COCHRAN: As noted before, the ADDs had to be adjusted to represent potential exposures that could occur at the maximum label-approved application rates. So these are the ones that we used for -- as the exposures.

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DR. COCHRAN: This slide shows a diagram of a structure that was treated with sulfuryl fluoride in Rancho Cordova. As before, the numbered circles around this structure depict the monitoring stations that were

set up at various distances from the fumigated structure.

In this case, aeration was accomplished using the tarpolin removal and aeration plan, TRAP plan.

This study involved two replicate fumigations, performed at one unfurnished home in Rancho Cordova in May of 1999. The application site data collected at the monitoring stations around this Rancho Cordova home were not used to estimate the upper bound and average bystander exposures in the present assessment because only two replicates were performed and we couldn't estimate the 95 percent upper bound.

Next slide.

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DR. COCHRAN: The data from phase 1 aeration by the TRAP indicated that after the 1st two hours of aeration sulfuryl fluoride was no longer detectable in ambient air samples collected. Therefore, the duration of bystander exposure during TRAP aeration would be assumed to be two hours for the exposures estimated.

In lieu of using the data from the application site monitoring stations, we use surrogate air concentrations derived from those measured during worker general detarping activities in an earlier study. These values were used as surrogates for bystander exposure during the TRAP aeration. A separate set of exposures

were not generated for the application phase, as the air concentrations are expected to be the same as those in a Stack plan model, regardless of which method is used afterwards.

--o0o--

DR. COCHRAN: This table presents the bystander exposures calculated at the maximal application rates during TRAP aeration. The acute two-hour ADD is the daily sulfuryl fluoride exposure that may occur during the 1st two hours of aeration and is calculated from the 95th percentile of sulfuryl fluoride concentrations as measured from the personal air monitoring done during the general detarping. This value was used since it was the greatest sulfuryl fluoride air level measured. And the bystander exposure level should not exceed that of the greatest level experienced by fumigation workers.

The exposure -- yeah.

CHAIRPERSON FROINES: I'm sorry.

In the work that Lynn and his colleagues are doing or have done, are they looking at both Stack and TRAP?

DR. COCHRAN: No, they're just -- the new study that they've done is the TRAP removal.

CHAIRPERSON FROINES: It's the TRAP. Because these numbers are relatively high, and so that's a matter

of some concern, I think.

DR. COCHRAN: Yes, which is one of the reasons why we asked them to do the study.

PANEL MEMBER BYUS: I have a stupid question.

What about when the wind blows? I mean how do you control for that? I mean it seems to me if the wind was blowing, depending on which way it was blowing, it would be diluted relatively quickly, but then it would make more -- as opposed to no wind at all, it might take a lot longer to --

DR. COCHRAN: That's a very good question. And as regulators, we're faced with some difficulty. We can't say which way the wind is going to be blowing. So we have to assume that the highest air concentrations that we're measuring -- and they're probably downwind, because there's always air moving, you're going to have to use those values; because it could go to the bystanders, I mean if they happen to be in that direction.

So although there will be a bias in your sampling procedure, because we have a number of different replicates -- again, we're always using the highest air concentration that we're monitoring and we're assuming that bystanders could be in that direction. But your question is correct.

PANEL MEMBER BYUS: Unless of course it was like

a Santa Ana wind blowing, in which case it would all get blown away before you could monitor it.

CHAIRPERSON FROINES: In Los Angeles of course you have the daytime western flow. But at night you have an offshore flow. So that what's downwind in the daytime is going to be upwind at night. So that its not quite as simple as -- it's not just a Santa Ana issue. It's essentially a daily occurrence.

DR. COCHRAN: Well, that's for the people that live over near UCLA. But if you're in the San Fernando Valley, you don't get that.

PANEL MEMBER HAMMOND: Well, you get a different -- they have a different kind of wind pattern that changes through the day.

DR. COCHRAN: That's right, right.

PANEL MEMBER HAMMOND: I mean it's not the same, but it's a different one.

DR. COCHRAN: But it's different.

PANEL MEMBER HAMMOND: But it does change; it's not the same. There's not one predominant wind direction.

DR. COCHRAN: Right. But what we're doing here is we're trying not to assume that people are going to get a break. We're trying to look at what the worst case situation is.

PANEL MEMBER HAMMOND: And hopefully that means

that you're keeping track of what the winds -- I mean we care about what the winds are when you're monitoring, right.

ARB AIR POLLUTION SPECIALIST BAKER: I was just going to add -- Lynn Baker again. I was just going to add that we collected on-site meteorological data during our two studies, which were -- both houses were of the TRAP method. And the winds during the venting -- during the venting and tarp removal were relatively light. And we ensured that we did have samplers downwind.

PANEL MEMBER BYUS: That's great.

PANEL MEMBER ATKINSON: Are there any conditions when they don't fumigate houses? I mean any meteorological conditions that stop them from doing it?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: I'm not sure if there are any label requirements. But I do know in high winds it's difficult to get the tarps in place. And so they won't do it for that reason.

PANEL MEMBER ATKINSON: What about rain? Any effect on rain apart from the miserable job of putting the tarps up?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: I don't think so.

CHAIRPERSON FROINES: But ARB wouldn't monitor during rain.

ARB AIR POLLUTION SPECIALIST BAKER: We didn't monitor during rain, no.

PANEL MEMBER PLOPPER: I have a question.

Could you define what you mean by a bystander? If you don't know what the concentrations are distances away from these houses, what is a bystander then?

DR. COCHRAN: There's no requirement on this, as far as I know, with the state as to how far buildings can be apart. It changes with jurisdiction. And some places you have trouble walking sideways between buildings. So I mean how -- what is a bystander? If you happen to be in the house that's right next door and there's only about six inches between your building and their building, you're still getting exposed or there's the potential to be exposed.

And it's true, I mean we're making the assumption that there's no different between indoor and outdoor air concentrations. I know of only one study in which something like that was measured. And that was done some years ago by my colleague here. And they looked at malathion concentrations outdoors and indoors while there was spraying going on. There was about a four-fold difference between indoor and outdoor air concentrations.

PANEL MEMBER ATKINSON: Yeah, it probably wouldn't apply for something like sulfuryl fluoride, which

is, you know, clearly gaseous. I mean if you look at things like ozone, there's only a difference of about 50 percent indoors versus outdoors particles viewed as being the same indoors and outdoors just due for --

DR. COCHRAN: Right, so we're not using it as --

PANEL MEMBER ATKINSON: So I would expect you'd have pretty well the same concentration of the compound indoors as outdoors, unless they're using an airconditioning system tightly sealed up.

DR. COCHRAN: I think that's a good point.

CHAIRPERSON FROINES: I have trouble with the term "bystander," which it sounds like you do too. It seems like there should be another term one could use, like "members of the public" or something like --

PANEL MEMBER PLOPPER: Just needs to be defined what it is. I mean is that somebody standing outside the building or two blocks away or --

DR. COCHRAN: I think it is defined in the document. But we'll check to make sure that --

CHAIRPERSON FROINES: No, no, I'm not quarreling with that. It's a term that gets used -- I've seen it in other documents not relating to pesticides. I've always had trouble with the word "bystander" as though it's somebody who accidentally happens to be standing there as opposed to somebody who lives next door, who is not

obviously a bystander, who's a --

PANEL MEMBER HAMMOND: Like a neighbor.

(Laughter.)

CHAIRPERSON FROINES: A neighbor, right.

Anyway, don't get sidetracked.

PANEL MEMBER GLANTZ: I just have one very parochial question. And I live in San Francisco where the houses are butted right up against each other. How do you apply this stuff in a situation like that, where you can't completely cover the house?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: For structures that cannot be tarped or are too large to be tarped, they have a method that they call tarp and spot -- tape and seal, where they put plastic and tape around all the doors and windows and seal up all the vents and then fumigate.

CHAIRPERSON FROINES: Let's go ahead.

DR. COCHRAN: Okay. Next slide.

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DR. COCHRAN: Finally, for non-worker bystanders proximal to non-food commodity fumigation sites, exposure may occur during the application and aeration phases of the fumigation. From the use reporting data I showed you earlier, you can tell that sulfuryl fluoride is not commonly used to fumigate non-food commodities.

Therefore, only acute and annual exposures were assessed for bystanders during a non-food commodity fumigation.

Because no air monitoring data were available, bystander exposure was estimated assuming a maximum ambient air level of 5 ppm, which is what's allowed on the label. For short-term exposures an upper bound was estimated by assuming that indoor air levels are equal to outdoor air levels and that an individual could be exposed for 24 hours. The annual exposure assumes that there is one exposure per year. As the pesticide use data indicate, that it's not likely again that you're going to see more than that.

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DR. COCHRAN: And, finally, these are the various areas of uncertainty in the estimate of the exposure. There are those technical issues that I discussed earlier concerning the monitoring data. And we have a lack of monitoring data associated with the maximum label approved use of sulfuryl fluoride, so we're having to make the assumption that we have a linear relationship between the amount used and the exposure level.

And as people on the panel have indicated repeatedly, that we don't have any data on the differences or potential differences between indoor and outdoor air levels, and we don't have any real data on the movement of

the sulfuryl fluoride as a plume off of the site.

Are there any questions that the panel would care to ask?

PANEL MEMBER BYUS: I just have one comment.

It's always -- It's interesting -- I mean you do a nice job in this part of the document on application rates. And applicators, do they just -- I'm a pharmacologist, so I'm always interested in the doses. When they decide to dose a house, do they calculate the volume of it first? Is that when they -- they measure in and calculate the volume and then they use -- multiply that out and that's how they decide how many pounds to apply?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: Correct. And actually, in the case of sulfuryl fluoride, it's quite a sophisticated method to calculate the correct dosage, not only the volume which they measure, but they also varied the application rate with the type of house, whether it's a slab or foundation, the temperature, how well the tarps are sealing the building. And so there are a number of different factors that go into the dosage.

PANEL MEMBER BYUS: And you do a nice job. You do discuss that in the document. And I think that's important.

And the other thing you state that's worth mentioning is that since this is a fairly expensive thing, they don't -- they're careful not to apply too much, because it -- not that they don't care, but it does cost them a lot of money. So they're going to only put what minimum amount that is going to do the job, unless there's a mistake, which is always a possibility.

CHAIRPERSON FROINES: Okay. Thanks Roger. That's very good.

As long as we're making -- are you the next speaker, Randy?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: Dr. Lim will be the next speaker.

CHAIRPERSON FROINES: I just wanted to put on the record officially, formally that Maryann Warmerdam, the Director of DPR, is here attending the meeting. I'm very pleased that she's here to see how this process actually goes on. And hopefully it will help as we proceed in the future.

Welcome.

(Thereupon an overhead presentation was Presented as follows.)

DPR STAFF TOXICOLOGIST LIM: Thank you.

I'm Lori Lim. I'm with the Medical Toxicology Branch. And I'm the author of the Executive Summary and

the Risk Assessment portion of the document.

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CHAIRPERSON FROINES: Do you want to take a break?

Let's take a five-minute break.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Can we get started following our five-minute break.

PANEL MEMBER GLANTZ: It all depends on how fast you move.

CHAIRPERSON FROINES: It's an Einstein relativity issue.

Lori, just -- well, let's wait. We have -- Charlie and Joe are out of the room.

PANEL MEMBER GLANTZ: And Kathy.

CHAIRPERSON FROINES: Oh, yeah.

Tobie, during the break Joe Landolph and Charlie Plopper raised questions about the bystander -- the exposure issue. And so I want to move ahead into the risk assessment. But we'll come back to that later, because I think they have some issues that they want to raise, really for clarification rather than anything else.

We didn't tell jokes, Kathy, while we were waiting.

PANEL MEMBER HAMMOND: I didn't know you were

waiting for me.

CHAIRPERSON FROINES: Lori, go ahead, please.

DPR STAFF TOXICOLOGIST LIM: Okay. This slide lists the drafts and the external review of the risk characterization document, RCD. This RCD is more complex than previous TAC documents because it was written to meet mandates of both SB 950 to address both occupational and general population exposures, and AB 1807 to address ambient air exposures.

The first draft dated March 2004 was sent to OEHHA and ARB for comments. The DPR responses to their comments are included in Volume IV of this current draft.

An August 2004 draft was sent to the SRP, ARB and OEHHA; and as well as presenting at the DPR's Pesticide Registration Evaluation Committee meeting and posted for public comments.

OEHHA provided draft findings based on the content of their draft.

The SRP leads, Dr. Byus and Dr. Atkinson provided us comments on the August 2004 draft. Their review resulted in an April 2005 draft. And after we made additional changes, the final draft was completed and stated June 2005 and is now being presented at this meeting.

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DPR STAFF TOXICOLOGIST LIM: Before I get into the specifics about sulfuryl fluoride, I want to give an overview of the risk assessment process and define some of the terms which I'll be using in this presentation.

The process starts with a question regarding toxicity and exposure. What is the toxicity of the pesticide? This is answered by reviewing the toxicology studies to determine the toxicity endpoints of concern. We use both published and registrant submitted studies. In this review we also seek answers to the question on how toxic is the compound. This is established by doing dose-response analysis of the data.

For exposure, the question is: What is the human exposure? The main divisions are the workers and the general population. As shown in Dr. Cochran's presentation, these two groups are further subdivided according to the age and exposure scenario.

These then lead to the question of: What is the risk of human health from exposure to the pesticide? We take into consideration the data on toxicity and exposure, as well as uncertainties and limitations of these data to come up with quantitative risk estimates.

At the conclusion of this process, recommendations are made to the risk management whether exposures need to be mitigated or not. For AB 1807 the

recommendation would include consideration about TAC listing.

In the next few sides, I will go over the steps on hazard identification, dose response assessment, and risk characterization in more details.

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DPR STAFF TOXICOLOGIST LIM: When we reviewed the toxicology studies for hazard identification, no-observed-effect levels, or NOELs, for treatment related effects are identified for each study. This is presented in the toxicology profile of the risk assessment document.

This step is tied in with the dose response assessment where we figure out the relationship between dose, response, and the duration of exposure. Out of this assessment is a determination of the critical NOELs and endpoints. The critical NOEL is generally the lowest NOEL of all available toxicology studies which did not cause any treatment-related effect for the duration of concern. Sometimes the lowest NOEL is rejected because of problems with the study. The critical NOEL would protect humans from effects at higher doses for the same duration of exposure.

One way to visualize this process is in terms of a sieve as shown in this slide, where 300 ppm is selected as the critical NOEL. The study with the critical NOEL is

referred to as the critical study or the definitive study.

This critical NOEL is used for two calculations to quantify the risk: Reference concentration and margin of exposure.

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DPR STAFF TOXICOLOGIST LIM: The reference concentration is the human exposure which should not be exceeded. It takes into account the differences in intake due to differences in inhalation rate between laboratory animals and humans, as well as between age groups in a population. For the latter case, infants have the highest inhalation per body weight, and would result in the lowest reference concentration.

It also incorporates uncertainty factors to account for uncertainties and limitations in the database. And this will be discussed further in the next slide.

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DPR STAFF TOXICOLOGIST LIM: This slide lists the three types of uncertainty factors used in the risk assessment. Each of the factor reduces the NOEL, with a default being a ten-fold factor.

First is the factor to account for the intraspecies variations between human individuals. This includes differences in response, which may be due to factors such as age, gender, genetic disposition and

health and nutritional status.

Interspecies factor is used when there is extrapolation data from laboratory animals to humans. This essentially assumes that humans are more sensitive than the most sensitive laboratory animal to the effects of a chemical. The default ten-fold factor may be further subdivided into a three-fold factor for pharmacokinetic and a three-fold factor for pharmacodynamic differences between species.

A third uncertainty factor is used when a required study has not been conducted, or a toxicity concern not addressed in the existing database. One example is the lack of a developmental neurotoxicity study for chemicals which cause neurotoxicity.

CHAIRPERSON FROINES: Lori, can I ask you one question?

DPR STAFF TOXICOLOGIST LIM: Yes.

CHAIRPERSON FROINES: The estimate of 18 percent that you used in your document, there's a paragraph where you talk about using a ten-fold safety factor to address the uncertainties in that 18 percent value. Is that the interspecies -- is that uncertainty factor that you've referred in the document the ten-fold interspecies docu --

DPR STAFF TOXICOLOGIST LIM: That's in addition to the adjustment for the absorption. We're talking about

the ten -- the interspecies ten-fold is taking care of age and gender, whatever that we don't know. That's in addition to it. And that 18 -- I'll talk about the 18-percent factor much more later.

CHAIRPERSON FROINES: Okay. Go head.

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DPR STAFF TOXICOLOGIST LIM: These are the equations to calculation the reference concentration. The first equation converts the NOEL usually from an animal study to a human equivalent NOEL. That is, we ask them the question: What would be the air concentration when inhaled by humans to get the same dose, given the differences in inhalation rates? This value is amortized for 24 hours so that the RfC is a 24-hour time-weighted average.

PANEL MEMBER GLANTZ: If I -- You used this equation in the -- I don't remember if it was the executive summary, but the beginning of the document where you have a typical calculation. And I think you need to put this in there, because I was sort of guessing what the numbers were.

I think the other thing that I guessed was the conversion between parts per million and mass per unit volume. So I think it would just -- I kind of got stuck there till I puzzled it out. You should include that.

Do you know the place I'm talking about?

DPR STAFF TOXICOLOGIST LIM: Yes, it is in the technical summary,

PANEL MEMBER GLANTZ: Yes.

DPR STAFF TOXICOLOGIST LIM: Yeah.

I have provided actual calculations in the appendix, but I could move it forward, cut and paste -- I mean copy and paste.

The second equation then applies -- oh, the last term on number of days is not used for a single day exposure.

The second equation then applies the uncertainty factors to the human equivalent NOEL to derive the reference concentration. This could range from a ten-fold when a human study is used to a thousand-fold when an animal study's used and there's a missing required study.

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DPR STAFF TOXICOLOGIST LIM: The critical NOEL and the reference concentration are used to quantify the risk of human exposure to the chemical. This risk can be expressed in two ways: As a percentage of the reference concentration or by a margin of exposure.

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DPR STAFF TOXICOLOGIST LIM: The first equation expresses the risk of human exposure as a percent of the

reference concentration. Both the exposure and RfC terms are in ppm's.

In the second equation a margin of exposure is calculated, is in the equation. When the human exposure is expressed as an absorbed dose, the NOEL is also converted to an absorbed dose. And I'll get into absorption factor effect on this equation later.

PANEL MEMBER BYUS: So in a sense the -- pardon, just to clarify -- the absorbed dose only -- the absorption -- the percent absorption number only affects the margin of exposure, not the reference concentration; is that correct?

DPR STAFF TOXICOLOGIST LIM: Precisely.

PANEL MEMBER BYUS: Everybody understand that? So that really the other --

PANEL MEMBER HAMMOND: What? Say that again please.

PANEL MEMBER BYUS: Why don't you say it, Lori.

DPR STAFF TOXICOLOGIST LIM: And you can see that in the reference concentration we used in only the air concentration. Whereas in a margin of exposure we put in the absorption factor. That's only if the human exposure term is expressed as absorbed. If it's not expressed as absorbed, then we will not adjust the NOEL as absorbed. So we're just trying to get it to be equal in the same

term.

So the absorption factor only affects the margin of exposure calculation in the sense that we put it there.

Is that clear?

PANEL MEMBER ATKINSON: Well, surely, doesn't that affect the reference compound as well? If it's taken from a rat model and humans are being exposed, if there's any difference in the absorption factor between the two species.

DPR STAFF TOXICOLOGIST LIM: Oh, definitely. I will talk about that later. But generally the reference concentration is an air concentration expression.

CHAIRPERSON FROINES: But it doesn't affect the MOE, Roger.

DPR STAFF TOXICOLOGIST LIM: Right.

PANEL MEMBER ATKINSON: I know.

CHAIRPERSON FROINES: Because you assume similar absorption too -- they assume similar absorption.

PANEL MEMBER ATKINSON: Right.

DPR STAFF TOXICOLOGIST LIM: Yeah.

Okay. These two terms --

PANEL MEMBER BYUS: Sorry. That's all right. Go ahead.

DPR STAFF TOXICOLOGIST LIM: These two terms are related. When a human exposure is at 100 percent of the

RfC, the MOE is equal to the total uncertainty factor used to calculate the RfC. And I have an example of math here on this slide.

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DPR STAFF TOXICOLOGIST LIM: This slide shows that if we assume that an infant exposure is at 0.12 ppm, which is the RfC, then taking it to -- express it in terms of milligram per kilogram per day using a default inhalation rate of 0.59 cubic meters per kilogram per day, that would result in an exposure dose of 0.30 milligram per kilogram per day. And you divide -- you're taking the NOEL of 300 milligram per kilogram per day, divide that by the human exposure, you would get the 1,000. So this does show that the math works out. So if the exposure had to be in 50 percent of the RfC, then the MOE would be 2,000.

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DPR STAFF TOXICOLOGIST LIM: This slide, with a backward number line and not to scale, illustrates where different levels are in terms of the NOEL, reference concentration, and the listing criterion. An animal NOEL of 300 ppm, on the far left, is equivalent to a human equivalent NOEL of 122 ppm for infants. This is adjusting for only inhalation rate between the animals and humans. When a 1,000 uncertainty factor is applied, it results in 0.12 ppm as a reference concentration. Taking it ten-fold

lower the list criterion is now at 0.012 ppm.

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DPR STAFF TOXICOLOGIST LIM: This slide shows the major section of volume 1, the health risk assessment, where the questions from the risk assessment process are addressed.

CHAIRPERSON FROINES: I should say just parenthetically that some years ago we had a workshop on these kinds of issues. And Dale Hattis from Clark University presented data, as well as some other people, and their -- they determined that sometimes our use of ten-fold safety factors is not adequate. So it's actually an open question that still is in the research rather than regulatory context.

DPR STAFF TOXICOLOGIST LIM: The hazard identification and dose response assessment in Sections III and IV. Risk estimates are presented in IV.C of other volume.

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CHAIRPERSON FROINES: I'm sorry. I brought that up because I wanted -- because there were so many important issues in the workshop on these kinds of risk assessment estimates. I think, Jim, that transcript from that meeting would be available for DPR to take a look at. Because it was a very, very important meeting in terms of

looking at some of the assumptions that go into these risk assessment calculations. So you might find it useful sometime.

Sorry. Go ahead.

DPR STAFF TOXICOLOGIST LIM: This slide highlights in red the areas which pertain to AB 1807 looking at the exposure of the bystanders. And they're the focus of the rest of my talk.

I will first summarize the findings from the toxicity studies in the toxicology profile. Then I will present the risk assessment for bystanders.

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DPR STAFF TOXICOLOGIST LIM: What is the toxicity of sulfuryl fluoride? The database -- that we have limited -- consists primarily of toxicology studies with laboratory animals exposed to sulfuryl fluoride by inhalation.

In 2002 U.S. EPA made a decision to require a developmental neurotoxicity study, but later waived this requirement when the registrant accepted an additional uncertainty factor of ten-fold instead of conducting the study. So in this risk assessment the factor is included in the determination of the reference concentration and the MOE for the general population.

There were reports of human toxicity to sulfuryl

fluoride due to intentional and accidental exposures when the house was tented for fumigation or when the treated house was not aerated sufficiently.

CHAIRPERSON FROINES: Is it common for EPA to do that?

DPR STAFF TOXICOLOGIST LIM: This is the first case.

CHAIRPERSON FROINES: That's a -- that's a -- to say, "Don't do the study, just throw in a factor of 10"?

DPR STAFF TOXICOLOGIST LIM: This is the first one that I know of.

CHAIRPERSON FROINES: Boy, it's a little shocking, isn't it, when you think about it, because it's so --

PANEL MEMBER HAMMOND: Well, especially because I think some of those accidental exposures had neurotox effects, right?

CHAIRPERSON FROINES: It would seem like a developmental neurotox study would be very useful.

Tobie.

DPR ASSISTANT DIRECTOR JONES: This is Tobie Jones. I just want to comment.

I think -- my toxicology staff may correct me, but I think the whole issue of EPA requiring developmental neurotoxicity studies came out of the Food Quality

Protection Act of 1996. And so I think, as Lori explained in this case, if a registrant chooses not to develop that study, then the Agency applies an additional ten-fold safety factor.

So I think -- it's a trade-off. But the developmental neurotoxicity studies as a regulatory requirement is a relatively new issue.

CHAIRPERSON FROINES: That's interesting.

Well, I think Kathy's point's very well taken. I mean to the degree that there is evidence of neurotoxicity, then you would like to see one.

DPR STAFF TOXICOLOGIST LIM: Yes, I would like to see one definitely.

(Laughter.)

DPR STAFF TOXICOLOGIST LIM: Okay. There reports of -- oh, I already did that. Let's see.

Study on workers involved in fumigation procedures suggest that some -- suggested neurological deficits. Unfortunately some workers in these studies were also exposed to methyl bromide, another neurotoxic fumigant, and their exposure to sulfuryl fluoride were not quantified.

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DPR STAFF TOXICOLOGIST LIM: In answer to the question of what is the toxicity of sulfuryl fluoride, the

first type of study we looked at is the pharmacokinetic study. There is only one pharmacokinetic study which was conducted in rats exposed to S35 sulfuryl fluoride by nose-only inhalation for four hours. When the rate of activity was measured seven days after exposure, the respiratory tract contained the highest level of radioactivity, with lower levels in the spleen, kidneys, brain and other tissues.

Fluoride, as the primary metabolite, were measured only in the plasma, kidney, brain and urine. Fluoride levels in these tissues returned to background levels after exposure. Fluorosulfate as an intermediate was also measured in the urine and blood. Sulfate was also detected. And the levels of these metabolites are on Table 2, page 26 of the document.

The primary route of excretion was via the urine, with some small amount in the feces.

The sum of radioactivity in the tissues at the end of seven days and the cumulative excretion of radioactivity in the urine and feces over the same seven-day period was added to a total of 18 percent of the administered dose. This is considered the absorption factor and used to estimate the human absorbed doses in the exposure assessment. The uncertainty associated with the use of this factor will be discussed further in this

presentation.

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DPR STAFF TOXICOLOGIST LIM: The toxicology database for sulfuryl fluoride showed three major target organs:

The Brain. Clinical signs were observed after acute and one to two weeks exposure at concentration of greater -- equal to or greater than 300 ppm. And these signs included tremors, lethargy, convulsion, hyperactivity, and motor incoordination.

Histologically, one striking finding is the vacuoles, a clear area in the cerebrum of all the species tested, the rats, mice, rabbits and dogs, after repeated exposure to a concentration generally less than 300 ppm for two weeks or longer. The cause and consequence of these vacuoles are unknown.

A second target organ is the respiratory tract where inflammation and alveolar macrophage aggregates were observed in lungs of rats and dogs after chronic exposure. These could be a result of chronic irritation.

Epithelial hyperplasia of the nasal tissues were reported in the rats and rabbits, again with repeated exposure.

As a result of exposure to fluoride, dental fluorosis was absorbed in animals after repeated

exposures.

Other effects involving the kidney, including hyperplasia and degeneration and glomerulonephropathy, as well as thyroid epithelial hypertrophy and body weight reductions.

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DPR STAFF TOXICOLOGIST LIM: This slide shows a picture of the vacuoles found in brain tissue of rats exposed to sulfuryl fluoride for 13 weeks. The vacuoles were localized primarily in the basal ganglia region of the brain. This and other studies showed that the increase in incidences were related to the dose and duration of exposure. The increase incidences, however, did not correlate with the doses which resulted in clinical signs. That is, some animals show vacuoles in the brain, but not clinical signs. It could be that more detailed neurological examination and/or extensive -- more extensive histopathology are needed. The nature of these vacuoles has not been identified. The inside of these vacuoles did not stain for lipids, myelin, glycogen, or neural tissues.

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DPR STAFF TOXICOLOGIST LIM: Here are the results of some types of studies in the database. Sulfuryl is not considered an oncogen or mutagen.

PANEL MEMBER LANDOLPH: Could you stop there a second.

DPR STAFF TOXICOLOGIST LIM: Sure.

PANEL MEMBER LANDOLPH: The discussion of carcinogenicity I think I would recommend making some modifications and through -- here and throughout the document. I would not say that those studies are negative. I would say that those studies actually have some positive results. You could say that they're not conclusive and they need to be expanded. But I certainly would not say that they're negative. In one study they were osteosarcomas and in another study they were benign bone tumors. Those are not negative studies.

DPR STAFF TOXICOLOGIST LIM: This is sulfuryl fluoride only. I think what you're referring to was fluoride.

PANEL MEMBER LANDOLPH: Oh, fluoride, yeah, which is a component of -- which it generates.

DPR STAFF TOXICOLOGIST LIM: Right. So what I need to do is add the fluoride carcinogenicity paragraph on to that section.

PANEL MEMBER LANDOLPH: Yeah, I've made some specific suggestions for that. I would do that.

I also think we might even consider recommending that sulfuryl Fluoride go to the NTP to have a full

carcinogenicity study on it. And the same thing -- I might as well do the genotoxicity now too.

Again, I think the characterization of that as negative is not precisely accurate. There were some positives in V79 Chinese hamster cells for mutagenesis and for chromosome breakage.

DPR STAFF TOXICOLOGIST LIM: Again, that's for fluoride.

PANEL MEMBER LANDOLPH: For fluoride, yeah, which is a metabolite of sulfuryl fluoride. So you might -- I would recommend that you'd qualify those statements. Because in some instance within the document the data on genotoxicity was called equivocal in your very nice fluoride appendix. And it's not really equivocal, because if it's positive in mammalian cells but negative in bacteria, it's just doing different things. The physiology is different. So I wouldn't call that equivocal.

And I would urge you to be cautious here. The reason why is underlying all this is if sulfuryl fluoride and/or its metabolites turn out to be genotoxic carcinogens, then you're talking about a three log or more shift in the NOELs and the dose response curve. We're not there yet. But I would urge you to be real careful on how you state that.

DPR STAFF TOXICOLOGIST LIM: Okay.

CHAIRPERSON FROINES: Can I ask a question about -- to Joe.

In the document that you wrote with your recommendations, is everything you just said included in that document?

PANEL MEMBER LANDOLPH: Yeah, a little bit in a more articulate fashion than the way I just said it. It's lengthier, but yes.

CHAIRPERSON FROINES: It is?

PANEL MEMBER LANDOLPH: It's more organized, yeah. It's all here.

CHAIRPERSON FROINES: I think that there is one sort of generic point, which is that we need to be -- we need to look at metabolites as -- when we -- I mean this came up with metam sodium, for example. And that clearly the metabolites were highly toxic. And so that it's important to -- as an overall policy I think to look at the toxicity of the metabolites as representative of the toxicity of the parent. Since we know there's a lot of fluoride released, to only look at the studies on the parent would underestimate the impact of the metabolites.

PANEL MEMBER LANDOLPH: And obviously the Bassin study, which unfortunately has not been published, from Harvard, which you were so kind to point out to us,

indicating that there might be some increased incidents of osteosarcomas in young males -- young boys. When you add all this together, it's beginning to get a little bit worrisome. So I would just recommend you encapsulate that all in the section. And I've made some recommendations to help you do that, which I e-mailed to Randy earlier.

DPR STAFF TOXICOLOGIST LIM: Yes, I do have it. And I have it here.

And now that we talk about it, I want to ask you a question on the Bassin study. So the thesis work is completed. Is the thesis available, do you know?

CHAIRPERSON FROINES: I don't know what you sent to Lori. But all I had was a newspaper article basically.

PANEL MEMBER BYUS: I can answer that question.

I called a friend of mine after you pointed this out to me at the EPA, who works on -- a toxicologist who works on fluoride in the water. She explained to me exactly what's happening with that study. That was a thesis study from Harvard. There's a National Academy of Sciences committee right now which is reviewing all the data on fluoride toxicity. It's looking over that study. She read that study. She couldn't get it to me electronically. She didn't have it electronically.

It was a study done by a woman, a graduate student who -- and it is unpublished currently. Very well

done, she said, where she used -- she analyzed other people's epidemiological data and put a fresh spin on it by bending it out by age, where she did find an increase in eight to nine year old males in osteosarcoma, not females. But she was very cautious in her writing and very careful not to draw any conclusions because of the exposure aspects of it, not knowing how -- because you can be exposed to fluoride from multiple sources.

And the National Academy of Sciences is looking over that -- this committee that's currently EPA has asked the NAS to do this -- just looking over that study in detail. It should be finished in February.

There is the other additional data, however, in addition to this that -- there's a significant amount of data with fluoride being used to prevent increased bone density. Ten years ago it was used a lot to increase bone density. They subsequently found out it was toxic. And so there's a whole plethora of sort of bolus fluoride use of data given to a huge number of people for that purpose. And they're also evaluating all of that data.

And so there will -- there should be early next year a whole new review of the current state of the art of where fluoride is, using that Harvard study, plus primarily this new bunch of human data with fluoride as a drug. Which has now been removed from the market because

they reviewed -- they found it was toxic.

CHAIRPERSON FROINES: So there is a National Academy Study. But that means that EPA probably has that epi steady.

PANEL MEMBER BYUS: It has the epi study. She was reading it to me from --

CHAIRPERSON FROINES: So maybe you -- I don't know where you would find it at EPA.

PANEL MEMBER HAMMOND: No, wait. If the dissertation is completed --

PANEL MEMBER BYUS: It's completed. You can get it.

PANEL MEMBER HAMMOND: -- then you can get it, right?

PANEL MEMBER BYUS: Sure. You can get it from Harvard. She got it from Harvard.

DPR STAFF TOXICOLOGIST LIM: That was my original question. If it's completed, then we could certainly ask a librarian to get it.

PANEL MEMBER HAMMOND: And that I think become a citable reference.

PANEL MEMBER BYUS: It's citable.

CHAIRPERSON FROINES: Okay.

DPR STAFF TOXICOLOGIST LIM: I just wanted to add that we're very fortunate that at our branch a fellow

toxicologist, Dr. Ruby Reed, is a member of the NAS Fluoride Panel.

CHAIRPERSON FROINES: So, she is?

DPR STAFF TOXICOLOGIST LIM: Yes.

CHAIRPERSON FROINES: That's great.

DPR STAFF TOXICOLOGIST LIM: And so she's my primary consultant on the fluoride issues.

CHAIRPERSON FROINES: Oh, she probably has the study.

DPR STAFF TOXICOLOGIST LIM: She's probably looking at it. While she cannot tell me any of their conclusions or deliberations, we're pretty much up on what's available. And some -- you know, I discuss these issues with her. Okay.

CHAIRPERSON FROINES: Yeah, she -- Joe.

PANEL MEMBER LANDOLPH: Yeah, also I noticed in your summation -- incidentally, which I thought was very nice on the oncogenicity of the sulfuryl fluoride, and all the -- the whole volumes were very well written -- I noticed there was also mentioned that sulfuryl Fluoride caused hyperplasia in lower animals and also hypertrophy of the thyroid and depletion of collagen of the thyroid in lower animals. So I would almost suggest a cautionary note that these effects have been noted, and we should look more closely to the future about whether there is a

potential for this to cause -- sulfuryl fluoride to cause tumors of the thyroid and/or the kidney. It's something we should be looking for.

CHAIRPERSON FROINES: Where's the hyperplasia?

PANEL MEMBER LANDOLPH: Hyperplasia of the kidney.

DPR STAFF TOXICOLOGIST LIM: I will add those points in my document.

Looking on page 2 of your comment on the second paragraph. Lets's see, that's 1, 2, 3, 4, 5 -- line 5 it says, "The fact that sulfuryl fluoride is positive in some types of assays and negative in other types of assays does not make an equivocal genotoxin." You mean fluoride and not sulfuryl fluoride, right?

PANEL MEMBER LANDOLPH: Yeah, probably fluoride, yeah. Sorry.

DPR STAFF TOXICOLOGIST LIM: Okay. And that also later on in that same paragraph about the oncogenicity, again that's about fluoride?

PANEL MEMBER LANDOLPH: That would be fluoride, yeah. Sorry.

DPR STAFF TOXICOLOGIST LIM: Okay. I just wanted to make that clear.

PANEL MEMBER LANDOLPH: Yeah, sorry.

CHAIRPERSON FROINES: I mean I think it's true --

I think it's fair to say that the number of chemicals that come before us that are themselves the ultimate toxicant is virtually zero, with the exception of ethylene oxide or other epoxides. But anything else requires some either enzymatic bio-activation or in this case hydrolysis.

So that in general we should treat the metabolites as representative of the parent compound.

PANEL MEMBER LANDOLPH: And, again, there's no data on whether sulfuryl fluoride can bind covalently to macro molecules. I don't think anybody's ever looked at it. So it's something that -- there's a lot of things that should be done.

CHAIRPERSON FROINES: Is that your impression, Lori.

DPR STAFF TOXICOLOGIST LIM: The genotoxicity studies show that these are negative. But you're correct.

PANEL MEMBER LANDOLPH: Yeah, nobody's looked at them, yeah.

DPR STAFF TOXICOLOGIST LIM: Right. Yeah, we could do literature search and try to get as much as we can, all that we can. And then we stop and -- documents.

CHAIRPERSON FROINES: Well, it's a problem because the -- you know, we're at a place where we have these historical genotoxicity studies that were basically products of the seventies that certainly don't reflect the

modern molecular biology that we use for looking at mutagenicity. So it's at this strange place where there's a gap between the research side of things and the regulatory side.

So go ahead.

DPR STAFF TOXICOLOGIST LIM: Let me just add that on page 47, which is a short blip on genotoxicity, there is one study that used isolated hepato -- and look at a scheduled DNA synthesis, and the study was negative.

CHAIRPERSON FROINES: So if you have -- so we don't need -- so you can take Joe's comments and consider making subsequent changes from that?

DPR STAFF TOXICOLOGIST LIM: Yes, I think for all the oncogenicity section. Right now I only talked about sulfuryl fluoride. So I could just tag on fluoride that discussion from my appendix and sort of copy and paste it there.

CHAIRPERSON FROINES: Yeah, I mean if you want -- I mean seems to me without getting into word processing issues, if you want to have some summary data in the main document and additional document in the appendix, that would seem to me okay. But it's your call, however you want to approach it.

DPR STAFF TOXICOLOGIST LIM: But the point's well taken. And I will add that information.

Let me just sort of start again.

So sulfuryl fluoride is not considering oncogen or mutagen. No tumors were found in rats on those oncogenicity studies. However, the findings of hyperplasia in the kidney and nasal tissues and hypertrophy in the thyroid epithelial cells indicate preneoplastic events.

It does cause reduced rabbit fetal and rat pup body weights in the developmental and reproductive toxicity studies.

--o0o--

DPR STAFF TOXICOLOGIST LIM: After the review of the toxicology database, the next step is to identify the critical studies with duration of exposure similar to those determined for human exposure. That is, if humans are exposed to sulfuryl fluoride for eight hours, ideally we should have a study that tells us what is the toxicity for that eight hours. In reality we have animal studies of predetermined exposure duration and many more human exposure scenarios.

--o0o--

DPR STAFF TOXICOLOGIST LIM: For bystander exposure during structural fumigation application and aeration, the air concentration declined with time, as shown in the second column. During application for the

first 12-hour period the air concentration was relatively constant. Then it declined over the next 12 hours. During aeration the highest exposure was measured at the first time point. For example, the first hour was Stack method and the first two hours with the TRAP method. With non-food commodity fumigation the assumption was 24 hours continuous exposure at 5 ppm.

There was an earlier question about the use on food commodity fumigation which was recently approved I think like three or four months ago about the exposure. The maximum limit for that use is set at 1 ppm right now, instead of the 5 ppm. So I would expect that the 5 standard exposure would be lower. However, with the food commodity fumigation you can have more frequent fumigation, so you would expect repeated exposure scenarios and more people would be exposed.

CHAIRPERSON FROINES: Well, one of the issues is -- as we all know, those of us who do this kind of work, inhalation toxicology studies are extremely difficult, very expensive and what have you. But, you see, this slide is really interesting insofar it shows the contradiction though that we get into, that we basically have high exposure at 12 hours or high exposure at 1 hour. And yet our database is based on these 6-hour studies. Well, the 6-hour studies is not a reflection of the actual

conditions in which people breathe this material. So that the toxicology and the exposure are discontinuous in that sense. And it's really unfortunate.

Although I also know how difficult it is to do inhalation toxicology where you would -- but it's not impossible. So that this is not -- has nothing to do with this document. It's just sort of a statement -- a general statement. But it does reflect -- the problem we have is that our toxicology does not necessarily reflect our exposure conditions.

DPR STAFF TOXICOLOGIST LIM: And with the pesticides -- because there's a part of the registration process is to require these upfront toxicology studies. And then later on you might discover additional human exposures in there that's not addressed.

So it should be a -- process, but it is actually more a sequential process.

CHAIRPERSON FROINES: Interesting.

DPR STAFF TOXICOLOGIST LIM: Since we don't have any toxicity studies with these same exposure conditions, we amortized the exposure for human and the animals on the daily basis, so that these two terms can be used for the calculation of the risk later.

--o0o--

DPR STAFF TOXICOLOGIST LIM: This slide is a

summary of the studies with acute effects. The study number refers to the reference numbers in the document.

The air concentration, ppm, from the studies were converted to exposure in milligram per kilogram per day term to allow comparison between studies which were conducted for different durations and different species.

Study No. 8, in blue --

PANEL MEMBER GLANTZ: I just have one question -- because I may have now figured this out. But in the study -- in the -- when you say NOEL/LOEL, are you saying that the NOEL is the first number and the LOEL is the second number?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER GLANTZ: Okay. I think when you have these tables, you need to make that clear, because I -- when I read it I thought you meant it was a NOEL or a LOEL, rather than that you were presenting a NOEL and a LOEL.

DPR STAFF TOXICOLOGIST LIM: Oh.

PANEL MEMBER GLANTZ: So I was -- I was all ready to like jump all over you.

PANEL MEMBER HAMMOND: Two columns.

PANEL MEMBER GLANTZ: Yeah, I think it would be clearer if you made it two columns.

DPR STAFF TOXICOLOGIST LIM: Well, if I added two

columns -- I don't know. It's more that I was trying to fit everything on one page.

PANEL MEMBER GLANTZ: I know. But it is totally --

DPR STAFF TOXICOLOGIST LIM: Like additional columns --

PANEL MEMBER GLANTZ: -- yeah, but it was like totally confusing.

DPR STAFF TOXICOLOGIST LIM: I could add a footnote.

PANEL MEMBER GLANTZ: Yeah, and that -- yeah, and it kind of looks like it could be a ratio.

PANEL MEMBER HAMMOND: Yeah, I could bring it as a ratio.

PANEL MEMBER BYUS: That is really -- it looks like it's a ratio. So you really have to fix that.

DPR STAFF TOXICOLOGIST LIM: Would a footnote do, or should I squeeze a column in there?

PANEL MEMBER GLANTZ: And the other thing is -- you know, because this was one of the things that really bothered me when I read the report. Like if you look -- so for rat number 7 there was no effect at 300, right?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER GLANTZ: And what you're saying is that the LOEL is a greater than 300, but there -- wasn't

actually measured --

DPR STAFF TOXICOLOGIST LIM: No.

PANEL MEMBER GLANTZ: -- right?

Well then I think you should just say "not available" or "not measured". And, likewise, for rat number 1, you know, which -- you had a LOEL at 334 and you don't really know what the NOEL is, because they didn't -- now that I understand what the table's showing, they didn't actually do a study where they actually found a NOEL. So I think for the ones where you don't have a NOEL, you should just say "not available," because people will know that the NOEL is going to be lower than the LOEL, but this makes it sound like you actually know what the no observed effect level is.

DPR STAFF TOXICOLOGIST LIM: Okay.

PANEL MEMBER LANDOLPH: No, but she's just saying that that's an upper bound. It's below that. I don't have a problem with that.

PANEL MEMBER GLANTZ: Yeah, I understand. But to me I think -- I mean I don't think what's written there, now that I understand it, is wrong. But I think it's misleading, because to me -- when you say to me something is a NOEL, what that says to me is that you did an experiment where you kept lowering the dose and you actually got to a dose where you didn't detect an effect.

So it's an affirmative finding and it's saying that that's a dose where you couldn't find anything.

When you have a LOEL, the LOEL that you present is actually a function of the experiment. Because if you say, you know, that the -- say in rat number 1 that the LOEL was 334. That's probably the lowest dose they had tried or lowest exposure level that tried. And so that's saying that that's the lowest level you looked at and you still found an effect. But the actual LOEL could be well below that.

So I really think that when you don't have an affirmative evidence that something is a NOEL, meaning you did an experiment at that dose and didn't find an effect, then you should say you don't know what the NOEL is. Even though -- I mean now that I understand this, I think it's not -- it's not a lie, but I think it's misleading.

CHAIRPERSON FROINES: Well, if it's a question of getting things on one page, I think you can put footnotes and it will be clear.

DPR STAFF TOXICOLOGIST LIM: Well, I will explain it one way or another.

PANEL MEMBER GLANTZ: Okay. But I feel really strongly. If you don't have a direct measured NOEL, then you shouldn't put a number there. I feel really -- because that looks very misleading.

DPR STAFF TOXICOLOGIST LIM: Okay. I could fix that.

CHAIRPERSON FROINES: It's one of these strange things that this kind of risk assessment is dependent upon the doses that you select for the study. So you're always limited by those doses. And so if it helps, I guess -- I mean you can put an NA or something in there. But I would have a footnote that says if there was not a -- there was not a dose below the level that was -- or something like that.

PANEL MEMBER GLANTZ: Or I would even say -- for the NOEL, I would say "unknown," because you don't know what it is because you didn't -- there's no data there.

PANEL MEMBER ATKINSON: But for rat 1 it's clearly less than 334.

PANEL MEMBER GLANTZ: Yeah, but that is given in the definition of what a -- a NOEL is always less than the LOEL. So if you're -- see, to me when you say the LOEL was 334, what that's saying is they did an experiment and that was the lowest dose they tried and they still found an effect. And that means the NOEL is somewhere below that.

If the -- on the other hand, in rat number 7, they're saying they tried 300 and they didn't find anything. So there are two different statements. And I

think to put a number in when you don't know what it is, I -- I think you should just say "unknown" or something.

PANEL MEMBER BYUS: Well, sometimes they experimentally test it and just didn't find it.

PANEL MEMBER GLANTZ: Well, no, that's right.

PANEL MEMBER BYUS: And in document she -- all the information is there. I do sort of agree with you. But I don't know exactly what term I would have used. "Not determined" maybe or "not observed" or whatever.

DPR STAFF TOXICOLOGIST LIM: I think somehow I could make that more exact.

PANEL MEMBER GLANTZ: Whatever terminology you want. But I just don't think there should be a number there if you don't know what the number is.

DPR STAFF TOXICOLOGIST LIM: Well, one of the things that I -- the other thing that I do is, other than the formatting, which is really minor, but it allows me to just look down on that column of the NOEL. That's the first set of number. And then you could easily pick out and say, "Well, this one is less than 200," just right there, and to say, "Okay, I need to deal with this study." As if I had like "NA" there --

PANEL MEMBER BYUS: See what she's saying?

DPR STAFF TOXICOLOGIST LIM: -- then I would say -- then I've got to look back to the LOEL and then

still have to come up with some idea.

PANEL MEMBER BYUS: She's picking less than 200 as the NOEL.

PANEL MEMBER GLANTZ: Yeah. But, you see, I think that -- that to me -- that's the thing --

PANEL MEMBER HAMMOND: It's a way to look down the column to get information.

PANEL MEMBER GLANTZ: Right. And what I -- the information that I think you should get looking down the column is that you don't know what the NOEL is in several of the studies.

DPR STAFF TOXICOLOGIST LIM: Right. But then the second purpose was to line them up and make a comparison, saying that of all these studies, where these things fall out. And so --

PANEL MEMBER GLANTZ: Right. But I think you could --

DPR STAFF TOXICOLOGIST LIM: A sort of visual tool.

PANEL MEMBER GLANTZ: Yeah. But I think it's -- I mean I can tell you when I read the report, I got totally confused by this. And I think that -- I think that what you should do is have two different columns, that are right next to each other so people can compare them, and then when you have -- and the only numbers that

are in the tables should be numbers that were actually observed. And so if they -- if the lowest -- if all you know is the LOEL, that's an important -- I mean that's interpreted very differently, which just says to me, "Well, the NOEL is somewhere below that." But you don't know if it's one milligram per kilogram per day lower or if it's way lower.

CHAIRPERSON FROINES: Lori, I think if you have -- what I would do would be to -- let's take number 1. So you have a column of LOELs. Under the column of NOELs I think it would be entirely accurate to say "not determined," because that's what actually happened. Nobody -- there was no experiment that determined that value. So if you say something like NA, not applicable, will just further confuse people, I think.

PANEL MEMBER GLANTZ: Well, I was thinking "not available." But "undetermined" is --

CHAIRPERSON FROINES: "Not determined" reflects what actually happened, because it is an experimental point. So I think that was -- that's a more accurate way of -- and so then the reader sees -- and you can put a footnote saying, "Where it is not determined, one would anticipate a lower value were it to be so," or something like that.

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: That's pretty clumsy language, but -- I don't know.

DPR STAFF TOXICOLOGIST LIM: I was anything about having --

PANEL MEMBER BYUS: In this case did you actually -- let me just add. I mean did you actually choose the NOEL less than 200?

DPR STAFF TOXICOLOGIST LIM: Oh, I'm going to go into it now.

PANEL MEMBER BYUS: Okay.

CHAIRPERSON FROINES: Let's go ahead.

DPR STAFF TOXICOLOGIST LIM: Right.

CHAIRPERSON FROINES: So the recommendation from the panel would be to make that modification in terms of the table.

DPR STAFF TOXICOLOGIST LIM: Right, to say "not determined."

CHAIRPERSON FROINES: Yes.

DPR STAFF TOXICOLOGIST LIM: Let's see, where am I?

Study No. 8, in blue, showed the lowest NOEL at less than 200 milligram per kilogram per day. This NOEL was not selected as a critical NOEL because of several limitations in this study. The effect was transient, occurring at the first one to two minutes of exposure.

And this finding would be difficult to use to extrapolate to hours of human exposure.

Also, the actual exposure concentration was not reported in the study.

And, three, there were lack of sufficient details in reporting of the data as the data was shown only in graphs.

At the next higher NOEL of 300 ppm there was three studies, number 7, 3 and 11, highlighted in yellow. And the critical study is number 7.

--o0o--

DPR STAFF TOXICOLOGIST LIM: Study 7 was selected as the critical study because --

CHAIRPERSON FROINES: Could you go back -- could you go back just -- here's an issue that we need to think about a little bit, I think, just as a prelude to this. You'll notice that your LOEL for number 1 is 334. And you chose the NOEL of 300. But if you apply a safety fact because number 1 is a LOEL, you're going to get a different RfC than you will if you used 300. And I think it will be lower. And so we have a problem of when we have a LOEL that you would normally apply even a three-fold safety factor or something -- whatever it might be, that may end up dominating your risk number as opposed to the NOEL that you selected.

Am I clear?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER HAMMOND: It's not even a safety factor. But you were saying, if you're going to make an assumption -- make sure I understand you. You're saying if you're going to make an assumption of a NOEL in the absence of data, based on a LOEL, that that assumed NOEL for this purpose would have been something that would have been at least effective two or three.

CHAIRPERSON FROINES: What I'm saying is that if you take -- if you take 300 from number 7 -- and I haven't thought about this before this minute, so pardon me for raising it. But it just popped into my head.

PANEL MEMBER GLANTZ: That's one of the vacuoles.

(Laughter.)

CHAIRPERSON FROINES: If you take the 300 and you divide it by your three uncertainty factors of a thousand, that gets you down to .3 -- .3. Pardon me. If you take the 334 and you use your safety factor of a thousand -- let's assume a safety factor of 3 for the LOEL to NOEL conversion. Then you're down basically three-fold below what you got from your number 7. So that there's -- So there's a contradiction.

PANEL MEMBER HAMMOND: I'm sorry.

CHAIRPERSON FROINES: Go ahead. I'm sorry.

PANEL MEMBER HAMMOND: Excuse me.

But I don't think you want to use the word "safety factor" because they're two different concepts.

CHAIRPERSON FROINES: Uncertainty factor.

PANEL MEMBER HAMMOND: Right.

I mean so I think that what one's saying is once you're going to make an assumption that the NOEL -- you're going to assume a NOEL based on the LOEL. And when you do that, if I'm hearing you correctly, you're saying you would typically divide by three?

CHAIRPERSON FROINES: Or ten.

PANEL MEMBER HAMMOND: Well, I mean whatever it is -- and that's what the whole thing has. It has nothing to do with where you go from there, because from there it goes the same way. But I think the real question is as soon as you assume there's any factor, whether it's 2, 3 or 10, that immediately anything that has an unknown NOEL in this table, like a 334, is immediately going to become lower.

CHAIRPERSON FROINES: Right. If you took --

PANEL MEMBER HAMMOND: As an assumed NOEL --

-- if you took the traditional approach -- if you took the traditional approach, the tradition approach would have you do -- the first step would be to take the 334 and divide it by 10, which would give you 33.4. You

would then divide by the thousand --

PANEL MEMBER HAMMOND: I mean everything has that happen.

CHAIRPERSON FROINES: -- and so you would be down to .0334 as opposed to .33.

PANEL MEMBER GLANTZ: But the problem I think with what you're suggesting, John, is that you do that when you don't have any direct observations of a NOEL. And here they do. And, you know, the NOEL --I'm going to go back and argue with you about the 200 in a minute. But if you just look at the other studies, you've got three studies, number 7, number 3 and number 11, which have a direct observed NOEL of 300, which is less than 334.

So I think that -- if you didn't have any directly observed NOELs, then I would agree with you. But since they've got a directly observed NOEL at 334 -- at 300, then, you know, it may be that that LOEL that they found is just, you know, barely above the level that you start seeing things. So I think, since they have directly observed no-effect levels, it's more reasonable I think to use the directly observed levels rather than an extrapolated level from a LOEL, because you don't know how much -- you know, when you get a LOEL, you don't know how much above the NOEL dose that experiment happened to be because you don't have any data.

PANEL MEMBER HAMMOND: But --

CHAIRPERSON FROINES: But, see, Stan, from a toxicologic standpoint -- what you just said is what a statistician would say. But from a toxicologist's point of view, it depends on what you decide is your most relevant endpoint. So it doesn't matter what's on that -- those numbers don't matter because you actually have to decide what is the endpoint that we consider the most important for purposes of this process.

PANEL MEMBER GLANTZ: Well, that's a different -- no, I agree with that too. But that's a third point.

But what I'm just saying is that if -- let's assume -- see, because then what you would be saying is the slight tremors, body-weight loss you think should be the most important endpoint. And if that's what you think, then I would say, okay, then you take the 334 and apply it through your uncertainty factor. But what I -- but if you were to take all of these things as -- you know, equally weighted, then I would take a directly observed NOEL over a LOEL as long as the directly observed NOEL was below all of the other LOELs, which except for Study 8, which we can come back to, is the case.

CHAIRPERSON FROINES: Well, actually there's a literature on this. And Kenneth Crump has written about it over the years. I understand, Kathy has written about

it over the years. And in his work on benchmark dose, he's been very articulate. And the problem with the NOEL is that it is also an experimental point, and it could be much too high or much too low. You never really know with a NOEL. What the NOEL is is you didn't find anything. The advantage of a LOEL at some level -- the advantage of a LOEL at some point is that you did find something.

And so I think we should go on and -- because this is a general discussion. But I think that the point is that we shouldn't necessarily lock ourselves into the NOEL unless it's the study that we think is the crucial endpoint that we want to establish. I think --

PANEL MEMBER GLANTZ: I don't want to beat this into the ground. But I mean if you were to take a LOEL and apply an uncertainty factor and end up with a level that was below all of the observed NOELs, I wouldn't object to that as a decision, because that's going to be health protective, you know. But what I'm just saying is all things being equal -- you see, and in this case -- see, the bigger problem I have is discounting Study No. 8. Because what happened in Study No. 8 is you got a LOEL that was -- with a relatively short-term exposure that was below the other NOELs.

CHAIRPERSON FROINES: Let's hold it --

PANEL MEMBER GLANTZ: You know, the question

there is --

CHAIRPERSON FROINES: Let's let Lori make her argument before -- because this poor woman is not a -- we're blathering away while she's waiting to make -- also, I want to make point, when I said something about you -- when I said something about you as a statistician, me as a toxicologist, that was a joke.

(Laughter.)

CHAIRPERSON FROINES: Go ahead, Lori.

DPR STAFF TOXICOLOGIST LIM: Actually I think Dr. Glantz now probably qualified like a risk assessment, because that's just one of the things that we do, think about that if you do have -- even if you have an experimentally determined NOEL, that gives you greater confidence of where the toxicity ends. And that's one of the key things we would consider. And I do agree with you also. It too could be -- they would be writing risk assessments in that we -- I did consider those numbers. And what if I apply uncertainty factors? So -- because both are correct in those two points.

But there's another thing that we also look at, is again the quality of the study. I tracked down this particular study, it's on page 27 on the bottom, for that Study No. 1. In this particular study, the animals were exposed to up to six hours to 1,000 to 15,000 ppm. So in

some way by presenting milligram per kilogram per day value is actually a little bit misleading. And that's my fault trying to simplify the table. And then they were -- so it was --

CHAIRPERSON FROINES: Which one are you referring to?

DPR STAFF TOXICOLOGIST LIM: Page 27 on the bottom.

CHAIRPERSON FROINES: The bottom one? Okay.

DPR STAFF TOXICOLOGIST LIM: Yeah, that last study.

PANEL MEMBER HAMMOND: Male rat, starting that paragraph?

DPR STAFF TOXICOLOGIST LIM: Yes, by Dow Chemicals, 1959. This one is acute toxicity studies where they're trying to figure out what the LD 50 levels were.

And then after two to three hours exposure to lowest dose of 1,000 ppm, this is where the rats starting to show the slight tremors and the slight weight loss. There's one death in this group after two hours exposure. Then there was an estimated LC 50. And this is how the NOEL was derived. And so --

CHAIRPERSON FROINES: That's very useful. I wouldn't use that study.

DPR STAFF TOXICOLOGIST LIM: You wouldn't use the

study?

CHAIRPERSON FROINES: Not that study, based on its design quality.

DPR STAFF TOXICOLOGIST LIM: Right. So that's why it was not used.

So, again -- so looking at the NOEL where there's experimental, we determined a lot in looking at the quality of the study. And that's how we come up with our final decision.

CHAIRPERSON FROINES: Go ahead.

DPR STAFF TOXICOLOGIST LIM: Dr. Glantz, do you want to talk about Study No. 8? Because I'm not going to go into that.

PANEL MEMBER GLANTZ: Yeah, because -- I mean just looking at the table, it would seem to me that you should use 200 or something less than 200 as a NOEL, because again the NOEL -- because something appearing in 20 minutes seems pretty fast.

DPR STAFF TOXICOLOGIST LIM: Yeah, again, that's my fault. Like I explained when I was reading this slide was the effect was actually transient occurring the first two minutes of the exposure. The total study was 20 minutes. But they found the effect in the first two minutes. And it would make it very difficult to extrapolate that finding to a human exposure that we're

talking about hours. So that's why that study was not selected.

PANEL MEMBER HAMMOND: You know, but I guess I'm confused. You're saying the rat was actually exposed for a short -- just for a very short period of time and the -- or the transitory effect just lasted a short period of time?

DPR STAFF TOXICOLOGIST LIM: Right. Just right after they got exposed they recorded that. And then they were normal after that.

CHAIRPERSON FROINES: But were they -- what was the measure?

PANEL MEMBER HAMMOND: But the duration of the exposure of the rat was how long?

DPR STAFF TOXICOLOGIST LIM: The study was -- it's on the bottom of page 28. The duration was 28 minutes.

PANEL MEMBER HAMMOND: Because one of the things -- and this gets back to what --

DPR STAFF TOXICOLOGIST LIM: I mean 20 minutes.

PANEL MEMBER HAMMOND: -- Dr. Froines was mentioning earlier about that issue of the disconnect between normally having these very long chronic exposures in the animals and our concern in a material like this of being short and acute exposures. This is an exception to

that, where we have an animal study that does look at an acute exposure, right?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER HAMMOND: Now, I don't know whether the transitory respiratory health effect -- how significant that was as a health outcome. But I do think that the fact that it was something that did happen there is important.

DPR STAFF TOXICOLOGIST LIM: Right, at 4,000 and 10,000 ppm the level would be way, way, way higher than we would expect. Because I think if that was done in a level that's closer to what we would expect humans, I think that would be an excellent study.

PANEL MEMBER HAMMOND: Right.

What -- you know --

CHAIRPERSON FROINES: But I wanted to say at 200 --

PANEL MEMBER HAMMOND: -- I never felt that very comfortable with this, what are the occupational exposures, which keep getting -- they really were never discussed carefully here. But is there a chance that some of the workers would have those exposures?

DR. COCHRAN: No. Not that kind of concentration. They would have to be in self-contained breathing apparatus.

PANEL MEMBER HAMMOND: You know, I did have discomfort throughout the document with the idea of saying: Since you're supposed to have self-contained breathing apparatus if it's over 5 ppm, they can't be exposed over 5 ppm. I certainly have observed in my career workers being exposed above the levels where they should be better protected. And I don't think we can assume that because they're not supposed to be exposed at a certain level that they're not in fact exposed.

I would be happier with data that showed that.

CHAIRPERSON FROINES: I'm confused. How do we get a LOEL of 200 out of this study?

DPR STAFF TOXICOLOGIST LIM: It's extrapolating from the time to 24 hour per day.

PANEL MEMBER HAMMOND: Those two are per day?

CHAIRPERSON FROINES: Oh, yeah, yeah. Okay.

DPR STAFF TOXICOLOGIST LIM: I should have included air concentration in that presentation there too.

In fact I have that in the actual table on page 33 that included the actual ppm concentrations for these studies. But it's already in tiny point. So rather than apologizing for not -- you're not able to see these slides, I -- you know, I was trying to truncate the table. So that's what happened.

CHAIRPERSON FROINES: Yeah. It seems to me that

that's the problem of this extrapolation to a 24-hour period where you're getting these what are clearly acute responses at 4,000 ppm. And then because just by adjusting you assume you're going to get a response at -- the same response at 200 milligrams per kilogram per 24 hours seems to me to be a stretch toxicologically.

DPR STAFF TOXICOLOGIST LIM: Right. And that's why we decided not -- this is not appropriate.

PANEL MEMBER GLANTZ: I'm convinced statistically.

(Laughter.)

CHAIRPERSON FROINES: Well, I --

PANEL MEMBER GLANTZ: No, no, I agree. I mean if you're giving this very high level for a very short time and getting a transient effect, I don't think it's -- I agree with you, it's not appropriate to assume you would get the same effect if you delivered that same dose very slowly.

PANEL MEMBER BYUS: Correct.

PANEL MEMBER GLANTZ: It's sort of pharmacologic point of view, I think.

PANEL MEMBER BYUS: It is -- I might add, it's much clearer -- well, it's clearer in the document than it is in these tables, the way she's just trying to show it in different ways on the bigger table. And on page 33 it

is clearer. And that was really probably why you discounted that study, not the reasons that you said.

(Laughter.)

CHAIRPERSON FROINES: So, Lori, at long last move ahead.

And there's always a certain degree of learning that we all do on this panel as we go through it, and so that it's useful. But it doesn't --

DPR STAFF TOXICOLOGIST LIM: Well, I learn too as I go through this document again and trying to reflect to the comments. So it's both ways.

Okay. Now, we can talk about the critical study for the acute exposure.

Study 7 was selected study as the critical study because of the quality of the study and the determined NOEL level. This study by Albee, et al., was an acute neurotoxicity study where female rats were exposed to sulfuryl fluoride six hours a day for two days. There was no treatment-related effect in the Functional Observational Battery, which contained 31 types of observations and measurements.

In addition, the animals were tested for grip performance, landing foot splay, motor activity and the electrodiagnostic responses examined within 24 hours after the final exposure. The NOEL was 30 ppm, or 300

milligrams per kilograms per day, the highest dose tested.

While the NOEL was from a two-day study, it was used as a single day acute NOEL because other studies, Studies No. 3 and 11, indicated that the acute NOEL should not be higher than 300 ppm. In particular, Study 11 showed that the mortality could occur at 600 ppm.

--o0o--

DPR STAFF TOXICOLOGIST LIM: With an acute critical NOEL of 300 ppm, human equivalent NOEL is 122 ppm using equation one that I've shown in the previous slide. The second term of the equation is the inhalation rate adjustment, with the rat inhalation rate of 0.95 cubic meters per kilogram per day and infant inhalation rate of 0.59 cubic meters per kilogram per day. The last term is the amortization for daily exposure.

The reference concentration for acute bystander exposure is 0.12 ppm after the application of the 1,000-fold uncertainty factor. This 1,000-fold uncertainty factor consisted of a 10-fold factor each for intraspecies variation, interspecies extrapolation, and a lack of a developmental neurotoxicity study.

--o0o--

DPR STAFF TOXICOLOGIST LIM: This slide shows the conversion of the 300 ppm to an absorbed dose using a default rat inhalation rate of 0.95 cubic meters per

kilogram per day and an 18 percent absorption factor. This value is used to calculate the margin of exposure.

--o0o--

PANEL MEMBER GLANTZ: Can you just go back. Because I -- could you go through -- because I couldn't figure this out when I read the report, how you got that 18 percent, again. Because I thought the 18 percent was some more -- oh, it was some more directly measured experimental number. Or, no --

DPR STAFF TOXICOLOGIST LIM: That came from the rat pharmacokinetic study.

PANEL MEMBER GLANTZ: I'm sorry.

Pardon me?

DPR STAFF TOXICOLOGIST LIM: That came from the rate pharmacokinetic study.

PANEL MEMBER GLANTZ: The 18. So that --

DPR STAFF TOXICOLOGIST LIM: Yeah.

PANEL MEMBER GLANTZ: Okay. I'm sorry. I misread this slide. So the 18 -- okay. So the 18 percent was a directly measured experimental value?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER GLANTZ: Okay. Never mind. I misread something.

CHAIRPERSON FROINES: It was -- but it's a measure of the sulfur -- radial labeled sulfur.

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: And whether or not it reflects, for example, fluoride may be a different issue.

PANEL MEMBER BYUS: Have you got that study, John? Did you get a copy of it? I heard you requested it.

CHAIRPERSON FROINES: Yeah, I did.

PANEL MEMBER BYUS: And did you look it over? Was it --

CHAIRPERSON FROINES: No, I haven't looked it over. But the --

PANEL MEMBER BYUS: Was it a -- Let me just ask that question, because I mean this has been a concern of all of ours, the 18 percent and the quality of that pharmacokinetic study, because it could affect these numbers to some extent, at least the margin of exposure numbers. Was it an integrated time dosed curve? You follow me?

In order to get extended absorption you integrate the curve over time, like the serum curve. That gives you the extent of absorption. Rather than measuring something at the end of seven days, which is what I -- you know what I'm trying to say? In order to get the true extent of absorption, fractional absorption of the applied dose you integrate the time concentration curve.

DPR STAFF TOXICOLOGIST LIM: Okay. This is back on slide number 15. The tissue level was the radioactivity measured at the end of seven days -- seven days after exposure. So it's not --

PANEL MEMBER BYUS: Right.

DPR STAFF TOXICOLOGIST LIM: Okay. And the urine and feces is a cumulative dose over that seven-day period. So they collected by hours.

PANEL MEMBER BYUS: Okay. So they know the total amount of radioactivity that came out in the urine and the feces --

DPR STAFF TOXICOLOGIST LIM: -- over that seven-day period.

PANEL MEMBER BYUS: -- over the seven days.

DPR STAFF TOXICOLOGIST LIM: Plus what's remaining in the tissue.

PANEL MEMBER BYUS: Plus -- okay.

DPR STAFF TOXICOLOGIST LIM: Does that answer your question?

PANEL MEMBER BYUS: All right.

PANEL MEMBER HAMMOND: And did --

PANEL MEMBER BYUS: Yes.

PANEL MEMBER HAMMOND: Sorry.

PANEL MEMBER BYUS: Go ahead.

PANEL MEMBER HAMMOND: In the metabolism, did

they actually observe that it was metabolized to fluoride and sulfate or deduced that?

DPR STAFF TOXICOLOGIST LIM: Those levels were measured, and --

PANEL MEMBER HAMMOND: So they measured the sulfate -- it was as sulfate?

DPR STAFF TOXICOLOGIST LIM: Yes.

PANEL MEMBER HAMMOND: It was actually sulfate and fluoride?

DPR STAFF TOXICOLOGIST LIM: Yeah, that's on page 26 table 2. But they only measure in the urine and blood and nowhere else. And only certain hours.

PANEL MEMBER HAMMOND: So is the assumption that the unabsorbed dose is exhaled -- just exhaled gas? But they didn't measure that ever? They didn't do a measurement of that?

PANEL MEMBER GLANTZ: How would you do that?

DPR STAFF TOXICOLOGIST LIM: It's labeled on S35 on the sulfur. So -- I think I mentioned something here.

Okay, wait. Radioactivity -- I mention in the study, radioactivity in the expired air was monitored for 24 hours and they did not detect any radioactivity. So they stopped monitoring.

PANEL MEMBER PLOPPER: So that's not what you got?

DPR STAFF TOXICOLOGIST LIM: No.

CHAIRPERSON FROINES: I think that the -- there are two issues from my standpoint. And I don't know about Joe, Charlie or others.

My sense is that you have this obligate nose breather, the rat, and it's breathing in this material. And I would guess that the 18 percent might be an upper bound. Because if you're a kid playing next door, I think you may have a tendency to breathe a lot of the sulfuryl fluoride. A lot of it's going to go out, and not as much is going to be absorbed. So the -- but I don't know. I don't have any idea actually. I don't think any of us can say what it actually is. One could even think that it might be higher. But in general I would think that it might be lower. The 18 percent might be an upper bound.

The important thing is that we acknowledge that there is uncertainty in this 18 percent. The problem with a bright line or specific value is that we assume -- you know, we don't really deal with inter-individual variability in humans. And so we have no idea what the range might be in a human population. So that this is a guesstimate which probably isn't unreasonable, but we don't really know. And so -- you do have a paragraph that you nicely talk about the uncertainty.

And the -- I had marked it. But then you talk

about a safety factor -- no, you say an additional ten-fold factor was included in the reference concentration calculation. Oh, no, I'm sorry. That's the developmental toxicity. But someplace in here I thought I remember -- and I thought I marked it.

PANEL MEMBER BYUS: She does. There is a paragraph. I can't find --

CHAIRPERSON FROINES: And I thought I marked it some -- that you had made some adjustment for the uncertainty in the 18-percent value.

Am I remembering it wrong?

DPR STAFF TOXICOLOGIST LIM: It's not an adjustment on the 18 percent but an adjustment to say that even though we think that there's an 18 percent, there are other things that could affect the actual internal dose. So we say that -- we applied -- we went ahead and applied the ten-fold interspecies extrapolation factor even though we already sort of make some corrections regarding the inhalation rate and consider the absorption. So this is another umbrella over everything else.

CHAIRPERSON FROINES: So the uncertainty in this 18 percent value is included within your ten-fold interspecies number?

DPR STAFF TOXICOLOGIST LIM: In sort of qualitatively, yes. We're saying that we still don't

know.

So the opposite way of looking at that is that just because we make corrections with our 18 percent, we didn't say -- we didn't decrease the ten-fold, saying, "Oh, we already took care of absorption, so it should be less than ten-fold" No, we're saying even though we look at the absorption, we're still going to want that ten-fold.

CHAIRPERSON FROINES: I can live with that.

DPR STAFF TOXICOLOGIST LIM: Okay. While the emphasis of this presentation is on acute exposure, I want to say a few words about the critical NOELs and effects for repeated exposures. For each of the duration the critical NOELs will protect against effects of the higher doses as indicated in the third column.

For one to two weeks of exposure the critical NOEL was 100 ppm based on brain lesions (vacuoles) found in rabbits exposed to 300 ppm for two weeks. These investigators also looked at the effects of sulfuryl fluoride in rats. While they did not find any lesions in the brain at 300 ppm, the kidneys showed changes described as hyperplasia of the collecting tubules, basophilic epithelial cells in the proximal tubules, and increased relative kidney weight. Reduced maternal and fetal body weights were reported in rabbits exposed during gestation

days stage 6 to 18.

For chronic toxicity the critical NOEL was 30 ppm also for brain vacuoles in rabbits exposed to 100 ppm sulfuryl fluoride for 13 weeks. At doses higher than the critical NOEL there was lesions in the rats, mice and dogs. Other effects involved the teeth, kidney and body weight.

For chronic toxicity, again there were effects in the teeth, brain, kidney and brain. The critical NOEL was 5 ppm based on lung inflammation in rats after repeated exposures in a reproductivity toxicity study.

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DPR STAFF TOXICOLOGIST LIM: The exposure assessment was already described by Dr. Cochran. For AB 1807, the group of concern is the bystander. In this group, the focus is on infants for this presentation because they had the highest exposure per body weight. And only their exposures are discussed further.

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DPR STAFF TOXICOLOGIST LIM: This is a summary table of the infant exposures which could occur while outside of a structure or commodity chamber during fumigation or aeration, as well as inside a residence during these activities.

These values were from the use of sulfuryl

fluoride at the submaximal application rate. And only submaximal application rate exposures are presented here because these exposures already pose potential health concern. These exposures are would be 10- to 14.5-fold higher if the fumigation were done with a maximally allowed application rate.

During fumigation the outside air concentration was 0.8 ppm during the first 12 hours -- these are time-weighted average numbers -- and 1.12 ppm during the entire 24-hour period. These were equivalent to 0.36 and 0.50 milligram per kilowatt per day absorbed doses respectively. During aeration, their exposures are much higher when the TRAP method was used and lower when the Stack method was used.

With non-food chamber fumigation the highest possible bystander exposure was 5 ppm, or 2.3 milligram per kilogram per day absorbed dose.

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DPR STAFF TOXICOLOGIST LIM: After the NOEL and reference concentration determined and the human exposures are estimated, the next step is to calculate the risk.

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DPR STAFF TOXICOLOGIST LIM: This slide is an expansion of the previous table to include the risk estimates, highlighting columns 3 and 5.

The 24-hour TWA human exposure in column 2 is compared to the reference concentration 0.12 ppm. The absorbed doses for these exposures in column 4 and the NOEL of 54 milligram per kilogram per day as an absorbed dose I used to calculate a margin of exposure.

In this table all exposures exceeded the reference concentration, and the margins of exposure were less than 1,000, the benchmark needed for acceptable exposure. At the maximal rate of application for structural fumigation, the risks would be substantially greater than those shown here.

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DPR STAFF TOXICOLOGIST LIM: The final step in the risk estimate is an appraisal of the risk, taking into consideration the uncertainties and limitations in the exposure and toxicology data.

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DPR STAFF TOXICOLOGIST LIM: In the calculation of the absorbed dose from the air concentration, an 18 percent absorption factor was used. This was from a rat pharmacokinetic study with the assumption that rat and human absorption are similar. Once absorbed, we assumed a three-fold difference in the pharmacokinetics of sulfuryl fluoride between species.

This factor -- this absorption factor is used to

convert both the critical NOEL and the animal study from human exposure to absorbed dose terms. Since the same factor is used for both the numerator and the denominator, it is cancelled out. So mathematically, the factor has no impact on the margin of exposure calculation.

The absorption factor is not used in the reference concentration calculation.

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DPR STAFF TOXICOLOGIST LIM: However, the magnitude of this absorption factor is important biologically if the absorption of so sulfuryl fluoride in humans and laboratory animals after inhalation exposure are different. This difference may be due to chemical or biological factors. The end result could be either higher or lower human absorbed dose compared to the current assumption.

For example, rat breathing frequency, about 60 to 100 per minute, is much higher than that for humans. The slower human rate means more residential time for the transfer of sulfuryl fluoride from air to blood in humans than in rat. A higher absorbed dose would be expected for humans.

On the other hand, the transfer of sulfuryl fluoride from the air to the blood could be limited by the chemical solubility between these compartments. While we

don't have data for sulfuryl fluoride, studies with volatile compounds show that rat blood/air coefficients are one and a half to two-fold higher than those for humans. This then could result in higher internal dose in the rat than in humans.

In addition, these studies show a direct correlation between rat and human blood/air coefficient. That is, for the compounds that were examined in the studies, the rat blood/air coefficient for a particular compound was predictive of the coefficient for the humans. These studies also showed that the octanol/water partition coefficients was not predictive of the blood/air coefficient.

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DPR STAFF TOXICOLOGIST LIM: This slide lists the uncertainties associated with the toxicology and critical NOEL selected.

First, effects observed in laboratory animals were assumed to also in humans. This was a necessity since we don't have human data to establish a critical NOEL. But we do assume humans are more sensitive than animals, using a ten-fold interspecies uncertainty factor.

Second, when the acute NOEL from a six hour a day study is amortized to 24 hours, the assumption is that the dose-time response is linear. This may not be the case as

the NOEL for a 24-hour continuous exposure, for example, could be lower than the amortized value.

Another certainty is the application of the NOEL derived from constant air level in the animal studies to human exposures with declining air levels, such as during application and aeration of structural fumigation. One would expect the NOEL to be higher if the laboratory animals were also exposed to decreasing air level.

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DPR STAFF TOXICOLOGIST LIM: And finally fluoride, which exposure was not assessed in this document. In the footnote of the risk assessment, I noted that the NAS work on fluoride, which started in 2003 at the request of the U.S. EPA, is still ongoing, with a new date of spring 2006 for completion. This work was to examine the drinking water standards and assess the total fluoride exposure.

Based on the comparison of toxicity with sulfuryl fluoride and sodium fluoride, it is clear that fluoride is involved in the dental fluorosis observed after treatment with either compound.

As for the brain vacuoles and lung effect, it is reasonable to assume that fluoride may be involved since the pharmacokinetic studies detect fluoride, which is inherently toxic depending on the concentration and

exposure duration. This fluoride would be expected to add to the total fluoride body burden.

In addition, the metabolic intermediate, fluorosulfate, may also be involved. There's little toxicology information on the toxicity of this compound. Or none that I could find really.

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DPR STAFF TOXICOLOGIST LIM: In order to see if fluoride is involved in the brain and respiratory effects, the individual animal data in the 13-week toxicity studies were examined. In these studies, increased incidences of effects in these organs were found in the dose groups with the elevated mean plasma fluoride level.

However, examination of the individual data showed some exceptions. The first column is the seven animals -- individual data for the seven animals treated at 300 ppm sulfuryl fluoride. For example, in this 13-week study with rabbits exposed to 300 ppm, the brain of animal #5 did not show vacuoles even though the plasma fluoride level was similar to other affected animals. The nasal effect severity was also not consistent in all animals.

This lack of direct correlation could be due to varying fluoride level intake from the drinking water and feed during the course of the study or individual

variations in response to fluoride. It could also be that the plasma fluoride level measured for only one time point was not a good indicator of tissue levels, especially after repeated exposures. Data on brain fluoride levels, especially in affected regions, would provide more definitive determination of whether and how fluoride was involved in the toxicity of sulfuryl fluoride.

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DPR STAFF TOXICOLOGIST LIM: While we don't know what the fluoride exposure levels were from the inhalation of sulfuryl fluoride, three scenarios for chronic exposures are provided in this slide using different assumptions regarding local exposure and residue in the tea leaves. These were singled out because of potential high exposures. Tea plants are known to accumulate fluoride from the soil. The constant sources of fluoride exposure were the dietary exposure, which is the sum from the uses of sulfuryl fluoride on food commodity fumigation, the use of cryolite which is metabolized to fluoride. And cryolite's used as an insecticide used on fruits and vegetables, primarily grapes, potatoes and citrus. It's a solid. It's not a fumigant.

PANEL MEMBER BYUS: What is it again -- what is cryolite, I mean, exactly? It's not -- do you know what the chemical is?

DPR STAFF TOXICOLOGIST LIM: The chemical formula?

PANEL MEMBER BYUS: Yeah.

DPR STAFF TOXICOLOGIST LIM: I don't remember what it is. But it is metabolized to fluoride. So it contains fluoride. It's a solid, and it is put on leaves. And it's also a naturally occurring compound.

PANEL MEMBER BYUS: Grapes? A lot of grapes?

It's a lot of grapes?

DPR STAFF TOXICOLOGIST LIM: Yeah, grapes, potatoes and citrus. Grapes, yes.

So the dietary included the uses of sulfuryl fluoride on food commodity fumigation, cryolite, and the background fluoride levels in food estimated by the U.S. EPA, as well as drinking water based on a 1 ppm standard. That's the fourth row there -- fifth row.

The maximum total fluoride exposure is shown in column 2 where worker exposure was set on the highest exposed group, which is the chronic exposure of the tent crew during applications of sulfuryl fluoride at the maximal application rate, and the maximum fluoride residue measured in brewed tea, assuming a consumption rate of two 8-ounce cups per day.

The average total fluoride exposure was based on the tent crew exposure at submaximal application rate and

average tea residue level.

And the last scenario used, in the last column, used the worker exposure set at the chronic RfC for sulfuryl fluoride in this document and an average tea residue. The total fluoride exposure in this scenario would be the U.S. EPA chronic RfC of 0.06 milligram per kilogram per day for fluoride.

PANEL MEMBER BYUS: I'd just like to commend Lori for doing this analysis, because -- and DPR, because they really tried here to -- the object of this was to determine really what the baseline fluoride was from all sources and through -- and then if sulfuryl fluoride really increased it significantly and what percentage -- would make it even more toxic.

And so I think we should commend them for really doing this kind of an analysis of this in terms of adjusting total environmental exposure.

DPR STAFF TOXICOLOGIST LIM: I need to share the spotlight with Dr. Byus, because he's the one who gave the suggestion.

(Laughter.)

DPR STAFF TOXICOLOGIST LIM: Maybe I wasn't supposed to say that.

PANEL MEMBER BYUS: But you did it. You did the analysis. And as I said --

DPR STAFF TOXICOLOGIST LIM: Maybe it was a setup.

PANEL MEMBER BYUS: -- I commend you for it, because it is very, very difficult, this sort of multiple exposure-type scenarios, and you ran this sort of -- and I think it was very -- because I didn't know how -- it could have come out significantly different.

CHAIRPERSON FROINES: It's clear we're creating a conflict of interest issue here.

(Laughter.)

PANEL MEMBER BYUS: Go right ahead.

DPR STAFF TOXICOLOGIST LIM: Okay. Based on the information currently available, bystander exposures to sulfuryl fluoride are of potential health concern. Even at the submaximal rate application, the exposures far exceeded the reference concentration, and the marginal exposures were less than the benchmark of 1,000 for acceptable exposure.

While not discussed in this presentation, the exposures of workers and residents reentering the fumigated homes under many scenarios pose health hazards and need to be reduced.

The recommendation is for sulfuryl fluoride to be listed as a TAC since the bystander exposures exceeded one-tenth of the RfC.

Additional toxicology and exposure data for sulfuryl fluoride and fluoride are needed to refine the risk assessment and to address the uncertainties in the risk estimates.

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DPR STAFF TOXICOLOGIST LIM: I'd lke to -- now, the final slide is to acknowledge the work of many toxicologists at the Medical Toxicology Branch who reviewed the toxicology studies used in this volume.

I also would like to acknowledge the reviewers of the draft documents from the Branch. And all the names are listed here.

And I need to add Dr. Ruby Reed's name on this list since she was my primary consultant on the fluoride issues.

Questions?

CHAIRPERSON FROINES: That's great. That was really a very fine presentation. Thank you very much.

Let me just deal with some administrative issues first. We would now normally go to Roger and Craig for any comments from them as the leads. And then we would go around the room and have comments from panel members -- or questions and comments.

So that would be where we are at right now. It's also 12:45. And so do people want to continue and pursue

that or do you want to break for lunch? Or what's everybody's interest?

PANEL MEMBER PLOPPER: Lunch.

PANEL MEMBER GLANTZ: Why don't we have a -- can we get lunch in the building?

Why don't we take a half hour break for lunch. And we could bring -- maybe finish eating here or something so we can move forward with this.

CHAIRPERSON FROINES: I don't think you can -- who's in this building?

PANEL MEMBER GLANTZ: Can't do that?

No canteen?

DR. ALEXEEFF: Directly outside, right outside to the right there's two places close by.

CHAIRPERSON FROINES: Could you bring it back in, George? Can you get something to bring it back in?

DR. ALEXEEFF: Yeah, you can bring it back in.

CHAIRPERSON FROINES: So is everybody comfortable with a half hour? Because --

PANEL MEMBER HAMMOND: Assuming you can bring stuff back here.

CHAIRPERSON FROINES: Or wherever. I mean the point is not to come back --

PANEL MEMBER HAMMOND: We can bring food back in, you're saying?

CHAIRPERSON FROINES: It's whatever you're interested in doing.

Tobie, are you happy with a half hour lunch and --

DPR ASSISTANT DIRECTOR JONES: That's fine.

CHAIRPERSON FROINES: Well, I think we have a consensus. Although everybody's kind of what, more soft spoken than they normally are.

So let's break. And let's come back here -- let's be ready to start by 1:30.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: So we're back to work again.

So to follow the traditional order here. Roger, you've been working on the exposure side. So the question is: Questions for DPR, comments, recommended changes, anything that you think is necessary.

PANEL MEMBER ATKINSON: Okay. As probably being somewhat evident, I've had a lot of comments to DPR during the process. Most of them have been taken into account.

The last lot we were on a conference call on Tuesday. So there's still some additional comments that are hanging from there, that I assume you are going to take into account.

My major concern at the moment is still the lack of data concerning the environmental fate of sulfuryl fluoride. I would urge you to look at the literature. I realize it's not -- there's no reference given in the actual text, but concerning the solubility and hydrolysis of the compound in water, to try and assess whether or not uptake by clouds and hydrolysis there will be -- they'll be important. If it isn't, then we've potentially got a greenhouse gas.

I see no -- I would not expect it to react with OH radicals, NO3 radicals or ozone, nor to fertilize. So

I would guess that if it doesn't get taken up by clouds with hydrolysis, then it's going to have a long lifetime.

And that's really it. Otherwise I'm fine with it as it stands now, subject to the things we talked about on Tuesday and I think an expanded version on the hydrolysis question.

CHAIRPERSON FROINES: To the degree that there's information available?

PANEL MEMBER ATKINSON: Yeah.

CHAIRPERSON FROINES: Let me ask you a pointed question then.

If we by the time -- when we finish going around the room, if there's a sentiment that the document -- that we would approve the document, or at least take a vote on the document, are you comfortable with them making the changes that you're talking about now, or would you require another meeting with another draft?

PANEL MEMBER ATKINSON: No, if we have sort of consultation from DPR -- or at least if I had some interaction with them on it, then that's fine. I'm perfectly happy with helping to assist on that specific question.

CHAIRPERSON FROINES: I'm not prejudging anything in terms of the discussion. I'm just saying -- I just want to be clear as we move around the room.

So Craig.

PANEL MEMBER BYUS: I really don't have anything to add. Most everything -- or everything I suggested that DPR do or change or add or the document, they did willingly. And I think it really made the document good and I'm happy with it.

CHAIRPERSON FROINES: So from your standpoint, you're at a place where -- leaving DPR aside -- in terms of the panel -- this discussion amongst the SRP, you're satisfied that the document meets the legislative criteria?

PANEL MEMBER BYUS: Yes.

CHAIRPERSON FROINES: Okay. Where to go next?

Stan.

PANEL MEMBER GLANTZ: All the things I had wanted to ask about have been discussed, and I'm satisfied.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: I just would like to just reiterate my concern about the exposures and both -- we have a small amount of data, which -- I know it's hard to gather this data. But I'd like to make sure that we understand better the peak exposures, the short-term exposures, the distances from this, and also the exposures of the workers. And I don't like making -- there being assumptions about what the exposures are based on what the

recommendations are.

Other than that, I'm fine.

CHAIRPERSON FROINES: Well, help me with what you want, having said that.

PANEL MEMBER HAMMOND: Well, I would rather, if the document -- if we don't have data on something, I would rather the document said that. If we don't know what the workers' exposures are, just say that. If we don't know something, we should say it. And I think it would just make -- that's all.

CHAIRPERSON FROINES: Is that clear for Randy and Lori and Tobie?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: Um-hmm.

CHAIRPERSON FROINES: Because Tobie's looking a little wide-eyed.

DPR ASSISTANT DIRECTOR JONES: Can you say that again.

PANEL MEMBER HAMMOND: I was concerned about parts of the document that make statements like -- the label says you shouldn't be exposed to more than 5 ppm's. So we assume that -- without self-contained breathing apparatus. Therefore, we assume that was the maximum. No one's exposed above that. I don't think that's an appropriate assumption.

So if the data don't exist, then I would rather you say that, there's no other data. And then you make some assumption. And I think it's good to call out when there's lack of data.

DPR ASSISTANT DIRECTOR JONES: I think the only caveat -- and I think the staff can work with that -- is since we're operating under a structure of the label is the law, those applying -- and there's statements on pesticide labels that say that very directly. So if in fact a company is allowing it's workers to go into an environment without the appropriate personal protective equipment and are being exposed, they have both a problem of legal consequences under our statute and under the Occupational Safety -- OSHA standards.

So I think staff can find a way to address it. But I think in terms of our looking at exposure scenarios, we have to assume that people are following the label. We understand that there are circumstances where they may not. But they are breaking the law, both from following pesticide law and from worker safety laws.

PANEL MEMBER HAMMOND: Okay. Maybe a better way for me to say that then -- okay, let me back it up -- is to say that in doing the risk assessment and for the documents and the assumption of the exposures, that the assumption -- that the assumptions are that first the law

is followed. And given that, that would lead us to this. But the way it's written, it actually at least appeared to me that you were saying that nobody was exposed above 5 ppm. And unless we know that, I wouldn't state that.

DPR ASSISTANT DIRECTOR JONES: I understand.

CHAIRPERSON FROINES: This is -- I mean this is clearly the classic problem of law versus science, where something that is truth in a legal sense may not be truthful in a scientific sense at all. And so we always live with different definitions of truth.

And so I think what Kathy is saying -- correct me if I'm wrong -- is that recognizing your constraints with respect to the law, it would also be reasonable to have some language about uncertainty, to say that the actual exposures may require further evaluation to ensure -- and so on and so forth -- to reduce the uncertainty about the...

So I think it's correct -- yeah.

PANEL MEMBER HAMMOND: Yeah, and I think the point for why you're doing it -- as I think about what you're trying to do in the document is you're trying to say, given that level, is there a residual health risk? That's basically in a sense what the document is trying to do. So you're saying if people are following the law, do we still have a problem? And that's what you're trying to

address in the document. So as long as it's couched in that way, then I feel fine.

CHAIRPERSON FROINES: Yeah, I think -- I don't think it takes a lot of writing. But I think it takes some pinpointing where you -- where there is uncertainty acknowledging it essentially. I think that's the -- what she's looking for.

Does that makes sense?

DPR ASSISTANT DIRECTOR JONES: Yes.

CHAIRPERSON FROINES: See, my job is to watch the heads nodding and then figure out where we are.

DPR STAFF TOXICOLOGIST LIM: At least for me I could tell that I could add that in my conclusion. That would be a big point.

PANEL MEMBER HAMMOND: Thank you.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: You want to do Charlie first?

CHAIRPERSON FROINES: Well, Charlie's the new scientist on the block, so I always want to give him, you know, some deference.

PANEL MEMBER LANDOLPH: I wanted to congratulate Dr. Jones and all the staff. I think you did a very nice job. The document's very detailed, it's very thorough.

I have given you my written comments to help you,

so it's easy to respond. And I would say certainly on page 4, paragraph 4, lines 3 to 5, I indicated that I thought this sentence on oncogenicity for fluoride should be moved to the end of the paragraph. And I would suggest reworking it, because it seems that there's almost already an upfront presumption that it would not be expected to be oncogenic in humans. I think that's maybe hanging yourself out there a little bit too far.

I would suggest something like: "The evidence for the carcinogenicity of fluoride, an active metabolite of sulfuryl fluoride, is therefore considered weak and not conclusive at present. Further studies are needed to conclusively determine whether fluoride is carcinogenic." That way you'll protect yourself, and just state it exactly the way it is without -- it almost sounds like you're making a pre-conclusion up front before we have enough data.

So I have a lot of statements like that. And I'll just be concise and not mention all of them.

On page 18 paragraph 3, it's just a fantastic section there which has human illnesses. And I wondered if you could discuss in a document whether the shortness of breath was reversible or irreversible in humans. As soon as I saw shortness of breath, I started thinking of RADS. And I wonder if anything like that has reared its

ugly head here. And you might just make a few sentences there.

And also answer whether the symptoms of numbness of the hands, confusion, memory loss, et cetera, are reversible or irreversible on exposure to sulfuryl fluoride, if that's known.

DPR STAFF TOXICOLOGIST LIM: May I explain?

PANEL MEMBER LANDOLPH: Please.

DPR STAFF TOXICOLOGIST LIM: I think Roger can talk about this data information from the Pesticide Illness Program, whether there's any follow-up on that.

Can either Joe Frank or Roger answer that question for you right now?

MR. FRANK: My name's Joe Frank. I'm responsible for the Exposure Assessment Program.

That's not a problem. We have a physician in our branch who will be able to answer the questions you would like answered. And we can put down the implications of those, whether they're transient, whether he thinks there's a -- you know, lasting effects.

PANEL MEMBER LANDOLPH: Yeah, thank you. I think that will be very important.

And while I've got you, also is it possible to extract or abstract any concentration data from those illness reports?

MR. FRANK: Generally not.

PANEL MEMBER LANDOLPH: Okay. Thank you.

And then on page 57, paragraph 1, line 4 --

CHAIRPERSON FROINES: Thank you.

PANEL MEMBER LANDOLPH: Thank you.

-- there's a statement that fluorosulfate was considered to be nontoxic. I would not put that statement in. I would say it's presumed a metabolite of this molecule, and studies need to be done to address whether or not it is toxic.

And also Dr. Plopper will get to you about sulfate as well. So I'll let him do that.

Then a question I had about the pulmonary edema. Since I saw that I started thinking of phosgene. And my question is: Are there then any parallels between this pulmonary edema and edema induced by phosgene? Is this a -- or is this a more prosaic type?

DPR STAFF TOXICOLOGIST LIM: I'm not familiar with the toxicity of phosgene. I can certainly look it up.

PANEL MEMBER LANDOLPH: And then a question: Is this pulmonary edema reversible or irreversible? That's something you might address in a document.

Let's see. I just have a couple more and then I'll stop.

CHAIRPERSON FROINES: That's okay.

PANEL MEMBER LANDOLPH: I thought the appendix review on fluoride was terrific. I really want to congratulate you on that. In fact, some of it's so good, like Dr. Froines mentioned earlier, I thought you might want to take a few sentences from there and put it up front, because if viewed that sulfuryl fluoride is a pro-drug for fluoride and other things, maybe a few sentences might come out of there. It's very, very well written.

And then you probably want to address somehow -- if you can get a copy of that PhD. thesis by Bassin, somewhere in there. Because I'm worried that there may be a potential lurking for oncogenicity of fluoride, which is a metabolite of this. With the appropriate qualifications. And then I mentioned the hyperplasia of the kidney and the collagen depletion, et cetera, as potentials for carcinogenesis.

And I already mentioned my comment about the genotoxicity assays, not to state that they're blanket. Overall equivocal, but they're positive in some assays. Because you have things like microtubule inhibitors, which are uniformly negative in bacteria because they don't have chromosomes, but they cause clastogenesis in mammalian cells. So please take that view.

And other than that, I have other small things, which you can look at yourself to see if they're helpful or not.

And the only final thing I'm thinking of would be somehow if you could write a short section or add to your section this discussion of the neighbor effect, we'll call it, rather than the bystander effect for clarity. I think it's our responsibility and yours to make sure that the neighbors would be protected if someone is fumigating a house. And a discussion we heard earlier that when the tent is up, there's leakage's that it's not airtight, worried me a little bit. And particularly Stan's discussion that the million dollar houses plus in San Francisco are right next to one another, I think somehow that has to -- we have to come to grips with that.

So if you could think of a concise way to put that in, particularly with the concentric circles of concentrations of the sulfuryl fluoride from the point of fumigation outward, I think that would be very helpful. If there's some kinetic data on how it dissipates, a few graphs would be very useful too.

CHAIRPERSON FROINES: That may be difficult because they really don't have the ARB data yet. And so maybe, if there is an update -- I don't know what you think. I don't think they really have the information

that you're asking for.

PANEL MEMBER LANDOLPH: Well, just tell us what they do have, and I'd be happy. It just seems to me -- you know, I was looking at Los Angeles County, and I mean there's just a truckload of fumigation going on. And it seems to me this should have all been sorted out a long time ago, before this molecule was put in the public domain like this. So I'm a little disappointed that that database is still in such a state of posity.

So I'll be delighted with whatever you find that you can put in there, and that would be helpful.

CHAIRPERSON FROINES: Well, what's the question you're --

PANEL MEMBER LANDOLPH: Well, I want to know how much is getting into, you know, proximate houses. Or are these levels serious? Should we not consider them? Or are they levels that should be considered in terms of the toxic --

CHAIRPERSON FROINES: So you're saying -- you're interested in the question of relative to the -- you're actually --

PANEL MEMBER LANDOLPH: Let me capsulate for you.

CHAIRPERSON FROINES: No, let me just say that we're on a little bit of a borderline here, because what you're asking is in fact a risk management issue. And so

it's not necessarily appropriate for this document. But what you're asking, if I understand it, is given the NOEL and the RfC, and given what we know about exposure, do we anticipate a public health problem in terms of proximity to Vikane use for fumigation? I think that's what you're saying.

PANEL MEMBER LANDOLPH: Yes. So if you fumigate your house and I'm living next to you are me and my family at risk of any health problems? That's realty the question.

CHAIRPERSON FROINES: And that's -- that is close to an issue for risk management in terms of setting the standards. So it's really out of our jurisdiction in a sense. But if you could put something in that showed a comparison of values that have been measured versus your NOEL estimates, something -- I think it shouldn't be overdone. I think if there's anything you could put in, it would be -- am I being clear?

PANEL MEMBER LANDOLPH: Yeah. Yeah, you're being very -- extremely clear.

And thank you for all your effort. It's a very nice document. And these are comments just intended to help you out a little bit.

DPR STAFF TOXICOLOGIST LIM: Can I add a little bit to this.

The way I understand the monitoring studies are done with a monitor from the structure away from in different directions. For every study, the highest point is not necessarily right next to the house. Okay? So being a neighbor you of course would be concerned. But that's not -- may not necessarily be the case. And there could be points, depending on the wind or whatever, that it could be away from the house. And we picked the highest point of that particular study when we did the exposure. If that helps.

PANEL MEMBER LANDOLPH: Yeah, it helps.

PANEL MEMBER BYUS: My suggestion would be to simply define what you mean by bystander in a clear term. Say, for example, these are the kinds of people or exposure scenarios for bystanders: Walking by while the house is being vented; living next door within X number of feet. Just explain what those scenarios are about what do you mean by bystander. Because I think -- I think that did come out of this discussion this morning, that it is kind of a misleading term. It means somebody who's sort of, to my mind, transiently walking around near there who isn't normally there. And that -- and you sort of think, "Well, what about the people that live right next door?" So it's sort of what are the kinds of exposures that might qualify under "bystander". That's how I would do it, and

not -- because we -- you know, not get into drawing more graphs or whatever.

DPR STAFF TOXICOLOGIST LIM: Well, we could clarify then the exposure assessment as though it's in the risk assessment.

PANEL MEMBER BYUS: Correct. I mean because you do it for the people that are putting the tarp on and off and that kind of thing. But "bystander," I think you just need a little bit more kind of relevant types of who those people might be.

DPR ASSISTANT DIRECTOR JONES: This is Tobie Jones.

If I could ask: If we clarified that and clearly indicated -- and I'll leave it to Lori and Roger to work this out -- that since we are not -- we are assuming that people inside neighboring houses are exposed to the same concentration as people outside, that we're trying to -- we're trying to account for this since we have no data to speak to that.

PANEL MEMBER BYUS: Right.

DPR ASSISTANT DIRECTOR JONES: And then clarify what we're including as bystander.

CHAIRPERSON FROINES: Yeah, that would be fine.

PANEL MEMBER BYUS: That's great.

CHAIRPERSON FROINES: That's good, because I

think this discussion clarified what Joe was really asking for. And I think -- it seems reasonable.

So you're okay, Tobie, on this?

DPR ASSISTANT DIRECTOR JONES: (Nods head.)

PANEL MEMBER LANDOLPH: And, yes, I'm happy that they go ahead and take care of business as they feel appropriate. Contact me if they need to. But I'm sure they can take care of it just fine, as Roger said.

CHAIRPERSON FROINES: You're volunteering your house to do studies when you --

(Laughter.)

PANEL MEMBER LANDOLPH: No, I'm volunteering your house --

PANEL MEMBER HAMMOND: Your neighbor's house.

PANEL MEMBER LANDOLPH: And that is a joke.

CHAIRPERSON FROINES: Charlie.

PANEL MEMBER PLOPPER: I'd just like to say I think it's an excellent document too. And I'm concerned about one thing and, that is, you're downplaying the acute responses to the respiratory things, because that happens with lots of toxicants. That's almost the respiratory system's response to a toxic stress. And when I -- and then you add pulmonary edema to that, you may be actually playing that issue down. I think that would be my concern.

And the other thing is the sulfates. And sulfates are lung -- or toxic compounds for the lung, and particularly if they're respired. And that's what that acute study would telling me. And I think you should just explain that, is what my concern was.

Were there any documents that talk about the workers on this that have any problems with the nasal cavity? Did they talk -- do they do tests for smell, for instance? Because there's a lot of literature now that suggests that when something has that kind of a toxic response in the nasal cavity, that it's carried by the nerves right into the -- goes through -- goes passed the blood brain barrier and straight into the brain. And that --

PANEL MEMBER BYUS: Is that true?

PANEL MEMBER PLOPPER: Oh, yeah. In fact --

CHAIRPERSON FROINES: When you drive on your freeway, all those ultrafine particles are going through your olfactory bulb into the brain.

PANEL MEMBER PLOPPER: Right, exactly.

PANEL MEMBER BYUS: Wow.

PANEL MEMBER PLOPPER: And most of those things are considered to be relatively inert as they go through. But this is not. And so I would be a little concerned about that. You know, there's probably no data, but it

would be interesting -- I wouldn't discount if they did any studies about anosmia or any other sorts of things, because that kind of a toxic response that soon would say to me that the nasal cavity was really attacked. And that could explain the difference in the -- between fluoride tests and tests with this compound in terms of nervous function -- or central nervous system function, different route.

DPR STAFF TOXICOLOGIST LIM: You're referring to the studies with the structural fumigator --

PANEL MEMBER PLOPPER: Yes. I mean I don't know if they did. But it would be worth knowing that, because --

DPR STAFF TOXICOLOGIST LIM: This is described on page 52. They did an olfactory study. In fact, that was reduce olfactory function. But I don't see any examination of the nose that's listed here. I could double check to make sure.

PANEL MEMBER PLOPPER: Well, I'm just bringing that -- because that's a -- turning out to be a very good sentinel, a very sensitive one. So if it's there, you should put it in. I'm more concerned that you might be erring on the side of being -- not setting your levels low enough. Just based on that.

So that's mainly my concern.

CHAIRPERSON FROINES: Well, let me try and -- the first thing you said was that there was less -- perhaps less than complete or under-interpretation of the data on respiratory effects. So just in terms of bringing -- so they understand what we're asking them to do, what would you recommend?

PANEL MEMBER PLOPPER: Well, I mean obviously there needs to be some more studies. But I think it would be worth not trying to downplay those issues and just treat them -- you know, you -- yeah I think you've done a reasonable job of picking your NOELs and discounting that study. But I don't think that you should throw that study out. You should just point out that the details are not there enough. Because from my perspective, that was -- that's the first entry point we use for picking a compound that's a respiratory toxin, is what happens when you give them a relatively whopping dose and you get -- that's how the respiratory system responds. And I can think of about six things that are now identified as toxicants that respond like that. And then you can take that and divide it -- that dose and divide it by a thousand and then you get a toxic -- a long-term toxic response.

DPR STAFF TOXICOLOGIST LIM: I have a section here on page 56 under "Hazard Identification with Respiratory System Effects."

CHAIRPERSON FROINES: Page what?

DPR STAFF TOXICOLOGIST LIM: Fifty-six, on the top part, where another -- we talked about this. It seems like it's -- I really need to talk more about it, because I just barely mentioned it toward the end of that first paragraph.

So would it be sufficient if I bring in the workers study information to say that during the -- but they didn't look at -- either they did or they didn't. And add more information to that paragraph?

PANEL MEMBER PLOPPER: That's what I was thinking of, yes.

DPR STAFF TOXICOLOGIST LIM: Okay.

CHAIRPERSON FROINES: Okay. And then the second thing you said was -- I'm sorry, I --

PANEL MEMBER PLOPPER: The sulfate issue. And I don't know -- I can't ask them to write a new document and I'm not -- I just think it's worth noting that --

CHAIRPERSON FROINES: If there's any literature. Well, I mean there's enormous literature on sulfuric acid and its carcinogenicity. But you're not talking so much about that, because at that pH you're not going to have a lot of sulfuric acid in the lung, I would assume.

PANEL MEMBER PLOPPER: Well, I don't know. I'm not a chemist. All I know is when you put sulfur and

oxygen together and you put it in the lung, you get problems. So I don't know about sulfate.

CHAIRPERSON FROINES: Well, that's a good question. At pH 7.4, thereabouts, if you have sulfate, you're going to have probably not a lot of -- I don't know. It's a good question.

PANEL MEMBER PLOPPER: Until it gets absorbed. And what happens when it gets absorbed? The doses that -- or the amounts that I saw bound in the nasal cavity and the respiratory system seemed very high because -- the estimates seem low because it's per gram. But you talk per surface. And per surface area that's a lot of material. Because that means almost all the cells have got it. Because it's not like a liver where it's in pieces. It's everywhere. And I thought that was a lot.

DPR STAFF TOXICOLOGIST LIM: So in terms of trying to add that type of information --

CHAIRPERSON FROINES: Are you more concerned about systemic sulfate effects or lung sulfate?

PANEL MEMBER PLOPPER: No, I'm just thinking in terms of what does it mean to have all this sulfate -- that much sulfate stuck in the tissues that long afterwards in terms of what that's doing to toxicity. Because it sounds to me like it's a lot. I think cells would have a difficult time dealing with that.

CHAIRPERSON FROINES: They would also have -- I mean there's the acute issue of what happens with sulfate uptake in epithelial cells, et cetera, et cetera, in the lung. And do you -- are we going to produce any sulfuric acid, which we know is problematic?

What I would do would be to do some -- a bit more literature work. We know that sulfuric acid when it's breathed as a fume is quite toxic. In fact, when I was on the NTP we considered sulfuric acid as a lung carcinogen. So that if you have a lot of sulfuric acid in the lung, clearly it's a carcinogen.

So in order to protect yourself, I think you should probably look at the sulfate literature a bit and decide what might be appropriate to --

PANEL MEMBER PLOPPER: Just mention it, because -- just for that, because it may turn out that that's what compounds the problems with the fluoride.

CHAIRPERSON FROINES: You think there -- we don't know how much sulfate is generated from this compound in the lung, do we?

DPR STAFF TOXICOLOGIST LIM: It was only measuring that urine and blood, as I recall. So we don't know the total.

CHAIRPERSON FROINES: So we don't -- there's probably no estimate of sulfate in the lung then, I would

guess.

DPR STAFF TOXICOLOGIST LIM: Not in this study.

CHAIRPERSON FROINES: And this is the only study. So we're sort of -- you may want to -- you may want to say this is the only study and this is an issue that's unresolved and further information would be helpful. I mean cover yourself by acknowledging that there is some uncertainty and that it's something that deserves further attention. Obviously sulfuric acid's quite toxic.

DR's. LIM: Would that be sufficient without any more reviews or -- how far do I need to go --

PANEL MEMBER PLOPPER: I think it would be. We don't -- I don't think the information is there, but it's certainly --

CHAIRPERSON FROINES: My guess is the information isn't there. And so what you're going to do is to make -- write a short statement that says this is an issue that deserves further study, and there is clearly toxicity associated with sulfates. And so --

PANEL MEMBER PLOPPER: Could you assume that if the -- whatever the fluoride burden is, if you divided it by two, that's the sulfate? Which is still -- it's quite a bit.

CHAIRPERSON FROINES: So you're just acknowledging that you're aware of the fact that this is

an unresolved issue, I think would be...

And there was a third -- you had respiratory sulfate and -- what was the third?

PANEL MEMBER PLOPPER: That's it. I think every else that I was concerned about somebody else brought up, so --

CHAIRPERSON FROINES: Okay. I'm the last one, and I'll be brief.

I think that it might be useful to -- your discussion of the two papers on page 52 is quite nice, I thought. And when you're over here talking about the risk assessment and you talk about selection of endpoints, I would actually put a -- when you're over here and you're in the brain vacuolation and malacia -- oh, you do? I'm sorry. What I was asking you to put in, you have put in.

(Laughter.)

CHAIRPERSON FROINES: My fault.

(Laughter.)

PANEL MEMBER HAMMOND: Smart.

CHAIRPERSON FROINES: Okay.

DPR STAFF TOXICOLOGIST LIM: I've got good leads.

CHAIRPERSON FROINES: All right. So that's good. We cleared that one up pretty fast.

(Laughter.)

CHAIRPERSON FROINES: I just wanted to make one

comment here. The Eisenbrandt-Nitschke article in -- it's in the published literature, it's on page 57 -- you have, "This discussion emphasized the role of fluoride in the toxicity of sulfuryl fluoride, but lacked detailed analysis. Indirect effects (adrenal cortex hypertrophy, hyperglycemia, and lymphoid tissue necrosis) observed with sulfuryl fluoride were attributed to fluoride ion as well as stress."

One, I think you can take the parentheses out of that sentence because I think it's all part of the sentence and the parentheses actually aren't needed.

But to the degree that sentence raises some fairly significant issues, namely, affects on the adrenal cortex and hypertrophy and hyperglycemia; and all I was going to say is that if there's anything else that you can say to fill that out a little bit more, it would be I think useful. It's not -- it may be that what you've got in there is reflective of the level of discussion in the paper.

DPR STAFF TOXICOLOGIST LIM: Right. That's why I said that they emphasized the role of fluoride in the toxicity but lacked detailed analysis of -- yeah, the role of fluoride in the toxicity -- of these in --

CHAIRPERSON FROINES: Yeah, that -- all I'm saying is that that sentence is so provocative that to the

degree that you can add anything more about those endpoints, it would be useful. So its really a writing issue, not more than --

DPR STAFF TOXICOLOGIST LIM: I'll reread the paper and see what I can find.

CHAIRPERSON FROINES: Yeah, just reread the paper.

And let me just -- I think that's it. I have all these places -- oh, the other issue that you raised was the nasal issue and the olfactory or other uptake.

PANEL MEMBER PLOPPER: Right. She was going to expand that.

CHAIRPERSON FROINES: Can you -- yeah, can you add something.

DPR STAFF TOXICOLOGIST LIM: Yeah, I'm going to go back to look at the papers and see what olfactory study was done to describe that a little bit more.

CHAIRPERSON FROINES: Okay. That's it. That's it for me.

So further discussion. And what we need to know is, given the discussion that the panel's heard as we've gone around the room, is the panel comfortable approving the document, recognizing that there are further changes that are going to be required?

Three nodded heads, four nodded heads, five

nodded heads.

PANEL MEMBER GLANTZ: Why don't you make a motion, Craig.

CHAIRPERSON FROINES: Do you want to make a motion?

PANEL MEMBER BYUS: Yeah, I'll move we approve the document subject to the changes that we've all discussed and given to you.

PANEL MEMBER ATKINSON: Second it.

CHAIRPERSON FROINES: Good.

Any further discussion?

All in favor?

(Hands raised.)

CHAIRPERSON FROINES: The vote is unanimous.

So we appreciate all your efforts.

PANEL MEMBER GLANTZ: Now, do we have to adopt findings?

CHAIRPERSON FROINES: Yes. And we agreed to -- we have some findings actually that OEHHA developed that will be useful for our -- to use as a starting point. And we're going to send those findings to the two leads. They can edit them and send them back. And then I'll edit them and then we can send them around and approve the findings at the next meeting.

And in the meantime I'm going to send a letter,

if everybody agrees, to Maryann that says -- it's just a one-page letter saying we've approved -- we voted to approve the document. And then they can get on with the regulatory process that follows. And that we will then send the findings subsequent to the next meeting, if that works for you.

Okay. And I think that what Craig and Roger are basically going to do is be responsive to the discussion here today, but also in the end cut down what is much longer than what we need. And then we'll send them around so everybody -- and Stan will clearly have edits. We know that.

(Laughter.)

CHAIRPERSON FROINES: No disrespecting hint?

And then I'll do it. And then we will approve them and send them out at the next meeting -- after the next meeting.

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: And so that's that.

We anticipate --

PANEL MEMBER BYUS: I think we're going with the new shortened review --

CHAIRPERSON FROINES: Well, that's right.

PANEL MEMBER BYUS: And so we're going with the new format -- new format findings -- findings format.

CHAIRPERSON FROINES: Basically a five-page document of that.

And we need to say something about the regulatory -- that the risk has been assessed to meet the statutory requirement. But I can work on that, so don't worry about it.

The second thing -- the last thing in terms of administrative matters, we are planning to have another meeting this year, perhaps in October or November. And we're going to be taking up another pesticide.

Tobie, what -- say it.

DPR ASSISTANT DIRECTOR JONES: Methidathion.

CHAIRPERSON FROINES: Right. That one. The M word.

And so here comes the hardest part of the day. We need two leads for this pesticide. And Craig and Roger I think have done their term. And so -- and Stan's certainly done his turn.

So, Charlie, would you be willing to do it?

PANEL MEMBER PLOPPER: I guess so, if I don't have to pronounce it.

CHAIRPERSON FROINES: And there's only one exposure assessment person left in the room.

PANEL MEMBER HAMMOND: So I do the exposure us assessment part?

CHAIRPERSON FROINES: Yeah. Would you?

PANEL MEMBER HAMMOND: (Nods head.)

CHAIRPERSON FROINES: I don't know anything about this chemical, so that I don't know how demanding it's going to be.

So it will be Kathy and Charlie, Tobie.

DPR ASSISTANT DIRECTOR JONES: Okay.

PANEL MEMBER ATKINSON: So what class of chemical is this? Is it an organophosphorus or what?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: It's an organophosphate pesticide.

PANEL MEMBER ATKINSON: Oh, okay. I'll be happy to assist on the environmental effect.

PANEL MEMBER HAMMOND: Oh, Good.

CHAIRPERSON FROINES: Good.

PANEL MEMBER ATKINSON: Since we've probably done all the published organophosphorus in the atmosphere.

CHAIRPERSON FROINES: The other thing for the next meeting is I would like to have a part-day workshop, if everybody agrees, on -- and I'll work on this with you and invite some people to come and present and discuss what substances would be appropriate -- should be taken up by ARB as future TAC candidates. And have Jeannette Brooks talk about their prioritization process, which has been -- we think is with about complete. Is that right,

Lynn.

ARB AIR POLLUTION SPECIALIST BAKER: Correct.

CHAIRPERSON FROINES: And so I think that we did diesel in 1998. We did ETS June 24th, 2005. That's a seven-year hiatus. But we did about 200 risk assessments in between that were the 2588 risk assessments. So that -- but the issue of what TAC's should be being brought to the panel -- and, for example, we might consider recommending ultrafine particles or we might -- you know, who knows, I mean. And so the issue of what compounds as scientists would we recommend, we can invite some people who could make some recommendations, if that would be reasonable.

PANEL MEMBER PLOPPER: That's a good idea.

CHAIRPERSON FROINES: So we will spend half a day on ARB issues and then half the day on DPR issues.

PANEL MEMBER HAMMOND: So this is all a one-day meeting.

CHAIRPERSON FROINES: One day meeting. And we would start it at 9, not 9:30, and so on and so forth.

PANEL MEMBER HAMMOND: 9 p.m.

CHAIRPERSON FROINES: So that's it.

Does somebody want to make a motion to --

PANEL MEMBER GLANTZ: I so move.

CHAIRPERSON FROINES: Second?

PANEL MEMBER BYUS: Second.

CHAIRPERSON FROINES: To --

PANEL MEMBER GLANTZ: -- adjourn.

CHAIRPERSON FROINES: To adjourn.

PANEL MEMBER BYUS: I'm sure that's what you meant.

CHAIRPERSON FROINES: Can we have a vote.

All in favor.

(Hands raised.)

CHAIRPERSON FROINES: We're adjourned.

Thank you very much. Very productive day.

(Thereupon the California Air Resources Board, Scientific Review Panel meeting adjourned at 2:20 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 21st day of July, 2005.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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