MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

SOUTH SAN FRANCISCO CONFERENCE CENTER

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PROCEEDINGS

CHAIRPERSON FROINES: I'd like to call the meeting to order.

We now have everybody here who's going to be here. We will be missing one panel member, Dr. Charles Plopper from UC Davis, who's traveling in Sweden.

And so at this point I'll open the meeting of the Scientific Review Panel on September 26th, 2007. And we have a quorum.

And so we should just begin with ethylbenzene. And, Andy, it looks like you're on target.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes. Well, we're going to get euphemistically -- we're going to get closer to the microphone first.

We're going to start with a brief presentation on our derivation of the unit risk factor for ethylbenzene, which is going to be given by Dr. Joe Brown here.

So I'll hand it straight over to you, Joe.

OEHHA STAFF TOXICOLOGIST BROWN: Thank you, Andy.

CHAIRPERSON FROINES: Excuse me. Paul wanted to ask a question.

PANEL MEMBER BLANC: Well, I was just going to say, Andy, you should give your full name, because otherwise on the transcript people may think your name is

Ethyl Benzene.

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, I've been called a -- I've been called a number of names in my time, but that is an innovation.

For the record, my name is Dr. Andrew G. Salmon, and I'm Chief of the Air Toxicology and Risk Assessment Section of OEHHA.

CHAIRPERSON FROINES: And you might -- one of you might just make sure that we all understand why this chemical is coming forward at this particular time.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Okay. Well, I think Joe will probably cover that. But in a nutshell, this is a chemical which is identified as a hazardous air pollutant by the federal forces; and, therefore, by definition is also a toxic air contaminant. It's a compound which is somewhat ubiquitous in the environment and from a various sources, as you will hear. And as a result of recent work, there are some carcinogenicity findings, which give us cause for concern. So this is what prompted us to derive a unit risk factor to assist the -- particularly the Air Toxics Hot Spots Program in any situations where they would want to warn or regulate a chemical.

CHAIRPERSON FROINES: Is there monitoring that's been occurring for ethylbenzene?

OEHHA STAFF TOXICOLOGIST BROWN: Yes, I believe so.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, they -- I mean that is something, you know, for the details we should defer to the Air Resources Board staff. But in a word, yes.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA STAFF TOXICOLOGIST BROWN: Thank you, Andy.

Let's get the next slide here, take a look at ethylbenzene.

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OEHHA STAFF TOXICOLOGIST BROWN: As you can see, similarities to benzene and styrene, two other compounds we're familiar with, were studied. And it is a federal HAP under the U.S. Clean Air Act, 1990, and therefore it's a toxic air contaminant.

Next slide.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: As Andy mentioned, many sources:

Industrial emissions, over 7 million pounds in 2002. Hopefully that's gone down.

Vehicle exhaust.

Wood burning.

It's a component of environmental tobacco smoke.

And we have a 2005 figure for ambient air concentration in California of .22 parts per billion or .96 micrograms per cubic meter.

Next.

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OEHHA STAFF TOXICOLOGIST BROWN: Just for reference, you know, established a chronic REL in 2000 of 2,000 grams per cubic meter, or 400 ppb, based on nephrotoxicity, hyperplasia of the pituitary gland, and other affects.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: Carcinogenicity. The gene tox profile for this we feel at this point is sort of inconclusive. However, the NTP in 1999 ran a full bioassay on this in mice and rats. They found:

Clear evidence of renal tubular adenoma or carcinoma and testicular adenoma in male rats;

Some evidence of renal tubular adenoma in female rats; and

Clear evidence for both lung and liver tumors in male and female mice, respectively.

Next.

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OEHHA STAFF TOXICOLOGIST BROWN: This gives a rundown of the actual quantal responses for the five tumor sites that were identified, from top to bottom mice to rats.

And in the first column there you can see that all of the tests gave significant trends for increases in the tumor incidents with dose. And also the top doses were all significantly different by the Fisher exact test.

And the denominators on these quantal responses ignored any animals that died before the first particular tumor was observed. So these are sort of adjusted by this.

Next slide, please.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. In terms of dose response methods, we actually apply two.

We use the sort of traditional approach, linearized multistage model, using the MSTAGE program of Couch, 1992.

And we also use the benchmark dose methodology first introduced by U.S. EPA in 1996, and using the EPA software. The latest version of this actually just came out last week. It's version 1.4.1B. But they keep

updating this as we go forward inside.

Now, we also use two different dose metrics. We use sort of an applied dose or a lifetime weighted average daily dose. And we also used a pharmacokinetic model to produce sort of a PBPK adjusted dose. And in extrapolating from the animal data to the human potency values or unit risks, we apply two different factors. For the applied dose, we used body weight human over body weight animal to the one-fourth power. And for the pharmacokinetic metric we used a smaller factor because we assumed the model would take part of that adjustment -- would take care of part of that adjustment. So we used a one-eighth power adjustment in this case.

PANEL MEMBER GLANTZ: That was one thing in reading the report I -- was that just --

MR. MATHEWS: Into the mic.

PANEL MEMBER GLANTZ: Oh, I'm sorry.

I didn't -- I mean what was -- other than just seeing what you just said that it seemed like less of an adjustment made sense. Is there any literature --

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, there was a rationale for that. The interspecies scale really is considered to be two components, pharmacokinetic component and a pharmacodynamic component. And, you know, it's an argument -- I guess we could argue how we should parcel

these two. We sort of assumed sort of arbitrarily that they're equal -- that they make equal contributions. Now, maybe that's not exactly true. But in this case, I think it's just an assumption of the assessment that we're doing here. That may not always be exactly the case. But in this case we're assuming that half of that interspecies correction is due to pharmacokinetics, which we're accounting for in the modeling. So this is more or less an assumption than assessment.

PANEL MEMBER GLANTZ: So it's just an assumption you made?

OEHHA STAFF TOXICOLOGIST BROWN: Yeah.

PANEL MEMBER GLANTZ: There's no data to --

OEHHA STAFF TOXICOLOGIST BROWN: It might not be half-half. It might be two-thirds and one-third.

Andy, do you want to say a word?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: As an aside, I'll just remark that the one-quarter power effect, which was the default for the applied dose method, is the recommended default for the new U.S. EPA 2006 cancer risk assessment guidelines. And it's what we are generally proposing to use ourselves for risk assessment at this point. So that is the underlying policy default.

PANEL MEMBER GLANTZ: Well, I think -- I mean I

think it would be helpful in the report to just make this clear, because when I read it I couldn't quite figure -- I mean I sort of generally remember that one-quarter number from somewhere a long time ago. But I think being explicit about where you got those from and what assumption you're making, I think would just make the report clearer, as I was very confused by that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: We'll clarify that.

OEHHA STAFF TOXICOLOGIST BROWN: So actually to recap here --

CHAIRPERSON FROINES: Let me just ask a question.

The difficulty I have, being the chemist in the crowd, is you say pharmacokinetic and pharmacodynamic, and I don't have anything to connect that to. I don't have any chemistry to connect what in fact you are talking about.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Let me try to explain that a little bit better.

The pharmacokinetics, you can view this as basically what the body does to the chemical. And the pharmacodynamics is -- you know, is the other way around. So it's the biological response as opposed to the metabolism and the distribution.

So pharmacodynamics is a response -- a biological

response to the chemical, what the chemical is doing to the body rather than what the body is doing to the chemical.

CHAIRPERSON FROINES: I think everybody at the table knew that. That's why we're here.

PANEL MEMBER BLANC: Oh, I thought that was a nice summary, to tell you the truth. I mean it was a nice way of saying it.

OEHHA STAFF TOXICOLOGIST BROWN: But that's the simplest way I can explain it.

So pharmacokinetics deals with uptake distribution and metabolism, but it doesn't deal with response per se or particular --

CHAIRPERSON FROINES: Well, let me give you -- I don't want to prolong this, but let me give you an example. When we did the pharmacokinetic modeling for methylene chloride, we were concerned about the glutathione pathway and the P-450 pathway. And here we have evidence for the formation of a hydroquinone as a metabolic pathway.

And so when you're talking about -- when you give the basic definition of toxicokinetics, the question is: What are the elements that went into developing the models besides in terms of your thinking? I mean I understand -- I understand that these are approaches that

one can take without taking into consideration the actual what does pharmacodynamics mean within this context.

OEHHA STAFF TOXICOLOGIST BROWN: Well I think it means the -- you know, the anticipated human response to this chemical, which we don't know for sure. So we're trying to adjust for, you know, how it might be metabolized and excreted. But we don't know -- we're not too sure about the response side of it, you know, what is happening in at a tissue level.

CHAIRPERSON FROINES: Okay. We'll just leave it as it is.

PANEL MEMBER FRIEDMAN: So I just want to make sure I understand it.

So you're saying that, you know, if you just took the human weight divided by the animal weight, a human so much bigger than a rat or a mouse, that you'd have a huge difference in effect; but you're saying that it probably has more -- we're assuming that it has more of an effect on the human than the rate difference -- than the weight difference would imply?

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

PANEL MEMBER FRIEDMAN: Is this just sort of a safety consideration or is this based on actual knowledge of the effects on humans versus animals?

OEHHA STAFF TOXICOLOGIST BROWN: Well, you know,

there are studies studying various scaling factors, mainly in sort of anti-cancer drugs and things like this. But when you get down to the environmental chemicals, it's a little bit more difficult to predict how the body's going to respond.

PANEL MEMBER FRIEDMAN: I didn't understand what you said.

OEHHA STAFF TOXICOLOGIST BROWN: When you get down to environmental chemicals like this, the not anti-cancer drugs that have been studied in humans.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: You know, there's a -- there have been a number of studies of the relative potency of carcinogens in animals of different sizes including humans. And as Joe says, the data set is defective in the sense that most of the ones obviously are drugs. But, nevertheless, there are actually quite a number of data points now. And there's a rather broad distribution of ratios that you see. But the three-quarters power or, you know, the one-quarter factor, as you see here, is a sort of midpoint in the range of actual observed differences. And it says that humans are somewhat more sensitive than the rodents on a per milligram, kilogram body-weight basis, but somewhat but not hugely. So that's -- there is a limited database to support the one-quarter power factor

used because of policy --

PANEL MEMBER FRIEDMAN: To me that sounds hugely rather than somewhat if you take that, you know, the quarter -- the fourth route.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, the possibilities which have been suggested cover an even wider range. Let's just say that.

You know, the suggestion has been made the difference in sensitivity might be, you know, all the way from nothing in the sense that the -- you know, the effects would be exactly the same on a per milligram, kilogram body-weight basis, all the way up to the -- you know, it might be several orders of magnitude higher in some cases. And there are a few chemicals where clearly humans are greatly more sensitive than animals. But for the most part, the difference falls into this range which is covered by the one-quarter power factor.

PANEL MEMBER FRIEDMAN: Thank you.

CHAIRPERSON FROINES: Did you want to say something?

PANEL MEMBER HAMMOND: I was just going to say -- I mean I think that also -- surface area is also a scaling factor as well.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: That was the previous default. And our original guidelines was the surface area assumption. That is also broadly consistent with the underlying data. But there's been a fair amount of discussion over the last couple of decades as to what is the best factor. And the sort of consensus position seems to have coalesced around the one-quarter rather than one-third choice now. Some of that is not, strictly speaking, based on the data of relative sensitivity to carcinogens but rather on the data for various enzymes and things like that, which seem particularly some of the xenobiotic metabolizing enzymes seem to cover the range using a one-quarter rather than the straight surface area basis. Not that that's a very good -- you know, that's not a very good reason, but it's one of the things which factored into the debate.

CHAIRPERSON FROINES: We should go ahead. I realize that these more or less standard scaling factors or more improved scaling factors are what we always use. And I was actually making a mistake by asking a question that was more about metabolism and downstream effects. And so it's really not particularly relevant to this particular issue. So let's go ahead.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: We will have further opportunities

to discuss this in greater detail in due course, I promise you.

OEHHA STAFF TOXICOLOGIST BROWN: Just to recap here. We basically have two dose response methods and two dose metrics. So that's like essentially four sub-analyses.

So if you go to the next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: This is just a reminder about the dose -- benchmark dose methodology.

Here we're fitting the observed data to a selection of models. And generally the ones that seem to fit best are the ones that are similar to the old multistage polynomial-type model. And we try to identify a lower bound on a dose that gives a 10 percent over-the-background response. And essentially that's our point of departure. And we essentially draw a straight line between that and the origin or simply divide 0.1 risk by the lower bound on that benchmark dose and that gives us a slope or potency.

And there's -- generally we've analyzed a large number of data sets. And frequently the results you get are very similar to the linearized multistage model. But there are some differences. The linearized multistage model is not really designed so fit doses in the upper

part of the dose response range. So you can get some differences, depending upon the data set.

And, also, the BMD method places a premium on the fit of the data. So you generally have a more stringent -- a fit criteria, a statistical fit criteria for a choice in model here. But generally that, as you'll see, the two different dose response methods give similar results.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. Some more on our pharmacokinetic assumptions for inhalation in mice. We used more or less standard response equations here and in rats. And to estimate low dose inhalation in humans, we used a pharmacokinetic model with human parameters in it.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. This is the first of four slides. There is a graphic coming at the end, so bear with me here. But this gives the actual numbers for the five different tumor sites that we evaluated.

In this first slide we're using the linearized multistage dose response method and the applied lifetime

weighted average dose. The figures in bold are for the male rat kidney tumors. We consider that site the most reliable of the five sites we looked at.

You'll see that the male rat testicular tumors give a higher value.

The fit of all of these data sets is excellent, as indicated by the P value. In this case P value of .1 or greater is considered an adequate fit.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: This is the benchmark dose approach, also with the applied dosimetry, a lifetime weighted average dose. And you can see the values are very similar. For example, the unit -- the projected unit risk for the male rat kidney is .0026 instead of .0025 previously. The fits are excellent across the board.

Next slide.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: Okay. This is the multistage dose response with the PBPK dosimetry. And here we're getting some of the lower values, but not lower by a lot: .0020 for the estimated human unit risk value for the male rats. And all the fits are adequate.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: And, finally, this is the benchmark dose with the pharmacokinetically adjusted dosimetry. And here we had a lower value, but still it's less than a twofold lower, .00164 for the human unit risk, and adequate fits.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: And then, finally, there's a graphic putting all these together. You can see along the bottom, we have the five tumor sites. And in the body of the graph you see the four different dose response and metric combinations. And the one on far left is the key site, the male rat kidney. And you can see that there's not much difference between the different methodologies used. On the Y axis we have the unit risk value.

So all of the methods we used gave fairly similar results.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: To summarize here, the 95 percent upper confidence bound on the unit risk value is similar at each site for the linearized multistage and the benchmark dose modeling methods:

Range of .00044 to .0066 per milligram per meter cubed.

So this includes methods for male and female mice and rats.

The male rat was the most sensitive sex and species tested. The kidney tumors again were judged to be the most reliable target site upon which to base the unit risk. The potency and unit risk values for the rat testicular adenomas, albeit higher, were complicated by a high background values for this fairly common tumor.

So even though we had higher values here, we didn't feel this was a good site to base the unit risk on because of those high backgrounds.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: Here's a summary of key values for ethylbenzene. Unit risk we chose .0025 per milligram per meter cubed or 2.5 times 10 to the minus 6 per microgram per meter cubed. And another way to express the would be .0087 per milligram per kilogram per day.

If you apply this to the average ambient value, you can project a population risk of 2.4 times 10 to the minus 6, which is, you know, fairly low.

PANEL MEMBER FRIEDMAN: Could you just remind me. Does that mean that two times in a lifetime --

OEHHA STAFF TOXICOLOGIST BROWN: -- lifetime

exposure --

PANEL MEMBER FRIEDMAN: -- of 10 to the 6 people, 2.4 cases were developed, is that what you mean by that?

OEHHA STAFF TOXICOLOGIST BROWN: Yes. You get 2.4 cases if you expose for lifetime at .96 micrograms per meter cubed, which is the average ambient value in 2005. So maybe its gone down, hopefully.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: We received --

CHAIRPERSON FROINES: So 20 million people you'd have 20 times that number.

PANEL MEMBER GLANTZ: So can I just ask one question before you get on to the comments?

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Let's go back.

PANEL MEMBER GLANTZ: In reading through the thing, in the PBPK model, you know, you have a lot of parameters you're pulling from various places in the literature to get the model and I mean that's the way those models are.

But the thing that I sort of kept asking myself as I was reading it is -- you know, you've got a lot of knobs you could turn in your predictions. And how sensitive is your result to the specific values that you

use? And how confident are you in them? Because you didn't really -- you just said here's a number from this paper and that paper, and sometimes the three or four significant digits which I always get anxiety attacks about. But I mean in the end -- I mean the fact that you ended up with very similar results with the two approaches was nice. But did you do any sensitivity analysis at all other than look at the effects of uncertainty in those parameter estimates

OEHHA STAFF TOXICOLOGIST BROWN: Well, you know, that's an area that we're trying to develop better techniques. One of the problems with the PBPK modeling is that you really need better statistical handles for uncertainty evaluation.

Now one of the comments was that the model we applied was not done in the rat that was used in the bioassay. It was -- in other words the parameters in the paper we used for our preliminary modeling was in a Sprague-Dawley rat, where there actually had been another publication which we didn't pick up on at the time where similar modeling, but not exactly the same, slightly different, was done in the F-344 rat, which we were actually using the bioassay.

So the commenter said, "Well, you've used the wrong model. And you also used the wrong parameter. You

used the human value for the blood air partition coefficient instead of the rat value," which was, you know, 60 percent different.

Well, you know we didn't think it would make a big difference. So we went and redid the whole modeling with the F-344 model, if you like. And there were some differences at the high dose level, but they really didn't affect the bottom-line value, what was going on at low dose, which really determines what the potency's going to be. So in a sense that was sort of like an uncertainty evaluation. We used basically two different models and got similar results, also with two different blood or partition coefficients, which generally have a stronger effect on these types of models than other factors.

So the short answer to your question is we did something of that nature. But we hadn't really done a systematic uncertainty analysis for this. And the actual number we picked was not actually based on a pharmacokinetic adjustment.

So I think what we're trying to do is develop models that have better statistical capabilities built right into the things like Monte Carlo. And we don't have that yet. The modeling software we have is relatively rudimentary but it's adequate for a lot of things. But that's certainly an area where we'd like to see

improvement in the future.

PANEL MEMBER BLANC: Can I ask a question. It may not be your bailiwick. But in terms of triggering hot spot -- a threshold for a hot spot concern, is the current public policy one case per hundred thousand or one case per --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: That's actually a decision which is made individually by the air districts. And it's the different air districts do have a somewhat different policy, depending on their individual circumstances of the --

PANEL MEMBER BLANC: What's the range?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Typically they start to expect some kind of action or notification either at 1 in 10 to the 5th or -- I think the South Coast has a somewhat higher trigger level because they have high background levels there. But essentially 1 in 10 to the 5th is the sort of default starting point. And the level of their concern obviously rises as the predicted risk goes above that level.

PANEL MEMBER BLANC: And can you just for point of reference, since we're talking about a cyclic hydrocarbon, give us the unit risk value -- the predicted

risk value -- I'm sorry -- for benzene as it currently stands?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Do we have that?

OEHHA STAFF TOXICOLOGIST BROWN: I'm going to have to -- I think we'll have to get back to you on that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yeah, we'll have -- well, we can look that up. I don't have it literally to hand at the moment, but I can look that up.

CHAIRPERSON FROINES: Is this room wireless?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY

BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: It's wireless. Then just go on your website.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yeah, we can do that.

PANEL MEMBER BLANC: The reason I asked the questions, because I'm just trying to get a sense of, just as a logic thing, has this -- where does -- does the value that you're coming at make some kind of biological sense -- in terms of biological public health sense in terms of what one would think was logical? And so I'd like to see how it plays against -- I don't -- do you have a cancer unit risk value for -- for the --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, the other two obvious comparisons are benzene, as you mentioned, and also perhaps another for naphthalene, which we developed a little while ago.

And this is in the ballpark. It's not -- we're not hugely far apart. But to give you the exact numbers, we're going to have to nip off line and do some homework.

OEHHA STAFF TOXICOLOGIST BROWN: I think it's lower than styrene, which is another chemical we worked on recently. But as Andy said, they're more or less in the same ballpark.

CHAIRPERSON FROINES: Well the methylene chloride document was -- if you use the applied dose, it was 10 times 10 to the minus 6; and if you use the PK model, it was 1 times 10 to the minus 6. So it was a factor of 10.

PANEL MEMBER LANDOLPH: In the write-up on the metabolism scheme, Figure 1, which I liked very much, I wonder if you would consider putting in there some putative oxygen radical intermediates, some putative quinones, because you mentioned that you're getting 8-hydroxy-deoxyguanosine and DNA. And you're also getting some chromosome breakage. And of course the ethyl side group is influencing the metabolism a lot, pulling it away from benzene. But there is some comparability there that

might be worthwhile just discussing concisely. Particularly if you're going to use that default linear no-threshold model, it would give you a little more justification for doing that.

OEHHA STAFF TOXICOLOGIST BROWN: Andy, could you bring up the metabolism slide at the end.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Sure, yes.

OEHHA STAFF TOXICOLOGIST BROWN: We do actually have -- it's not in our --

CHAIRPERSON FROINES: We can come back to -- I'm going to raise the same issue. So why don't you go ahead and we'll come back to it, unless it's coming up next.

OEHHA STAFF TOXICOLOGIST BROWN: This is the slide. This is sort of a classic thing we took out of Angstrom.

And I think you're right in a way. Maybe we ought to have a second figure that really focuses on this oxygen and, you know, the quinones and the possibility -- there's a few in the literature of generating a reactive oxygen species.

PANEL MEMBER LANDOLPH: Because you're getting chromosome breakage in the workers and you're getting, you know --

OEHHA STAFF TOXICOLOGIST BROWN: This is sort of

a general slide basically to show the chief urinary metabolites, the mandelic acid.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: This is the ones which you actually identified --

OEHHA STAFF TOXICOLOGIST BROWN: Right.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: -- as I understand, rather than the reactive intermediate --

OEHHA STAFF TOXICOLOGIST BROWN: The route at the bottom, which -- the ring oxidation route leading to ethylphenol there and also these other suspicious oxidation products are relatively small metabolites. These are less than 1 percent generally on the bottom there.

But I think you're right. I think we ought to have a slide there, because there are a couple that we could possibly produce that would elaborate a little bit more in this area.

CHAIRPERSON FROINES: Well, as long as we're -- am I interrupting you?

Go ahead.

PANEL MEMBER LANDOLPH: Just one second.

And it would give the document just a little bit of elegance if you just compared that to benzene. Just a

paragraph, a short paragraph would be useful.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Okay. I think we mentioned it in our response to comments, but we didn't cover it perhaps with as much detail as we should in the documents. So we can add that.

Do you want us to proceed with the response to comments at this point?

CHAIRPERSON FROINES: Well, let me just make my one comment, and then maybe we won't come back to it.

I agree with Joe. And I've already told Melanie that I'm going to bring it up. And, that is, one of the things that's interesting -- and this is for further discussion over time -- one of the things that's true about IARC documents, as you know, is that they now take into consideration mechanism of action as one of the criteria for ranking. And it seems to me that that would be a good approach for us to be taking, and in some respects we have in the past. And in this case, this cries out for a brief discussion -- because way back at the end of your discussion on metabolism and mutations and what have you, there's this paper by Midorikawa in 2004, and the thing that's important is he does see oxidative DNA damage, as Joe just pointed out. But more importantly, he sees the metabolism -- the metabolites are

not those. Those to me are benign. I don't think any of those are particularly worrisome.

But I do think that the ethyl hydroquinone, the catechol and the quinone are probably the causative agents for the carcinogenicity, either by reactive oxygen species generation -- but the ethyl hydroquinone will form irreversible bonds with amine groups on DNA. And so you have two possible mechanisms with the quinone -- the quinone or the catechol, namely, the reactive oxygen species being formed, which is what the deoxyguanosine would tend to indicate that you're getting some superoxide radical anion; and, secondly, that these are going to be powerful irreversible electrophile inhibitors like benzoquinone is. Benzoquinone is very active in binding proteins and DNA.

And so I would just give the benzoquin -- the ethyl benzoquinone a little bit more tension than this one little paragraph here, because this is the one metabolite which you can say without any question is potentially carcinogenic?

OEHHA STAFF TOXICOLOGIST BROWN: Well, I believe there were some in vitro follow-up studies there where they actually found adducts being formed --

CHAIRPERSON FROINES: Yeah, yeah. But I think I -- rather than putting it at the end sort of buried, I

would say mechanism -- potential mechanisms. And those aren't going to make it in your --

OEHHA STAFF TOXICOLOGIST BROWN: Well, actually that particular paper has a diagram in it which I was thinking about when you were asking the question. So I think -- I think we could come up with something that would expand that graphically with a figure to try to emphasize a potential mechanism that could support a linear --

PANEL MEMBER LANDOLPH: I agree with that also. And also the fact that you're finding some chromosome breakage in the peripheral blood lymphocytes of exposed workers, that's very similar to what you see with benzene. And that likely would lead the MOA to segueing from the oxygen radical generation into the chromosome breakage, which is how benzene predominantly works.

PANEL MEMBER BLANC: I'm not sure -- I understood your comment to be you're thinking that maybe in addition to this figure you would put in the other figure?

OEHHA STAFF TOXICOLOGIST BROWN: Add another figure, yes.

PANEL MEMBER BLANC: But I actually think it would be far better for you to take this figure and adapt it -- you already say that you're adapting it from --

OEHHA STAFF TOXICOLOGIST BROWN: Well, it says

adapted. Actually it means copied.

PANEL MEMBER BLANC: Well, I would suggest it. Because if you show two different figures with two different metabolic pathways, it's going to confuse rather than elucidate. I mean I think you should integrate a metabolic drawing that is the presumptive metabolic model that you believe based on best science exists. I'm just emphasizing what John said. But I have to say that coming at it as a -- from my end I would be very confused to see this figure and then another figure which purports also to be the metabolic pathway, which --

OEHHA STAFF TOXICOLOGIST BROWN: The rationale for this figure is the urinary excretion data, a percent, you know, of the metabolites comprised with mandelic acid and so on. I mean those ones across the top, you know, make up like 95 percent of the actual metabolites identified in the urine.

Now, there are other intermediates and ring oxidation products which we're concerned about. But I don't know if it's going to give the right quantitative idea if we just scrap this thing. Now, I don't know, I mean we'll certainly --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- we'll have to work on that, yeah, and see what we can --

OEHHA STAFF TOXICOLOGIST BROWN: We'll have to work on that. But I certainly agree we need another figure to focus on the potential mechanism of action of these quinones.

CHAIRPERSON FROINES: Well, this is important. And let me give you an example. Roger McClellan in 1983 wrote a paper on putting benzo(a)pyrene on carbon black. And when they looked at the metabolites, when they looked at the products after the experiment, and they exposed animals to them and then looked at the products, what they found was no products whatsoever from the diol epoxide that everybody has in every toxicology textbook in the country. So that what everybody believes is the mechanistic pathway for the carcinogenesis was BAP going to a diol epoxide, they found nothing. And they found 20 percent of the benzopyrene quinone.

And so one has to ask the question -- you know, every textbook in the United States has this one pathway and they didn't find a single bit of evidence.

So, when we start to put in metabolism, I think it's worthwhile to put in information that helps lead you to your ultimate conclusions. We don't really need review documents. It's good to have some level of review, there's no question about that. But I think, and the Panel may disagree with me, that highlighting those

elements of your report that lead to ultimate conclusions is much more insightful in terms of the Panel understanding how you got from point A to point Z.

PANEL MEMBER LANDOLPH: And that statement on the summary of the Ethylbenzene genotoxicity I think is accurate. But I would recommend breaking out into separating the oxygen radical stuff into a separate paragraph. So although you correctly point out that there's no gene mutation in the lower organisms, and some of the in vitro studies stress, that there is oxygen radical data, chromosome breakage, which may well be thought to be the ultimate mechanism by which it had carcinogenesis or something like that.

PANEL MEMBER BYUS: I agree with you because -- I think you did a very nice job discussing the mechanism of action in response to the comments, but it's not actually in the document. So it goes along exactly with exactly what John says. You want to use that belief of what the mechanism of action is to lead through the thought processes on your conclusions. You do it in the comments. You do it nicely. I think the comments -- it's a very nice, interesting scientific interchange back and forth and it's well thought out and I agree with your conclusions. It's just it's not in the document anywhere in a logical precise manner, as another paragraph or in

conjunction with an additional metabolism slide that really gets to the crux of the mechanism of action in terms of metabolism rather than the clearance, which is part of the PBPK modeling and whatever. And important -- it isn't that important, but it's -- you need to make that distinction in terms of the amount of the metabolite that might be responsible for the mechanism of action of the carcinogenicity. See what I'm saying?

So that really just needs to be clearly documented in the main document. It's all in the comments, if you care to read it back and forth and find it. But that's really not where it ought to be.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: I think our initial approach was that we would do the -- we would do the unit risk the way we did it regardless of whether we felt that we knew what -- that that was the mechanism of action. But having explored the issue in some length, I think we're coming around to the view that this is highly plausible even if we don't feel either the right or the need to absolutely hang our hat on, as it were.

CHAIRPERSON FROINES: Well, you have -- you know, all of this requires you to be strategic. And when Melanie is sitting back there and she says, "Oh, my God, this thing forms a quinone. Froines is going to jump all

over us, because that's his pet compound." So you say to yourself, "Maybe we better put it in the document because he's clearly going to come back and haunt us on it."

Go ahead. I'm sorry.

PANEL MEMBER BLANC: This figure that you adapted, in the adaptation was there -- I assume there was a label for the lower calicle that was dropped through a technical --

OEHHA STAFF TOXICOLOGIST BROWN: Probably.

PANEL MEMBER BLANC: And is that then -- am I understanding that that as shown is 4-ethylphenol?

OEHHA STAFF TOXICOLOGIST BROWN: That's correct.

PANEL MEMBER BLANC: And then that 4-ethylphenol, which is not labeled, is then purportedly on its way --

OEHHA STAFF TOXICOLOGIST BROWN: -- on its way to produce --

PANEL MEMBER BLANC: -- to one -- an alternate to going to glucuronidation as going to this epox -- further epoxification and then to a catechol or whatever.

OEHHA STAFF TOXICOLOGIST BROWN: A catechol or a quinone.

PANEL MEMBER BLANC: And, therefore, in addition to the arm that goes to 4-ethylphenol, there's another arm not shown that we now know goes to 2-ethylphenol?

OEHHA STAFF TOXICOLOGIST BROWN: Yes. And that

would be the subject of a second slide -- or a second figure.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Expansion --

OEHHA STAFF TOXICOLOGIST BROWN: -- or expansion of --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- of this one if we can figure out how to do it.

PANEL MEMBER BLANC: You probably -- there's probably an 18 year old intern on your staff who could --

(Laughter.)

OEHHA STAFF TOXICOLOGIST BROWN: I'm sure there is. We need a young brain on this one.

PANEL MEMBER BLANC: I mean that's the problem, right?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, it is.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We have our ways of doing these things. So we'll have to look at that.

PANEL MEMBER BLANC: Or someone's kid maybe.

PANEL MEMBER LANDOLPH: Is there any data on leukemia induction in animals at all? I didn't see any mention of it. Is there anything in the literature?

OEHHA STAFF TOXICOLOGIST BROWN: I didn't come across that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Are we done on metabolism? Because I just have -- we've managed to do our homework here, and I just was going to report that we have -- for benzene we have a unit risk factor of 2.4 times 10 to the minus 5 per parts per billion or 2.9 times 10 to the minus 5 per microgram per meter cubed, which is about 10 times the potency of ethylbenzene. And given that there's 3 or 4 parts per billion of benzene in the air, that gives you actually a background risk of about 1 in 10 to the minus 4. So clearly Benzene is a bigger problem than -- then this is not a completely negligible problem.

PANEL MEMBER BLANC: Good. Well, that's helpful to me. I don't think that's something that needs to be in your report, but it's still helpful for me then.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: But, you know, I'm -- I mean I'm sorry we didn't have it right away. We should have got it done.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Let's go back to the first of the comments slides.

We received only one comment, but it was very voluminous. And so those sort of boil down the responses

for this overall.

Probably one of key comments was that the commenter believed that ethylbenzene is largely non-mutagenic and should be assessed with a nonlinear dose response, a threshold-type of approach. And we've mentioned this a little bit.

At this point we think that ethylbenzene hasn't been adequately tested for genotoxicity, particularly for oxidative damage to DNA. Therefore, the possible role of genotoxicity is inconclusive in terms of supporting a particular mode of action at this time.

Next slide.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: Second comment basically focused on the mode of action for the kidney tumors. And the comment was that ethylbenzene causes kidney tumors via 1-phenylethanol induced chronic progressive nephropathy (CPN). Some data was supplied.

We thought that the causal relationship between CPN and kidney tumors was not established. Furthermore, there was a relatively high background of CPN, which made it difficult to use it.

So that was detailed in our responses to the comments.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: Third one, liver tumors in female mice are due to increased cell proliferation and the development of altered hepatic foci.

The data supplied showed a weak increase of foci with females and no effect in males.

We OEHHA was not convinced that this potential MOA is operating or how significant it may be. So we just thought that was sort of inconclusive.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: And, finally, lung tumors in male mice are due to the formation of ring-oxidized metabolites including catechols and quinones.

And our response: It's possible that cytotoxic quinones may be involved in an MOA for lung cancer, or possibly other cancers. However, in our view this has not yet been established. So we just sort of talked about that possibility, how we should expand on that in our document. But as yet, we don't have that established mode of action for any particular --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think the commenter's point was that they were arguing that the quinones were causing cytotoxicity rather than genetic damage. And that was

what we felt was frankly unsubstantiated. And it was as likely, if not more likely, that the quinones were having a genotoxic effect.

PANEL MEMBER LANDOLPH: Well, they likely do both.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Absolutely --

PANEL MEMBER LANDOLPH: But the key here --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- as do most full service carcinogens.

PANEL MEMBER LANDOLPH: But in the contest of carcinogenesis, the genotoxicity is certainly more important, I think.

PANEL MEMBER BLANC: Can you clarify for me when they kept harping on the term "modified Hill criteria," do they mean modified Bradford Hill criteria?

OEHHA STAFF TOXICOLOGIST BROWN: Yes. Yes, epidemiological according to --

PANEL MEMBER BLANC: Perhaps you could inform them that Bradford Hill was his full last name and that Bradford was not his first name, that his name was Austin Bradford Hill.

(Laughter.)

PANEL MEMBER BLANC: Or am I missing something?

Was there -- has there been some, you know, promulgated guideline that uses that terminology and has chopped off his name?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: No, I think it's a rather widespread misapprehension. We all know that he was of course Sir Austin Bradford Hill, the last two being sort of final names.

PANEL MEMBER BLANC: Yeah, Sir is not his first name either.

But thank you, Ethyl, for pointing that out for me.

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Ethyl strikes again, yeah.

(Laughter.)

CHAIRPERSON FROINES: It is true that when I keep seeing this Hill, Hill, Hill, I wonder if it's some molecular biologist, you know, down at Cal Northridge or something. And obviously it's not.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: But not to be confused with author of the Hill equation either.

(Laughter.)

OEHHA STAFF TOXICOLOGIST BROWN: I think that's

the last slide we have, other than the metabolism slide, which we sort of chewed over.

So I guess we -- if you have additional questions or comments or suggestions for improving the basic document, I think we'll go back and address the concerns you've already mentioned to us and try to come up with a better figure or figures to --

CHAIRPERSON FROINES: Stan.

PANEL MEMBER GLANTZ: I just had -- this is sort of a point I was confused on. If you look on page 14, and then there's a bunch similar tables following that. I wasn't sure what -- you have a column there called "Statistical Significance," and I wasn't quite sure what you were -- what the hypothesis was.

PANEL MEMBER FRIEDMAN: I couldn't figure it out either. The footnote since explained it. But --

PANEL MEMBER GLANTZ: Well, no, I couldn't figure out the footnote either.

PANEL MEMBER FRIEDMAN: Oh.

PANEL MEMBER GLANTZ: Oh, okay. Well, then it's my shortcoming here.

But, you know, one of the things, it says their pairwise comparisons to controls using the Fisher exact tests. But I presumed that the controls were the ones that were unexposed.

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

PANEL MEMBER GLANTZ: So how can you have a P value for the first line in the table?

PANEL MEMBER FRIEDMAN: It says the P value listed next to the control group is a result of trend tests.

PANEL MEMBER BLANC: You know --

PANEL MEMBER GLANTZ: Where did it say that?

PANEL MEMBER BLANC: Down below.

But, Stan, I had absolutely the same reaction. I mean I finally understood it. But you really should not -- there's no hope in the footnotes to help you here, although they could be a little clearer. But I think that wherever it is you put the P value for the test for trend, please don't put it in the first row. It's just completely confusing.

PANEL MEMBER GLANTZ: Yeah, I think you should just put another line at the bottom that says test for trend or something.

PANEL MEMBER BLANC: And each of the tables has that. It was completely --

PANEL MEMBER GLANTZ: Yeah, that's right. I was totally -- well, at least one member of the panel was smart.

PANEL MEMBER FRIEDMAN: Well, that was one of the

few things that I was very concerned about too. But I just read the footnote and I finally understood --

OEHHA STAFF TOXICOLOGIST BROWN: You just happened to read the footnote and find --

PANEL MEMBER FRIEDMAN: Yeah. Well, so I mean -- so I agree with better communication now.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We will clarify that.

PANEL MEMBER GLANTZ: Well, I read the footnote too and I completely didn't get it.

So, anyway, the other thing about this table and the others is I think it would just be helpful in kind of thinking about the dose response -- and then this actually is a whole bunch of places in the report where you do this -- where you have the tumor incidents and, for example, for the controls you have 3 over 42 and for 750 ppm it's 21 over 36, I think it would be helpful to add another column that just has what that ratio is. You see what I'm saying? Take out the calculator and figure it out. Because that -- I mean I think you want to keep what you've got because it shows you, you know, the actual numbers, which I think is important. But just adding -- and this applies to the other tables -- you know, just so you don't have to take out your calculator.

PANEL MEMBER LANDOLPH: And in that footnote for

tumor incidents, under D, could you just define that as total number of tumors over total number of animals, just to be brutally clear.

PANEL MEMBER GLANTZ: In other words, presented this way, two out of three panel members were confused?

PANEL MEMBER FRIEDMAN: I was -- the third one was too.

PANEL MEMBER GLANTZ: But you figured it out. So two out of three were terminally confused.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's 66.67 percent.

(Laughter.)

PANEL MEMBER HAMMOND: It was the 95th percentile.

PANEL MEMBER FRIEDMAN: You were really good about defining your abbreviation, but you didn't define NTP, at least that I could find. So I didn't know what it was until I found the reference.

OEHHA STAFF TOXICOLOGIST BROWN: That's true.

PANEL MEMBER FRIEDMAN: And then I would just like to suggest you could -- it took me a minute to figure out what MO -- it may be everybody here knows exactly what MOA is. But it took me a minute to figure out it was mechanism of action. So I'd like to do -- try to avoid these action items.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Let's do a jargon hunt to make sure we have --

PANEL MEMBER HAMMOND: -- have in place jargonisms.

(Laughter.)

PANEL MEMBER GLANTZ: Yeah. I absolutely had the same thing with MOA where I actually guessed what it was.

PANEL MEMBER FRIEDMAN: Ah, you see. So sometimes --

PANEL MEMBER GLANTZ: If you're given enough monkeys and enough typewriters. But, yeah, I agree. I think --

OEHHA STAFF TOXICOLOGIST BROWN: NTP is identified in the references, by the way. So if you got that far --

PANEL MEMBER FRIEDMAN: I finally found it there. But --

PANEL MEMBER GLANTZ: Well, I had the same thing with LTWA. I had to kind of look around to figure out what that was.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. We'll try to fix those deficiencies.

PANEL MEMBER LANDOLPH: You know, but I want to say overall I liked the report. These are things that can sharpen up. I think it's written very well. It's done

competently. It's got a lot of the correct background literature. So I was very pleased with the document in general.

PANEL MEMBER BLANC: Are these your comments, Joe?

PANEL MEMBER LANDOLPH: Yeah. I forgot to sign them.

CHAIRPERSON FROINES: Does the Committee want to approve the document pending changes, or do you want to delay a vote until you see the next --

PANEL MEMBER BLANC: No, no. I'll be happy to make the motion that we approve this document as submitted, presuming the minor changes are made.

PANEL MEMBER LANDOLPH: I'll second.

CHAIRPERSON FROINES: Conversation, comments?

All in favor?

(Ayes.)

(Hands raised.)

CHAIRPERSON FROINES: The vote is unanimous for approval of the document on ethylbenzene.

Want to take a break?

THE REPORTER: No, I'm fine.

CHAIRPERSON FROINES: That went by so easy, it was disappointing.

OEHHA STAFF TOXICOLOGIST BROWN: After 20 years

on this, we're getting better at it.

(Laughter.)

CHAIRPERSON FROINES: Do you want to take a quick break?

PANEL MEMBER BLANC: Yes, sure.

CHAIRPERSON FROINES: Okay. Five minutes.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: May we reconvene?

Drs. Glantz, Salmon, Friedman, Hammond.

In my office we have a jar. And if you use a colloquialism, you have to put a quarter in for an end-of-the-year party.

(Laughter.)

CHAIRPERSON FROINES: So we should have a jar for people who don't come back to the table at the end of the break.

PANEL MEMBER LANDOLPH: Do we get to take money out if we come back early?

(Laughter.)

CHAIRPERSON FROINES: Great.

Tobi.

PANEL MEMBER GLANTZ: Are you an economist too?

PANEL MEMBER LANDOLPH: No, just poor, just poor.

(Laughter.)

PANEL MEMBER HAMMOND: Just a professor at UC.

CHAIRPERSON FROINES: Thank you, Tobi.

DPR ASSISTANT DIRECTOR JONES: I'm Tobi Jones, Department of Pesticide Regulation. I want to thank the Chair and members of the Scientific Review Panel for providing DPR the opportunity to present our risk assessment on endosulfan and our proposal to list endosulfan as a toxic air contaminant.

Endosulfan is one of the few organoinsecticides remaining in use in the U.S. While endosulfan's use continues to decline, it is still a preferred insecticide for certain crop pest combinations in California. This continued use means that there is still sufficient ambient air exposure to warrant endosulfan as a toxic air contaminant.

DPR is aware of a recent report by the Department of -- California Department of Public Health on the association of the use organochlorine pesticides, including endosulfan, with cases of autism, and we will work with Department of Public Health on this issue.

Since DPR's public comment period on endosulfan ended late in August, we have not completed our responses to the received comments. We will provide those comments and our responses to the Panel in the near future.

I'd like to turn this over to the three DPR staff who are authors of the risk assessment. Dr. Shifang Fan

will present the environmental fate and use of endosulfan. Dr. Sheryl Beauvais will discuss the assessment of exposure to endosulfan. And Dr. Marilyn Silva will discuss the human health assessment and conclusions about the proposal to list endosulfan as a toxic air contaminant.

CHAIRPERSON FROINES: Welcome.

(Thereupon an overhead presentation was Presented as follows.)

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: The environmental fate of endosulfan.

Endosulfan is a pesticide belonging to the chemical family of organochlorine, and the sub-class chlorinated cyclodiene, with only one double bond. Its molecular structure has two stereochemical isomers, alpha-endosulfan and beta-endosulfan. The alpha-endo isomer is asymmetric; the beta-endosulfan is symmetric.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Endosulfan is poorly soluble in water, but readily soluble in common organic solvents. Alpha-endosulfan has higher vapor pressure, so it's more volatile. And the beta-endosulfan has higher adsorption coefficient. Therefore there's more affinity onto soil particles.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Endosulfan is a broad-spectrum non-systemic insecticide and acaricide with contact and stomach action. It is used to control sucking, chewing, and the boring insects on a wide variety of vegetables, fruits, cotton, and trees. Currently, there are six registered products containing active ingredient of endosulfan in California. Formulations include emulsifiable concentrate, wettable powder, and the technical grade endosulfan. The technical grade endosulfan is used to formulate the end-use products. All labels bear a signal word "Danger" and "Poison." It is a restricted pesticides in California.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: In recent ten years, annual endosulfan use decreased from more than 200,000 pounds in 1997 to about 83,000 pounds in the year 2005. The 2005 is the latest year when the use data was completely compiled.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Here is Endosulfan use distribution map. The top use counties are Fresno, Kings, Imperial, Kern, Tulare, and the Riverside in San Joaquin Valley and the Imperial Valley.

CHAIRPERSON FROINES: Does anybody look for it in the Colorado River?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Pardon?

Colorado River, no.

Sorry. It takes a while for the next slide because it's the map side-by-side comparison.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: This side-by-side comparison of use map with the same scale showed the decreased endosulfan --

PANEL MEMBER GLANTZ: Could you back up?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: It's taking a while to get back to it.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Okay. That map has the same scale, shows that decreased Endosulfan use in 2005 was mainly due to reduction of the cotton crop in the San Joaquin Valley.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: This monthly use for the entire state showed that the peak use months were from June to September. For the top six use counties the peak use months varied from county to county within June to September.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: In California, endosulfan was mainly used on cotton, alfalfa, lettuce, tomato, and the melons.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Endosulfan fate. The physicochemical properties of endosulfan determine its fate in environment. The fate here includes inter-environmental media transportation and the inner-media transformation.

Endosulfan is released to the environment almost exclusively from pesticide applications. And there is no known natural source of Endosulfan. But it was found in almost all environmental media and all over the world. As we mentioned previously, the alpha-endosulfan is more volatile and the beta-isomer is more adsorptive and persistent. It's overall moderately volatile property enables it to be transported as vapor and spray drift to multiple media. Its moderately adsorptive and persistence properties enable it to stay in the environment for an extended period and it can be transported via runoff to the surface water bodies or via dust dispersion to atmosphere and the redeposit to off-target areas.

Therefore, Endosulfan has been detected in areas where it was never used, such as Lake Tahoe Basin and

Sequoia National Park, and even in the Arctic.

Endosulfan degradation come via biotic or abiotic process in aerobic and anaerobic conditions. Both alpha- and the beta-endolsulfan can be oxidized to endosulfan sulfate via biotic metabolism. Endosulfan sulfate is of comparable toxicity as its parents and more persistent. They all can hydrolyze abiotically or biotically to endosulfan diol. Endosulfan diol is more hydrophilic and less toxic. They can be further metabolized to various intermittent metabolites and eventually mineralize to release carbon dioxide. But the processes are slow. Therefore, most common chemical forms found in the environment are alpha- and beta-endosulfan, endosulfan diol, and endosulfan sulfate. Alfa- and beta-endosulfan and the endosulfan sulfate are toxicity concerns.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: In soil. Adsorption immobilizes the endosulfan to be leached to groundwater. So leaching is not important. However, both dissolved and the particle-bounded endosulfan can be transported via runoff to rivers and lakes and eventually to the ocean.

Endosulfan can volatize to the atmosphere from the soil water surface driven by Henry's Law constant. Study showed that approximately half of the amount of

endosulfan applied to surface soil was lost via volatilization in three to five days for alpha-endosulfan and five to eight days for beta-endosulfan. Endosulfan bounded on soil particles can also be transported as dust to the atmosphere from dry soils.

Endosulfan degradation in soils depends on many factors, such as soil type, organic carbon content, pH, temperature, moisture content, microbial population, and the biomass. Reported half-lives vary from 28 days to more than 200 days and typically it's 50 days.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Endosulfan contaminated to -- okay, in water. Endosulfan contamination to surface water bodies is mainly due to spray drift and the runoff transportation. Spray drift consists alpha- and beta-endosulfan from applications. Runoff events can carry all three types of toxic endosulfan. And most likely to be dominated by endosulfan sulfate due to its more persistence.

Endosulfan loss from water involves adsorption and volatilization. In a laboratory study, 24 hours evaporation at room temperature resulted in 26 to 27 percent of alpha-endosulfan loss, but 95 to 98 beta endosulfan remained in the incubation vials.

Endosulfan hydrolysis favors in neutral to alkaline water. Half-lives varied from hours to more than 200 days, depending on pH and temperature. At acidic water, oxidation becomes the main degradation process.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: In atmosphere. Volatilization and the vapor transportation are the main processes for the endosulfan entering to and moving in the atmosphere. When endosulfan is applied onto crop, volatilization starts and the vapor is transported by wind and turbulence. The continuous volatilization and the vapor transportation eventually remove up to 50 to 70 percent of total endosulfan deposit on the crop surface. Volatilization from soil solution and free water surface also contributes to the atmospheric endosulfan but at much lower rates.

Spray drift can result in endosulfan intentionally moved to off-target areas. There were many spray drift events reported in eighties and nineties. The spray drift is manageable via regulations and the technical improvement.

Another source of atmospheric endosulfan is from dust dispersion and transportation. Its importance depends on regional weather, geographic and topography conditions, and human activities. Dust transport can

carry all three toxic forms of endosulfan, but much lower in magnitude than spray drift and the vapor transport.

CHAIRPERSON FROINES: Question. I have just one question.

I wasn't quite clear on your spray drift. You then say manageable. And I wasn't sure what you meant by that.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: Let me give you -- in 1988, the California Department of Food and Agriculture monitored aerial application of endosulfan to three fields in the most 19 drainage area in Monterey County. Endosulfan was found on deposit sample location 18 feet from the application field. This information was used to develop education measure to reduce off-site movement of endosulfan.

And the U.S. EPA started the 300 feet of buffer zone. And California Pesticides Regulation Department have like a certain times to have some regulations, and certain time you can spray and, you know, what kind of wind or the weather conditions you can spray. And if the wind exceeds some criteria, and then you cannot spray. Something like that, the regulation managing the spray drift.

And the technical improvement I think of the aircraft type and the nozzle and the drop letter size, all

that, have some experimental data and that they set some regulations for that.

PANEL MEMBER BLANC: I think what Dr. Froines is getting at is that you're mixing two different issues. If you're presenting the technical atmospheric fate data, then clearly it's easily entering into the atmosphere via drift. Whether or not there may be administrative recommendations in order to reduce that problem is an editorial comment, which I don't think belongs in the environmental fate. The environmental fate is not that because this is a big problem, there have been a number of regulations that have been introduced. The environmental fate is that it easily is distributed through drift, end of story. I mean you could say because of that various regulations. But if you just say, "and that's a manageable problem," well not really. It seems like it's a problem that's substantive enough that there have been all of these steps that have been recommended. And since we all know that things that are recommended may not happen, and since you're talking in general terms -- I mean I hope I'm not putting words in your mouth, but I think that's where you were going with this comment.

CHAIRPERSON FROINES: I think it's a potential can of worms to get into that discussion of what somebody means by manageable, because then you have to deal with

the issue of evaluation and validation, and that's really out of the scope of this discussion. So we --

PANEL MEMBER BYUS: I have another question though.

So when you spray -- so I just want to get clear in my mind the difference between drift and volatilization, and then what happens to that volatile chemi -- what happens to endosulfan once it's volatilized?

So I imagine you mean by drift, you're talking about during the spraying process, actual drift of the particulate spray?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: That is one thing that happens in the application.

PANEL MEMBER BYUS: During application.

But the volatilizations, so you're saying that 50 to 70 percent of what is sprayed on plants doesn't stay on the plant, it goes back up into the air through --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: Yeah, because of the -- they volatilize from the -- surface and turbulence and the wind dilutes the -- took away and then volatilization continues. There is probably in a few days -- in two to three days. That depends on the weather and two to three days or three to five days, yeah, probably 70 percent -- 50 to 70 percent

will eventually volatilize from the surface of the crop. That I got from the literature.

PANEL MEMBER BYUS: But that's not considered part of your actual drift concern?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: It's not drift. It's volatilization. It's volatilization.

PANEL MEMBER BYUS: And the reason is because it's more diluted, is that the -- I mean --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: The volatilization is their -- their property. But if the weather condition -- if the wind turbulence is strong and then if -- it moves away fast and then comes in. The volatilization is also driven by the -- because -- if continue to dilute, they will continue to volatilize if the partial pressure here is high and the volatile is lower. But it's already diluted and it's -- it's low, but it's high and fast.

PANEL MEMBER BYUS: Okay. So let me ask -- I guess the question that we ask is --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: The volatilization is just like the dissolution in the water. It's driven by the concentration. Though for the air it's driven by the partial pressure I think.

PANEL MEMBER BYUS: Right. But say you were standing next to a field that had been sprayed and you were downwind of it for the next day, say you lived 50 -- or beyond the 300 feet, would it blow down in your direction following the volatilization? Would it be a significant exposure to you, to someone?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: They do 300 feet, I think they'd probably have the data support it.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: Sheryl will be talking about that later.

PANEL MEMBER BYUS: Right. But I mean that's what -- I'm just trying to get this straight in my mind, when you're talking about the environmental plate and the drift versus volatilization and we talk about exposure, where all this falls.

DPR ASSISTANT DIRECTOR JONES: This is Tobi Jones. Let me just see if I can clarify.

I think within DPR in our regulatory structure we use spray drift terminology exactly as you indicate, Dr. Byus. And that is off-site movement during or as a result of application. If after material has settled on to plant or soil surfaces and it then volatilizes off, we're not currently calling that drift.

And I would say to the Committee, there's currently a discussion with environmental groups about that definition of drift as regulators use it, not just DPR but also U.S. EPA.

So I think what you have surmised from this is the case, that we're -- for the environmental fate of endosulfan, Shifang is talking about the material that comes off after the application, not during the application. And I think that's where her terminology on spray drift during the application being manageable by the kinds of technologies that she described is the case.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: Yeah, and Sheryl later will be giving results of an ARB study done. And actually concentrations after the application were higher in the air than during application. So as the volatilization is more --

CHAIRPERSON FROINES: I would argue that this is an issue that -- I mean you put your finger on what is a contentious issue and that there is a current policy, as Tobi just said. But this is, for example, particularly problematic when we get to fumigants like Telone, where it's injected into the soil, and as it vaporizes out of the soil and ends up in urban areas, do you call that drift or do you call that just happening to, you know, blow that way?

So I think that when you have something like a fumigant where it volatilizes and ends up in Bakersfield, I think one's going to have a hard time not calling that drift. And so this is an issue which I think we don't need to pursue today, but it's a policy issue of some consequence.

Go ahead.

PANEL MEMBER GLANTZ: If I can -- Because I remember a very hot meeting with DPR in San Diego a long time ago where there was a huge fight about this. But I think though that you are saying, whether you call it drift or banana, that this stuff is moving off site as a result of its application -- even if it is applied correctly and in accordance with the current standards, it moves off the site. But what you call that movement, you know, but it is moving off, you know. If it's blown off while it's being applied, that's one way to move off. But you're saying even if it doesn't blow off while it's being applied, it's going to volatilize and the volatilized stuff is going to blow off. So what you call it -- I never quite could figure out why this was such a hot issue. But it's clearly moving all over the place.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: They both move the toxic to off-site areas.

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER BYUS: In pharmacology we would call this redistribution.

(Laughter.)

PANEL MEMBER BYUS: So in a sense it's a good term, redistribution. It's redistributing from where you applied it.

PANEL MEMBER GLANTZ: And DPR might even want to use that term.

(Laughter.)

PANEL MEMBER BYUS: Oh, probably not, but...

CHAIRPERSON FROINES: Stan just proved two things: One, there is no issue that we haven't dealt with at some time in the past that will come up again and again and again. But this issue actually does have to come up again, because there is -- I think when you get into the risk management phase, there is some need for consistency of definition and what we're talking about. So let's not worry about it here today, but it is an issue which in the outside world that we never -- this group never sees is -- there is discussion about.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Okay. The wintertime dormant spray may result in wet atmospheric endosulfan in rain and snow.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: In atmosphere. Endosulfan is not susceptible to atmospheric degradation. The cloud droplets and the rainwater usually are acidic. Therefore, hydrolysis is not a common process in atmosphere. Endosulfan does not absorb --

CHAIRPERSON FROINES: I'm sorry to interrupt you again. I don't mean to be rude.

The lead for exposure on this Committee was Kathy. And so -- and Roger's usually the person who deals with atmospheric chemistry. So I assume that since you're not raising a complaint, that you're comfortable --

PANEL MEMBER HAMMOND: No, I assumed that the fate was being -- that was assigned to someone else, I thought.

CHAIRPERSON FROINES: Jim.

PANEL MEMBER HAMMOND: Well, I thought that's what you just said. So I didn't do fate.

I thought I was doing exposure, which is --

CHAIRPERSON FROINES: Was Roger to look at this point?

PANEL LIAISON BEHRMANN: This is Jim Behrmann, liaison to the Panel.

No, we only assigned two leads in this -- for this report, exposure and health. And so if there's a miscommunication, I apologize. You know, we did not --

PANEL MEMBER HAMMOND: That's my fault then --

PANEL LIAISON BEHRMANN: -- I did not assign fate specifically to Dr. Hammond.

CHAIRPERSON FROINES: So we will get -- we will have to do findings on this chemical at the next meeting. So in the interim we can deal with the photolysis. So that -- oh, I'm not saying you're wrong. I'm simply saying the Panel should review the photolysis -- the atmospheric chemistry issue, and it hasn't been done by us.

PANEL MEMBER HAMMOND: My fault.

PANEL LIAISON BEHRMANN: I apologize. It was my error in not clarifying that with Dr. Hammond. So we can work with Dr. Atkinson to, you know, also do that.

CHAIRPERSON FROINES: All right.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: Endosulfan does not absorb solar radiation of the troposphere, so photolysis can also be negligible.

Indirect photo-oxidation with hydroxyl radical may result in endosulfan sulfate and endosulfan diol susceptible to photolysis. However, they are not abundant in the atmosphere. Therefore, half-life was estimated to be 1.5 years for alpha-endosulfan.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Air concentration of endosulfan. Endosulfan concentration in air depends on the distance from the application sites. For short-range transportation, seasonal variation typically mirror the agricultural practice. Temperature and the application frequency mainly drive the air concentration in the area. For regional range, the joint U.S. EPA and the Environment Canada monitoring project investigated atmospheric toxic contaminants to the Great Lakes region. The vapor phase results showed a distinct annual cycle with peaks in summer one or two orders of magnitude higher than in winter. Summertime average concentrations was 80 picograms per cubic meter for alpha-endosulfan. Concentrations for beta-endosulfan and the endosulfan sulfate were generally lower. For long distance transportation to the Arctic, average air concentrations ranged from 1 to 10 picograms per cubic meter. As part of Toxic Air Contaminant program, Department of Pesticides Regulation provided endosulfan use report and the air monitoring recommendations to Air Resources Board for documenting the airborne endosulfan concentrations.

ARB monitored an endosulfan application in San Joaquin County in 1997, and conducted an ambient air monitoring in Fresno County in 1996.

Our next speaker, Sheryl, will present more

details for these monitoring studies.

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DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Here is just a brief summary of the ARB's monitoring results. For application monitoring of total 28 samples, 96 percent had alpha-endosulfan above the quantification limit. The highest individual concentration was 38 nanogram per cubic meter. Only 57 percent sample had beta-endosulfan above the quantification limits. The highest concentration was 200 nanogram per cubic meter. Endosulfan sulfate was detected in 7 out of 28 samples, but less than the quantification limits.

For ambient monitoring study, of total 75 samples reported, 88 percent had alpha-endosulfan above the quantification limits. And the highest one-day concentration was 140 nanograms per cubic meter. Only 3 percent samples had beta-endosulfan greater than the quantification limits. And the highest one-day concentration is 26 nanograms per cubic meter.

PANEL MEMBER FRIEDMAN: Could you explain what the LOQ and LOD are? I don't quite understand that.

MR. FRANK: Okay. LOQ is limit of quantification. LOD is the limit of -- detection limit.

PANEL MEMBER FRIEDMAN: What does that mean?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: The use of the -- is the instrument -- the smallest amount in the instrument that can detect it. If they can't detect it, they cannot quantify it --

PANEL MEMBER FRIEDMAN: You mean because it's so high --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: -- reliably. So they set it -- sometime they set it at 1 to 5 times of the LOD. So they feel confident it can reliably quantify. But that the measurable amount is just the same. So LOD and LOQ is the same. But for the endosulfan I think it's different.

PANEL MEMBER HAMMOND: No, it couldn't be the same if you have --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: No, this one is not. For some chemicals.

PANEL MEMBER HAMMOND: Oh, for some. Okay.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Yeah.

PANEL MEMBER HAMMOND: Yeah, here it's not?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: For this one it's not, right.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Yeah, the one level is the level they can actually -- they'll see within their blip on their

thing. And the other one is where they can actually quantify. So in between those two levels there's kind of a gray area where they know it's there, but they can't give you a quantifiable amount.

PANEL MEMBER FRIEDMAN: So they're both low?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Yeah.

PANEL MEMBER FRIEDMAN: One is so low you can't --

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Right.

PANEL MEMBER FRIEDMAN: -- and the other is so low you can't be sure of it?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: But we know there's something there, but they can't measure it.

PANEL MEMBER BLANC: So I'm confused. Someone else is going to be presenting in more detail the sampling data?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Um-hmm, Sheryl will --

PANEL MEMBER BLANC: And that's the next speaker?

PANEL MEMBER BYUS: Right.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: She will give you more detail about how to

correct the data, how to --

PANEL MEMBER BLANC: I just want to make an observation though. We have a hundred samples on which we're basing the data. Is that all the sampling we're going to hear about?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: For the assessment, yeah.

PANEL MEMBER BLANC: So we have approximately one sample for every 15,000 pounds of this toxin that's been used over the last ten years?

There's on average 15,000 pounds used per year, or is it 150,000 pounds used per year based on your previous slide?

CHAIRPERSON FROINES: 2004 was 150,000 pounds.

PANEL MEMBER BLANC: Right.

PANEL MEMBER HAMMOND: But now it's greatly reduced from before.

PANEL MEMBER BLANC: I understand that. But the last samples you have are from 1996 and 1997, and altogether we have 100 samples that we've had ten years of use in the interval, have at least 150,000 pounds a year. So we approximately have one sample per every 150,000 pounds.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST FAN: Oh, this use not the way. This is just the

sample taken from one study -- one application, one ambient study.

PANEL MEMBER BLANC: So we'll be hearing -- that's why I asked. Are we about to hear about other sampling as well?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: It's going to be the ARB sampling that was done. That's where we're going to get the results the assessment are made on.

PANEL MEMBER BLANC: So why did you present these sampling data here? What was the purpose of these sampling data if you're about to --

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: That was a summary of the ARB sampling that was done. And Sheryl will be giving you more in-depth concentration --

PANEL MEMBER BLANC: -- of the same hundred samples?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: Yes.

PANEL MEMBER BLANC: So we have a hundred samples over ten years in total, that's all our sampling?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: Yeah.

PANEL MEMBER BLANC: I just want to be clear.

But I'll make my critique on that later. I just want to make sure --

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: This one is done completely on the ARB study that was done.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: We only do one sample for ten years. But some other people did a lot of studies.

PANEL MEMBER BLANC: In other states?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Yeah.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah, I was also assigned to help out on this document too, mostly the health effects, I'm sure.

This third volume I thought was written pretty well. I particularly liked that figure 10 on the degradation in the water.

One comment I would make is, throughout not only Volume 3 but the other volumes, if you could include some concise discussion of the enzymes that metabolize endosulfan in bacteria and in mammals, that would be very helpful, because there's a lot of metabolites but there's no enzymology and that's sorely lacking. So if you could add that in 3 and in the other volumes, that would be very

helpful.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Yes. I think that's a very good point. We'll address that when we do the revision for the final.

PANEL MEMBER LANDOLPH: I have to apologize for not getting my comments to you earlier. You sent me the first volume and then he said, "Don't do this one. We're going to send you a second copy." And then it got buried under a blizzard of paper.

CHAIRPERSON FROINES: I just wanted to -- I'm curious as to -- I'm looking forward to the next presentation, because the numbers that were on the screen were not the numbers that you actually said.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: The numbers she gave were actually summations between the different isomers. So you're --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: What, this one?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Yeah, the ones you composed.

CHAIRPERSON FROINES: Those two numbers that are on the screen were never mentioned in what you said. They were other numbers. And so as far as I know, I have no idea what anything is at this point.

Am I --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: This one is not a concentration. Because Sheryl will talk about your detail about a concentration. I just give the summaries how many samples we have taken and how many above the quantification limit, that there is 96 percent. I didn't put a lot of column here because I don't want to have the whole slide full of the numbers and confuse people. Actually this way you have to have a calculator.

So 96 percent of 20 -- I do have it -- 27 out of 28 is above the quantification limit that's spent for 95 -- 96 percent of the sample above the quantification limit. And the 1 percent -- 1 of the 28 is 4 percent.

Is that clear?

PANEL MEMBER BYUS: My question --

CHAIRPERSON FROINES: No, I don't want to -- no, my point is very simple.

PANEL MEMBER GLANTZ: I think the point they're trying to make here is that they found a lot of them.

CHAIRPERSON FROINES: What I want to say is a matter of presentation, not a matter of the content. What I want to see on a slide is what I'm going to be told in words. I don't want to have to do calculations. You're doing calculations in your head as you speak. And I don't want to do that. I want to see slides that reflect what

you're saying. And if you have to have five slides, that's fine. But it's -- I have no idea what has been said up to now on this issue, because I don't remember those numbers that you said. I can't.

Stan may, but that's another question.

So let's go ahead.

PANEL MEMBER BYUS: Just a minor question. I think the point is, what are you concluding by this slide? What's your conclusion? I mean you present this. Now, what's your conclusion? In one or two sentences, what is the conclusion of this what you just presented here?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Yeah, I just give the fact, what is from this application -- this monitoring the results is like that. That means that most of alpha-endosulfan we can -- is volatilized as to the air, and the less beta-endosulfan, and in the application study. But in the ambient study we also get most of these alpha-endosulfan and much less in beta-endosulfan.

PANEL MEMBER BYUS: Okay. So that's your conclusion?

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: Yeah.

PANEL MEMBER BYUS: Okay.

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: But the concentration -- we don't have the concentration because Sheryl will talk about it. And we don't want to repeat, so we cut that off.

PANEL MEMBER BLANC: I think we should just move right into the next presentation. That would be awfully helpful to the --

DPR ASSOCIATE ENVIRONMENTAL RESEARCH SCIENTIST

FAN: It will be interesting.

DPR STAFF TOXICOLOGIST BEAUVAIS: Thank you.

PANEL MEMBER BLANC: You're welcome.

(Thereupon an overhead presentation was Presented as follows.)

DPR STAFF TOXICOLOGIST BEAUVAIS: I'm Sheryl Beauvais from the Department of Pesticide Regulation, and I'll be talking about data and assumptions used to estimate exposures. And part of that will be a more detailed discussion of the studies that Dr. Fan was just talking about.

PANEL MEMBER LANDOLPH: Can I ask, which volume are you referring to now?

DPR STAFF TOXICOLOGIST BEAUVAIS: This is exposure assessment, which is volume 2.

PANEL MEMBER HAMMOND: Two.

DPR STAFF TOXICOLOGIST BEAUVAIS: Thank you.

Okay. Estimates were based monitoring done by

the Air Resources Board of endosulfan concentrations in air. Both ambient and application site monitoring was done using the sampling arrangements shown. And to start with I'll focus on the little sampler here.

This is the air sampling tube. It has two sections of sorbent, which was in this case XAD sorbent. This is the top end of the tube. This is the end that gets connected to the pump here. Tubes were connected to flowmeters and then on to the sampling pump here with Teflon tubing.

And during -- I want to highlight a couple of points during the methods validation portion when they were validating analytical methods. There were two pieces of information that I just want to pass along to you:

The first being that they did breakthrough testing, which is something you want to make sure basically that the sorbent that once it captures the analyte, the analyte stays there and doesn't simply pass through the tube and on out the pump. And in order to do that, what they do is spike the top end of the tube and run -- attach this to a sampler pump, in this case for 24 hours at 2 liters per minute in the laboratory. And then at the end of that time analyze the two sections of sorbent separately. What you want to see is your analyte in the primary section and not in the back-up section.

And that's what was found here. There was no detectable amounts in the back-up section.

CHAIRPERSON FROINES: I have a question.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

CHAIRPERSON FROINES: When we do air sampling, what we do, we use something called the Tisch sampler. And the Tisch sampler has a filter for collecting particulate. And it has a Tisch -- an XAD resin tube. And so we're collecting both particulate and vapors. And obviously the reason for that is -- I live in Los Angeles and we have lots of particulate. But unfortunately you guys live up in the area that now has heavy particulate as well.

And so the question is: Have you ever done any studies in which you've actually collected particulate and extracted things like endosulfan off the particulate?

DPR STAFF TOXICOLOGIST BEAUVAIS: I don't know.

CHAIRPERSON FROINES: Lyn?

DR. BEAUVAIS: The answer's no.

CHAIRPERSON FROINES: Why? With the levels of particulate that you have, you need to worry about adsorbed vapors.

ARB AIR POLLUTION SPECIALIST BAKER: Hi, Dr. Froines, members of the Panel. Lyn Baker with the Air Resources Board.

And we have in the past used a filter in front of the adsorbent resin when we were trying to differentiate the particulate phase from the gaseous phase of something. But then for an exposure assessment they've usually added it all together. So we typically have not been requested by DPR to differentiate. So we've usually just collected the -- with this type of an adsorbent tube, which is not obviously designed to collect particulate, but it will collect particulate, and we know that because the top of the adsorbent often is brown, where the adsorbent is white. So it's trapping some of the particulate.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: There actually have been study looking at how well the adsorbent tubes -- this is Kathy Hammond, I'm sorry -- how well the adsorbent tubes collect particles. And there actually is a very high level of pass through, of the particles passing through the tubes. Intuitively you might think that particles are well adsorbed by the tubes or collected, but they're not. So, since even a volatile material -- you would have two things. You might have particles that contain endosulfan at the beginning and then you also might have vapor phase, endosulfan that condenses on to the surface of a particle. And those particles then could pass through this tube, and then you could underestimate exposure, which I think is

what Dr. Froines was talking about.

ARB AIR POLLUTION SPECIALIST BAKER: We certainly recognize there is some pass-through. But we know that the resin does trap some of the particles because we see a layer of particulate at the top of the bed of resin.

PANEL MEMBER HAMMOND: True. But you don't know what percentage that is.

ARB AIR POLLUTION SPECIALIST BAKER: Exactly.

PANEL MEMBER HAMMOND: In study -- I don't know -- for these materials I haven't done the studies. But for other studies, other kinds of tubes, charcoal tubes, which are similar designs, as much as 80 percent of the particles have been found to pass through, which I have to say I was surprised when I first saw it, those data.

CHAIRPERSON FROINES: I didn't want to hold it up any further. But I think this is an issue, Lyn, that we should come back to; and, that is, the generic issue of particles versus vapors. Because if you have an ultrafine particle with Telone on it, that's going to have a very powerful electrophilic effect in the lung. And since the ultrafines are absorbed into the cells, you're actually putting particles into the cells in the mitochondria and other places. And so this is an issue which hasn't been looked at to any degree. And I think it's an area of

pretty significant -- could have a significant impact.

PANEL MEMBER HAMMOND: May I, as long as you're on that part.

It also -- if the material itself is not very water -- not very soluble in the blood and not taken up quickly from the lung into the blood, if it's in the vapor phase it may be exhaled in a very high proportion; where if it's in the particulate phase, it might be trapped in the lung and therefore the dose -- the actual dose may be higher as well.

ARB AIR POLLUTION SPECIALIST BAKER: We'd certainly be happy to talk with you and DPR more about this.

CHAIRPERSON FROINES: Yeah. I mean your assumption that everything's going to get trapped on the XAD resin of course is the fundamental assumption. And it's just something that needs some experimental investigation, I think. It's not a fault. We're not under that.

So thank you.

DPR STAFF TOXICOLOGIST BEAUVAIS: But I can see that this is a source -- potential source of underestimation that will need to be mentioned in the exposure appraisal section of the document. So I'll add that in there.

CHAIRPERSON FROINES: Thank you.

DPR STAFF TOXICOLOGIST BEAUVAIS: Thank you.

The second point that I wanted to make on this slide is that -- or second comment about method validation, I'm going to highlight the fact that we did have acceptable recoveries of both alpha- and beta-endosulfan from these resins. And I'm mentioning that because in some of the field studies I'm about to show you the recoveries were not so good in a couple places. And I just want to point this out as part of the overall picture that we looked at when reviewing these data.

Next slide, please.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. First I'm going to talk about the ambient air monitoring study in 1996. And the purpose of ambient air monitoring is really we're trying to get a sense of what the concentrations are in an area of high use. So we asked ARB to do monitoring at a time when we anticipate use to be high and in an area where we anticipate use to be high. And this is based on pesticide use data from previous years.

So in this case, the use was done -- or the monitoring for endosulfan was done in Fresno County in --

from the end of July through the end of August. Sampling was conducted four days a week, and these were approximately 24-hour samples.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And to give you sort of a comparison here, this is the pesticide use report to summary of how much endosulfan was applied in Fresno County each month in 1996, in thousands of pounds here is what we're looking at here. And as you can see, we did -- the sampling did capture a high use period. But the high use actually occurred slightly before the sampling began in June and July.

Although we did -- we captured a high sampling period, it's questionable whether we captured the potentially highest concentrations. So that's a point that needs to be made.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And the sites for the air sampling, there were four sample sites. These were in Fresno County. Each of these was a sample mounted on top of the roof of a school. And then the background site was the ARB ambient air monitoring station in Fresno. This was an area where endosulfan use was not anticipated, and in fact the background samples collected at the site did not have endosulfan greater than the limit of

quantitation. It was below the LOQ for all samples for both alpha- and beta-endosulfan.

And the highest concentrations occurred at the San Joaquin Elementary School site.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: Limit of detection. Just quickly acquaint you with this. The analytical limit of detection for alpha-endosulfan and beta-endosulfan are shown here. And then the limit of quantification in this case, to answer your question with numbers, in this case was 3.3 times the detection limit divided by the volume of air sampled.

So this is an analytical detection limit for the samples themselves, the resin. And then this is -- we get the LOQ. So the LOQ would depend on how long the sample was running. And this gives you a sense of what the LOQs are for the 24-hour samples.

And I'll point out here that endosulfan sulfate was analyzed, and all samples were below the LOQ. And so I'm not going to talk about that any further.

Endosulfan sulfate concentrations were not included in the total endosulfan. We looked only at the alpha- and beta-endosulfan in some of those to get total endosulfan concentrations for the exposure estimates.

PANEL MEMBER BYUS: And what was used for the

detection? What was the method?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST WOFFORD: The analytical method?

PANEL MEMBER BYUS: Yeah, just -- what was it?

DPR STAFF TOXICOLOGIST BEAUVAIS: Electron capture detector. Unless you know that, my mind just went blank. It's in the document. I just went blank.

Sorry about that.

Okay. Quality assurance included collocated samples that will run each week; a trip blank, all of which were below the LOQ, which is what we want to see. And then now I need to talk about the spiked samples.

As I mentioned, we did have some recoveries that were very low. In the ambient air sampling, there were low recoveries in the field lab and trip spikes. These were all prepared at the same time at the start of the study and then stored until they were used. And all of them were, you know, 50 percent or lower and. The mean field spike recovery was 44 percent. It ranged between 38 and 54 percent.

And -- yes.

PANEL MEMBER FRIEDMAN: What is a trip blank?

DPR STAFF TOXICOLOGIST BEAUVAIS: A trip blank goes along for the ride basically. It goes into the cooler where the samples are going to be put. And it

doesn't leave the cooler. So a field spike is one that goes and is hooked up to a pump. And in this case the field spikes during the ambient air monitoring were done in the Fresno -- or in the ambient air background site, a place where you don't anticipate endosulfan.

PANEL MEMBER GLANTZ: Now, when you say a field spike, does that mean you --

DPR STAFF TOXICOLOGIST BEAUVAIS: You spike it in the lab. You put a known amount of the endosulfan -- alpha-endosulfan and the beta-endosulfan into endosulfan sulfates on each of the tubes and then see that you can recover the same amount when it comes back. So the spikes are analyzed along with the samples. And the trip blank is going along with it. It's looking for contamination in the handling process basically. So the trip blank is not connected to a pump, the field spikes are.

And so all of those were low. And then the lab spike is testing the analytical process, so it doesn't leave the lab. So in this case, the endosulfan recoveries -- alpha-endosulfan recoveries were all low.

But as you can see here, this is the mean alpha-endosulfan recovery and the beta-endosulfan recovery in the ambient air monitoring. And then for comparison I'm showing the application site means as well. And, again, the alpha-endosulfan was back up there again.

There was a quality assurance audit done of the procedures of all the study trying to detect what happened -- and trying to determine. And they came upon -- they didn't find any problems with their procedures or anything basically, but they determined that it was possible that what happened was that there was -- the solutions were spiked with a commercially purchased -- commercially purchased solutions of alpha- and beta-endosulfan. The manufacturer of the solutions recommended that they be stored at room temperature, and the laboratory stored them in the refrigerator. Now, what the laboratory procedures would have them do is warm them up to room temperature before use. But that -- and so that's a possibility. They essentially weren't able to determine exactly what the cause was there.

PANEL MEMBER HAMMOND: But did they spike the ambient and the application site samples at the same time?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, these are two different times.

PANEL MEMBER HAMMOND: Was the same -- but --

DPR STAFF TOXICOLOGIST BEAUVAIS: They were started at two different times, in that ambient air monitoring was done in 1996 and application site monitor was done in 1997. And all samples were analyzed within 20 days of collection. So, no, those are two different sets.

PANEL MEMBER HAMMOND: And do you know if the procedure for storing the standard was the same, or did they not refrigerate it in the second year?

DPR STAFF TOXICOLOGIST BEAUVAIS: That's a good question, and I can't answer that off the top of my head.

PANEL MEMBER HAMMOND: And it would certainly seem to me in -- if that happened in my lab, I would have done a little experiment to find out if refrigeration had that effect.

DPR STAFF TOXICOLOGIST BEAUVAIS: And they did. And I think they were getting equivocal results.

What?

Oh, here we go.

ARB AIR POLLUTION SPECIALIST BAKER: I'd just like to add, the analytical work and the spiking for these were actually done by two different labs, the Air Resources --

PANEL MEMBER HAMMOND: You mean for the ambient and application?

ARB AIR POLLUTION SPECIALIST BAKER: -- and application, yes.

Yes, the ambient was done by the Air Resources Board lab and -- the Air Resources Board staff did all the field sampling. But the Air Resources Board lab did the analysis for the ambient samples and the spiking. And so

it was our lab and our quality assurance audit of our lab that found this possible problem.

The Department of Food and Agriculture lab actually analyzed the samples for the application site monitoring a year later. And --

PANEL MEMBER HAMMOND: But ARB lab still spiked the samples?

ARB AIR POLLUTION SPECIALIST BAKER: No, the spikes were done I believe by the Department of Food and Agriculture lab.

So apparently it was something that our lab did inconsistent with the way they analyzed the samples when they actually spiked them. Because as the audit report for the study showed, the storage stability samples where you spike samples, put them in a freezer to make sure that you're not going to have degradation of the samples before you get them analyzed from the field, those results were all good. They were over 80 percent recoveries. So they apparently spiked the field samples differently than they spiked the storage stability samples.

So they have no reason to think that there was a problem with the actual ambient samples. They think the audit concluded that there must have just been a problem with the way they spiked the spiked samples for the ambient study.

PANEL MEMBER HAMMOND: I hear all that. I'm saying, if I thought that, then I would take the next step and just do a little experiment to see if that had an effect.

DPR STAFF TOXICOLOGIST BEAUVAIS: They did do a comparison.

PANEL MEMBER HAMMOND: Because one of the problems also, I understand it, is that in the recovery studies there's a very wide variation. It wasn't just that it was 44 plus or minus 2 percent, right? It was a huge variation in there. And that makes it very difficult to interpret the ambient air monitoring data.

DPR STAFF TOXICOLOGIST BEAUVAIS: True.

PANEL MEMBER HAMMOND: I mean I understand what you're saying and, you know, it may be okay, but we really don't know.

DPR STAFF TOXICOLOGIST BEAUVAIS: We don't know, that's true.

ARB AIR POLLUTION SPECIALIST BAKER: So Sheryl will explain the -- they accounted for our poor recoveries.

CHAIRPERSON FROINES: They what?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, they didn't actually.

ARB AIR POLLUTION SPECIALIST BAKER: No, no, you.

You did.

DPR STAFF TOXICOLOGIST BEAUVAIS: Oh, I see what you're saying, what -- the next step, the procedure here.

What this slide is actually concluding is that we actually --

PANEL MEMBER HAMMOND: -- divided by .44?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, we went ahead and corrected for these spike recoveries.

PANEL MEMBER HAMMOND: But you used .44?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: But you did have some of -- some of your spiked samples have recoveries of 10 percent, right?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, and that's -- if we'd back up for a slide for a minute here. And I want to -- what we did was we corrected for mean field spike recovery, which had a range of 38 to 54 percent. That's typical of what we would do. The labs -- and, you know, and that's another thing that I don't know the answer to and, that is, whether lab spikes were done at -- were analyzed after or before --

PANEL MEMBER HAMMOND: I think that really levels the trip blank if I remember from document --

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. Maybe it was the trip --

PANEL MEMBER HAMMOND: I think the lab was okay. I think it was -- it was either the field or the trip -- the field and the trip were different from each other.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: And I forget which was the lower one. But --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, I'm --

PANEL MEMBER HAMMOND: But they didn't make sense anyway.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER BYUS: So why did you choose 44 percent and not the lowest recovery to be held protective? I mean that's just --

DPR STAFF TOXICOLOGIST BEAUVAIS: Well, to be health protective again, because the field spikes are the ones that went out in the field and were treated exactly the same as the samples. Those are the ones that --

PANEL MEMBER HAMMOND: Did you draw air through the field spikes?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes. Yeah, those --

PANEL MEMBER HAMMOND: So you do them for 24 hours?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes. Yeah, the ambient air -- in this case for the ambient air study the

field spikes are done alongside the background sampling and --

PANEL MEMBER HAMMOND: Okay. Let me just postulate something.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER HAMMOND: I'll just -- you know, if we don't -- but I will postulate.

The trip blanks that had no air drawn through them had only 10 -- I think they had like 10 percent recovery.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER HAMMOND: The ambient air samples maybe also had 10 percent recovery. But because they were drawing air, you assume that air had no analyte there. But maybe it had analyte there and that's why it had a hard recovery.

DPR STAFF TOXICOLOGIST BEAUVAIS: No, they run concurrently with the background samples that had no -- where the endosulfan was below the LOQ, which is what you want.

PANEL MEMBER HAMMOND: Which is in the same location?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: They're collocated. Okay.

PANEL MEMBER BLANC: Yes. But you don't know

that the reason that the background samples were below the LOQ was because your recovery was so poor.

PANEL MEMBER HAMMOND: You get in a circle there.

DPR STAFF TOXICOLOGIST BEAUVAIS: Ah, I see what you're saying. You're right.

PANEL MEMBER HAMMOND: Yeah, it's just a circle. You just can't tell what you've got.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, you're right.

PANEL MEMBER HAMMOND: And also, it's not only that it's poor, but what makes it really even worse is that it's highly variable.

PANEL MEMBER BYUS: Right.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER BLANC: And just in your opinion, were these monitoring data to be submitted for publication, given what you're telling us about the variability of the adjustments that you made? Do you think it would be accepted for publication? Do you think peer-reviewed --

DPR STAFF TOXICOLOGIST BEAUVAIS: I have seen samples that go through contortions like this get published, yes.

(Laughter.)

DPR STAFF TOXICOLOGIST BEAUVAIS: And not

ideally, yeah.

Well, I think we can agree these data are less than ideal, yes.

PANEL MEMBER BLANC: And, Dr. Hammond, if you were reviewing this, you know, would you --

PANEL MEMBER HAMMOND: I would have difficulty -- I'd have serious difficulty with knowing how to interpret the data. And I'd feel that it would be very, very difficult to have any understanding.

And I guess the other question I would have is -- these things happen. I mean this happens, right? But then why was the ambient sampling not repeated? Especially since you're going back in the field to do application site sampling the following year, I would think then you would do ambient air monitoring again.

DPR STAFF TOXICOLOGIST BEAUVAIS: And I can't answer that question.

PANEL MEMBER HAMMOND: I mean it's probably -- you know, it's probably ancient history now.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: But it seems like --

DPR STAFF TOXICOLOGIST BEAUVAIS: Resource allocation, I don't know.

PANEL MEMBER HAMMOND: Yeah. And this may go back to Paul's earlier question about the number of

samples too.

And let me be clear. We know this isn't necessarily you personally, but we're just --

DPR STAFF TOXICOLOGIST BEAUVAIS: Sure.

PANEL MEMBER HAMMOND: But it seems like ambient air's an important measurement, important enough to decide to measure it. There were problems. It happens to me, you know. And those are the data that we say, "Okay, that was a pilot run and we have to figure out what went wrong," and then we repeat it. And this is -- to say the only data we have are data that are highly questionable is I think of concern, and I'm disappointed that that set of measurements wasn't repeated to understand.

CHAIRPERSON FROINES: Well, just -- I'd like to move on. But I think the Panel -- this Panel needs to think about this. Because, as we all know, endosulfan is a very, very dangerous pesticide. It's banned in most countries -- many countries throughout the world. And we're just talking about its regulation. So when we talk about health, we don't have any doubt that it's problematic from a TAC standpoint. So we need to decide what is -- what are we willing to accept in the exposure assessment so that we're comfortable with any determination we make.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, and

includes -- this is the application site data that I'm about to present under consideration. Because what happens to the monitoring adjacent to an application, the concentrations are higher, the risk numbers are -- of course it's much worse, you know, much lower MOEs for the application site monitoring for the bystander exposures. And any mitigation measures that we take to cover them -- to bring down bystander exposure would then involve a lessening of the ambient air as well.

PANEL MEMBER HAMMOND: Except for the volatilization that was mentioned earlier that might happen over the next several days afterwards.

CHAIRPERSON FROINES: And that might underestimate it.

PANEL MEMBER BYUS: And it won't affect it at all.

CHAIRPERSON FROINES: That would underestimate it.

PANEL MEMBER BYUS: Theoretically --

DPR STAFF TOXICOLOGIST BEAUVAIS: Well, because it would involve decreased application rates, for example, decreased numbers of applications that are allow, the source of things that --

PANEL MEMBER HAMMOND: Well, that kind of --

DPR STAFF TOXICOLOGIST BEAUVAIS: That kind of

mitigation measure, yeah. Yeah, I'm sorry. I'm speaking regular --

PANEL MEMBER BYUS: But 50 to 70 percent of what you spray under ideal conditions revolatilizes, is going to contribute to the ambient air. Nothing you can do other than reducing the amount of total exposure is going to affect that. Am I wrong on that?

PANEL MEMBER HAMMOND: It reduces total application?

PANEL MEMBER BYUS: Huh?

PANEL MEMBER HAMMOND: Reduced total application.

PANEL MEMBER BYUS: Reduced total application. So nothing other than reduced total application is going to reduce theoretically, since you have such a high percentage of it that goes into the air and then it has such a long half-life. So really nothing you're going to mitigate other than reducing the total amount that you spray is going to really affect that. And then of course but then your ambient air data is kind of weak, so -- or nonexistent. But that's okay.

I just want to make sure I have it clear in my mind.

CHAIRPERSON FROINES: Let's go ahead, because we are going to have to deal with the issue of the MOE, and the MOE depends upon what we're going through right now.

So let's --

PANEL MEMBER HAMMOND: What the E is.

CHAIRPERSON FROINES: What?

PANEL MEMBER HAMMOND: It depends on E. MOE depends on E.

DPR STAFF TOXICOLOGIST BEAUVAIS: Exposure.

(Laughter.)

CHAIRPERSON FROINES: I can't keep up.

(Laughter.)

CHAIRPERSON FROINES: Let's go ahead.

But I'm just putting those words out so people are thinking about them as we go forward.

DPR STAFF TOXICOLOGIST BEAUVAIS: Next slide.

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DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. These are the ambient air concentrations. And this is -- each of these are the sites. And this is the San Joaquin County Elementary School site.

On the Y axis, this is a mean concentration or the concentration of micrograms per cubic meter. Each bar is -- this is -- the blue bars are alpha-endosulfan and the red bars are beta-endosulfan. Arrow bars are standard deviation.

So to get the concentration used in the exposure estimate from this, I took the mean alpha-endosulfan and

added it to the mean beta-endosulfan. So mean total is .062 micrograms per cubic meter. So you'll see this again momentarily when I'm talking about exposure estimates.

And in calculating the mean and standard deviation for any samples that were below the LOQ, I used half the LOQ.

So, again, when we're talking about that gray area between detection and quantification, take half the LOQ assigned to that or substituted for that.

PANEL MEMBER BLANC: And can you tell me what the median values were?

DPR STAFF TOXICOLOGIST BEAUVAIS: Off the top of my head, no. But --

PANEL MEMBER BLANC: Was it skewed to the right?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER BLANC: So it was skewed towards higher concen -- skewed this way, right?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, exactly. There's a long tail on -- a lot of non-detects.

PANEL MEMBER BLANC: Oh, so it's skewed towards --

DPR STAFF TOXICOLOGIST BEAUVAIS: A low LOQ, yeah.

PANEL MEMBER HAMMOND: No, that makes it high here and it stems out. So you're still --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, what you're saying is correct. Yes, it is skewed.

PANEL MEMBER BLANC: I mean was the median higher than the mean? Maybe I should be asking it that way.

DPR STAFF TOXICOLOGIST BEAUVAIS: I wouldn't -- no, I wouldn't think so. It should be lower.

PANEL MEMBER BLANC: Okay.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, because --

PANEL MEMBER HAMMOND: It usually is --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, it would be lower. The median is going to be the center --

PANEL MEMBER BLANC: Right. And --

PANEL MEMBER HAMMOND: The median could have been less than detectable.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, exactly.

PANEL MEMBER HAMMOND: I don't know the lots, but it could have been.

PANEL MEMBER BLANC: No, because we had the numbers -- most of them were detectable at least for the --

PANEL MEMBER HAMMOND: Right. Well, I don't know, do we -- were those percentages from the previous speaker's slides the percentages for these samples?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, for the

part that she talked about for the ambient air, which was just the bottom half of her slide.

PANEL MEMBER HAMMOND: So something like 96 percent were detectable, do you think?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, that's the application site that that's true of.

PANEL MEMBER HAMMOND: Oh, okay. But it's 8 -- I think it's still pretty high.

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BRANCH CHIEF MARTY: 88 percent for alpha.

PANEL MEMBER HAMMOND: 88 percent?

Yeah, 88 percent are greater than LOQ for alpha.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: So these are exactly the same data as these that you're talking about?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, this is the same data, yes.

PANEL MEMBER HAMMOND: So these are 75 ambient samples, is that right?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: This is 75?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, the N on each of those bars is 18 or 19 samples. So 18 or 19 samples per site.

PANEL MEMBER HAMMOND: So these are mostly

detectable, unquantifiable?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER BLANC: I guess my question is related to -- since so much of the -- leaving aside all of the other error factors, these mean values are going to be driving a lot of your future calculations?

DPR STAFF TOXICOLOGIST BEAUVAIS: For the ambient air it does, yes.

PANEL MEMBER BLANC: So is -- maybe, Kathy, you'd want to comment on this. Is the mean the most conservative public health protective metric to use, or should it be the 75th percentile?

PANEL MEMBER HAMMOND: Compared to the median, yes.

PANEL MEMBER BLANC: And what about compared to the 75th percentile?

PANEL MEMBER HAMMOND: Well, I mean I think what I -- I was going to wait till I got to hear what's being said, to give her a chance to give the talk.

But I mean I think one of the things to talk about from what I read here is this 95 percent value that's in there. I mean all of these are going to have to be looked at --

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER HAMMOND: -- and how they're used.

But I think one -- the mean is -- if you want to know what the mean, you know, exposure is. But if you want to take a look at what's the public health protective, you have to go to something higher, like a 95th percentile, or even a -- and I actually think that maximum concentrations should be reported. That was one of the questions, is that are your whiskers there, are those to the maximums? Sometimes those are like times so many standard deviations or inter-quartile. Actually it turns back -- because you don't standard definitions.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, the air bars in this case are standard deviations. So --

PANEL MEMBER HAMMOND: So that's only the standard deviation?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Oh, oh. Then do you have the maximum value for those samples?

DPR STAFF TOXICOLOGIST BEAUVAIS: I can tell you. I think it was the point --

PANEL MEMBER GLANTZ: Yeah. Boy, I'll tell you if those are standard deviations, then they're very skewed as to --

DPR STAFF TOXICOLOGIST BEAUVAIS: And actually what I would like to do to -- before we spend a lot of time on this --

PANEL MEMBER GLANTZ: If those are the standard deviations, they're very skewed distributions, and it doesn't really even make sense to talk about the mean. You really ought to be presenting this as --

PANEL MEMBER HAMMOND: Well, you know, let me just say -- and I'm sorry that we're kind of jumping around a lot while giving your presentation -- as long as we're saying this, I would expect it to be extremely skewed. There's certain tables in here that surprised me because the standard deviation is equal to the mean, and that to me is too small. I would expect it to be higher in this kind of -- these kind a data, because we're talking here -- you say, well, four days a week for the entire month of August, right? -- Monday through Thursday the entire month. And I think you do not have the data, if I understand from this -- or maybe you do -- as to whether or not any endosulfan was actually being applied during that time, I mean to the days you can't associate the sample --

DPR STAFF TOXICOLOGIST BEAUVAIS: We cannot, no.

PANEL MEMBER HAMMOND: -- that's sprayed in it?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, because the use report data are only reported to within a square mile.

PANEL MEMBER HAMMOND: I understand that. But I mean you don't even know if they were applied that day --

day by day, do you?

Was any applied in the entire county or in that square mile --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, there was.

PANEL MEMBER HAMMOND: You do have that information?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, I do.

PANEL MEMBER HAMMOND: Because I think that that's another way that these data need to be looked at. But, you know, certainly there were days in which there was no application, right, in which you have sampling. So that's going to give you -- you know, stand the, you know, real low values. And then you're going to have days the application might have been very nearby.

So I would expect if you had 10,000 samples collected in Fresno, you would have a very wide range, you know, highly dispersed data.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: I mean that's what one would expect here.

CHAIRPERSON FROINES: Keep in mind, Kathy, one thing, that they are using one half of the LOQ for their --

PANEL MEMBER HAMMOND: I understand. But they only have 12 percent of the samples that are -- for which

that's true. So that's not affecting much. It has very --

CHAIRPERSON FROINES: It's not affecting much. But it's different than calling it zero or ignoring --

PANEL MEMBER HAMMOND: But it really has no effect on the data here. If they then made it zero, it wouldn't change really, because -- but if -- so you do have a -- you started to look up, before we kind of truck you in 14 different directions, the maximum values.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah. And it's -- I've got a good size table here and so I can tell you this in a little bit. But --

PANEL MEMBER HAMMOND: Or maybe you can do that later --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: -- after a break or something. Maybe you need to get through your talk or something. But I do think that understanding what the maximum values are --

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. Yeah, I'm seeing values here around .3 -- .31, .28. And so we know that they go at least that high. And I think that might be the highest.

PANEL MEMBER HAMMOND: .3, .38?

DPR STAFF TOXICOLOGIST BEAUVAIS: .28, .31.

CHAIRPERSON FROINES: Gary, did you --

PANEL MEMBER FRIEDMAN: I was just thinking -- maybe you're going to get to this.

PANEL MEMBER HAMMOND: Yeah, I am.

PANEL MEMBER FRIEDMAN: But do you know the days that --

DPR STAFF TOXICOLOGIST BEAUVAIS: Probably -- hey, if we let you.

PANEL MEMBER FRIEDMAN: If you know the days that they're spraying, maybe, you know, if you look at that day and the next day, get at the question of volatile -- you know, spread a volatile material versus the drift issue.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. And I have not done this specifically with endosulfan. I did this with the last compound I came before this panel with, which was Methidathion. And you have -- it's difficult to interpret because you have, you know, maybe two or three applications that happened a day or two before the monitoring started and it's difficult to determine how far away you should go from the sections -- the one-square-mile sections. I mean within the county certainly there's applications on a daily basis. Fresno County in 1996 was using a lot of endosulfan.

So the question is: How close do I need to get? And then how many days before and after? And within

those -- so I can certainly do that work. But I guess to also clarify that we -- when we look at this from a regulatory standpoint, we're focusing -- the worst case scenario for ambient air is for the person who's adjacent to an application. And so that's where we're using the upper bound estimate from the application site monitoring to cover that. And then these -- we have seasonal estimates for application site as well as for ambient air.

CHAIRPERSON FROINES: Let's go ahead.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. Now I'm going to talk about application site monitoring. This occurred in 1997. And ARB monitored an application of endosulfan to an apple orchard. And the applied rate was 1.5 pounds of endosulfan to acre -- per acre. And the maximum allowed on apples is 2.5. So for the short-term exposure estimate for that acute I accounted for that difference. And I'll be talking about that in a minute.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: There were -- in this application site study there were four sampling stations that surrounded the orchard. The wind direction was from the west during the application and for several hours afterwards. And so this east sampling site had the

highest concentrations of endosulfan.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And this is showing the samples. Sample No. 1 is the application. And then these are the post-application samples. And earlier when Pam was saying that the highest endosulfan concentrations occurred after the application, that will be the next graph that I show you here in a minute. But I'm just going to let you know -- just sort of orient you as to what these sample intervals are. There were a total of seven. The first five covered the first day essentially. It's 26.75 hours by the time you total all these hours.

And as you can see, the wind was directly out of the west during the early part where these highest concentrations were happening.

And then we have -- after that first day we have sample 6 and 7, each of which was a 24-hour sample. So we had a total of three days.

So I have a 24-hour time-weighted average that covers this first 26.75 hours. That's samples 1 through 5. And then a three-day time-weighted average that I'll be talking about for the seasonal and annual exposure estimates that incorporated these last two as well.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And analytical detection limits were similar in this study to the previous one. And again all samples were below the LOQ for endosulfan sulfate, so only alpha-and beta-endosulfan were included in the total endosulfan estimates. Total endosulfan concentrations used estimate exposure. Again, we had duplicate collocated samples. And background and trip blanks were all below the LOQ.

In this case we had acceptable recoveries for the field lab and trip spikes. Alpha-endosulfan mean recovery of the field spikes was 85 percent. The range of all recoveries was 78 to 90. And the range was 57 to 66. So we had a lower recovery for beta-endosulfan in this study.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. And this is a summary graph of the application site concentrations, where each of these sets of bars is a sample -- represents a sample interval. Concentrations are given in micrograms per cubic meter. And each of these bars is the total alpha plus beta endosulfan, with the red bars being from the -- this east sampling site. The little bars on the left are from the north, and yellow and the dark -- black I guess are from the south and west respectively.

So, again, the east's sampling station had the highest endosulfan concentrations. And to determine the

24-hour total endosulfan that we used for short-terms exposure estimate, just multiply the concentration of each interval at that east station times the time and then divide by the total time.

And so you get the -- this 24-hour time-weighted average was 1.63 micrograms per cubic meter, and then it was adjusted for the fact that this wasn't a maximum allowed application rate. So it was multiplied by that 1.67 the ratio of 2.5 to 1.5 pounds they had per acre. So this is the concentration that is used in the short-term exposure estimates.

And then for long-term concentration, which is going to be the three-day time-weighted average I used to calculate seasonal and annual exposures, this is all the -- average calculated like that for all seven samples.

PANEL MEMBER HAMMOND: I think this is very interesting. But I'm looking at -- you know, I just quickly looked up. So your three is -- the top bar there is the two to six hours after application.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah. That's a four-hour sample, yeah.

PANEL MEMBER HAMMOND: So we're seeing quite a bit after application; one is during the application?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: And then sample 4 is 6 to

14 hours, you know, which -- I'm trying to see this one panel. But number 6 is your 24 to 48 hours. And number 7 is your 48 to 72 hours. And what I noticed there is that those two numbers aren't changing.

So, if you had to guess what 72 to 96 hours was.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: So we -- you know, everything you have there is correct. But if we were to think about what's the long-term exposure, not a three-days but if we were to say two weeks, it might be that it might actually be continuing, that may be a very slow --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah. And actually for my long-term calculations I'm using a month for that.

PANEL MEMBER HAMMOND: And you keep it at level 7?

DPR STAFF TOXICOLOGIST BEAUVAIS: I use that three-day time-weighted average and multiply that by a month.

PANEL MEMBER HAMMOND: Oh, I see. You say that's the level of those for a month.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: Now, the other thing that's happening is presumably there are other fields

being sprayed.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, right.

PANEL MEMBER HAMMOND: And so that's the other part that goes into that assumption?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

And the background -- now, there was background sampling done, the pre-application samples, and no alpha-endosulfan -- I'm sorry -- no endosulfan. All the pre-application samples were below the LOQ.

PANEL MEMBER HAMMOND: And so there were not -- no other fields just had -- you were talking earlier about there might have been other fields that have been sprayed or had applications and --

DPR STAFF TOXICOLOGIST BEAUVAIS: Well, I can't address whether or not there was a field, for example, on day two during this sample interval 6. There could have been a field somewhere around there that was being sprayed. I don't know. We only --

PANEL MEMBER HAMMOND: But it is interesting that there was nothing at all beforehand.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah. They were below the LOQ, yeah.

PANEL MEMBER HAMMOND: That's very interesting.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. Those are the data that are used to calculate exposure. And to calculate exposure, we would estimate absorbed dose for the bystander and ambient air estimates as a total, alpha plus beta endosulfan. Assume a hundred percent of the inhaled pesticide is absorbed. And so it's simply air concentration times the inhalation rate for adults. And infants we use slightly different inhalation rates. And these are the ones that we typically use in calculating exposures.

The air concentrations again. For ambient air we use the data from the highest sampling station, which was the San Joaquin Elementary School. And for bystanders, that east station application monitoring.

And then also, we don't know -- people could be potentially exposed to endosulfan every day of the year. You know, that's sort of like the background assumption. We really don't know what individual exposure patterns are. What we do is we take the use data and we make an assumption here that exposures are less likely to occur during months when there's very little use. And in this case we use an arbitrary cutoff of 5 percent of the annual total that was used during that month.

So we don't have great resolution. And so we just simply take a monthly total here. And this -- so

what you're looking at here is a graph that's a five-year average between -- in this case, between the years 2000 and 2004 of how much endosulfan was applied in Fresno County each month by all methods on all crops. And then the question is: How much of it was applied in February and March and so forth. And what we find here is that that 5 percent cutoff, seven of these months are above that. And so we say that the exposure's most likely to occur during those seven months. And so that's when we annualize. We say that seven months is the 7 out of 12. And I'll show you here in the calculations.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: For the seasonal -- we do both seasonal and annual. And I'm not doing a short-term ambient air concentration because I'm using the bystander -- the application site data to cover for that. So we're assuming that that's the worst case for an ambient air, is somebody who's adjacent to applications.

And so for the seasonal it's just simply the concentration times the inhalation rate.

And then the annual, we annualize it by saying that, well, they have these high use months. So 7 divided by 12 in this case here. And so this the concentration. This mean concentration from the San Joaquin Elementary

School site times the inhalation rate times that 7 over 12. And so this is how the annual average daily dosage is calculated.

And the next slide.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And bystander calculations. Now we have a short term that's also going to cover the ambient air exposure. And here we have this short-term concentration, which was the 24-hour time-weighted average that was adjusted again upwards for the application rate. And so the short term is simply this concentration times the inhalation rate, which is higher in infants than adults.

Season and annual average daily dosages were calculated in the same way as for ambient, except that we were looking at the pesticide use report data at how many applications are made. We don't know where the sites are located, but they give us site identifiers, field locaters. And so from that we're seeing that you don't see the same one popping up over and over again over a period of months.

And in most cases there's a limitation as to how often you can apply endosulfan per year. In fact, I think it's all but tomatoes you have like at most one or two applications I think that is -- that are allowed.

So for the bystander exposures we're assuming one month rather than seven months, because the person -- there is no evidence to suggest that there be multiple locations or multiple uses at a location over a seven-month period.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And these are the exposure estimates. So for the short-term exposures, again for the ambient air we're taking the bystander estimates to cover those and then seasonal and annual exposure estimates.

Next slide.

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DPR STAFF TOXICOLOGIST BEAUVAIS: So to talk about some of the uncertainties, which we have been talking about, the recoveries for the alpha-endosulfan during -- spikes during the ambient air sampling were low. And so to -- and they were unable to confirm the reason in the quality assurance audit -- determined that it possibly had to do with the refrigeration of the spiking solutions.

But we did the -- we corrected for the field spike recoveries. And this is the effect that you get on the concentrations. These are the uncorrected and then the corrected for field spike recoveries.

So this is just a graph that you've already seen.

And this is what it would look like without the correction.

--o0o--

DPR STAFF TOXICOLOGIST BEAUVAIS: And, finally, ambient air. Now, as we -- a couple things that I need to say on this slide. The first piece is what's already up there, which is that the ambient air exposure estimates could have been overestimated, because again, as we've seen earlier, use has been decreasing annually since the monitoring was done in 1996.

However, as I showed on the earlier slide, we didn't necessarily capture the highest use period. And so there's possibility that it was underestimated. And there may be other reasons as well.

And I have some other things here that I obviously need to talk about now in the appraisal.

And that is it. Do you have any other questions?

PANEL MEMBER BYUS: Just one quick question. I mean you showed the picture of the airplane spraying versus that thing.

Do airplanes spray endosulfan?

DPR STAFF TOXICOLOGIST BEAUVAIS: Sure. There are applications, yes.

PANEL MEMBER BYUS: Do you have some feeling about drift compared to airplanes versus whatever that is?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, that's an air blast that you're looking at there.

PANEL MEMBER BYUS: Air blast. What's your --

DPR STAFF TOXICOLOGIST BEAUVAIS: This is what you would see in an orchard application. So this is the type of application that was monitored.

There are some studies where they have looked at both air and ground methods. And air blast is in those studies. And this isn't endosulfan. This is other active ingredients. But it's in the general range of the aerial. Sometimes it's higher, sometimes it's slightly lower.

And then when you talk about the ground being sprayed with methods where they're -- you've got the boom that's pointed downwards. In this case you've got a spray that's going upwards. And it's with air jets that are basically trying to deposit it all over these leaves and move the leaves around. So you've got quite a cloud going into the air there.

But when you've got the spray boom where the spray's pointed downwards and you're trying to minimize this off-site with the sort of management methods we we're talking about earlier, those off-site concentrations are lower. So --

PANEL MEMBER BYUS: So this is kind of more of the -- it's I mean the maximal dispersion and drift,

whatever?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, for ground methods this would be the worst, yeah.

PANEL MEMBER BYUS: What'd be their worst case scenario of an application? That's my question.

DPR STAFF TOXICOLOGIST BEAUVAIS: Pretty close, yeah.

PANEL MEMBER LANDOLPH: In that air blast is he wearing -- the person spraying it, are they wearing respirators? And do they ever get sick? Any toxicity symptoms from spraying this stuff?

DPR STAFF TOXICOLOGIST BEAUVAIS: They can -- now, in this case I think this individual's in an enclosed cab. If they're not, they're wearing a respirator.

PANEL MEMBER HAMMOND: It seems to me -- this is a question -- going back to Craig's question.

In the text -- I'm not going to be able to find it now -- but I think I remember seeing and being surprised to see that the flaggers had lower exposures -- these were personal samples on the -- occupational exposures -- that the flaggers had lower exposures than the pilots of the planes. And I was always traditionally taught that they would -- the flaggers would have much higher exposures except for when the planes crashed --

(Laughter.)

PANEL MEMBER HAMMOND: -- which happens, and it's more frequently than one would expect.

DPR STAFF TOXICOLOGIST BEAUVAIS: Now, the flagger data set that we have access to is a fairly small data set. And so it may be an artifact of that small monitoring data set.

PANEL MEMBER HAMMOND: Okay. Because that was like a very surprising kind of finding. Because usually it's like much higher because they're on the ground getting sprayed. And it makes you -- and if you're in the plane, you're not getting. Going back over your path, but --

DPR STAFF TOXICOLOGIST BEAUVAIS: Well, in this case I'm also assuming an open cockpit plane. I'm not assuming an enclosed cockpit at all.

PANEL MEMBER HAMMOND: So --

DPR STAFF TOXICOLOGIST BEAUVAIS: So this is someone that could conceivably turn around and drive right back through their own swath.

PANEL MEMBER HAMMOND: So you basically were working from the means of your values when you did all these calculations?

DPR STAFF TOXICOLOGIST BEAUVAIS: What we do for short-term exposures, we try to come up with an upper

bound estimate. And that's where that 95th percentile comes in.

PANEL MEMBER HAMMOND: So that was a question I had. Was that an observed 95th percentile or the calculated estimate of the 95th percentile value? Or was that the 95th percent -- upper confidence limit for the mean value?

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. No, it's -- what that is is that is an upper bound -- it's a 95th percentile using log normal methods, if I remember right. I'll have to check that for these. But that's -- but that is of the data set.

PANEL MEMBER HAMMOND: It's trying to estimate --

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: -- the 95th percentile statistically from the data?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Okay. That's what you're trying to do?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Okay. And those were the numbers that you used to do all these calculations?

DPR STAFF TOXICOLOGIST BEAUVAIS: For the short term. And then for long term -- basically what we're trying to do for the short-term exposures, we're trying to

get a reasonable worst-case estimate. For long-term exposures we're assuming that not every exposure's the maximum. And when you look at the pesticide use report data you find that, that a lot of times they're applying it half the maximum allowed application rate or sometimes less. So we're going for more of a typical exposure for the long-term estimates.

PANEL MEMBER HAMMOND: Using the mean?

DPR STAFF TOXICOLOGIST BEAUVAIS: And that's where we're using the means, yes.

PANEL MEMBER HAMMOND: So let me go back to the bystander for just a minute just to keep -- before we get too confused.

DPR STAFF TOXICOLOGIST BEAUVAIS: Sure.

PANEL MEMBER BYUS: Saying that at the bystander where you've got your estimate of 95th percentile, did you ever go back and look at your maximum measured value to see how that related to your estimated 95th percentile value? Because one of the things -- I mean I think it's worthwhile trying to do. And the reasons given in the report, and they do make sense, are the -- with the small number of samples, it's hard to know where your 95th percentile value is. You're probably better calculating it. And the reality is if you do a lot of looking at exposure data, especially when it's so skewed, as these

data would be and would be expected to be, that it's very unlikely, very unlikely that if you do a hundred samples, which is more than what was done here, if you collect a hundred samples you're unlikely to actually get things in the upper 5 percentile. Even though you might think you would, you're actually unlikely --

DPR STAFF TOXICOLOGIST BEAUVAIS: So your upper bound estimate is oftentimes above --

PANEL MEMBER HAMMOND: Right. You're actually underestimating the upper bounds if you do it from sampling data directly. But it's also, I always think, still useful to look at your data. But, you know, it's specifically to look at those maximum values and see.

But it's very difficult to actually capture the true maximum values. But at least look at the maximum to see, because you might for some reasons have missed some behavior or something that's happening that can lead to those higher values.

And certainly when one's looking at chronic effects, which I assume is what you're -- when you're doing your annual levels, you're talking about chronic effects -- then mean values are the -- what you want to know are people's mean exposures through the year and using an arithmetic mean as the appropriate...

PANEL MEMBER LANDOLPH: Okay. I've just got a

quick question.

On page 11 under "Reported Illnesses," which is a very interesting section, I noticed there are a couple sections in volume 2 where you mention that with just endosulfan alone, one illness injury is occurring as a result of exposures to the field residues. And then with endosulfan plus the others, out of 56 cases, 43 are occurring as a result of just exposure to field. That surprised me. Is that not well appreciated? I mean I would --

DPR STAFF TOXICOLOGIST BEAUVAIS: I'm not sure I understand the question.

PANEL MEMBER LANDOLPH: Well, I think it's fascinating data. And it surprised me that, you know, the levels were so high that when people are going out to harvest the crops, they're getting sick from exposure to this stuff. And is that well recognized within DPR?

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay. I guess to clarify, when we -- these illness reports that we show here include the possible, probable, and confirmed. And in many cases they don't necessarily confirm that it was endosulfan or another chemical. But, you know, you can't necessarily know. But you go in and analyze field residues perhaps. These are -- so when we're talking about field residues, we're talking about folks that have

gone into harvest or to do some sort of field work afterwards. And it's on a field that was treated -- if it's included in here, it was treated with endosulfan and possibly two or three other compounds as well, possibly simultaneously or, you know, it's in a tank mix or sometimes over a period of days. Or the crew may have been in more than one field and then gotten sick. And so they're looking at what possible exposures they were at.

And so when you see these multi -- you know, endosulfan with other pesticides, this is a -- you know, we include it because it may be due to endosulfan, but we can't decide it for sure.

PANEL MEMBER BLANC: Can I ask why this section is in this volume, when I would have expected it to be under the "Human Exposure" -- "Human Illness" section?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER BLANC: Was there some -- I mean --

DPR STAFF TOXICOLOGIST BEAUVAIS: There may be a reason. I'm not -- I can tell you that the data are coming from the same branch that this -- and this is all worker health and safety data. And so it may be there for that reason. It's also included in the human health.

PANEL MEMBER BYUS: It's in the risk characterization as well.

DPR STAFF TOXICOLOGIST BEAUVAIS: It is in there

as well.

PANEL MEMBER BLANC: Where -- I was just looking --

PANEL MEMBER BYUS: Because I had some concerns about that too.

PANEL MEMBER BLANC: I was just looking at page 86 where the human data are.

Is there another place in the risk -- in the medical toxicology in the --

PANEL MEMBER BYUS: Page 21 of the other volume.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, it's in both volumes.

PANEL MEMBER BYUS: "Reported Illnesses," page 21.

PANEL MEMBER BLANC: Oh, I see. Gotcha.

Okay. Never mind.

PANEL MEMBER BYUS: If you'd read that.

PANEL MEMBER BLANC: I did see it.

PANEL MEMBER HAMMOND: It's hard to read.

PANEL MEMBER BLANC: But I got confused now.

PANEL MEMBER HAMMOND: You know, your presentation was all about airborne exposures.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: And -- well, Ms. Fan stated a couple of ideas here. And one question is -- and

I can't remember if this holds for the airborne data. It's for a lot of the other data, the dietary data. There were corrections made for what percentage of crops were treated and there are various things about the decline -- the use of this material has declined.

And actually the total amount used in California has declined quite a bit, correct?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Why is that?

DPR STAFF TOXICOLOGIST BEAUVAIS: It's a combination of newer chemicals coming into play and -- you know, the neonicitinoids, for example. And in the most recent decline in the 2004 to 2005 data, they attributed it very much to the decline in cotton acreage, which was one of the crops.

DPR ASSISTANT DIRECTOR JONES: This is Tobi Jones. Let me make one comment that was reflected in the discussion in our public meeting on this issue. And this was offered up by our representative from the County Agricultural Commissioners back in the -- and I'll look it up with Pam here -- probably the early nineties there was a substantial effort to reduce service water contamination with endosulfan. So --

PANEL MEMBER HAMMOND: Which contamination --

DPR ASSISTANT DIRECTOR JONES: Surface water

contamination because endosulfan is highly toxic to aquatic organisms.

And so the uses were more highly controlled at the county level through our permit system, and uses fell off as a result of that also.

PANEL MEMBER HAMMOND: Okay. This is kind of a question more for the Panel or for John. But one thing I've been a little unclear about as we think of a toxic air contaminant is how to think about something where the use is declining, but it's not really just one kind of decline. As I looked at the data, sometimes it goes up and sometimes it goes down. And some crops started using it more than other crops.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: And so the popularity of using a particular pesticide in a particular year shouldn't be driving whether or not something is a toxic air contaminant. And at some level if you want to think about what -- you know, if something's a toxic air contaminant, it may also depend on what the potential exposure would be if it were used more rather than -- you know. And I'm not sure how exactly we deal with that, but I want to put that out there; that a lot of the evaluations that have been done in the report are looking at what is the exposure today. But there are these --

although the ambient airs were based on ten years ago.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Right. And I do acknowledge that. But some of the other data were based on other things. And so I think that's one thing to -- at least we need to bear in mind as we look through these data.

DPR STAFF TOXICOLOGIST BEAUVAIS: Well, and actually the way that we adjust for the use -- and I showed you that slide with the use pattern, the percent that was used each month. And what's happening --

PANEL MEMBER HAMMOND: Yeah. But that's to get your annual.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes. And that's the only point in which we're considering use in our exposure estimates is during -- is to determine what portion of the year might they be exposed. We're not dialing it down because --

PANEL MEMBER HAMMOND: Right, because you're not looking at how many people are exposed.

DPR STAFF TOXICOLOGIST BEAUVAIS: No. Right, exactly. And so that's -- and what happens as the use drops off is that it takes -- that tends to even out and you tend to have more months that go above 5 percent. And it just tends to, you know -- instead of having that tall

peak where, you know, you've got a 40 percent in two or three months, you end up with everybody getting a little closer to 20 percent or 10 percent. And so it tends to -- we tend to actually estimate exposure more as the pesticide use drops off, for the annual exposure.

PANEL MEMBER HAMMOND: I had questions and comments about some things -- both the dietary and the reentry issues.

DPR STAFF TOXICOLOGIST BEAUVAIS: No, to clarify the dietary's going to be in the next portion.

PANEL MEMBER HAMMOND: That's what I wasn't clear about.

And the reentry, anything on that?

DPR STAFF TOXICOLOGIST BEAUVAIS: No, the reentry's here. So reentry --

PANEL MEMBER HAMMOND: This would be the time to talk reentry?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: Okay. In the report, the comment is made that the reentry time for endosulfan is two days in California.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: One day outside. But in California it's two days.

And then there's the pre-harvest interval, PHI.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes.

PANEL MEMBER HAMMOND: I'm terrible at these acronyms.

Pre-harvest interval, and which might be for some crops as one day and some days are seven days.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: You know, they're varying. And that's the -- that I think is based on the dietary issues, right?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah, controlling residues, yeah, right, exactly.

PANEL MEMBER HAMMOND: This is to control residues.

So that all makes sense. And then there's a statement made in the document a couple of times that when you're looking at reentry, you assume either it's the reentry interval of two days, or if the pre-harvest interval is longer, it's the pre-harvest interval time and then you add five to seven days to that.

DPR STAFF TOXICOLOGIST BEAUVAIS: Okay.

PANEL MEMBER HAMMOND: And --

DPR STAFF TOXICOLOGIST BEAUVAIS: I can clarify that.

Okay. To clarify, we use the reentry -- the restricted entry interval, the REI, which is the two-day

interval, for all activities except harvesting; because we assume that if you're harvesting a food crop, you're not going to harvest it before you can sell it, before it will have -- at a time when it would still have legal residues -- potentially have the legal residues.

So we set the harvesting at the pre-harvest -- the expiration of the pre-harvesting interval. And for the short-term exposures we set it right at the expiration of each of -- of either the REI or PHI. But for the -- again, for the -- when we're looking at these annual and seasonal estimates when we're looking at more of a typical exposure, there's no reason that people need to go in as soon as this expires time after time after time. So we assume that they don't go in right at the expiration period and we add a few days. And --

PANEL MEMBER HAMMOND: Well, it's like five to seven days, which the half-life is actually -- but on the other hand, it might well be that there's weaving or there's other -- I mean I don't know, but I would think that that's the kind of work that you'd almost --

DPR STAFF TOXICOLOGIST BEAUVAIS: And, again, this is only for the seasonal and annual.

PANEL MEMBER HAMMOND: And you almost have to talk to a agricultural specialist to know how the crops are handled. But it just concerned me, because that could

represent a significant underestimate.

And then going back to the comment that was made where there were illnesses reported that were related to reentry, that would also seem to create some of that problem.

So I just was concerned that that -- I mean maybe that's true. And I just don't know. But I -- in the lack of -- lacking knowledge, I would be setting -- I'd be using the two-day reentry. Except I understand for the pre-harvest. If it's harvesting, and entering the harvest crops would have to be after the pre-harvest interval.

DPR STAFF TOXICOLOGIST BEAUVAIS: Yeah.

PANEL MEMBER HAMMOND: But you don't say after that. You say five to seven days -- the pre-harvest interval plus five to seven days or the reentry plus five to seven days.

DPR STAFF TOXICOLOGIST BEAUVAIS: To try to get at a more typical event. And we --

PANEL MEMBER HAMMOND: But do we know that that's typical? I mean where does that come from that makes that typical?

DPR STAFF TOXICOLOGIST BEAUVAIS: What we know is when we have information from crop specialists about when certain events typically occur.

PANEL MEMBER HAMMOND: So that is how that was

done? For each crop the actual number of days was --

DPR STAFF TOXICOLOGIST BEAUVAIS: No. We know that weeding is done at a certain time. And it's going to vary by crop, you're right. And so we set an arbitrary interval that we expect is going to be shorter than when these activities -- you may need to only go in and weed by hand once or twice. I mean it's depending on the crop. It depends on the sensitivity of the crop and whether or not it can handle equipment. And, you know, it's going to vary widely.

PANEL MEMBER HAMMOND: I can certainly understand that that varies widely. And I certainly know it's outside of my -- the direct information's outside of my knowledge base.

DPR STAFF TOXICOLOGIST BEAUVAIS: And this is again only for the longer-term exposure estimates. We always have a short-term estimate that is done at the expiration of the REI or the PHI. There's always that.

PANEL MEMBER HAMMOND: Okay.

DPR STAFF TOXICOLOGIST BEAUVAIS: Whether or not -- and in some cases if we have no indication of long-term use -- or frequent use on a crop, then we don't do long-term estimates.

But we always have a short-term estimate. So that estimate is always there. So we always have an

estimate that involves --

CHAIRPERSON FROINES: I think, Kathy, if you have suggestions in this area, you should provide them to DPR, and that would be useful. I think that whether the specific recommendations have bearing on the MOE and the actual determination of TAC, you should state the implications when you provide the information.

PANEL MEMBER HAMMOND: Yeah. I mean because the other question I had in terms of toxic air contaminants -- it sounds like it's an air exposure. But the crop residue is another exposure. Dietary's another one, which we'll get into. But on the other hand you have to look at people's total exposures, right, you know, when we're looking at the toxicity eventually. So is that the reason we're looking at these others as well -- these are the exposure routes -- so we have the full exposure, even though we're looking at a toxic air contaminant? We're not just -- we're saying, what is that adding to the base that the people have from other sources?

CHAIRPERSON FROINES: I think that -- that's why I'm a little hesitant about this right now, to tell you the truth, because it doesn't get factored in in terms of the actual numbers that form the basis of the MOE. And if it doesn't get factored in, then either we should tell them that that should happen or we should go with the

numbers that they have.

PANEL MEMBER HAMMOND: Well, that's part of what I was confused about and how to look at that.

CHAIRPERSON FROINES: And I think this is up to the panel, but my sense is that -- I don't really know what my sense is, because I think the issues you're raising are very good. I think my sense is that this becomes -- this issue and the dietary issue becomes something that one talks about qualitatively in terms of the fact that this may under-represent exposure to the public, but that the MOE gets calculated by the actual airborne concentrations that we have. But that's just my sense of it. I need -- you know, but we need to decide how we want to address that issue, because the way they're doing it is -- the way they have reached the designation of recommending this as a TAC has been based on the airborne concentrations and none of these other factors. And so it's up to the panel to decide what you think is most appropriate.

PANEL MEMBER LANDOLPH: Well, also in that second document, you got a nice five-page section on pharmacokinetics. Could you again -- I could recommend, please put some of the enzymology in and point out what the toxic metabolites result to be. It would be helpful.

CHAIRPERSON FROINES: What do you all think? I'm

trying to raise a question and I get absolute silence.

PANEL MEMBER BLANC: Well, I guess there's a -- I have a regulatory question in response to your question.

It's always been somewhat challenging, because the approach that we deal with outside of the pesticides is a completely different endpoint in the way in which the question is arrived at. And I'm not really -- it's not really clear to me that from a statutory -- I always understood it that the reason you have this sort of odd ratio with the 100 to 1 and 1,000 to 1 derived from a statutory guideline of some kind. But it's an internal DPR decision that that's how you do it? So if you wanted to do some kind of ratio that included the total body burden of exposure by all routes, you could do that too? And if the airborne exposure tipped you over to 100 to 1 or 1,000 to 1, then that would still reach your threshold for recommending labeling as a toxic air contaminant?

DPR ASSISTANT DIRECTOR JONES: Well, I'm not sure I can answer your question directly, Paul. I think to be clear, DPR has chosen over the last two years to present to the Panel our comprehensive risk assessments, which cover the statutory requirements we have in other venues. I know sometimes that has created some discomfort for presenting you a lot information. That's why we didn't provide the complete appendix on the dietary analysis.

But it wasn't our intent to include that as a means of making a determination on presenting this as a toxic air contaminant. I mean I think prior to presenting -- probably sulfuryl fluoride was the one we first did that, you know, where we split our documents.

So we basically had two risk assessments. And we had one focused on ambient air and one focused on all exposures, an aggregate consideration of inhalation, dietary, and occupational exposure.

So, you know, no, I don't believe that we would -- our regulation giving us a higher margin of exposure standard by which to make a determination on proposing a toxic air contaminant is based on ambient air exposure.

CHAIRPERSON FROINES: Based on what? I'm sorry.

DPR ASSISTANT DIRECTOR JONES: Based on ambient air exposure.

So the other information that we include in the document is our management's decision to present comprehensive risk assessments and not expend the resources to break out the ambient air exposure versus other routes of exposure.

And I think at the -- I mean I'm kind of posed to dilemma because of the discussion of Methidathion. I believe Dr. Byus was identifying that it was a good thing

that we included other exposures and considered aggregate exposures. So for kind of broad or regulatory purposes we are considering aggregate exposures. But for purposes of listing or proposing listing a compound as a toxic air contaminant, we're focusing on the ambient air exposure.

CHAIRPERSON FROINES: I would like -- Paul, I'd like to defer a discussion what came about to describe for a period of time between now and the next meeting. And I'll tell you what that is. Under AB 1807, there's a definition of a toxic air contaminant. That definition is very broad. It says that there may be the potential for health effects. And so it's -- as you know, it's a very broad -- the Legislature created a very broad definition.

DPR as a matter of policy uses the MOE. But there's no place in 1807 that says that there has to be an MOE to meet the criteria for a TAC. That's a DPR policy. And whether -- and we have disagreed with that for -- Stan and I --

PANEL MEMBER GLANTZ: Forever.

CHAIRPERSON FROINES: -- for 20 years.

(Laughter.)

CHAIRPERSON FROINES: And so I don't want to take it up now. It's an issue -- it's a matter of agency policy versus legislative mandate. And I'd rather deal with Methidathion -- endosulfan and deal with the legal

issues outside of here for at least this particular meeting.

Is that all right with you folks? It's a can of worms to get into right now.

PANEL MEMBER BLANC: Yeah, that's fine.

Well, then the answer I think would be that for the purposes of our discussion here, although it's too -- it's in our interest and it's helpful to hear about the other scenarios of exposure, that in fact what we will focus on for right now will be the inhalation route of exposure.

CHAIRPERSON FROINES: Yeah, I think that your -- see, if I had my choice about your documents, I would have a document that started out with some general information, and then from then on provided information that lead the agency to their conclusion. In other words, that it became focused, so that when you were seeing studies, the studies you were seeing were the studies that formed the basis for the ultimate decision; not a literature review, but a strategic document that said, "Here's how we got to this endpoint"; and it should be very focused.

So in that respect, what I'm doing is agreeing with you and saying that we don't really need to do dietary and --

PANEL MEMBER HAMMOND: -- crop residue.

CHAIRPERSON FROINES: What?

PANEL MEMBER HAMMOND: Crop residue --

CHAIRPERSON FROINES: -- crop residue issues.

And that DPR obviously disagreed with those in terms of having more than one document, as Tobi said. But my sense is that there should be -- you know, my guess wish list I would want a document -- when I wrote the lead standard, I wrote the whole -- the lead standard so it would go so that when you read the last sentence, you knew why you got there from the first sentence. And that seems to me to be the way we should do it.

PANEL MEMBER BLANC: But I do want to clarify something, because you had used the term "ambient air." But did you mean inhalation? Because doesn't the bystander -- in your terminology you differentiate between ambient air and bystander. But those are inhalation exposures and in fact --

DPR STAFF TOXICOLOGIST BEAUVAIS: That's correct.

PANEL MEMBER BLANC: -- the bystander inhalation exposures also are applicable to the determination of toxic air contaminant recommendation.

DPR ASSISTANT DIRECTOR JONES: Yes.

PANEL MEMBER BLANC: But I do want to clarify that.

There's something else I want to clarify. And it

may not be the point at which to do it. It may more reflect the third presentation. But the other scenario aside from dietary and bystander and occupational and ambient that you deal with is the swimmer scenario?

DPR STAFF TOXICOLOGIST BEAUVAIS: That's here.

PANEL MEMBER BLANC: And that consistent with this definition would not be relevant to our toxic air contaminant determination. However, based on the physical properties of this chemical and the fact that your toxicology data, which we're going to come to in the next talk, are clearer for inhalation and more potent for inhalation, wouldn't the route of exposure that would matter for a swimmer be inhalation of droplets and aerosols rather than the dermal exposure of a swimmer? Isn't the swimmer -- isn't -- no, not ingestion.

DPR STAFF TOXICOLOGIST BEAUVAIS: It's included -- inhalation is included in there.

PANEL MEMBER BLANC: So therefore is the --

DPR STAFF TOXICOLOGIST BEAUVAIS: This was based on EPA's model, the swim model, which includes inhalation and ingestion as well as dermal. So all three exposure routes are there.

PANEL MEMBER BLANC: So then does that -- does the swimmer -- therefore is part of the swimmer model -- how do we know which part of that parse out in terms of --

isn't part of the swimmer model therefore applicable? Your swimmer model came out with an MOE -- a low MOE, right? Or is that wrong? Am I wrong about this?

DPR STAFF TOXICOLOGIST BEAUVAIS: I think that the exposures were very low in swimmers.

PANEL MEMBER BLANC: So that no matter how you cut it, the swimmer wouldn't have had a --

DPR STAFF TOXICOLOGIST BEAUVAIS: -- were fine, yeah.

PANEL MEMBER BLANC: Then it's probably not applicable.

And the model that you used that includes the inhalation piece of it takes into account the specifics of this chemical; is that correct? That varies by chemical?

DPR STAFF TOXICOLOGIST BEAUVAIS: Yes, it does.

PANEL MEMBER BLANC: Okay. Thanks.

CHAIRPERSON FROINES: Gary's gone. So just for the record, Gary Friedman has left for the day.

It's 12:43. Should we break until 1:30 for lunch?

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: Yes. I don't think we need a motion. Let's just break.

So we're going to go then to the third speaker?

Cool.

Thank you.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: Welcome. We're ready to get started, so let's go.

DPR STAFF TOXICOLOGIST SILVA: Are we starting?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: Actually I've been asked for the public record to introduce myself.

I'm Pam Wofford from the Department of Pesticide --

CHAIRPERSON FROINES: Wait, wait, wait. Start over again.

PANEL MEMBER HAMMOND: I'm sorry. I apologize.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: I've been asked to introduce myself since I forgot to earlier.

PANEL MEMBER GLANTZ: We're just obsessing. It's okay.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

WOFFORD: My name is Pam Wofford. I'm with Department of Pesticide Regulation, the Environmental Monitoring Unit.

(Thereupon an overhead presentation was Presented as follows.)

DPR STAFF TOXICOLOGIST SILVA: I'll be presenting evaluation of endosulfan as a toxic air contaminant.

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DPR STAFF TOXICOLOGIST SILVA: And this slide summarizes the steps to the risk assessment process, and is a road map for my presentation.

Sheryl and Shifang already presented --

CHAIRPERSON FROINES: Marilyn, could you put the mic closer to your mouth. I can't hear you.

DPR STAFF TOXICOLOGIST SILVA: Sheryl and Shifang already presented the exposure assessment and fate. I'll be going through hazard ID and dose response assessment to identify the endpoints and the no-effect levels, or NOELs, for inhalation.

Finally, the risk characterization is generated through a culmination of information gained from the toxicology and the exposure, and these data determine the risk for humans.

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DPR STAFF TOXICOLOGIST SILVA: The toxicology profile contains evaluations of all available toxicity studies for endosulfan, and they include acute studies submitted by DPR -- submitted to DPR by registrants, toxicity studies submitted to DPR to register under SB 950, and literature studies.

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DPR STAFF TOXICOLOGIST SILVA: These are the general pharmacokinetics for endosulfan.

The oral absorption according to a rat gavage study's 87 percent and is assumed to be 100.

Dermal absorption, 47.3. Sheryl's already talked about that.

Inhalation is assumed to be 100, and so on.

The primary metabolite is endosulfan sulfate. But also the diol and the lactone have been observed.

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DPR STAFF TOXICOLOGIST SILVA: This just shows the pathway for endosulfan metabolism. And the sulfate is the main product, but you'll also see endosulfan diol and endosulfan lactone.

CHAIRPERSON FROINES: You have a mistake in at least one slide. The endosulfan diol is not CH3OH.

DPR STAFF TOXICOLOGIST SILVA: Oh, did I put that? Sorry. I can change that.

CHAIRPERSON FROINES: See here?

DPR STAFF TOXICOLOGIST SILVA: Oh, yeah. Sorry about that.

CHAIRPERSON FROINES: I passed my graduate orals --

(Laughter.)

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PANEL MEMBER GLANTZ: I'm impressed, I have to say.

DPR STAFF TOXICOLOGIST SILVA: That he could see it? I know.

(Laughter.)

CHAIRPERSON FROINES: Normally when gamma-amino butyric acid, or GABA, binds its receptor, activating the GABA receptor, chloride ion binding complex, the chloride ions flow across the cell membrane to neutralize the cell interior and terminate fast signaling or cell excitation.

When endosulfan blocks the chloride channel, or otherwise interferes with the binding complex, the nerve stimulation remains, manifesting the clinical signs of neurotoxicity such as convulsions or tremors.

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DPR STAFF TOXICOLOGIST SILVA: In the hazard identification section, we want to find the critical endpoint and do the NOEL selection. And this is done after having reviewed the available literature and identified the toxic endpoints.

We need to select the NOELs to calculate the risk. And these are referred to as the critical NOELs. They're generally the lowest NOEL, with the critical endpoint considered to be the most sensitive endpoint. So

that its use will protect other effects, for example, endocrine effects induced by endosulfan at higher doses.

We also look at the durations of exposure of the studies and select one that matches closest with human exposure duration.

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DPR STAFF TOXICOLOGIST SILVA: These are the key studies for the acute endosulfan treatment. And the green shows the oral -- the oral NOEL, 0.7, in the rabbit developmental study. And there's also -- and that really doesn't come in very clearly on this, but it's an acute LC50 study. And there was no NOEL in that study, but there's a NOEL -- or a LOEL of 0.5.

Okay. So this study, while we didn't obtain a NOEL, will be used in the final decision on the NOEL for inhalation -- acute inhalation.

And, by the way, all these studies are used -- are performed with a mixture of alpha- and beta-endosulfan.

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DPR STAFF TOXICOLOGIST SILVA: In this slide, we ended up using finally the Subphrenic inhalation for our critical NOEL, but used also the acute LC50 study and the Subphrenic range finding. And the treatments are listed there and all the doses. And you might notice that the

LOELs for all three studies are very similar. But in the Subphrenic we didn't see any signs or effects before I think it's day 12. And -- or actually no effects prior to day 9. And yet all the LOELs were very similar for the three studies.

So we propose for the acute critical study to use the Subphrenic inhalation.

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DPR STAFF TOXICOLOGIST SILVA: The advantages to the Subphrenic inhalation are the following:

All three LOELs were similar.

More animals were treated in the Subphrenic; 15 per sex per dose versus 5 per sex per dose.

The Subphrenic used a 29-day recovery with 5 per sex per dose. And the acute had a 14-day observation after the dose.

0.194, which was the NOEL in the Subphrenic study, is reasonable based on the LOELs from the other studies -- or from all three studies.

And 0.194 is a conservative estimate for an acute NOEL, since acute NOELs are usually higher than Subphrenic or chronic NOELs.

And I'd like you to note that the three studies were from the same laboratory and in the same timeframe, within six months.

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DPR STAFF TOXICOLOGIST SILVA: So the next is selecting the NOELs and endpoints for Subphrenic exposure. And the green shows the dietary, where we chose the two generation repro study with a NOEL of 1.18. And the red, again, is the same Subphrenic study that I mentioned before, with a NOEL of 0.194.

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DPR STAFF TOXICOLOGIST SILVA: And here's a summary of the Definitive Subphrenic Inhalation Study. And as I showed before, it's aerosol, nose only.

And there are clinical signs of neurotoxicity, decreased body weight, decreased food, increased water intake, clinical chemistry effects that were reversed at the end of recovery.

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DPR STAFF TOXICOLOGIST SILVA: For the chronic there were no inhalation studies available. However, for the dietary we used the one-year dog study with a NOEL. We went with the lower NOEL of 0.57.

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DPR STAFF TOXICOLOGIST SILVA: So for the chronic NOEL we decided to go with the same Subphrenic inhalation in the rat. Only we extrapolated from Subphrenic to chronic to obtain an effective no-effect level.

So --

PANEL MEMBER LANDOLPH: Could I ask you a quick question?

Could you please define ENEL in words.

DPR STAFF TOXICOLOGIST SILVA: I did. I got your comment.

PANEL MEMBER LANDOLPH: Thank you.

DPR STAFF TOXICOLOGIST SILVA: Its just Equivalent No-Effect Level.

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DPR STAFF TOXICOLOGIST SILVA: The other endpoints:

Oncogenicity. There was no evidence of oncogenicity in animal studies.

Genotoxicity. We considered equivocal evidence from in vivo and in vitro gene tox studies.

And endocrine disruption. Endocrine effects were observed in male rats only at doses surpassing neurotoxic doses.

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DPR STAFF TOXICOLOGIST SILVA: The exposure assessment covers information already given by Sheryl. And for my work I used the corrected values that she showed previously.

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DPR STAFF TOXICOLOGIST SILVA: And this is a table that she already presented.

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DPR STAFF TOXICOLOGIST SILVA: Because during the Methidathion panel discussion someone said that they appreciated seeing the aggregate exposure, I included this dietary summary, and chose for adults and infants the highest exposure in diet.

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DPR STAFF TOXICOLOGIST SILVA: For the aggregate exposure to the public, I needed to look at the ambient air and the air for bystanders at work sites. So the air aggregate was the inhalation exposure plus the dietary exposure.

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DPR STAFF TOXICOLOGIST SILVA: And here is, using Sheryl's data and the dietary data, the results of exposure -- aggregate exposure. And in parentheses there are -- it's the percentage diet of the overall exposure. And you can see that the diet comprises a pretty high percentage.

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DPR STAFF TOXICOLOGIST SILVA: To characterize the risk, say, what is the risk to humans, we look at a combination of hazard identification, exposure assessment,

and uncertainty factors to determine the margin of exposure to characterize potential risk to humans.

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DPR STAFF TOXICOLOGIST SILVA: The risk for non-carcinogenic health effects in humans is expressed as the margin of exposure, or MOE. The MOE is the ratio of the NOEL to the exposure level in humans.

The acute, Subphrenic, and chronic NOELs employed for the characterization of the risk exposure to endosulfan were derived from studies performed on laboratory animals.

When the NOEL is derived from an animal study, generally an MOE of at least a hundred is desirable assuming humans are ten times more sensitive than animals and that there's a tenfold variation in the sensitivity of the human population between the lower range of the normal population and sensitive subgroups.

In other words, we generally want the potential human exposure level to be at least a hundred times lower than the NOEL in animals.

Criteria for listing a pesticide as a TAC is when the MOE is less than 1,000 when based on an animal NOEL.

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DPR STAFF TOXICOLOGIST SILVA: And here are the margins of exposure that we got for the inhalation groups.

And in green you can see all that are below 1,000, but all are greater than 100.

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DPR STAFF TOXICOLOGIST SILVA: And then for the dietary, just for your information, the MOEs are very high for Subphrenic and chronic and over 100 for acute.

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DPR STAFF TOXICOLOGIST SILVA: So just to give you a perspective here. To calculate the margin of exposure to the public where we have inhalation plus diet, the following is the formula we use.

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DPR STAFF TOXICOLOGIST SILVA: And for aggregate air and diet for endosulfan we have the following MOEs: There's -- all of them are over 100 except for infant short-term bystanders.

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DPR STAFF TOXICOLOGIST SILVA: So this is DPR's summary of the studies we're using, the critical studies for our NOELs. Dietary. And then on the bottom we're basically using one study for the acute/subchronic. And then we have a safe -- an additional 10X safety factor for the chronic.

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DPR STAFF TOXICOLOGIST SILVA: And just for your

information also, this is what U.S. EPA is using.

They don't have a chronic NOEL for inhalation or an acute. So they're basically just using the Subphrenic as occupational for seasonal exposure to workers.

But you might note that our acute neurotoxicity -- or our acute NOEL for inhalation is much lower than the acute neurotox that they're using. And also our acute dietary is half as much, our Subphrenic is much lower, and our chronic is in the same ballpark as their dietary.

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DPR STAFF TOXICOLOGIST SILVA: Focusing again on the air exposure. Here are the calculations for the reference concentrations. Air concentrations below the reference concentration, or RfC, are generally considered sufficiently low to protect human health.

The RfC's were calculated for acute seasonal and chronic exposure to endosulfan by dividing the inhalation NOEL by the respiratory rate in humans to obtain the equivalent human inhalation NOEL.

And at the bottom we have the -- Sheryl's already shown these -- the respiratory rates for infants and adults.

And, again, inhalation absorption is assumed to be 100 percent. Human equivalent inhalation NOEL was then

divided by an uncertainty factor of 100, described earlier when the NOEL is derived from animal data.

To convert RfC from microgram per cubic meter to parts per billion, the value was multiplied by the molecular volume and divided by the molecular weight of endosulfan.

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DPR STAFF TOXICOLOGIST SILVA: So acute and Subphrenic RfC's are 3.3 microgram per cubic meter for infant, 6.9 microgram per cubic meter for adult. And the extrapolated values for chronic are a factor of ten less.

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DPR STAFF TOXICOLOGIST SILVA: The DPR toxic air contaminant listing criteria is shown in this figure. Listing is considered when the exposure exceeds one-tenth, or 10 percent, of the reference concentration for acute and Subphrenic inhalation exposure to endosulfan.

This listing criteria limit is 0.2 parts per billion, 0.4 parts per billion in adult. And for chronic it's a factor of 10 lower. And I've shown micrograms per cubic meter in very tiny print there. And we will basically be regulating on the infant values, which are lower.

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DPR STAFF TOXICOLOGIST SILVA: The risk

appraisal. Based on the previous slide, this table using the corrected exposure value shows the MOEs for the various exposure scenarios along with the percent RfC. The percentage should be approximately 10 percent or less in order to avoid listing as a TAC.

In red are the scenarios that do not exceed the threshold; that is, they're less than 10 percent. It's evident that the majority of conditions do though.

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DPR STAFF TOXICOLOGIST SILVA: So the risk characterization summary using the corrected exposure values shows that the MOEs that are greater than a thousand are just ambient air, seasonal in infant and adult, and annual for adult.

But the majority of the MOEs are less than 1,000, ambient air for infant; bystander, all values.

Any questions?

CHAIRPERSON FROINES: I just have one question at the outset, and then I'll turn it over to Joe, who was the lead for it.

What are the elements in the MOE of a thousand? You have intraspecies and interspecies. And what's the other factor of 10?

DPR STAFF TOXICOLOGIST SILVA: That's -- I think that's the criteria for listing that the -- where is that?

Okay. For DPR the criteria for listing is when exposure exceeds one-tenth, or ten percent, of the reference concentration. One-tenth of the reference concentration. So it's a thousandfold. So you have interspecies, intraspecies, and then an additional tenfold below the reference dose. So that's a thousand.

CHAIRPERSON FROINES: Okay. Can you and perhaps Melanie help me. Because in the OEHHA comments, they suggest in calculating an RfC OEHHA would add an uncertainty factor to protect infants and children due to their greater sensitivity to the endocrine disrupting and neurotoxic effects of Endosulfan. So it sounds as though this factor of ten is not part of your thousand.

DPR STAFF TOXICOLOGIST SILVA: No, I think that -- I don't really know about their extra 10X factor.

DPR ASSISTANT DIRECTOR JONES: Just let me clarify.

The proposed listing criteria is an additional tenfold safety factor. It doesn't have anything to do with OEHHA's recommendation. So I mean I think that is a separate issue.

OEHHA DEPUTY DIRECTOR ALEXEEFF: George Alexeeff with OEHHA.

Yeah, just as a clarification, I think what DPR is describing is their normal procedure for listing

something as a toxic air contaminant. It simply adds a tenfold -- if it's within tenfold of the margin of exposure, then that's a condition to allow them to proceed in the regulation to list.

For calculating the RfC, well, they can describe how they calculated it, which is a slightly different matter. Okay?

CHAIRPERSON FROINES: I don't know.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Well, the RfC they calculated -- I don't want to put words and describe. But as I understand, the RfC they calculated used the standard two uncertainty factors. So --

CHAIRPERSON FROINES: But why -- I'm confused. What is the policy of DPR and OEHHA on a tenfold safety factor for children?

DPR STAFF TOXICOLOGIST SILVA: According to -- the infants and children is a different issue, and that's not something that we deal with at DPR.

The criteria for identifying pesticides as a toxic air contaminant, do you want me to read that?

CHAIRPERSON FROINES: (Shakes head.)

I mean maybe the Panel does, yes. I know it.

Go ahead with the criteria.

DPR STAFF TOXICOLOGIST SILVA: Do you want me to read this?

CHAIRPERSON FROINES: Yeah, please read it.

DPR STAFF TOXICOLOGIST SILVA: Okay.

"A pesticide shall be identified as a toxic air contaminant if it's concentrations in ambient air are greater than the following levels: (For the purposes of this section, a threshold is defined as the dose of a chemical below which no adverse effect occurs.)

"For pesticides which have thresholds for adverse health effects, this level shall be tenfold below the air concentration which has been determined by the Director to be adequately protective of human health.

"For pesticides which do not have thresholds for adverse health effects, this level shall be equivalent to the air concentration which would result in a tenfold lower risk than that which has been determined by the Director to be a negligible risk."

CHAIRPERSON FROINES: And is that a regulation?

DPR ASSISTANT DIRECTOR JONES: It's not a policy. It's a regulation.

CHAIRPERSON FROINES: It's a regulation that you passed?

DPR ASSISTANT DIRECTOR JONES: Yes.

PANEL MEMBER BLANC: Well, that answers the question I had earlier, doesn't it?

CHAIRPERSON FROINES: What's that?

PANEL MEMBER BLANC: That was the question I was trying to ask earlier, I think.

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER BLANC: You know, before lunch I asked whether it was policy or regulation. It sounds like the answer is it's regulation, the hundredfold business.

PANEL MEMBER GLANTZ: Right. But it's their regulation. It's not law. It's their regulation. Which I'm being very restrained because we've had huge fights about this in the past.

CHAIRPERSON FROINES: Well, I'm just -- George, then I'm confused. Why would you have put this recommendation into your findings if you knew what has just been said? It seems like you're making a recommendation for which there's no apparent basis or there's -- I don't know. Help us here.

OEHHA DEPUTY DIRECTOR ALEXEEFF: I'd be happy to help you.

Okay. So the problem is we're a little bit -- and Tobi can help clarify in case I'm a little off base. But there's a little bit of confusion between the regulatory basis that Department of Pesticide Regulation uses for determining that something is a toxic air contaminant versus the risk assessment procedure.

So, the comments that we submitted are on the

risk assessment procedure and are not commenting on the regulation that had been developed. So what we're referring primarily there is development of a reference dose. So if -- our comments on that has to do with how we felt the margin of safety or of the uncertainty for calculating the reference dose. That's what is being referred to there.

So I don't know if that helps clarify. We'd be happy to explain why we have that opinion, if that's the question that you'd like us to answer right now.

CHAIRPERSON FROINES: Well, having gone through SB 25, we know why you have this opinion.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Okay. Well, I thought the specific reasons for this particular compound, if that --

CHAIRPERSON FROINES: Yeah, go ahead.

OEHHA DEPUTY DIRECTOR ALEXEEFF: I'll have our staff person -- I mean Dr. David Ting, he's our new section chief for our branch -- our section that reviews the Department of Pesticide Regulation risk assessments.

OEHHA RISK ASSESSMENT BRANCH CHIEF TING: Hi. My name is David Ting and I'm with OEHHA.

OEHHA agrees with the toxicology evaluation carried out by DPR. And we agree with the selection of the critical animal studies and identification of the

NOELs in the risk assessment. However, after looking at some of the red studies that indicate young animals could be more sensitive to some of the health effects resulted from endosulfan exposure, OEHHA would apply an additional uncertainty factor to the risk assessment.

CHAIRPERSON FROINES: Thank you.

So I understand, so that the issue is a risk assessment approach, methodology, policy, however you describe it, compared to what the regulatory requirements are for DPR. Is that a correct way of saying it?

OEHHA DEPUTY DIRECTOR ALEXEEFF: Correct. So whatever the -- George Alexeeff. Whatever the resulting number is, in this case as Dr. Silva read about the significant risk that's determined by the Director. We would suggest the significant risk level should be threefold lower based -- not threefold? -- whatever -- some additional factor lower to protect infants and children. And then the regulatory requirement would play out the way it normally would. That's to try to resolve the confusion.

CHAIRPERSON FROINES: Yeah, that would require a change in their regulation.

OEHHA DEPUTY DIRECTOR ALEXEEFF: No, we're not changing their regulation, no. She could read the regulation again to clarify it. It basically says that

they apply an additional tenfold factor to the level determined to be -- an insignificant risk or significant risk? -- by the Director.

DPR ASSISTANT DIRECTOR JONES: Significant risk.

DPR STAFF TOXICOLOGIST SILVA: Wait.

PANEL MEMBER BYUS: Negligible.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Negligible risk?

DPR STAFF TOXICOLOGIST SILVA: To be -- yes.

PANEL MEMBER GLANTZ: Yeah, I think that the --

DPR STAFF TOXICOLOGIST SILVA: -- determined by the Director to be a negligible risk.

PANEL MEMBER GLANTZ: So, John, I think what they're saying is that the -- the difference in opinion is what level of exposure constitutes a negligible risk. And OEHHA's suggesting that should be a lower number than DPR is, because they're saying that you need to take into account that -- not only the differences in breathing rate with infants, but at the same level of exposure there's going to be a bigger effect in the infant.

And then after you have that, then the regulation sort of sets where you put the line. So they're changing the risk estimate that is then applied to the -- the regulation is then applied to. They're not differing on what the regulation is.

Is that right?

OEHHA DEPUTY DIRECTOR ALEXEEFF: Correct. Yeah, we're not changing. We're just raising an issue with regards to the risk, yes.

PANEL MEMBER GLANTZ: So that explains the thing you were asking me about.

It's a very soothing noise, wherever it's coming from.

PANEL MEMBER BYUS: Puts you right to sleep.

CHAIRPERSON FROINES: Are there any comments on this particular issue before we go ahead?

Joe?

PANEL MEMBER LANDOLPH: On this specific issue?

CHAIRPERSON FROINES: No.

PANEL MEMBER LANDOLPH: Or generally?

Yeah, I want to comment.

Yeah, I wrote some comments, about three pages, and I gave them to DPR. And I'll just try and summarize them.

You know, I want to congratulate Marilyn and colleagues for writing such a huge document. It's a lot of hard work. In general it's pretty well written. Wherever possible, if you can, I'd recommend some condensation just by a little more concise writing, because otherwise -- well, this is a problem with every document that gets big. It kind of puts you to sleep if

it's not a little bit concise. So do the best you can.

Regarding the chronic -- the toxicity and the oncogenicity studies, I went and did a hazardous database substance search and a tox line search. And they seem to indicate that -- I guess it's EPA according to the American Conference of Government Hygienists calls endosulfan not classifiable, A4, as to carcinogenicity. So you might want to put that statement in there discreetly somewhere. That doesn't mean it's not a carcinogen. It just means the database is not good enough to decide one way or the other.

And I would buff that up, and I'll give you some more comments there.

On your discussion of the genotoxicity, I would recommend revisiting the way you look at that data. In my opinion -- on page I guess it was 64 or so there's a big table where you have a lot of data. And that data indicates about 12 of the 25 tests -- 13 of the 25 tests are positive. So to me as a genetic toxicologist, I wouldn't call that negative or equivocal. I think there's data there.

And when you look at different types of genotoxins, sometimes some are odd like this. They don't show up in every test. That just means they have a more specific mechanism of action. So I think it is genotoxic.

And you have statements in here that it forms DNA adducts too.

So I think it is genotoxic. And I'd recommend you revisit that in your writing, both in the executive summary and in the text. And I made some suggestions as to how to help you out there.

I'm convinced that it causes, from your writing and the literature, chromosome aberrations, micronuclei, and mitotic gene conversion and reverse mutations in yeast. And that's all positive.

It also does inhibition of gap junctional communication. It's a tumor promoter. Now, that hasn't yet crossed the line into a carcinogen until the studies really show that definitively it is. But it's worrisome that it's got some genotoxic activity and tumor promoting activity. So just mark it as it is. It's not going to change your risk assessments now, because you can't do that until you get carcinogenicity data. But I would bulk those sections up and list them a little bit more specifically.

Let's see, what else?

Oh, and you go through the FIFRA acceptable many times. Tell you the truth, I don't know what FIFRA acceptable is. Are there concise guidelines?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER LANDOLPH: Maybe you might want to append those to the document or something.

And I don't -- this is a personal bias. I wouldn't throw a study out just because it's not FIFRA acceptable. I would --

DPR STAFF TOXICOLOGIST SILVA: No, that's not -- one of the things about FIFRA studies that's very useful is that there are specific guidelines. And so you know exactly what there is. Everything is complete. You have all the -- you have acquired a number of animals. You have a required protocol. There's quality assurance, there's GLP. There are individual data for each animal for every parameter.

And then, one of the purposes of the FIFRA studies is to get a NOEL, which often times in literature studies they're not looking for specifically a NOEL but they're looking for, you know, one certain aspect.

No, but we don't --

PANEL MEMBER LANDOLPH: Yeah, just the reason I bring this up, it's just mentioned so many times, it gives the reader the impression that you're trying to knock out studies that are not FIFRA acceptable. I mean certainly you can weight them downward. That's okay. But maybe one way to do it is just put it in parentheses or something like that, so you have to say it so many times.

DPR STAFF TOXICOLOGIST SILVA: Okay.

CHAIRPERSON FROINES: Wait. I'm sorry. They cannot weight studies down that aren't FIFRA guidelines. Absolutely not.

PANEL MEMBER LANDOLPH: Well, if you're convinced they're fatally --

CHAIRPERSON FROINES: The problem we have here is that what they're doing is they're mixing 950 documents with 1807 documents -- 1807 process.

Pardon me?

PANEL MEMBER HAMMOND: Translate.

CHAIRPERSON FROINES: There is nothing in 1807 that requires the use -- that a paper meet FIFRA guidelines. There is no requirement. That does not -- the definition, as I said earlier, of a toxic air contaminant is very clear, it's very broad. There is not a word in AB 1807 that says you have to have FIFRA guidelines. They have to -- in fact, what is -- the criteria that this panel uses for determining the quality of studies is whether they are in the peer-reviewed literature, right? That's always been our policy, and I've been on this Committee since '83.

So since 1983 the criteria has been peer-reviewed publications and not reports. And 1807 doesn't require FIFRA guidelines. Therefore, the trouble with pushing

these two documents into one is they're using the FIFRA guideline requirement under 950 but it's not in ours. So that we end up having to read all that stuff about FIFRA, when in fact it's not a requirement under 1807.

And therefore it would be much better -- and we've talked about this in the past -- if we had two documents. I mean word processors would seem to be able to take something out of here and put it in another section. Right? It seems to me that that's a word processing problem, so that we wouldn't have to read under -- I mean in this document it was almost every paragraph talked about FIFRA guidelines. And it's not a requirement. Okay.

So it does mean that we have the problem of having to go through for $100 a meeting an enormous number of sections which has nothing to do with this Panel. Which we shouldn't really have to do. We shouldn't have to read occupational studies in here.

DPR ASSISTANT DIRECTOR JONES: John, I'll carry back to my managers your desire to see a separate document. We will continue to use studies that we receive in DPR that we have to make a determination on acceptability under the SB 950 statutory language.

CHAIRPERSON FROINES: Sure. I'm not quarreling with that at all.

DPR ASSISTANT DIRECTOR JONES: But I think in order that -- let me just say one thing to Joe.

Joe, I would be reluctant to advise Marilyn to include the FIFRA guidelines because it's very voluminous, and you're after trying to get us to reduce documents. We can provide a web link to both EPA's data requirements, which DPR uses, and to the guidelines which provide guidance to those conducting the studies.

PANEL MEMBER BYUS: I have a question.

CHAIRPERSON FROINES: Go ahead. I'm sorry.

PANEL MEMBER BYUS: Your stakeholder toxicity studies, you know, the ones that aren't in the public literature, are they FIFRA guidelines? Do they follow FIFRA guidelines?

DPR ASSISTANT DIRECTOR JONES: What do you mean stakeholder --

PANEL MEMBER BYUS: Don't you have the -- you know, don't your stakeholders do toxicity studies themselves and then, you know, they have that -- the database that you use, there's a database of animal toxicity studies and --

DPR ASSISTANT DIRECTOR JONES: Right. And based on individual companies, they may or may not publish those, you know. But they don't -- they are not required to publish those, but they are required to present them to

us.

PANEL MEMBER BYUS: Right. But are they FIFRA -- do they use FIFRA guidelines or not? All of them? Is there a policy -- I mean it's just a statement.

DPR ASSISTANT DIRECTOR JONES: Not to dwell on this, but a law contemporaneous with 1807 required us to have studies that were acceptable under the FIFRA guidelines. We have a term, "complete valid inadequate." It's in the law, that we had to go through and judge the studies.

CHAIRPERSON FROINES: The what? I'm sorry.

DPR ASSISTANT DIRECTOR JONES: And we continue to receive those studies from registrants who want to register compounds in California.

CHAIRPERSON FROINES: What did you say about 1807 and FIFRA?

DPR ASSISTANT DIRECTOR JONES: I said a law contemporaneous with 1807.

CHAIRPERSON FROINES: Oh, contemporaneous. But it's contemporaneous --

PANEL MEMBER BYUS: They do use -- when they provide these studies, they must follow FIFRA guidelines.

DPR ASSISTANT DIRECTOR JONES: That's right.

PANEL MEMBER BYUS: And you said -- and she's saying yes. That's what I --

DPR ASSISTANT DIRECTOR JONES: On an individual basis we may consider studies that are presented in the scientific literature, we may consider studies that are done under the guidelines for European Union. But I think that's -- in answer to your question, yes, they use those.

PANEL MEMBER LANDOLPH: And then just a few more quick comments.

CHAIRPERSON FROINES: Wait. Let me just -- since I started this. I think within the context of our criteria of peer-reviewed studies, we should know whether a study is peer reviewed or not. And if it's a company study, we should know that. Because if we know it's a report, we may weigh that differently than a peer-reviewed study. And that's -- see, that's the difference we have here. We have a 950 where the FIFRA guidelines are the key factor. But this Panel hasn't worked that way. And so there's this paper, for example, that wasn't in the document, genotoxic effects of endosulfan and beta-endosulfan on human HEPG2 cells. This is in environmental health perspectives. This paper was not in the document. It clearly is a good, solid peer-reviewed publication.

DPR STAFF TOXICOLOGIST SILVA: I think -- I wrote in an e-mail to you that I just missed it. And it was not left out because it wasn't a FIFRA guideline study. I

just missed it.

CHAIRPERSON FROINES: Oh.

PANEL MEMBER BLANC: Joe, do you want to finish up your thing too?

PANEL MEMBER LANDOLPH: Yeah, thank you. I'll be brief.

And I would recommend under biotransformation -- again, it's throughout the whole document, this is Part 2 -- that you please list and refer to the enzymes that metabolize endosulfan, whether they're P-450s or other enzymes, which ones, and glutathione transferases and which ones. And there's a statement that these enzymes were induces non-specifically. I didn't know what that meant. You might -- if you could clarify that for us, that would help.

And then pull forward into the executive summary, and I would recommend a concise capsulation of the genotoxicity studies and the gap junctional communication inhibition in the tumor promotion studies, just very concisely.

And I think that would take care of it. And thank you.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I have a question that doesn't pertain directly to your presentation, but it just

pertains to material here.

But before I go there, the first slide that you showed that related to studies that you selected, and there was the inhalation --

DPR STAFF TOXICOLOGIST SILVA: Oh, the table?

PANEL MEMBER BLANC: It was like the sixth slide or something. There was an inhalation study that you summarized. But then in the end that wasn't the inhalation study that you used.

Before the Subphrenic.

DPR STAFF TOXICOLOGIST SILVA: The acute --

PANEL MEMBER BLANC: The acute rat where all the doses -- there was a LOEL but no NOEL.

DPR STAFF TOXICOLOGIST SILVA: Right.

PANEL MEMBER BLANC: And then you didn't end up using this. You ended using the Subphrenic. But you said this study was from the same lab as the Subphrenic?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: And because that study did have a NOEL and this only had a LOEL, you preferred to use that?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: But what wasn't completely clear to me was, had you used this LOEL and then done the extrapolation to get to a NOEL, what would the number have

been?

DPR STAFF TOXICOLOGIST SILVA: Well --

PANEL MEMBER BLANC: You would use a factor of 10?

DPR STAFF TOXICOLOGIST SILVA: Well, in general, yes. But the thing is is usually the acute NOELs are higher than the Subphrenic. And so that's why, you know, in the past we've just used the Subphrenic NOEL. And based on the three --

PANEL MEMBER BLANC: But wouldn't this then be .056?

DPR STAFF TOXICOLOGIST SILVA: Yeah.

PANEL MEMBER BLANC: And what is the one that you got based on the --

DPR STAFF TOXICOLOGIST SILVA: .19.

PANEL MEMBER BLANC: So this would be 50 percent less if you used this?

And so your rationale other than it giving you a lower number is what?

DPR STAFF TOXICOLOGIST SILVA: Well, okay, if you look at the Subphrenic study, you can see that even on a Subphrenic basis -- and I think you need to go up another couple of slides. Up the other way, yeah.

See, if you look at the Subphrenic, you'll see that you're not seeing any effects prior to day 9. And

that was at .387, which is the LOEL. Whereas, at 0.44 in the range finding, which was not a detailed study, that was just, you know, a summary, but they had these effects. So at .44 you're seeing decreased body weight gain.

And then the LOEL for the acute, which was .567. And that dose was used only in females. You can see that there are a lot of effects at that slightly higher dose. At 28 minutes females are showing clinical signs neurotoxicity.

So it seems like it's a reasonable selection for a NOEL considering the effects you see on a Subphrenic study, that, you know, going from .38, .44, .57, how steep that is, it seems very reasonable to choose .194 as a NOEL.

PANEL MEMBER BLANC: But let's say you had two studies that weren't from the same lab and one was an acute study and one was a Subphrenic study, and the Subphrenic study said, "Well, we didn't see anything at dose" -- oh, let me make it an even clearer example. Suppose you had two acute studies, and one had an apparent NOEL that was at .1 but the other one had a -- didn't have it. I mean I'm not sure that you have a rational basis for discounting the study at which you have the one acute study that you have, which has a LOEL but not a NOEL, and instead using the NOEL from a study which wasn't designed

to look at acute effects even though it has some comments on what happened in the first nine days.

DPR STAFF TOXICOLOGIST SILVA: Okay. Look at the -- could you go to the next slide.

No, back. Yeah.

The advantages to using that I listed here, that how similar the three NOELs were but how steep the curve seemed. But also in the Subphrenic study we're treating 15 per sex per dose along with a 5 per sex per dose follow-up, versus the acute where there's only 5 per sex per dose used.

PANEL MEMBER BLANC: But I'm not sure that I would be compelled either because of what -- you're seeing an effect. That would be a compelling argument to me if you had -- if you were making the reverse argument and trying to say that something was a no-effect level in a study with only 5 and then you had 15 where you saw an effect, because there'd be a statistical -- more of a statistical chance of not seeing an effect in only 5.

DPR STAFF TOXICOLOGIST SILVA: But then you're not seeing anything on a Subphrenic basis of .19.

PANEL MEMBER BLANC: But it was a study designed to do different things. I mean am I -- are you assured -- but let me ask the question again the way I would.

If you still -- if you had two studies, one of which didn't see something but the other one which did --

DPR STAFF TOXICOLOGIST SILVA: Okay. You're going to have to be looking at, you know, when it was done, the lab it came out of, how many animals they used, a lot of things. I mean it just depends. You know, I have to look at the studies.

PANEL MEMBER BLANC: I know.

Does anybody else have the same question that I have? Is this -- I mean I'll drop it if I'm out of line.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: I don't have any problems with it. I think it's fine. I mean I think it's a matter of judgment. And this LOEL versus NOEL, I mean obviously when you have the low effects and then trying to extrapolate to no effects is not as satisfying always as something that actually -- a series of doses where someone actually measured no effects. That's the other issue.

So I mean I think it's always a -- it's a judgment here and, you know, I don't think it's that far off I mean without getting all the -- you know, reading all the studies in detail. I mean it's rational.

DPR STAFF TOXICOLOGIST SILVA: Yeah, there just aren't many studies out there at all on inhalation for endosulfan.

PANEL MEMBER BLANC: No, I understand. The reason I asked the whole series of questions is since it's a 50 percent lower level than if I carry the math through for things for which you had a ratio of a thousand five hundred, which you say wouldn't cut muster to be a TAC recommendation, now would suddenly be less than a thousand. So I don't know how -- I don't remember exactly how close some of your numbers were. So --

DPR STAFF TOXICOLOGIST SILVA: Actually though there's no short term for the ambient air. Only for bystanders. And those were all less than a thousand --

PANEL MEMBER BLANC: -- anyway.

DPR STAFF TOXICOLOGIST SILVA: Yeah.

PANEL MEMBER BLANC: Okay. So let me ask my other question, which was just the question that didn't refer to your slides. It has to do with mechanism, which as I understand it is -- as you emphasize, the GABA-mediated pathway. Why is it that in some of the animal studies there were decreased acetylcholinesterase levels? And it was in more than one of your studies. You don't comment on it at all. It's just reported, and I was --

DPR STAFF TOXICOLOGIST SILVA: It was mainly in the Subphrenic rat study. And we didn't see it in the chronic. It was -- you know, I added all that, but those

things weren't observed in later studies. It doesn't seem to be --

MEMBER BLANC: And it's in the cat study too, right, your report?

DPR STAFF TOXICOLOGIST SILVA: But wasn't that -- I think that was like an IV study or a really unusual route.

PANEL MEMBER BLANC: Yeah, but I mean -- yeah, but I just didn't -- I was completely confused by it and thought, boy, did I -- was there some section I missed here about its mechanism of action?

DPR STAFF TOXICOLOGIST SILVA: I don't think so. I think --

PANEL MEMBER BLANC: I think that it would be worth having a couple of sentences that say, "Although this was observed, it wasn't consistent. We don't think that it's" -- because otherwise it's just hanging out there.

DPR STAFF TOXICOLOGIST SILVA: Okay.

PANEL MEMBER BLANC: And then in terms of the human health effects, I know that the pesticide illness reporting system appears two different places. We've already commented on this before. The way those data are described, they're pretty useless from a human health understanding, because systemic, skin, eye --

DPR STAFF TOXICOLOGIST SILVA: Yeah, right, right.

PANEL MEMBER BLANC: I know that some of that has to do with coding. But in fact there are narratives for those case reports. And since we're talking about six in which -- six case reports in which there was pure endosulfan and not some mix, don't you think it would be worth it to go back, pull those reports, and actually summarize, since your entire human case literature otherwise is one report from India and one report from southeastern United States? I mean why have that elaborate pesticide illness reporting system if you -- isn't this the ideal time you'd want to actually use the data?

And also in the "Human Section" on page 86, actually I think that's where it should go since it's the only -- some of the only human data you have, or you should refer back to it.

But the first paragraph there, I think there might have been a word processing error or something. Can you see where the report describes six patients?

DPR STAFF TOXICOLOGIST SILVA: Uh-huh.

PANEL MEMBER BLANC: There's no reference and I don't know what the report is.

DPR STAFF TOXICOLOGIST SILVA: Oh, I'm sorry. I

must have just -- yeah.

PANEL MEMBER BLANC: Is it possible that that's the Eli report from '67? It's not referenced anywhere. I mean there was an old report in literature, E-l-i, Charlie Hine was a coauthor.

DPR STAFF TOXICOLOGIST SILVA: Oh. That sort of rings a bell.

PANEL MEMBER BLANC: I think it got chopped off inadvertently or something at some point, and then the reference died with it.

DPR STAFF TOXICOLOGIST SILVA: There have been so many drafts of this thing that sometimes I wonder where things go.

Okay.

PANEL MEMBER BLANC: You might also want to take a quick look at Schaumburg and Spencer's second edition. Boy, there's a fairly erudite discussion of this class of pesticides. And some of their citations are not exactly journal articles. There are other texts which seem -- but based on the way they're citing them, they seem to be texts which actually have primary data in them or something. I can't really tell. That may not be the case. But you should look if you have that reference and just double check.

CHAIRPERSON FROINES: Their first book came out

about 1980. So this is one that came out in the latter '90s I think. So I wouldn't get confused because the old book has been around for a long time.

PANEL MEMBER BLANC: Right. But those were the things that confused me.

PANEL MEMBER BYUS: I have a few comments.

CHAIRPERSON FROINES: Please.

PANEL MEMBER BYUS: I agree with the tumor promotion. Under genotoxicity comments I had exactly the same thing. The data's not totally definitive but there's plenty of indication. So you really need to make a little more definitive statement about that.

I have one question about the pharmacology, your first slide or whatever is there on the first -- about the absorption.

No, keep going backwards.

That one.

And I kept reading it over and over in the -- and, again, maybe I'm just not getting it. But generally if 75 percent -- if you go to the bottom -- by oral gavage shows up in the feces, that's indication of poor bio-availability, not a lot of absorption. I mean otherwise if 75 percent of what you missed are showing up in the feces, that's not a hundred percent absorption. Yet oral absorption, rat gavage, 87 percent, assume 100

percent. I kept reading it over and over again and I don't know what it is. So I don't understand.

DPR STAFF TOXICOLOGIST SILVA: Well, I think that --

PANEL MEMBER BYUS: I understand blocking off bile duct and looking and see what you got. That was good. But I don't get the -- to see what -- you know, you're getting enteropathic circulation.

DPR STAFF TOXICOLOGIST SILVA: Yeah, I think they're recovering total radioactivity rather than metabolites per se. So 13 percent of administered radioactivity's coming out in the urine and 75 percent in the feces.

PANEL MEMBER BYUS: So that if you increased the amount, then that process saturates and all of it gets absorbed. I don't know what the mechanism is. It just doesn't -- you know, it's just -- it doesn't make sense to me. I mean it might make sense. I mean it may really make sense.

So clear that up, would you, because it just -- it just stands out as something being inconsistent completely.

DPR STAFF TOXICOLOGIST SILVA: Okay.

PANEL MEMBER BYUS: I have just a couple more comments, one about the reproductive toxicity. You know,

it actually seems like this is a fairly reproductively toxic compound, if you read it study after study. Test is spermatogenesis, all of the -- all kinds of -- now, again, these are occurring at higher doses than you're picking here, correct?

DPR STAFF TOXICOLOGIST SILVA: Right.

PANEL MEMBER BYUS: But still I mean when you conclude on page 67 in your summary, "Many studies obtained from the open literature showed direct effects on the male reproductive tract, although these effects did not alter reproductive performance," and I don't really know where that is. I mean there's some statements in here that -- sperm count in gavage deference was significantly decreased and their motility was sluggish.

DPR STAFF TOXICOLOGIST SILVA: Well, we're actually going to be revising that section, because I've put together all the pertinent studies and -- to show the studies, the duration, the author, the --

PANEL MEMBER BYUS: Okay. Because it says -- you know, you conclude there are no effects in the reproductive parameters for either sex. I mean I don't -- it just seems inconsistent again to me.

DPR STAFF TOXICOLOGIST SILVA: Yeah. I'm going to get --

PANEL MEMBER BYUS: I mean after study after

study after study you list all these effects, every study is showing reproductive, particularly in the male.

DPR STAFF TOXICOLOGIST SILVA: But it's the dose and the route and --

PANEL MEMBER BYUS: But you should make some comment that at the doses used in these studies you're seeing that. But that, you know, at much lower doses that you might see with exposure, this is way, way above what you'd see. Something like that.

DPR STAFF TOXICOLOGIST SILVA: Yeah, I'm going to be -- no, I have another table and adding to the section or revising the section.

PANEL MEMBER BYUS: And then I do have --

CHAIRPERSON FROINES: Can I just comment just --

PANEL MEMBER BYUS: Oh, sure.

CHAIRPERSON FROINES: I would agree with the two of you about that, because obviously the estrogenic effects, the reproductive effects, all of this is emerging science. And my experience is that as the science emerges, you tend to get more, not less; hence, our view of lead compared to 50 years ago. And that I would actually put a paragraph in the document someplace that acknowledges the reproductive and endocrine effects as an emerging science to be taken seriously.

PANEL MEMBER BYUS: And of course stress the

dose, as you say. Because if these are all occurring at extremely high doses --

CHAIRPERSON FROINES: No, I think the endpoint that they chose is exactly the right one.

PANEL MEMBER BYUS: And then my last concern I have -- I just want to echo. The reported illnesses, the human data, struck me exactly the same way. I mean there must be narratives, I mean these several individuals who were exposed. I mean I have notes here like what concentrations were they exposed to? Was this the concentrate or was this the diluted form? You know, and what happened to them? I mean they died. One person died. And the other person had permanent --

PANEL MEMBER HAMMOND: Did you find that paragraph?

PANEL MEMBER BYUS: Right, exactly. I mean permanent paralysis, irreversible. I mean these kinds of things are, you know, very, very important, one would think.

So I mean you just need a little bit -- you know, in terms of the -- again, back to the toxicology, back to the dose, what was -- you know, even if you don't know exactly what the exposure was, you can get some --

PANEL MEMBER HAMMOND: What were they doing?

PANEL MEMBER BYUS: What were they doing? Sure.

I mean --

PANEL MEMBER HAMMOND: What was the time reentry in the field?

PANEL MEMBER BYUS: Exactly, time, that kind of thing. I mean all those things I think are really relevant to this toxicology for the extent that it exists. So I would do that as well.

CHAIRPERSON FROINES: Since I had mentioned that one study that you said you missed, I just wanted to comment that I went through all the reproductive and endocrine studies that I could find on this compound, and I checked your references. And Basically as far as I can tell, you got most, if not all, of them. So I think -- it isn't as though it's not there.

DPR STAFF TOXICOLOGIST SILVA: But it's not -- you'd like it more concise, and it will be.

CHAIRPERSON FROINES: I'd like one paragraph that says, "This is emerging science that we need to follow up on over time."

PANEL MEMBER HAMMOND: Yeah, I would second that, because I think that there is that kind of interest in endocrine disrupters and in the reproductive effects. And who knows where it will go eventually. It's nice to at least have laid out what's known at this point. And you can conclude by saying it's not the most sensitive

endpoint, but that those effects are there. I think they're worthwhile --

PANEL MEMBER LANDOLPH: And, Marilyn, when you put those enzymes down that are thought to be involved in metabolism, if it's known what receptors they bind to and how they activate the metabolism, you know, maybe by binding to a receptor, translocation to the nucleus, new RNA, if that's known, if you could just sketch a couple sentences there, that would help out too.

PANEL MEMBER BYUS: My last comment was simply about the P-450 induction. I mean there must -- you mention it, it induces P-450. But does it -- do you know what isozymes it induces, those kinds -- I mean -- and, again, I'm not trying to just -- so based on evident -- you know, the mechanism of action-based analysis for everything is very prevalent. And so this is -- I mean if you remember that this was the previous thing we were looking at, it's all laid out of which of the isozymes are -- again, it's very important.

DPR STAFF TOXICOLOGIST SILVA: Okay.

PANEL MEMBER BYUS: It's not trivial.

CHAIRPERSON FROINES: Can I disagrees?

PANEL MEMBER BYUS: Oh, all right.

CHAIRPERSON FROINES: And I want to defend --

PANEL MEMBER GLANTZ: No.

(Laughter.)

CHAIRPERSON FROINES: -- the DPR folks, because --

PANEL MEMBER GLANTZ: He doesn't pay any attention to us.

CHAIRPERSON FROINES: What?

PANEL MEMBER GLANTZ: Nothing.

You said, "Can I disagree?" And we both said no.

(Laughter.)

PANEL MEMBER GLANTZ: And you just kept going anyway.

(Laughter.)

PANEL MEMBER GLANTZ: I know it was a rhetorical question.

CHAIRPERSON FROINES: I think that the document -- the strength of the document is that it gets -- it basically focuses on getting where they want to go, and I think that's a very good thing. Because I think that's what these documents should be about.

You two are basically wanting her to make this a literature review.

PANEL MEMBER BYUS: No.

PANEL MEMBER LANDOLPH: No.

CHAIRPERSON FROINES: And I think that you should -- I think if you want to put P-450 and which

isozymes are important, so on and so forth, I just think it should be limited and not ask her to do a whole thing on P-450 chemistry. I just don't think it's valuable.

PANEL MEMBER LANDOLPH: You can say it in a short paragraph.

DPR STAFF TOXICOLOGIST SILVA: Yeah, I have some good papers that --

PANEL MEMBER LANDOLPH: And if there's a review, just cite it and write three lines or four lines and that's it.

PANEL MEMBER BYUS: One sentence. In the sentence --

DPR STAFF TOXICOLOGIST SILVA: And I can add them to the --

PANEL MEMBER BYUS: Add it to the sentence.

DPR STAFF TOXICOLOGIST SILVA: -- the metabolism thing, yeah.

PANEL MEMBER BYUS: Right.

CHAIRPERSON FROINES: The hell with you two.

(Laughter.)

PANEL MEMBER GLANTZ: I was told to point out the previous statement was a joke for the record.

(Laughter.)

PANEL MEMBER BYUS: Please, put that down.

(Laughter.)

CHAIRPERSON FROINES: We have -- Paul's left. We're down to four people plus -- five.

We're a quorum?

PANEL LIAISON BEHRMANN: Yes.

CHAIRPERSON FROINES: Now, shall we continue now or shall we take it up next time?

PANEL MEMBER GLANTZ: Next time.

CHAIRPERSON FROINES: Next time.

PANEL MEMBER GLANTZ: I have one question. Are you going to do another draft of the document based on --

DPR STAFF TOXICOLOGIST SILVA: I sure am. Oh, yeah.

CHAIRPERSON FROINES: And we have --

PANEL MEMBER GLANTZ: Now, will we also for the next meeting have the public comments and the response to comments too?

Yes. Okay, good.

PANEL MEMBER HAMMOND: This is by the December meeting?

CHAIRPERSON FROINES: I would still argue to -- because given the tone of your voice, I would argue keep the rewrites limited and meaningful so we don't -- all due respect to my two friends here, you know, that we keep it within confines.

PANEL MEMBER GLANTZ: And maybe use the famous

red line strike-out method so people can see -- you know, so you don't have to read everything again.

DPR STAFF TOXICOLOGIST SILVA: I see, yeah.

Are you -- I mean are we going to pursue the endocrine or are we going to -- I mean do you want --

CHAIRPERSON FROINES: I say, as far as I'm concerned, it should be a paragraph.

DPR STAFF TOXICOLOGIST SILVA: Okay.

CHAIRPERSON FROINES: A paragraph.

DPR STAFF TOXICOLOGIST SILVA: How about a table?

CHAIRPERSON FROINES: Whatever you -- that's right. A table that says here are studies and we'll look forward to emerging science. Just in a sense note that you're aware of this emerging field. And so when it comes up again in the future, and of course it's going to in some chemical or other, that we have it in the document. That was all I -- I wasn't trying -- I certainly don't think you should get into a whole discussion on endocrine disruption. I mean --

DPR STAFF TOXICOLOGIST SILVA: No, I prepared --

PANEL MEMBER BYUS: No, and my -- yeah, and my concern about that was not his concern that you talk about endocrine disruption. It just seems like you listed nicely all the endocrine effects and then sort of wrote them off. And the reason is is because of the dose, that

they're all occurring at very high doses. If that's the reason, that's all I would need in the summary, to say, yes, these things all occurred, but they occurred in animal models at very high doses that are tenfold or hundredfold -- whatever it is -- higher than these other effects.

So, you know, that's all I want to see.

CHAIRPERSON FROINES: But I would argue something different, which is interesting. Because as we move into -- as we move into what people are calling the new science, and we've lived through chronic animal bioassays and acute bioassays and Subphrenic bioassays since the seventies and eighties and even up to the present, but, you know, everybody's talking about new high through-put systems for doing short-term testing. And so the science may not be ready for prime time, but it's coming along. And at some point we're going to be making decisions about dose response, not based on an animal NOEL, but it's going to be based on some, you know, oxidative stress measure or NRF2 measure or what have you, and that's going to be a different -- there the dose situation's going to be quite different because it's going to be quite low. And so we're going to have to figure out how we're going to deal with that coming down the road.

So I think that just the issue of NOELs is

a science -- you know, it's from 1950.

PANEL MEMBER BYUS: I wouldn't argue with you, but --

CHAIRPERSON FROINES: Yeah. So I think it's --

PANEL MEMBER BYUS: -- we're always going to have to deal with the dose though. The dose is going to be the key issue no matter what the assay is. It's relative to exposure.

CHAIRPERSON FROINES: Yeah, but all I'm saying is that I think that ten years from now we'll be looking at things differently in terms of dose response.

PANEL MEMBER HAMMOND: I think that's all true. But I also think that it's important to at least lay out what are the categories of health effects that occur from something.

CHAIRPERSON FROINES; Yeah, of course.

PANEL MEMBER HAMMOND: And even if they're not the critical ones upon which you set the dose. Just so the people know that these are other -- the categories in the general things. But, again, it doesn't have to be a full 20-page section. What works best for you in how to present it. But I think just presenting that information is useful.

CHAIRPERSON FROINES: Are we --

DPR ASSISTANT DIRECTOR JONES: Let me just ask

one question of the panel.

Did it work previously on Methidathion when staff went back and took your ideas and thoughts and incorporated and we provided you an annotated highlighted copy that showed the changes and tried to summarize that?

Because we'll -- And, John, assuming that we will be discussing this in December 4th, that we'll get you a copy of that well in advance of the meeting and also provide you the comments and response to comments prior to that.

CHAIRPERSON FROINES: I don't think I'm overly optimistic to say that I think we can complete this document. And so one of the things we'll want to do perhaps, if it's okay with the Panel, is work on the findings between now and the next meeting as well. And then hopefully we can -- then we'll be in good shape.

(Laughter.)

PANEL MEMBER BYUS: With the comment that --

CHAIRPERSON FROINES: I can see why this document -- I can see why she would like this document to go away.

PANEL MEMBER BYUS: The comments are crucial. I mean as you know the Panel spends a lot of time reading and analyzing the comments. We take them very seriously. In fact, it is usually what I -- when I'm reading these

documents, what I read first. I know Stan taught me that many years ago, and I still do it. And I use the comments and then I read the document.

So they are very important and we really do listen to them and we really do consider them in depth. So they really are very important and it is nice to have them generally ahead of time before we have the document, because it sort of saves -- at least in the way I do it, it saves me some time and energy. But that's okay.

PANEL MEMBER GLANTZ: Yeah. Another thing related to that is this difference of opinion with OEHHA and how to handle exposure to children or infants, and how much of a correction factor to put in that. It would be nice if that got resolved. Or at least, if you can't come to an agreement, have the arguments on both sides laid out and then we'll decide what to do.

CHAIRPERSON FROINES: Well, I think it's -- I think it's internal. Yeah, I don't think we could in a sense define it.

Do we -- I want to delay us one minute longer.

I might like to borrow some of your slides for my risk assessment class. Those were really nice slides.

(Laughter.)

CHAIRPERSON FROINES: Can I get an adjournment.

PANEL MEMBER GLANTZ: I move we adjourn.

CHAIRPERSON FROINES: Second?

PANEL MEMBER BYUS: (Raised hand.)

CHAIRPERSON FROINES: All in favor?

(Hands raised.)

CHAIRPERSON FROINES: I would never stop using Andy Salmon's slides, but those were good too.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 3:00 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 4th day of October, 2007.

JAMES F. PETERS, CSR, RPR
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