MEETING

OF THE

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

CALIFORNIA AIR RESOURCES BOARD

MILBERRY CONFERENCE CENTER

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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TUESDAY, FEBRUARY 1, 2000

9:00 A.M.

Janet H. Nicol
Certified Shorthand Reporter
License Number 9764

APPEARANCES

MEMBERS PRESENT:

Dr. John Froines, Chairman
Dr. Roger Atkinson
Dr. Paul D. Blanc
Dr. Craig Byus
Dr. Gary Friedman
Dr. Anthony Fucaloro
Dr. Stanton Glantz
Dr. Peter S. Kennedy
Dr. Hanspeter Witschi

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD:

Mr. Jim Behrmann, Manager
Mr. Bill Lockett, Deputy Ombudsman, Northern California
Mr. Peter Mathews, Office of the Ombudsman

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. George Alexeeff, Deputy Director for Scientific Affairs
Dr. James Collins, Staff Toxicologist
Dr. Melanie Marty, Senior Toxicologist
Dr. Andrew Salmon, Chief, Air Toxicology and Risk Assessment

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Mr. Paul Gosselin, Assistant Director
Dr. Andrew Rubin, Staff Toxicologist

ALSO PRESENT:

Ms. Elinor Fanning, UC Berkeley

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P R O C E E D I N G S

CHAIRMAN FROINES: Welcome, everybody.

This panel has had approximately a two-month break, so that everybody should be really raring to go.

Melanie doesn't want to hear that.

DR. GLANTZ: I just thought of a wise crack, but I won't make it.

CHAIRMAN FROINES: The first item, there's no other information I think that's particularly relevant at the beginning, so we might as well just go right into the agenda.

So we're going to continue to consider the draft report, 23 of the first 43 compounds.

DR. MARTY: I'm Melanie Marty from the Office of Environmental Health Hazard Assessment, and we're going to present today the revisions made to the document based on the panel's comments from the last three meetings or so.

Today we're talking about the technical support Document for the determination of chronic reference exposure levels for airborne toxicants.

This slide presents the definition of the chronic REL. Essentially the chronic REL is the concentration in air at or below which no adverse health impacts are anticipated following long-term exposure. It is meant to protect most people, including sensitive individuals,

although we are obviously unable to account for idiosyncratic responses.

Exceedance of this REL does not necessarily result in adverse health consequences, until you reach a high enough level to see adverse health connections. I think that's important that people understand that.

We made a number of revisions in the document. This slide summarizes the revisions in the introduction.

We changed the uncertainty factor for interspecies extrapolation when you're using primate data to three from ten. This was based on comments from the panel that they felt primates were close enough to people that perhaps we shouldn't have lumped them together with rodents.

We added a brief discussion of hyperplasia as a toxicological endpoint. That's on page 17 of the introduction.

We also reworded our discussion of the benchmark concentration approach on page 19 and in particular talked about the difference between how US EPA does benchmark concentration and how we have proposed to use it.

The difference being primarily that they are looking for a benchmark which is the 95 percent lower confidence limit on the dose that produces a ten percent response rate. We felt that was closer to a LOAEL rather than a NOAEL. We would rather use the 95 percent lower

confidence limit on the dose that produces a five percent response rate. So that's one difference between our approach and their approach.

We added an equation for unit conversion from ppm to milligrams per cubic meter. That's on page 30.

We also on page 30 clarified our discussion of the use of US EPA RfCs. Essentially what we have stated is that we have a evaluated the US EPA RfCs. In many cases we agree with the choice of the key study, but we have somewhat different approaches to the use of uncertainty factors and we're also more consistent with what we describe as a chronic toxicological study. So we actually have criteria for the duration of the exposure.

We also made a number of generic revisions to the toxicity summaries in the RELs. We responded to all the panel members' comments.

We added emissions information from the air toxics emissions database, which is the Air Toxics Hot Spot Program's database of emissions reported by the air districts and facilities.

We also added, where available, ambient concentration data, which we intend to update to whatever we can -- the latest year from the Air Resources Board. I doubt they have their '99 all pulled together, but at least we'll get the '98 emissions in. I'm sorry. In '98, the

ambient concentration data.

We added more description of key studies, and that was in response to most of the panel members' concerns about us not describing enough the information that was available.

We added comparison reference exposure levels where you could have chosen one study or another with some discussion of why the study we chose we chose.

We also added a section, strengths and limitations of the data, and essentially organized some material that was already in there into that section so it was easy to find and describe, and we bolstered that section in a number of cases.

The panel had directed us to go back and look at our US EPA RfCs that we proposed just adopting. So we did do that. And in fact with a number of the studies we agreed with the choice of the study made by US EPA, but we would have applied different uncertainty factors.

One of the things we did was drop the modifying factor that EPA uses in a number of their RfCs. This changed the chronic REL for ammonia, EGME, mercury and MTBE. In general it went up, because they added an additional modifying factor of three, which they of course divide through by. And we removed that modifying factor so the numbers went up a little bit. With rounding it ends up being about a twofold, depending on the numbers.

In the case of mercury, we actually used different uncertainty factors than US EPA. We dropped the modifying factor, but we actually used a different uncertainty factor so the number changes, it actually drops.

DR. FUCALORO: Can I ask a question? How does three round to two? I'm not quite sure.

DR. MARTY: If you go through the calculation and then round the final number, we rounded it to one significant figure, so it ends up if you do the calculation and round the final numbers, the difference isn't quite three.

DR. SALMON: Like ammonia was 70 and 210. Went from 70 to 210, so we rounded 70 up and 210 down.

DR. MARTY: Other changes --

DR. GLANTZ: Where is the limitations section?

DR. MARTY: It's section 7 of each toxicity summary.

DR. GLANTZ: Okay.

DR. MARTY: I'm sorry. It's not in the introduction. The last section, before the references.

DR. GLANTZ: I see them.

DR. MARTY: Other changes that were made in response to our re-review of some of these issues, for chlorine we used a benchmark concentration approach. This approach we discussed quite a bit and essentially most

everyone agrees it's better than just using the NOAEL, LOAEL divided by uncertainty factors approach.

In so doing, the reference exposure level changed from .06 to .2 micrograms per cubic meter, and we did use a benchmark concentration for a five percent response rate.

In the case of ethylene glycol monoethyl ether, we actually read some studies that were suggested by Dr. Blanc. They were human studies. They indicated to us that the interspecies uncertainty factor should really be higher than what we had initially proposed. So this dropped the reference exposure level to 70 micrograms per cubic meter.

The original number was an EPA RfC. We used the same study and kept the key study, but rather than using an interspecies uncertainty factor of three, we used ten, even though we had a human equivalent concentration adjustment. And that's basically as a result of us evaluating a series of studies by Welch and Cohn, which couldn't themselves be used because of uncertainties in the information, but indicated that humans might actually be pretty sensitive to the reproductive toxicology effects.

Ethylbenzene is another chemical that was suggested we go back and look at the new chronic NTP bioassay, which came out in the middle of last year. We did that and revised the REL using that study. And the REL

changed from .2 to .4 parts per billion. The original proposed REL was an EPA RfC based on developmental toxicity.

If we had used the EPA study and done our methodology, we actually would have had an even higher number. So we're not uncomfortable that -- we think we're protecting against developmental effects.

In the formaldehyde summary we added a table with comparisons of the REL, which was based on a human study to RELs based on 13 animal studies. And essentially they bracket that human REL. Some of them are lower, some are higher. So it just strengthens the argument for the use of those studies.

For hydrogen chloride we updated the RGDR from what was originally in the document. Originally we proposed to use an EPA RfC and, when we evaluated it, the RGDR was changed and we also changed the low observed adverse effect level uncertainty factor from ten to three in the process, so the REL changed from seven to nine micrograms per cubic meter.

In the case of methyl ethyl ketone, we went back and looked at a study which I believe Dr. Blanc had suggested us to look at it.

Mitran et al, 1997, is a study of exposed cable factory workers and we replaced the rat study which we had used, which in essence was actually a subchronic study. And

the REL changed. It actually dropped from 10,000 to 500 micrograms per cubic meter. So this was a significant change and we were impressed by that and thought it would have been much better to use that human study in this case.

In this case these workers were only exposed to MEK. They did not have other solid exposures, and the exposure assessment seemed to be relatively good for a human study.

DR. FUCALORO: Curiosity on that, I mean, that's a 20 to 1 change. Now, the US EPA has any data? I mean, how did they handle methyl ethyl ketone? I mean, something is that big a change, I mean it's -- you have to understand what that -- what other people think of that change.

DR. MARTY: The RfC for methyl ethyl ketone that was developed by EPA in '92 has been withdrawn, and we don't -- they don't have any number.

DR. FUCALORO: What was theirs and why was it withdraw, by the way?

DR. MARTY: I think the methodology changed between when they had developed it.

The original study that we proposed for the REL was a rat study with whole body inhalation for 90 days, and the toxic endpoint noted was increased liver weight and relative kidney weight in the male and female rats.

In contrast this Mitran et al study, which looked

at people, was looking at neurotoxic endpoints. They had a battery of neurobehavioral tests which obviously has some -- there are problems in interpretation of those tests, but in addition they conducted motor nerve conduction velocity tests, which are not subjective, at least near to the degree that the neurobehavioral battery tests are. And they got significant decreases in measured nerve conduction velocity in three nerves.

So we felt that that was important information. The Cavender study really didn't look at neurotoxicities, so they have been missing the more important endpoint in this case.

CHAIRMAN FROINES: I'm sorry. Where is that described?

DR. MARTY: Page A-182, methyl ethyl ketone derivation of chronic reference exposure levels.

And then the Mitran study is described on page 180.

CHAIRMAN FROINES: I'm sorry, Melanie, which is the study with the nerve conduction velocity change?

DR. MARTY: That was Mitran et al, 1997. It's described under effects of human exposure on page A-180.

These were relatively long-term exposures. The average length of exposure was 14 years.

CHAIRMAN FROINES: Did they control for alcohol?

DR. MARTY: Jim is looking at the study.

They did have 41 exposed workers and 63 controls, which they say were matched for age, physical effort at work, work shift and socioeconomic factors.

I'm not sure that they specifically addressed alcohol. You would have to assume, though, that the alcohol usage was different in the 41 subjects and 63 controls if it were to impact the results.

CHAIRMAN FROINES: The historical problem with neurobehavioral occupational studies is always this problem of alcohol, not controlling for alcohol consumption.

DR. SALMON: That isn't such a big problem now with the neuroconduction velocities studies.

CHAIRMAN FROINES: I understand.

DR. SALMON: Which was one of the reasons why we focused on that endpoint rather than the neurobehavioral studies, because, as you correctly point out, the number of variables and confounding factors which need to be taken care of.

CHAIRMAN FROINES: It's also true that hexane produces a distal axonopathy, as you know, and that myelin changes are a late stage of that process, and so motor nerve conduction velocity changes are in fact late stage change in hexane exposures. So it may be that because you've got 14 years' exposure, you've got myelin damage as well as axonal

damage. That's the assumption, I assume.

DR. MARTY: Yes.

CHAIRMAN FROINES: Tony, question?

DR. FUCALORO: No, I'm done.

DR. MARTY: In the case of PGME, we originally used a subchronic study for the REL, and there was a submission to us from industry of a chronic toxicity oncogenicity, two-year bioassay, that we read and have incorporated into the document. And the result is that we used it as the basis of REL rather than the subchronic study, and the result is that the REL went from 0.6 to 2 ppm.

CHAIRMAN FROINES: The record should show that Dr. Friedman is here now.

DR. COLLINS: The original study was subchronic and the new study was chronic.

DR. MARTY: Correct.

For phosphoric acid we originally had an EPA number which was based on a benchmark concentration, but the benchmark concentration used again the 95 percent lower confidence limit on the dose for ten percent response rate. We went back and calculated that using the LCL on a five percent response rate. The result was the REL changed from 10 to 7 micrograms per cubic meter.

That's it for the changes to the document.

I did want to -- maybe I should wait if there are any questions.

I did want to talk about the next steps for this document to clarify that, at least what we're thinking.

Okay. We will --

CHAIRMAN FROINES: The panel sees this as our rock of Sisyphus, you know.

DR. GLANTZ: What's the rock of Sisyphus?

DR. BYUS: It keeps rolling. Roll it up there and it comes back down.

CHAIRMAN FROINES: Who was condemned to roll the rock up the hill, he gets it to the top of the hill, it rolls back down, and he has to start over again.

And the chronic REL document has some of the qualities of that.

DR. GLANTZ: I was actually going to speak to that, but not as eloquently.

DR. MARTY: We need to incorporate any additional comments that we get from the panel today and finalize the methodology section and these first 23 chemicals.

We will then address the rest of the first batch at the March 7th SRP meeting, so the panel will be receiving the last 16 of the first 40 chemicals and with changes that we have made pursuant to all the comments that has gone on for the last three meetings. So you should be receiving

that very shortly.

CHAIRMAN FROINES: Help me. This next 16 are chemicals that we have already discussed, you've made changes?

DR. MARTY: Correct.

CHAIRMAN FROINES: And then they'll be coming back to us again?

DR. MARTY: Correct. Just like this first 23. We wanted to get all 40 to you, but December got in the way.

DR. GLANTZ: I had asked Melanie about this before the meeting, why we didn't just get all 40 back, and I was told that, as she just said, that they just didn't have time to integrate the comments from the last meeting.

So what I would like to suggest is that subject to any further discussion we approve the document as it's before us, which is a method, a basic methodology in the first 23, and then the rest of the 16 or 17 that they didn't get to will just come in and maybe be incorporated as an addendum, but appropre of the rock of Sisyphus, I'd like to approve this document.

And unless people have -- I read through it. I thought it was fine.

And so the subsequent chemicals that we will deal with would be treated as additions to an approved document, rather than hold the document up. Because this is going to

go on for a long time as we add more and more compounds.

CHAIRMAN FROINES: We have 80 more to go.

DR. GLANTZ: Yeah. But I'd like to have this be finished and approved so they have a finalized document and then we'll just add chemicals to it.

CHAIRMAN FROINES: Do you want us to then take up the 16 at a subsequent meeting?

DR. GLANTZ: Yeah. I mean, what she just said is that they'll bring the rest of those back to us at the next meeting, and I would expect that since they were discussed at length already, hopefully it will be like -- at least when I reviewed the document, I looked at it and said, yes, they made the changes we suggested. I couldn't think of anything else, so I'd like to approve it, unless someone else found anything they wanted to do.

Then as the additional chemicals come, the next 16 we would take, approve unless there's still a problem, and that would be treated as an addendum to this document. But this document would be done and then the third batch or the second batch and the third batch, as those come to the committee and are discussed and dealt with would simply be added to the approved document, rather than have the document continue to wait.

CHAIRMAN FROINES: So you're basically proposing a two-vote sequence?

DR. GLANTZ: Well, I'm proposing that we vote, unless people have objections to it. I have no concerns remaining with this document. That we approve this and finalize it. And then as additional chemicals come to us, that when those are approved they be added to the approved document, rather than holding the document until all 120 or however many there are compounds that will be dealt with.

CHAIRMAN FROINES: Comments on that?

DR. FUCALORO: I have no problem. There are a few things that almost fall into the category of typos that I can talk to her later about.

DR. GLANTZ: If other people have problems, then, fine, but I don't personally have any problems with the document as it stands now. If they do, they should be dealt with.

DR. WITSCHI: I have a question about the future of this document. What's the mechanism or the process? If new data become available, which should be used to modify what's already in it, because, you know, I've seen a few examples where like this 1999 stuff which you didn't have the last time, so as things -- if we approve it, you know, as times move along, what's the mechanism to take care of new developments?

DR. MARTY: We intend to keep relooking at these chemicals as time goes on, for that very reason. There are,

as you pointed out, a number of examples in here where we found new studies.

DR. WITSCHI: Yes. Will you bring those changes before us?

DR. MARTY: Yes. We have to bring the chemicals and the revisions before the panel.

CHAIRMAN FROINES: I guess I would suggest that if you are going to make revisions that you make the revisions over a period of time and bring as a block of chemicals. The last thing I think we want to see is a chemical dribbling in here and there.

DR. COLLINS: Chemical of the month problem.

DR. GLANTZ: Could be the pebble of Sisyphus.

DR. MARTY: That makes a lot of sense to us too. Bring it in batches.

CHAIRMAN FROINES: I think that this then it does begin to feel like an endless process.

DR. WITSCHI: Won't it give some mandate to them to -- OEHHA gives us an update every year, every two years, something like this.

DR. COLLINS: An annual update.

DR. WITSCHI: At one of the meetings.

CHAIRMAN FROINES: That make sense? That's good.

So, Melanie, I think you're still -- this is a little bit -- should have come at the end of your

presentation rather than here, so why don't you go ahead.

DR. MARTY: Okay.

CHAIRMAN FROINES: Unless you are finished.

DR. COLLINS: We have no objection.

DR. GLANTZ: I actually thought she was finished. I'm sorry.

CHAIRMAN FROINES: No, no.

DR. MARTY: I'm almost finished. I have four more bullets.

As Stan noted, I talked to him a little earlier, we wanted to address the rest of the first batch on March 7th, and then I think it's a great idea to have that added as addendum.

We have to review the public comments on the second batch of 40. We started that process, but we need to keep going and make changes to those second batch of 40 based on the public comments, and also on the panel's comments from the last several meetings. So in other words all the things that we changed in these chemicals, we've got to go back to the second batch and make those similar changes. And then we were hoping to bring them to the panel for review in June.

Then we have the third batch which has not even gone out for the second public comment period yet, so that's down the line.

CHAIRMAN FROINES: Now, the panel may not remember this, but the chemicals have been assigned to the various members of the panel. And I guess I'll ask Peter to make sure everybody has that so they're reminded.

DR. GLANTZ: Why don't you give them, since some of us have short memory, I guess -- no jokes, I'm sorry. He can just give them to me again.

This is the current set. Okay. I can remember this. I was going to say, as we get -- you haven't assigned the second or third batch, have you?

CHAIRMAN FROINES: The second are assigned.

DR. GLANTZ: I thought my memory had completely --

CHAIRMAN FROINES: The second are assigned.

DR. GLANTZ: The second are. Okay. Maybe what you should do is when we get the report from OEHHA on the second batch, maybe you should send the assignments around.

CHAIRMAN FROINES: I'll redo it.

Peter or Jim, we've sent the assignments out, but let's redo it.

DR. GLANTZ: For the second batch.

CHAIRMAN FROINES: For the second batch.

DR. GLANTZ: Why didn't you send that out concurrently when you send the second batch out.

DR. MARTY: Okay. That's it for talking about this document.

I have three more overheads, but it's actually going to the second agenda item.

DR. GLANTZ: Let's finish with this before we go on.

CHAIRMAN FROINES: You're moving -- the last overheads are for the second agenda item?

DR. MARTY: Yes. These last three are really the second agenda item, updating the panel as to where the rest of all the hots spots guidelines are.

DR. GLANTZ: Let's finish this.

CHAIRMAN FROINES: In that second -- we had talked on the telephone about you're talking about the implications of what we've all done and that's what's coming?

DR. MARTY: That we should do now. That we should do now.

What's coming is where is Part 4, where is part 5 in the process.

CHAIRMAN FROINES: No. But I mean these three overheads.

DR. MARTY: Yeah. That's basically what else we have to do for the Air Toxics Hot Spots Risk Assessment Guidelines, but it's not the discussion of how you use the numbers in this.

CHAIRMAN FROINES: Let's follow Stan's -- let's go to Stan. Does that make sense?

DR. MARTY: Yes.

Unless you wanted to talk about issues of the hazard index approach and how we used the numbers, some issues have come up with the panel.

CHAIRMAN FROINES: Let's -- but that doesn't -- we can have a discussion after we've actually approved the document.

DR. MARTY: That's fine.

CHAIRMAN FROINES: Let's do that. So I guess the thing to do is to ask panel members if they have comments on anything that's been presented or changes that have been made.

Let's start out with Stan.

DR. GLANTZ: No, I'm happy with the document.

CHAIRMAN FROINES: Gary.

DR. FRIEDMAN: I have no suggestions.

CHAIRMAN FROINES: Peter.

DR. WITSCHI: No problems.

DR. ATKINSON: I have three minor changes on the physical and chemical properties, if I can just give you those.

DR. BYUS: That's fine. Very good.

DR. FUCALORO: I have some changes, but they're minor.

DR. GLANTZ: Just for the record, these changes

that Roger and Anthony mentioned, those are just minor editorial corrections, there's nothing substantive; is that correct?

DR. ATKINSON: There is a wrong vapor pressure in one of them.

DR. FUCALORO: There's one -- is that formaldehyde?

DR. ATKINSON: Yeah.

DR. FUCALORO: Formaldehyde is clearly wrong and the number hasn't changed.

DR. ATKINSON: Yeah.

DR. FUCALORO: Other than that, they're mostly typos.

DR. ATKINSON: Typos.

DR. GLANTZ: Well, then, I'd like to move that we approve this document and finalize this document.

DR. KENNEDY: Second.

CHAIRMAN FROINES: Is there any further discussion?

Then all in favor.

(Show of hands.)

DR. GLANTZ: It's unanimous.

CHAIRMAN FROINES: So the rock is tilting, holding in place.

DR. MARTY: Okay. The next --

DR. GLANTZ: This is, by the way, a very nice piece of work. And I think it continues the very high-quality work that you guys have brought before us, after we make you suffer appropriately. But it is very very well done and it's just a massive undertaking.

DR. MARTY: That it is.

DR. GLANTZ: Very well done.

CHAIRMAN FROINES: I also think the panel gets credit, though, for having been very thorough in their review of this. That's been, I think, important so that the public has trust in the deliberation that results in these numbers being solidified.

Why don't you tell us what the meaning of all this is.

DR. MARTY: I can go through these slides and that will help focus that discussion.

Basically what we just approved today was Part 3, the determination of chronic reference exposure levels. And we will, as the discussion reflects, be adding chemicals as we move along in over time.

We also have -- Judy, can I have the next slide.

As we just discussed Part 3, what we're going to be doing, Part 4 is the technical support document for exposure assessment and stochastic analysis.

And Dr. Glantz is the lead on that document. He

has received a copy and is plowing through it now.

The panel will receive the document mid February, along with our responses to the comments. The public comment period occurred a couple of years ago and then the document sort of got -- well, we lost a lot of staff and diesel exhaust got in the way. So we are now getting back to the -- we responded to the comments. Everything is ready to go, but we didn't want to give it to you before this meeting to avoid a paper blizzard.

We intend to make an overview presentation of the document and some discussion of the changes that were made since the last version, which was presented by OEHHA to the panel in March of, I think it was 1997.

So we had an overview of the document already given to the panel. There was some discussion at that meeting. And then we have made quite a few changes since then to that document, so we'd like to just re-present the document and talk about some of the key changes.

And then we anticipate that by the time the May meeting rolls around the panel will have had enough time to look at the document and we can start discussion by the panel.

CHAIRMAN FROINES: In March?

DR. MARTY: In May. March 7 we'll present an overview, but you folks will only have had the document a

couple of weeks at that point.

DR. GLANTZ: We're not meeting in April?

DR. MARTY: I don't know. I looked at my latest notes indicating no April meeting. So that I'm just throwing May out there, because I didn't realize there was an April meeting.

CHAIRMAN FROINES: Jim.

MR. BEHRMANN: The next meeting date beyond March has not been set yet.

DR. GLANTZ: I would think, I mean, I'm about a half, a third, or halfway through the revised document, and I would think that it could be discussed. I think it's a long, complicated document, but it's, I think if there's a presentation in the March meeting, then it would be reasonable to have a discussion in the May meeting or rather at the next meeting, whether it's in April or May.

I think that there have been a lot of changes to the document. This is the one where they're trying to model population variability, and rather than looking at single numbers, take into account variability of breathing rates, variability of how much dirt you eat, all of that sort of variability, weather conditions, and there are a lot of, you may recall, political problems with the document before where there was some modeling going on, and as far as I am able to detect it's now back to being based on science.

And but I have not had a chance to go through the public comments. And I was just looking at the document, but it is about three inches thick, three or four inches thick.

Because there's a methodology is laid out and then they go through, it's sort of like what we've been doing with these chemicals, except looking at different biological parameters and there are a series of studies discussed and distributions involved.

But I think it's like the one we just approved, it's going to represent a substantial contribution to improving the quality of these risk assessments.

But I think that the plan, since it is complicated, to have it presented at one meeting and give people some time to think about it before we actually discuss it is a good idea.

But I have, in going through it so far, I haven't found any major problems, although I'm not finished.

DR. MARTY: Okay.

CHAIRMAN FROINES: Can I ask you one question before we go on.

One of the issues that emerges when you do stochastic modeling and you've looked at the population distribution of risk, that gives you a whole series of data which you then use in your ultimate risk management

determinations.

Here we come up with 3 times 10 to minus 4 for diesel, and then unfortunately, in my view, people tend to use that as a bright line.

Now, with stochastic modeling, you come up with a wide range of values, based on the different distributions, and then somebody has to decide what is the level of protection that you should afford the public, given those distributions.

And so it would be very useful when we actually get around to discussing it, I don't want -- the panel can't get into the risk management issue, but if you can give us some sense about how you developed this mass of data, how people are going to interpret it for public health consideration and control use, because if you have 25 numbers or ten numbers or one number or hundred numbers, somebody still has to decide what is the -- what do you use when you make decisions.

And so at some level just because you can do stochastic modeling doesn't mean that things get necessarily better, unless you have a clear, coherent policy framework to offer. So it seems to me it would be useful to have some sense for the panel to have some sense of that, so they have a sense of how you're actually going to use that information.

DR. GLANTZ: I'll let Melanie talk here, since she wrote the document, but that's in there actually. You know, where they in fact have some discussion of when it's worth the trouble or suggestions on how to decide whether or not it's worth the trouble to use this more complicated modeling approach. I don't recall anything about where you should draw the line.

DR. MARTY: Right. We actually presented tiered approach in there to risk assessment, with four tiers. The first being just a deterministic approach where you have one input value for an exposure parameter, and that would be the simplest form.

And what we did was we used our analyses of the distributional characteristics of the data, for example, for breathing rate, to say where we think those point estimates should lie and we present a mean or a central tendency estimate and a high end estimate, which in this case is the 95th percentile on the distribution.

And then we do have discussions of when it makes sense or doesn't make sense to do a more complicated risk assessment using the full distribution.

We do -- we don't have anything in there about how the risk manager then chooses where on the distribution they're going to protect people. And we did that in a sense on purpose because we're trying to just look at the science

and say this is the 50th percentile, this is the 75th, this is the 90th, this is the 95th, rather than getting into the risk management end of things.

However, both the Air Board and several of the districts have had some discussion about this issue and I anticipate a lot more discussion in the next six months or so of what to do with the numbers.

In essence to have the distributional characteristics better defined helps the risk managers, because right now the deterministic methodology is based on estimates that might be a combination of the 50th percentile and the 75th and the 95th here and maybe the 99th there and you really don't know where you are on the distribution without doing a really thorough analysis. So that's one of the issues that we tried to address in this document.

CHAIRMAN FROINES: Go ahead.

DR. MARTY: Okay. And then Parts 1 through 4 represent the technical support documents, with lots of information that eventually gets distilled into Part 5, which is risk assessment guidance manual. The guidance manual is just that, it's a step-by-step incorporates all the information from Parts 1 through 4 and gives instructions for conducting site-specific health risk assessments in the Air Toxics Hot Spots Program.

And we have worked with ARB on this and will

continue to do so and also with the California Air Pollution Control Officers' Association.

We're hoping that the manual is ready by this summer.

There was some discussion about the role of the panel, but we think that the panel needs to look at the manual.

That's all the overheads that I had.

DR. GLANTZ: That's all the work you have for us?

CHAIRMAN FROINES: So panel will see the manual this summer?

DR. MARTY: Yes.

DR. COLLINS: Jim Collins, OEHHA.

I'd like to say that some of the acute RELs are already being used now in risk assessments that the districts are submitting to OEHHA, so the numbers that were approved last March have been actually used in actual risk assessments or as an index or acute index.

CHAIRMAN FROINES: So, Melanie, you were going to say?

DR. MARTY: There were some concerns on a couple of the panel members regarding the use of the chronic reference exposure levels. And I don't have overheads for this, but I think I wanted to talk through it.

In particular, since some of these chronic

reference exposure levels are fairly close to measured ambient concentrations in the South Coast Air Basin, the question arose, well, what does the risk manager do with that.

The hazard index approach, as you'll recall, is where you ratio the modeled ground level concentration from what you estimate using modeling the air dispersion of chemicals from a specific site. You ratio that to the reference exposure level.

If that number is one or less, then the typical risk management decision has been that the facility is fine and it poses no public health risk.

It's when this number goes above one that flags get raised. Different risk management, just different risk managers will use that number in different ways. The 35 air pollution control districts all have to have a regulation as to what they do for the hot spots program when that number goes above one.

In the notification provisions of the statute, the district can require facilities to notify the surrounding community of their emissions and what those emissions are, what the potential health impacts are.

It's up to the district whether they notify and who notifies.

The ARB back in '92, I think, came up with a

notification guidance, and in the guidance they recommend that OEHHA be contacted if the hazard index goes above one. And there was a lot of discussion and still is a lot of discussion about what to do when the hazard index goes above one. And the primary issue is, well, there's uncertainty in those numbers. Those numbers are meant to protect basically everybody, so when you start exceeding those numbers, how much do you have to exceed them before you actually have endangerment of the public health.

Of course we have included information in there to protect sensitive subpopulations.

So there have been many instances where the districts have a facility where a hazard index is above one and they've called us and said what is the uncertainty in this number and we've walked them through the derivation of the reference exposure level.

If we have an uncertainty factor of a thousand and the hazard index is two, that doesn't give me very much heartburn and generally doesn't give the risk managers very much heartburn.

If you have a hazard index of two or three or four and your uncertainty factor was only cumulative uncertainty factor of ten, then in most instances most districts would require that facility to notify.

So it's not hard and fast. Some districts have --

at least one district, Sacramento Air Quality Management District, the hazard index has to reach ten before they require notification.

I don't personally necessarily agree with that, because that erases all of the uncertainty factor for some chemicals, but for others that may be adequate. So therein lies the rub of how to use these numbers.

DR. FUCALORO: So the reporting of a number, of course, is one-dimensional object element. Why not report numbers with uncertainty factors?

DR. GLANTZ: They are.

DR. FUCALORO: They do that? So they say contact you and ask you what the uncertainty factor is. It seems to me they should have the information --

DR. GLANTZ: It's in the documents.

DR. MARTY: They have the documents. They have the documents. It's just usually a question, it's an engineer who is calling and they're unsure of the meaning and the toxicology of the compound and want to know a little more. That's generally what happens.

DR. FUCALORO: Also I mean an argument for a case-by-case basis, not only knowing a number and an uncertainty factor, also the toxic endpoint is important.

DR. MARTY: Yes.

DR. FUCALORO: If it's sneezing, it's one thing.

If it's something neurological damage, it's quite another.

DR. MARTY: Yes, yes. I think most risk managers get a little more nervous if we're talking about developmental toxicity and irreversible impacts, versus eye irritation.

CHAIRMAN FROINES: But there's also the issue of variability versus uncertainty.

DR. FUCALORO: That's a good point. That's a good point.

DR. MARTY: Yes.

DR. GLANTZ: And the stochastic model or document goes on in some length about that, actually.

CHAIRMAN FROINES: So is there -- do the local districts -- let's assume if the local districts then have the company or whoever notify the public who are quote, "overexposure," is there any other legal requirement for control to reduce that level?

DR. MARTY: Yes. There is a requirement that the districts, if they deem the health risk to be significant enough, institute risk reduction audits and plans, so the facility has to go back and look at their process and decide where they can reduce emissions.

To my knowledge, there have been very very few facilities in this state that have had to do risk reduction audits and plans, and it's always been based on the

carcinogenicity, or the carcinogenic risk from the emissions. I'm unaware of any risk reduction plans that have been triggered by a hazard index exceeding one.

DR. COLLINS: They could be.

DR. MARTY: Yes, they could be, but I'm unaware that that has happen.

I think in most cases they have a different trigger level, so, for example, the notification, the trigger level might be a hazard index of two or five, but the risk reduction trigger level is much greater than that. They've done that also with the cancer risk estimates from facilities. Most facilities have to notify when the cancer risk is above ten to the minus five, but risk reduction doesn't kick in until the cancer risk is above ten to the minus four. There's a parallel. Each district has their own regulation, so I don't know what all the regulations are, but there's a parallel process for the hazard index.

DR. COLLINS: The South Coast is currently looking at revising the hazard index, get your hazard index below five, and now they're thinking of getting it below three, so that's part of the rule 1402 that we're looking at right now.

CHAIRMAN FROINES: Well, it's interesting -- Peter.

DR. WITSCHI: These are great documents. Are they

are going to be available in some electronic form?

DR. MARTY: Yes. They'll be posted on our Web page, so people can just download them from the Web page, from OEHHA's web page.

DR. WITSCHI: Are they going to be searchable in these form?

DR. MARTY: Are they going to be circulated?

DR. WITSCHI: Searchable.

DR. MARTY: Searchable.

DR. WITSCHI: The reason I'm bringing this up, I once came across documentation which was on a disk, but it was in pictures. It was totally useless, because you couldn't search it.

DR. MARTY: You know, I have to ask our Web master.

Andy says there is a search tool on our Web site, but I personally never tried it, so I don't know how good it is.

DR. SALMON: It's a basic text search function at the moment. I think they're looking into getting more sophisticated database type structure built into the site, but it's not there at the moment.

DR. WITSCHI: Because the data you have in those documents, they really could be used to do some very interesting research and reexamination, re-evaluation of

some of the assumptions, because we have so many data on them.

DR. SALMON: It's a basic long-term objective to get all these numbers into a database format, so it would be actively searchable off the Web site, and that's something which they're working on at the present time.

DR. MARTY: I think there's another issue to sort of tie it in there, what do you do when your reference exposure level is pretty close to ambient measured concentrations. And it's really parallel to if you look at the criteria air pollutants we do have some RELs for the criteria air pollutants, basically they're the ambient air quality standard. And many times they're exceeded in the basin.

Some years back, the districts required facilities to also in this program look at their criteria air pollutants emissions and add them into the hazard index approach, and in the South Coast Basin that almost always kicked people over one for respiratory and eye irritation, so the district made the decision not to require people to notify based on a criteria air pollutant emission if that exceeded that, the ambient air quality standard.

And part of their logic was, well, we have other ways of dealing with that, we don't need to deal with that through the Air Toxics Hot Spots Program. There's a whole

nother program that deals with criteria air pollutants.

So in the case of formaldehyde there may be for this chronic REL, it's fairly close. It's actually the ambient levels measured in '98 are right on top of what we're proposing as the chronic reference exposure level.

So it may turn into an issue for the risk manager of whether they want to do something about that or not.

CHAIRMAN FROINES: I have just one more question, which is let's assume that you have a plant that's using toluene diisocyanate, which is a strong sensitizer, that the effects are very low levels and so on and so forth.

How does anybody know that plant X, which used the TDI, and how does anyone know what that dispersion concentration is? In other words, how does one determine the numerator in your hazard index, and how is -- are the local districts responsible for determining that those values for industrial sites and so they have to know what chemicals are being used? I don't understand how it all works, frankly.

DR. MARTY: The districts are required to obtain information on emissions from the facilities themselves that are under their purview. And there are cut points in terms of if the facility emits greater than 25 tons per year of criteria air pollutants than they were in the first phase. And there's the first phase, the second phase and the third

phase, basically go by size of the facility.

The districts generally have gone by which facilities have permits. So that's how they've tracked facilities down. They work with the facility operator to come up with the emission estimate, and they're responsible for making sure that the emissions estimates from each facility are accurate.

For a small district that's a small workload. For the South Coast Air District that's been a huge workload.

If the facility is required to conduct a risk assessment, and only those that fall within a certain category in the district's prioritization are actually required to write a risk assessment, for those facilities the risk assessment uses an air dispersion model to estimate what the ambient concentrations are in a grid surrounding the facility. That air dispersion model is reviewed by the local air district engineers and approved.

So and also the Air Resources Board is sometimes called in for some of the more -- the larger facilities that had to use fancier modeling.

So that's how the numerator is derived. It's basically based on estimates of emissions and air dispersion modeling.

CHAIRMAN FROINES: Further questions? Are there further questions for Melanie?

Okay. Thank you.

Can we take a ten-minute break before we switch over to pesticides.

(Thereupon a short recess was taken.)

CHAIRMAN FROINES: Everybody has a copy of the January 5th letter to Paul Helliker and Mike Kenny that transmitted the findings from our two -- our workshop that had two parts, one on prioritization and one on exposure estimation. And so you've had that before, so this is just give it to you again.

It seems to me that that process worked out very very well.

So the point of this part of the agenda is for a discussion to see if the panel has ideas for any subsequent workshop activities that we might consider to further improve our addressing of pesticide-related issues.

And I think that the other part of this would be for Elinor to work with DPR staff to further develop ideas and generate suggestions.

And I think what she's going to mention this morning is not a direct result of a conversation with DPR, but in a sense her own activities. But that one of the things we did was to ask Elinor to work with staff at DPR to develop workshop ideas so that we're all in sync on this.

She has some suggested ideas for future workshops,

the dates of which are to be determined.

And basically she thought that we never completely finished the issues surrounding organophosphates.

So, Elinor, why don't you talk about the things you've been thinking about?

DR. FANNING: Do you want to start directly with the organophosphate idea, or do you want to open for a more general discussion of more a brainstorming for future workshop topics? We can do it either way.

CHAIRMAN FROINES: Either way. Go ahead.

DR. FANNING: Okay. I had via Jim Behrmann for input before today's meeting from either panel members or agency staff for ideas for future workshops.

I think perhaps the time was a bit short, and I haven't heard a lot of feedback yet.

But we can have a general brainstorming session today in which we can identify topics that might be helpful to discuss in a workshop format. And I think the idea is if we can anticipate the issues, scientific issues, that are likely to arise in the evaluation of documents that are coming to the panel, then I can work to develop an agenda and identify some speakers who can address those topics and get to some consensus and clarification before we actually get into long snarls with various documents.

Maybe it is most effective if we begin with the

one idea that I came up with, and then we can take a minute afterward to develop this idea further and also see if there are other topics that people would like to suggest.

So this is the one-page outline that Peter should have, I believe, handed out to everybody.

Okay. What this is is essentially an idea to take a short session, probably just a couple of hours, to follow up on some of the recommendations that came out of our earlier workshops held in October in South San Francisco.

Specifically from workshop Part A on pesticide prioritization from October, the second recommendation from the panel is to consider a batched approach for listing of high priority or organophosphate pesticides.

And the idea there is to see if DPR would consider developing a document similar to what you're seeing for chronic RELs that would essentially address a number of the organophosphate pesticides in one document and thereby streamline the process of evaluation. Many of these pesticides have similar toxicological properties.

So I would envision -- this is just sort of brainstorming of my own, and I think it would be good after I go through it to see if DPR might have some comment on what they think would be most useful out of this.

But I envisioned beginning with DPR staff coming with a status report on the organophosphates, going through

which ones are their highest priority for assessment at this point, which have been monitored in California. And I believe the majority of the high-priority organophosphates, there is some monitoring data available.

Furthermore, there are toxicological and health effect assessments from US EPA, and we had a speaker come to our workshop to discuss those tolerance reassessment documents with us. So there are quite a bit of background data that may or may not be useful for the DPR assessment, and I'd have to get DPR to comment on that.

And after we began with an identification of which organophosphates might be useful to address in a batch, then I envision that we could go on and discuss some of the key toxicological issues with assessments to these pesticides, perhaps bringing in outside speakers if that is useful.

And the toxicological issues that came to my mind right off the bat, first are the issue that we've had several times before of cholinesterase inhibition. It's not clear to me whether it's completely resolved, how the panel and DPR want to handle evaluation of cholinesterase inhibition data, and whether it might be useful to develop a discussion to develop a standardized approach to those data. Most of these pesticides are cholinesterase inhibitors. So that would be the first of those issues.

We can talk about that a little bit more, what

specifically you'd like to see addressed, and then I can work to try to identify appropriate speakers for it.

Secondly, I identified metabolism and toxicokinetics as an area that might benefit from some workshop type discussion before preparation of a document. There's quite a bit of information on paraoxonases, enzyme in humans and interindividual variability due to polymorphisms in the gene for this enzyme, that may affect the population distribution of sensitivity to organophosphate pesticides.

So I had identified that as a potential area to bring in a speaker and have some discussion.

And the third toxicological issue that I have on this relates to a discussion that I believe has also come up with the panel before of acute and reversible health effects versus chronic delayed health effects and how those data would be treated in the risk assessment.

Item No. 3 would then progress to sort of a discussion of method, what type of format for a batched document would be most useful for the panel and most efficient for DPR to develop some discussion on how to, what type of outline would be most effective.

Then the final issue that I thought we may want to include is some discussion of whether or not it's useful to try to address co-exposure to multiple organophosphate

pesticides in this document.

We had some discussion of multiple pesticide exposure in our workshop. We had the follow-up session at Claremont where Randy Segawa from DPR presented some alternative ways of grouping pesticides. And one of his alternatives was in chemical family types such as organophosphates.

So we may want to develop that idea a bit further, but I believe it would require quite a bit of discussion about how to do an exposure assessment for mixed pesticides. We need to look into the feasibility issues there.

So that's a brief presentation of the idea that I had for that workshop.

And I'd be interested in hearing feedback whether people think it's useful, whether there are issues you particularly like to see. And I don't know if perhaps DPR might want to comment.

MR. GOSSELIN: Thank you, Elinor.

I thought this was a real good outline. It's consistent with the findings from the workshop from last fall and some of discussions we had. And I think even thinking about the discussion you just had with the OEHHA documents and how they've gone through a pretty lengthy process and batching of many many compounds for consideration, and given the parameters of what the law

allows us to do and what would meet the scientific expectations of 1807 could we do something similar. Because I think as a finding, grinding out single documents is kind of a long process. And if there's a more efficient means while maintaining a full scientific scrutiny of the pesticides we're dealing with, we should probably look into that, and I think this might be a good opportunity to do that, looking at the OPs.

Another cut on this is that we also have a list of HAPs listed toxic contaminants. Those are out there, some of which we do have risk assessments completed on, some of which because of their use or potential to get into air or other things that we don't have any activity on, but eventually we may have some air issues with them and should there be a means of us going through a similar process you went through with OEHHA of coming up with a summary document and getting RELs established for those compounds.

And almost as a sideline is this project we're working on with ARB, OEHHA and some other agencies down in Lompoc, that's going to expand this spring, we're going out and monitoring for upwards of 50 pesticides in a community.

CHAIRMAN FROINES: 15?

MR. GOSSELIN: 50.

CHAIRMAN FROINES: 5-0 or 1-5?

MR. GOSSELIN: 5-0.

The staffs from OEHHA, our staff and DHS and the county have gone through and using best professional judgment have come up with sort of preliminary RELs that would be used as screening levels for these numbers.

So this is almost getting into sort of the cutting edge where pesticide air exposures are getting to the communities, looking at multi-residues.

The big advent is going to be that there's going to be multi-residues screens developed for air monitoring that's going to allow us potentially to use these methods in various places, which is going to necessitate having some scientific notice to evaluate whether we need to take any mitigation measures.

But I think with this, whatever choice we make on going with OPs, which is a good one, or HAPs, or some other cut, I think looking at the document you've just gone through and approved is almost a template for us to try to emulate, would be a suggestion on how to go.

CHAIRMAN FROINES: When you say multi-residue screens, are you doing essentially micro-environmental monitoring to look at contamination of soil, contamination of water?

MR. GOSSELIN: The one down in Lompoc is strictly air.

CHAIRMAN FROINES: Air.

It's an interesting issue when you think about it. If you've identified 50 pesticides that are used in Lompoc that you can sample for, that gives us some sense of the scope of this problem we're dealing with. It would be interesting to see a protocol for what this is.

MR. GOSSELIN: Actually, one of the things we're interested in with this project and the protocol is having, and this was just discussed at the interagency panel, was having some external peer review of the work that staff had been doing, so that's real critical. And if that can be brought forward here to evaluate, at least the methodology on how the monitoring is designed and the thought process and screening levels, I think that would be real helpful.

CHAIRMAN FROINES: On the HAPs, you know what would be useful, it seems to me, would be to have Elinor work with your staff to look at the use patterns for the various HAPs, as well as the chemical structures for the HAPs. In other words, are there unifying elements that would help pick -- we were talking last night about compounds that contain chlorine and bromine, for example, as one structure issue. And but I don't know the pesticide HAPs, so it would be useful to do some background to look at structure activity issues and to look at use patterns.

DR. FANNING: Is there a sense of whether it would be -- I think this idea of looking at HAPs or looking at the

group of chemicals being monitored at Lompoc is very interesting, and is there a sense of whether we would want to focus on one of those issues first or the organophosphate groups, or which would be most useful?

MR. GOSSELIN: There are down in Lompoc it does capture a lot of OPs used in one of the screens.

DR. GLANTZ: Why did you pick Lompoc, just for curiosity?

MR. GOSSELIN: Given we only have the rest of today, I don't have all the time.

DR. GLANTZ: Can you give us, you know, the classic comic book explanation of why you picked Lompoc?

MR. GOSSELIN: They picked us. It was a community that had housing right next to agriculture in the Valley, and fairly small community, moderate size, fairly moderate size agriculture in an enclosed valley, right next to Vandenburg Air Force Base.

There was a lot of concern about various health concerns in the community and one of the concerns was some pesticide use. And one of the things that had not been done was very extensive or any pesticide monitoring of agriculture in that area.

So it became chicken and egg about which products about the 140 that are used there, what to monitor for and whether they had any direct bearing on the health effects.

And that sort of discussion went on for a while and then about three or more years ago we ended up forming an interagency work group with state scientists and brought in some local people to kind of craft out a consensus on what they would like to see.

That did go beyond pesticides. There was a silica plant that eventually shut down and they were having a lot of problems and a variety of other things.

And there's a big health survey going on also.

CHAIRMAN FROINES: But my sense is that we can follow that operation going on there, but it seems like that wouldn't be part of something we would do as a workshop unless -- it seems to me like the outline that you came up with for this makes more sense, at least from our standpoint.

MR. GOSSELIN: The cholinesterase policy probably be something very relevant and specific, that we've had sort of our paper written on. I think EPA has held at least one scientific advisory panel on that, with issue papers. I'm not sure if they have a report out yet.

DR. FANNING: They do have some kind of risk assessment approach to cholinesterase data.

MR. GOSSELIN: Right.

And some of the members that sat on the SAP could come out for that also.

DR. BYUS: I really like this outline for the organophosphate. Lot of these issues we dealt with and are very important. It's still not clear that -- I really think it would be an excellent idea to have a workshop on this, on the organophosphates. I don't know what the order would be, but it's certainly a pressing issue. There's many of them. And all of these issues, toxic mechanism, toxicokinetics, plasma versus red blood cell, versus brain, delayed neurotoxicity versus immediate, and also the carcinogenicity of these things is complicated. It's variable.

And then the multiple exposure issue, God only knows. I mean, I think I still say somewhere in food residue is some answer to that question, because at least you know that these were all applied at one point. If you work your way back from that, in addition from forward from how you've sprayed them, you can work your way backwards, because you know they're actually there.

So all of these things are very important and since there's a lot of organophosphates, I think just the science discussion would be very important to the panel.

DR. FANNING: Okay.

CHAIRMAN FROINES: I frankly think this issue, the more I read about pesticides, the more impressed I am with the tremendous challenge that we have, because the data we have to work with is so limited. We're constantly trying to

ask questions and there's no data because people do science for regulatory purposes rather than science for NIH.

And so you just don't have the kind of -- I mean, just look at the database on butadiene or perchlorethylene or asbestos or lead. I mean, it's thousands of papers.

And with pesticides, there's just a few papers and they're not in the peer-reviewed literature. Relatively few in the peer-reviewed literature.

We can try and look at all these issues, which I think is good, but part of the problem is what we have to work with is so small. I wish there was a way to stimulate more research on a lot of these issues, because I think we have a real limiting factor.

But having said this, I think there's a third issue that is a little different from what Elinor said, which is I take the issue of chronic health effects from OPs as being different than acute effects as being different than delayed neurotoxicity, and that is the long-term chronic neurological effects from organophosphates, irrespective of the delayed neuro effects is still an issue that is not well defined, I think. So that's another.

DR. FUCALORO: I'm a little unsure as to what we're supposed to be deciding here. This looks like basically, it seems to be some agreement, at least from those who spoke, that the document presented to us would be

a good working document for the next workshop, and I guess you come back with some modifications for our review, I guess through you, John.

CHAIRMAN FROINES: I think basically Elinor is doing her best at trying to get feedback from this panel and so she's dragging --

DR. FUCALORO: Well, it's such a well-thought-out document, it's hard for us to say other than it seems good and we should proceed. But actually you heard some comments.

DR. FANNING: Yes, the feedback is useful.

In addition, I had hoped to get a sense from Paul, from you, how important this issue was versus other issues that you may have in your minds, other questions, other possible workshop topics that you'd like to address.

What I'm hearing, I think, is that most people think this would be a good idea to go ahead with as our next workshop. Is that --

DR. KENNEDY: Unquestionably.

DR. FANNING: Okay.

CHAIRMAN FROINES: I think the other thing is it's important to get a lot of feedback input from DPR, because there are lots of scientific questions that they've been wrestling with for longer than this panel has and the panel becomes a place in which those questions can be aired and so

it's maybe it's useful to us then, as well as for panel deliberations.

DR. FANNING: Exactly. I anticipate that we'll work together closely and essentially have DPR staff identify and help sort of frame these issues in a more specific way. So we'll plan to work together on that.

DR. WITSCHI: You know, you comment about not so much science, this is science, may be true, but there used to be a very extant volume and it was called "Pesticides, a Study in Man." And it was edited by Jake Hayes, who has been dead for about seven, eight years or so. But I think we should make an effort, because to the best of my knowledge somebody is continuing this work, and that is for our purposes the first thing to look for to get information is what are the data out there about toxicities of pesticides as we can derive from man. And I would expect that much of the old information might actually still be valuable.

CHAIRMAN FROINES: That's true. There's been a consistent level of research.

DR. WITSCHI: Yes, yes.

CHAIRMAN FROINES: However --

DR. WITSCHI: I don't know, I think somebody has created this, but I'm not quite sure, but this could be found out.

CHAIRMAN FROINES: On MITC, the person who is most often quoted is Dr. Alexeeff. He has the most references, I think, of anybody. So we expect to hear from you today.

Thank you, Paul.

Thank you, Elinor.

I think we're finished on that.

DR. FANNING: Yeah. I think so. We'll work together and send something around with a more detailed proposal after we have worked it out and propose a date and see if you have input about speakers or want to help refine the agenda.

CHAIRMAN FROINES: I think that I'm interested in paraoxonase polymorphisms, but I think that you should try and keep the context clear, which is how does the paraoxonase polymorphism or other interindividual variability issues affect the risk assessment process. So it's not just simply an abstract scientific issue.

DR. FANNING: Sure. I think as I stated here, the idea is can the data on paraoxonase polymorphisms be used to perhaps adjust or at least provide a reality check on the use of default tenfold interindividual variable protection factor. Perhaps that would help bracket it a bit. One of the goals of discussing it is that very concrete risk assessment issue.

CHAIRMAN FROINES: One of the things we might hope

to come out of some of these things is questions that we can send to US EPA to say we need to know how many people in the population have this genetic change, and EPA should be funding work to find that out. I mean, in other words, it's not -- we don't necessarily have to see this as a totally internal process, because if we raise important scientific questions, then in fact those should go to a place like EPA for them to think about it. California tends to be ahead on this stuff to some extent, rather than behind.

DR. FANNING: Thank you.

CHAIRMAN FROINES: Peter and I, we're talking because we were -- Paul Blanc is doing his -- is on the wards at this point, so he can only be here for an hour or two, because he's actually seeing patients. And he played a fairly strong role in the last meeting on MITC, so we were hoping to have him here, but I don't think he can be here until 12:30 or 1:00, so I think what we should probably do is start with MITC, take a lunch break and then finish up. So we don't sort of delay everything just to get one person to the meeting.

So, Paul, let's do MITC.

MR. GOSSELIN: Staff are getting ready to come up.

And, thanks.

This is continuation of the discussion on the MITC document.

What we had planned on doing, instead of going back over the entire document, is do a couple things.

One, just summarize the relevant issues for the toxic side in the document and also kind of focus on the issues. I think Elinor summarized some key issues that were raised from the last meeting and a couple of the other ones that have been raised since that time, and also talk about sort of the status of where we are on looking at what exposures are occurring out there from the data we have had and data we got in December.

And also I think Tom is going to look at adjustments to, possible adjustments, to some of the longer-term exposures based upon new use data.

A couple things on the importance of this document are twofold, beyond just the consideration of listing MITC as a toxic air contaminant. Your review's also going to be used by us as our external peer review to help support formal rulemaking that may need to occur based upon the issues, the scientific issues raised in this document. So the full review and the consideration of these issues are real critical, not only for the listing process, but also for our regulatory process.

With that, and I know there's a lot of issues, I'll turn it over to Andy Rubin.

CHAIRMAN FROINES: Just one comment.

Remember at the last meeting in November in Claremont, we only got about halfway through, so we haven't really dealt with the risk characterization and risk assessment issue and I think we did some work on exposure, but not enough, I think.

And why don't I stop there.

But the issue of clearly you've seen what Elinor has raised, but one of the major issues that we need to decide upon is what goes into our -- what goes into our findings, which will then go to Paul Helliker, and in that regard this becomes -- I just want to say this for the panel, because this is an extremely complicated chemical.

We have metam-sodium, which has its own toxicologic properties. We have MITC, which has its own toxicologic properties. We have methyl isocyanate, which has very significant toxicologic properties, as everybody knows, because of Bhopal. We have carbon disulfide, and we have hydrogen sulfide, just to list the ones I can think of off the top of my head. Plus I have no doubt that there are others. This is a very reactive compound, series of compounds.

So that we're really dealing with a quite complex series of compounds and their breakdown products, and so the panel is going to have to address that particular issue when we send our findings forward.

This is not -- we're not dealing with a chemical here. We're dealing with at least five. And so it's important for us to think about that as we think about how we transmit this, whatever we intend to transmit.

DR. RUBIN: My name is Andy Rubin, and I'm going to be reviewing the health aspects of the MITC document.

In view of the fact, as Dr. Froines mentioned, we did start the discussion of the toxicity of MITC at the last meeting on November 17th, and I gave a fairly complete summary of MITC's toxicity profile, I thought what I would do today was instead of spending a whole hour discussing it, the toxic profile again, I would quickly recap what we discussed there to get us all on the same ground, because I know at least one or two members of the panel weren't there.

And then probably the most important slide that I'll show you is to introduce you to some of these difficult, what I call discussion decision points with this chemical, some of which have already been mentioned now by Dr. Froines.

Then I'm going to take up probably -- well, the issue that we were discussing back on November 17th when we had to stop, and an issue that Dr. Witschi has encouraged me to look at in a little more detail, and that is whether MITC itself could possibly be considered an oncogen, and I'm going to take a detailed look at that, at that particular

study.

Then we'll go through the margin of exposure calculations, the reference exposure calculations, hopefully we can do that fairly quickly.

And then mention some of the toxicity of some of the other metam breakdown products, in particular methyl isocyanate, MIC, and hydrogen sulfide.

And then wrap it up. Okay.

By way of recap, if you remember, MITC reached the public consciousness back in 1991, July, when 19.5 thousand gallons of 32.7 percent metam-sodium were spilled in the Sacramento River, causing a release of gaseous MITC and exposure of many people in the local area, particularly around Dunsmuir, to irritating concentrations of MITC.

The conclusions of the several papers that came out of the epidemiology on that spill were that despite the fact there were no good measurements for two or three days after the spill, the estimated levels of MITC in the Dunsmuir area, the high estimates, ranged between 140 and 1600 ppb.

These levels, whatever they are, sent 705 people to the hospital complaining of eye irritation, nausea, throat irritation, with one -- with a possible long-term sequela of condition known as RADS, or reactive airway dysfunction syndrome, a kind of chemical asthma.

In setting or beginning to set the acute levels, the acute endpoint levels, we looked to a human eye irritation study. This was a study conducted at UC Davis Medical Center, using about 70 individuals.

We came up with a NOEL value of 220 ppb, a LOEL value of 800 PPB.

Interestingly, this turns out to be right in the level, these two values, right in the area of the estimated values of MITC in the Dunsmuir area after the spill.

CHAIRMAN FROINES: Can I ask a question about that?

DR. RUBIN: Yeah.

CHAIRMAN FROINES: I'd like to come back to the RADS later, but in your document you say the following. Interestingly, complaints of abdominal pain, diarrhea, rash and cough continued after ambient levels had hit below the published reference level of .4 parts per million, recalculated to .5 parts per million in Alexeeff, et al, 1994.

That report by George, I haven't read, and my question is that would indicate a LOEL of about .5, compared to your NOEL of about 220, which you select. If you take a LOEL of .5, that gets you down to a NOEL of about .05, so there's a fourfold difference between what your document says George says, and he may want to comment on this, and

this value that you select.

So I couldn't -- the Alexeeff document seems to suggest significant complaints, abdominal pain, diarrhea, rash and cough, at levels of .5 parts per billion.

DR. RUBIN: Parts per million.

CHAIRMAN FROINES: Yeah. As opposed to your NOEL of 220 parts per billion.

So there's obviously in your own document a major discrepancy.

DR. ALEXEEFF: George Alexeeff with OEHHA.

Actually I would probably agree with Andy Rubin on his assessment of that, because what you said is correct, in terms of .5, .4 parts her billion, and having those effects. However, the exposure occurred over several days. So actually we have a longer exposure than this particular study conducted. Okay.

So there is one is the length of the exposure.

The other thing is the issue that in the actual incident that occurred, people were possibly exposed to a higher concentration at first and then a lower concentration. So there's that whole exposure, it wasn't .4, .5 over two or three days, it was some higher concentration and then a lower concentration.

Then the other thing points again to your previous comment that the issue of are we talking about exposure to

MITC or metam-sodium breakdown products. And those are two different questions.

And what happened in the Dunsmuir incident was exposure to metam-sodium breakdown products, of which we think MITC is the primary one, but how do those other ones interact. And that's another question there.

So this study here is strictly MITC.

So I think it is all consistent, but I think it also shows the variability that we have on some of these questions, exposure time, the other things that are in metam-sodium breakdown products and how do they interact. The issue that this particular exposure study was eye irritation only with an eye mask versus whole body exposure.

But I think, surprisingly, is actually to me I see this as consistent, as opposed to really a big discrepancy, but it just points out the variability in responses.

And also you can look at that issue as well as the variability aspects where we have a population exposure versus, I forget the individuals, the college students that were involved in this study.

DR. KENNEDY: You're also looking at physiologic manifestations of possible antecedent injury, which can come after the fact.

CHAIRMAN FROINES: Now, I want to, I really do want to emphasize for this panel to be thinking about what

are we taking up here. Are we taking up metam-sodium, which is used at 15 million pounds a year in California, or are we taking up MITC, which is not used at all, essentially. So we have zero versus 15 million pounds.

And what we send forward to Paul Helliker, I think should reflect the issue, which -- and I'll leave it at that.

But, George --

DR. GLANTZ: Can I ask a question about that? And that is does MITC come from anything but metam-sodium in any amount? And I remember I think the document addressed that, but I can't remember what it said.

DR. RUBIN: There's, to my knowledge, there's one other pesticide that generates MITC upon breakdown and that's dazomet.

DR. GLANTZ: That's right. And that's in the document.

DR. RUBIN: Yeah. That's in the document.

CHAIRMAN FROINES: Very low.

DR. RUBIN: Very low compared to the very high levels of metam that are used.

MR. GOSSELIN: John, if I can clarify. It's true MITC as an active ingredient is hardly used and is inconsequential across the state. But the risk numbers and this assessment, the way we're going to use it in regulating

is to look at the sources of MITC principally from metam-sodium. So this is actually going to be used by us to regulate metam-sodium use, because of the principal effect of its breakdown products, MITC.

CHAIRMAN FROINES: We're going to have to come back to that. This is clearly the fundamental issue for this panel to address. There's a high ridicule value of listing a chemical that's not used, and ignoring a chemical with 15 million pounds, and so we'll come back to that.

DR. GLANTZ: Just on that point, I mean, given what Paul said, I mean couldn't this issue be, to some extent, resolved by just changing the title of the document to say metam-sodium and the other compound, what was the other one?

DR. RUBIN: Dazomet.

DR. GLANTZ: Dazomet and MITC.

CHAIRMAN FROINES: Well, I think we can -- I would like, my strategy is I would like us to, if we can, to not send the document back for multiple rewrites, so it never -- the next time it emerges we'll all be retired. I'd like to try and see, this is an important chemical, a really important chemical. It would be nice to move the document forward, but we have to be sure in our findings and in terms of how we title the document, and all we can do is recommend is that we address this issue.

DR. FUCALORO: Well, I'm not sure if we have legal constraints or just a matter of title. I'm not sure about the legal constraints, but it seems to me we're looking at MITC from all sources, whether it's directly applied from metam-sodium or the other one that I can't recall, or in the future some other brand name comes up which produces MITC at a very high concentration. We certainly want this document to cover that, because MITC is toxicological, and so it would, barring legal constraints, you can say MITC from all its sources.

Is that fair enough? I don't know.

CHAIRMAN FROINES: Well, no, that's not quite right.

DR. FUCALORO: Okay.

CHAIRMAN FROINES: As we go further into, and this is why we should go ahead and not get into this discussion right now, because the toxicity of MIC is so profound --

DR. FUCALORO: That's where really it really comes from, yeah.

CHAIRMAN FROINES: We're going to have to deal with that in the context of this too. So MITC breaks down to MIC -- so I'll just -- I still want to follow up George's comment, which I never did.

At some level we set a NOEL of 220. It would be nice, however, to see some language in the document that

said -- but given that the Nesterova work and given the Alexeeff work, there could be a NOEL that's much lower. I mean, the trouble is we set these NOELs as though they are in stone and in fact there's a hugh uncertainty in these values, as we know. They're defined by, as we all know, from reading Kenny Krump's paper, by the dose choices that people make in setting up the experiments.

So it's worth thinking about. It seems to me that we think about sometimes putting in ranges of potential NOELs, as well as -- and then perhaps do your calculation on the MOE, looking at some values. In other words, there are -- it doesn't have to be quite so rigid.

Go ahead.

DR. RUBIN: I might add to that the other aspect that is very determining in NOEL is the endpoint, and when Russell and Rush, who did the study at UC Davis, chose eye irritation using a set of goggles, that they had made essentially the implicit choice not to expose the subjects via the lungs.

So we have -- there's a major uncertainty here that perhaps lung effects could occur at lower MITC levels, not even speaking of any other breakdown products.

DR. WITSCHI: Just in interest of precision, I do not think that it was eye irritation. I think it was just blinking, which is not the same thing. And if you sell this

study as having shown eye irritation, you open yourself up to criticism, because some people question whether increased blinking rate is an adverse health effect.

DR. RUBIN: Right. It was increased blink rate, as well as subjective sense of eye irritation. In other words, people were blinking harder and marking a little bit higher on the scale as to how well they felt, how well their eyes felt in relation to a midpoint of how would you feel if you were cutting an onion.

DR. WITSCHI: I know. But that's not quite eye irritation as people would look for into these kinds of things.

DR. RUBIN: Okay. Moving on to perhaps even more troublesome area, which we discussed in detail last time, the setting of a subchronic inhalation level at one ppm based on effects measured at ten PPM in rats, at 12- to 13-week rat inhalation study.

Here what we're looking at are systemic effects, a decrease in weight gain, a decrease -- or an increase in water consumption, and decrease in serum protein, that might be argued as fairly marginal. But in the absence of any other data on subchronic or chronic exposures to MITC via the air, we felt that we had to rely on this study and these endpoints.

And I covered these in the last meeting.

Chronic effects will -- this issue will take more significance when we have the chronic exposure values. There are of course chronic effects of exposure to MITC. We have no inhalation exposure, which is where the primary human exposure is going to come from. There are fairly serious effects in the dog, vomiting, very pronounced toxicity vomiting, salivation, liquid feces, et cetera.

But I want to come back to that when we have chronic exposure data.

Next slide.

This I think will accent what Dr. Froines has said. There are a number of catch points in this risk assessment that we've struggled very hard with, we've made some conditional decisions and we're interested in the view of the panel on these issues.

The first, the use of the Russell Rush human eye irritation study, the preferable use of that, over the Nesterova cat study to establish an acute endpoint NOEL. That we discussed last time.

Number two, we also discussed last time the use of the rat 12- to 13-week inhalation study to establish the subchronic endpoint NOEL, were the endpoints serious enough to base a NOEL and LOEL determination on.

Number three, this issue came up from Dr. Witschi in the last session, is MITC itself an oncogen, and I'm

going to present that data today, and how we're looking at that. And I'm actually going -- this is one area where there actually is some change in our thinking from the document that you have in your hands.

Number four, this is a big one, metam and MITC have different toxicologic profiles. Metam, unlike MITC, is a pretty frank carcinogen, causes angiosarcomas in male mice, hemangioma sarcomas in male rats. They're related tumors.

It is also an embryotoxic and clastogenic, none of which we see in any clear way with MITC.

How do we handle this?

The way I've handled it up to this point is simply to include the metam risk assessment as an addendum to this document.

I've also got a summary of the metam's toxicologic properties in the MITC document.

But we're definitely interested in what the panel thinks about this issue.

Then some typical risk assessment conundrums.

If we're going to calculate chronic MOEs, do we use a subchronic inhalation study, which we have, or do we use chronic oral data?

Number six, use of a tenfold default uncertainty factor to establish the chronic REL for MITC from the

subchronic data.

It's been argued that perhaps we should be using a threefold uncertainty factor, for instance.

And then number seven, the toxicologic implications of other degradation of products.

These are the big issues.

Okay. The issue of MITC's possible oncogenicity came up in the last session. I had a summary slide at that time that expressed the neoplastic situation in rats that had been exposed, these are CD Sprague-Dawley rats that had been exposed to MITC through the drinking water. I had expressed it at that time in terms of benign and malignant tumors.

Upon going -- basically I'm going back to the study and reviewing the study in detail, we decided that it's more helpful to look at the actual histological tumor type, instead of just classifying as the registrants or as the contract lab did, by whether they were supposedly benign or not.

This study the rats were exposed to zero, 2, 10 or 50 PPM MITC in the drinking water. At the end of two years the survivors were sacrificed. Most of the animals that died, died during the second year.

What caught our attention in this study was an apparent rise in multiple benign tumors of the mammary

gland.

When we went back and looked in detail at the path report, which is quite voluminous on this study, we found that almost all of those multiple benign tumors were fibroadenomas. Fibroadenomas occur in Sprague-Dawley rats at levels as high as 50 percent, and in this study as high as 70 percent. So this is a tumor type that is pretty darn common even in untreated animals.

A fibroadenoma is a considered a, quote, "benign," to use a very non-benign term, a benign tumor by all pathologists. However, it has the capacity to progress either to carcinoma, which would be epithelial in nature, or sarcoma in rare instances.

I think most pathologists take fibroadenomas seriously. It has the capability of developing into a malignant cancer.

What sort of raised our eyebrows on this study was the incidence rate shown at the very top.

Something -- I don't know about operating this. Maybe it's too bright in here.

What we see in this study is a 23 percent incidence rate in the controls, rising to 40 percent at 2, 44 percent and 47 percent in the dosed animals. A Fisher pair wise comparison at the high dose compared to the control comes out with a P value of .054. This raised our

eyebrows.

I don't pretend to be a statistician, but when I see a P value that close to .05, it's interesting.

What I went therefore and did was classify all the related tumors that I could find.

DR. GLANTZ: What's the C-A?

DR. RUBIN: That's a Cochran Armitage trend test.

DR. GLANTZ: You say greater than .05, was that like that .051?

DR. RUBIN: In those tests we come up with Z values and it says come up with a Z value above something, it's greater, it's greater than .05, and I hope I don't have to comment on that any more.

DR. GLANTZ: Don't happen to remember what the Z value was?

DR. RUBIN: They're incredibility low in all of these.

DR. GLANTZ: You mean the Z's are like around zero?

DR. RUBIN: Or less than zero. They come out negative.

What that points out is that we can't see any obvious dose relation with this effect.

DR. GLANTZ: Well, it could be. I mean, you don't want to get carried away with small numbers, although those

aren't really small numbers.

First of all, .054 is close enough to .05 to bother me, and I do know something about it.

But the interpretation that I would put on that would be to say that it looks like you get an effect at very low doses and then it tends to saturate, which may be why you're not seeing a trend effect, but it may be that you've still got -- if you get any of this stuff it tends to be bad, and then maybe there's something in there saturating or something.

DR. RUBIN: Yeah.

DR. WITSCHI: These are endocrinic-dependent tumors, so your point is well taken.

DR. FRIEDMAN: It might helpful to see the actual P value rather than just .05. If it's a .06 we'd feel a lot different about it than if it was .5.

DR. RUBIN: I think the way to do it would be to put the Z value on this, but I'll go back and look at that and talk to --

DR. GLANTZ: It might be interesting to just pull all of your -- to take zero and everything else and to just pool them.

DR. RUBIN: Right.

DR. GLANTZ: And, you know, and at that point I bet you would get a pretty significant effect of exposed

versus unexposed.

CHAIRMAN FROINES: Well, there's a couple of other comments I'll make since you did that.

The second date, they clearly have small numbers here. We don't like 20 animals.

DR. WITSCHI: Group of 50.

CHAIRMAN FROINES: This is surviving. In my laboratory we have a hard time picking up cancers in dead animals, animals that are found dead. So there's that problem. So the numbers are small.

The other thing is that the animals clearly didn't like the taste of the water, and so that there's going to be a fair degree of variability, or at least uncertainty, in the amount of water that they actually got in.

So when you look at this 40 percent, 44 percent and 47 percent, it's not clear whether the mice, the rats, at 50 parts per million didn't hate the drink taste so much that they weren't drinking as much water and therefore their dose was lower. So there could be some simply dose-related issues at the three dose levels, given the taste of the water.

In our arsenic work right now we have to work our tails off to get the animals to drink the water. They don't like the taste of the arsenic. And this is clearly the same kind of phenomenon, so that the trend test, given the

circumstances of the study, I think one has to be careful overinterpreting that.

DR. RUBIN: Can I respond to that?

CHAIRMAN FROINES: Sure.

DR. RUBIN: I calculated the statistical values based on the calculated intake of MITC based on the observed water intake. It is very true that any time you put metam or MITC into the water the rats stay away from it. They don't like it. It smells like a rotten egg. However, we do have water consumption values here, so we do have MITC intakes.

CHAIRMAN FROINES: Well, I agree. And in the experiments that we're doing currently right now on 400 animals and 60 animals per test group, we are collecting water data and the animals knock the water -- they don't like the water, so they knock the bottle, they do all sorts of things.

So when you actually do this for a living, you have to have some humility about these water intake numbers that you get.

DR. FRIEDMAN: I'm confused now, because what you're showing across the top is concentration. It doesn't show the total intakes. So how do we know that that's the total intake?

DR. RUBIN: It's in the document.

DR. FRIEDMAN: It isn't the concentration, you're looking at the total amount consumed?

DR. RUBIN: What we're looking at here is the concentration in water in PPM. We make a calculation and the register -- the contract lab also makes a calculation of the amount of MITC that the animals actually consumed, based on the amount of water that they drank.

So those figures are the relevant figures for calculating any statistical values, recognizing that there is a big variation in the amount of water intake even within the same dose group.

DR. FRIEDMAN: But it would be helpful to see a table like that based on intake. Do you have those data?

DR. RUBIN: I have them, but I don't have a slide on them.

DR. FRIEDMAN: Do they show similar finding with sort of the threshold and then leveling off or what?

DR. RUBIN: That's what they show. I mean, I'm not sure what you're getting at, but the intakes do vary, I'd say 20-fold. The intakes vary, the mean intakes vary 20-fold from the lowest to the highest dose.

So it's not terribly skewed to say just present the concentrations, although I would be quite willing to.

DR. FRIEDMAN: The intake was fairly similar across those three?

DR. RUBIN: Yes. But they're big big --

CHAIRMAN FROINES: Big concentration.

DR. RUBIN: Big.

CHAIRMAN FROINES: And therefore the data is probably skewed, so some animals are going to be having a much higher dose than others or a much lower dose than others.

DR. BYUS: Within a group, you're saying?

CHAIRMAN FROINES: Yeah.

So all I'm saying is we need to interpret this data with some caution where you have obvious evidence that the animals had difficulty drinking the test chemicals, that's all.

DR. FRIEDMAN: Another point is that we're focusing on the multiple tumors on the top line, but the second row shows singles where there seems to be no effect at all. I'm a little bit confused as to how to interpret all this.

CHAIRMAN FROINES: Can you say something about that? I don't understand this focus on single tumors. I don't understand the relevance of it.

Do you, Peter?

DR. WITSCHI: No. You can have one tumor or seven tumors. Look at tumor-bearing animals, not the number of tumors.

DR. RUBIN: This is tumor-bearing animals.

DR. WITSCHI: What's the difference between the rat that has one tumor or three tumors or four tumors?

DR. RUBIN: I made that division because partly because the division is made in the data itself. The way this experiment is done this is quite interesting. The pathologist comes along and he sees a big lump in the animal. These fibroadenomas are huge. And while there's one lump, there's a single adenoma. If there are two, it's multiple.

The reason I expressed it here was I thought that it might provide -- the reason I went to look at it was that I thought that single fibroadenomas if they were being stimulated by MITC would also show an increase.

Perhaps it's irrelevant.

CHAIRMAN FROINES: I would draw the conclusion, I'd say the more potent, the greater the dose, the more tumors you're likely to see.

DR. WITSCHI: You're right. There are certain systems where tumor multiplicity is really an index of carcinogenic potency. And in this case I really do -- I do not see any reason to separate the animals in the single ones.

DR. RUBIN: They're all added up.

DR. WITSCHI: If you look at the bottom line,

that's very close. If you just add up the tumor-bearing animals, first of all, regardless of whether it's benign or malignant, I think that when we in science and judgment in risk assessment there's a statement that you really should not make a difference between benign tumors or malignant tumors in evaluating bioassays, because uncontrolled growth is uncontrolled growth. And that's where I come from. This is for animals.

And then if you really look at the bottom line, that was my point, the ones which have been exposed to have more.

Now, you also brought in the historical background. But, see, there's one thing we do not know. Does a carcinogenic treatment increase tumors proportional to the number of spontaneous tumors or does it add tumors?

In other words, if you had a background of ten and you have 20 tumors or an incidence of 20, does this mean the incidence was doubled or if you would have only the percent incidence you would have 11 percent in the treated ones. You do not know what is the proportion to the background or something that's being added.

And again we're looking at this from a frankly from a conservative standpoint.

DR. RUBIN: Yeah. Yeah. I'm well aware of that and I've --

DR. WITSCHI: Then the other one, this seems to be a tricky compound, because if you look at the hemangiosarcomas in the metam and your rats have exactly the same phenomenon, you have the paradoxic one, you have a dose response and you have a small increase. Knowing the metam, you actually added the mouse study showed a carcinogenic response, therefore you said the data in the rats mean it's a carcinogen, but if you look at table 9 in your metam and compare it with the human data, they're as good or as lousy as they are --

DR. RUBIN: Oh, yeah. This is very real-world data.

DR. FRIEDMAN: If we take then the tumor-bearing animals are the criterion, the best criterion to use, then the findings there in the third row are not significant. That's bottom line, the multiple plus single.

CHAIRMAN FROINES: Which one are you at?

DR. RUBIN: In the third row from the top, right?

DR. FRIEDMAN: Yes.

DR. RUBIN: When you add all animals bearing fibroadenomas, at least fibroadenomas that can be palpated, you don't get a statistically significant response, although you do still get a slightly higher response in the dose downs.

DR. FUCALORO: If I understand Hanspeter, you look

at the bottom line, which contains not only the benign, but the malignant, and the same conclusions I think statistically at least from my eye, there's not much response.

DR. KENNEDY: Has this been done, Hanspeter, in a strain that does not produce spontaneous fibroadenomas?

DR. WITSCHI: What?

DR. KENNEDY: Has a comparable study been done on a strain of rat that does not have spontaneous fibroadenomas?

DR. WITSCHI: I don't think so, no.

DR. KENNEDY: Clearly could be a hormonal effect rather than a direct effect. Very interesting to evaluate it. And one can actually make an argument that the vascular tumors are also at least in part hormonally mediated, because it's angiosarcomas of the breast are rare, but not vanishing, where in humans it occasionally will have receptor-specific hormonal --

DR. WITSCHI: Your point is very well taken, but then we have to answer that question, we have to go into the mechanisms. They're facing the same situation as we are facing with certain steroid tumors, where we do get more lumps, but it's clearly a non-genotoxic mechanism and it's the MITC only to answer this question.

DR. RUBIN: This is the data for MITC right here.

DR. WITSCHI: Yes, I know.

DR. BYUS: I have one question. There were really 50 animals per group, 26 were live at the end?

DR. RUBIN: There are 60 animals per group, yeah.

DR. BYUS: So why are they all dying? What are they dying of? I mean even in the control, the control is zero, you're saying to me that there are 60 animals in the group and only 26 of them lived to the end of the study?

DR. RUBIN: That's right.

DR. BYUS: In my opinion that makes this study virtually useless. Why are the animals dying? You don't want more than half your animals dying before the end of the study of something that's not related to the cancer. I mean, it becomes -- it's a worthless study. You shouldn't even be, perhaps I'm exaggerating because I didn't read the study, but the last thing you want is animals dying. The fewer the better, unless they're dying of the cancer, in which case you make -- that pathologist makes that diagnosis.

DR. RUBIN: Right.

DR. BYUS: If the animals happen to die during the study, you autopsy them immediately and hopefully determine what the cause of death was and hopefully it's because of the cancer that you're looking for and not something else.

If it's something else, you try to make a

diagnosis if you can.

But I mean to have that many animals dying, this skews all the data completely. You can't get any incidence values that are meaningful out of a study where more than half are dying.

CHAIRMAN FROINES: Well, the problem is that when they do die, unless you can pick them up right when they die, you know, everything turns liquid in their insides and so you can't really do pathology. You can find big tumors, but you can't do as precise a pathology as you could do if you sacrificed them.

So you really lose data with these animals that are dying from virus infections or whatever is causing it.

DR. BYUS: It skews the value --

CHAIRMAN FROINES: They are down to a point where -- I have talked at great length with the National Institute of Environmental Health Sciences precisely about this issue, because my current mice are in 16 months and they're dying off, and I wanted to figure out how to deal with this issue.

They said we will look at the data down to about 20 animals, but below that we won't use it.

So that these numbers here are really on the border. And so one has to worry about interpretation. So it seems to me that one can say that there are some trends

here, but my concern is that the overanalyzed data, like looking at single versus multiple, it doesn't help. It doesn't tell you anything when you're all finished.

And I'm speaking not now as a scientific reviewer, but as somebody who actually does this in the lab, as Peter does, and these are issues that are real, not abstract.

DR. BYUS: I'm still saying if your mice are dying of viruses or whatever, something not related to the chemical, and they have this high of percentage that are dying, it skews -- the data becomes meaningless. I do the studies too. And if my animals are dying in this high amount I cancel the study and conclude it, end it. You don't know why they're dying.

CHAIRMAN FROINES: You must have much more money.

DR. BYUS: I have a very good animal facility.

DR. FRIEDMAN: In human studies we deal with this all the time.

DR. BYUS: But not in animal studies where you're designing an experiment to assess the carcinogen incidence, incidence in a lifetime and you're doing lifetime studies, which are hard to do. The last thing you want are the animals dying of some other cause other than your chemicals.

DR. FRIEDMAN: If you do, it would --

DR. BYUS: They might have gotten the cancer, they might have not. They died early from a virus that could

have gone on to develop a tumor. You really don't know.

DR. FRIEDMAN: There are statistical methods for dealing with this when you -- they're censored at the point that they die and you just take into account the time of follow-up. We have in human studies we have life table analysis and so on to deal with that.

DR. BYUS: When you are doing large numbers, but small numbers you cannot do it.

DR. FRIEDMAN: If you get too small a sample, then you're in trouble, or if you require that they all live to a certain point, then I see that you're in trouble.

CHAIRMAN FROINES: Can I ask you --

DR. GLANTZ: Actually, though, I'm sitting here doing some arithmetic on all your numbers. But Gary raises an interesting question, why don't you do a life table on these animals, because you can, if they've lived to a certain point and then died from an unrelated cause, that's exactly what a life table analysis is for, is to take advantage of the fact that you've been able to follow them up to some point and --

DR. BYUS: The beauty of doing an animal experiment is it's a controlled experiment. You're designing it to get rid of all these variables and if you don't get rid of the variables your experiment isn't valid.

DR. GLANTZ: Right. But if the animal dies of a

viral infection or some unrelated thing, you can still take advantage of the fact that --

DR. BYUS: A small number. Out of a group of 60 you probably would not want more than five die from viruses.

CHAIRMAN FROINES: No, no.

DR. BYUS: That's all I ever had.

CHAIRMAN FROINES: No.

DR. BYUS: Many lifetime --

DR. WITSCHI: I would have to take issue with what you said. In a study like this, you do not necessarily expect the animals to die from your carcinogen, because it makes a difference if the animals dies from the tumor or whether it dies with the tumor. If it dies with the tumor, that's --

DR. BYUS: The zero group is not getting any chemicals and two-thirds of the animals are dying. That's not good.

DR. WITSCHI: We don't know if they were dying --

DR. BYUS: It doesn't matter when they died, they're supposed to live a lifetime of two years.

DR. WITSCHI: No, no. This table doesn't tell you whether the ones who died before terminal sacrifice died a couple of weeks or a couple of months before.

CHAIRMAN FROINES: Anyway, this is the only study we have.

DR. RUBIN: Right.

CHAIRMAN FROINES: We don't follow your point of view and throw it out. You have to use it for whatever we can get out of it and the life table analysis is the classic way that one would evaluate data where you have changing mortality.

And so that's that. So I don't think we have another choice.

And I think that there are a couple of issues that we'll talk about a little bit later. I mean, one should look at this data precisely because we have metam-sodium data.

One has to be thinking about the question of is the MITC the carcinogen, since it is a primary breakdown product, how does its carcinogenicity compare to the metam-sodium carcinogenicity and that's a question that requires some analysis.

But I don't understand what the decedents are.

DR. RUBIN: These are the animals that died, most of which died in the second year.

CHAIRMAN FROINES: You're right. I certainly wouldn't include them.

DR. RUBIN: No. You can tell, the fibroadenomas are much lower.

CHAIRMAN FROINES: Of course they're dying before

you want the study is over, so you can't look at them in terms of any kind of trends. You have to be very lucky or have a very powerful carcinogen.

DR. WITSCHI: What really we should do is look at compared when they died off with other studies. In very few studies you get your 60 animals to the ripe age of two years. It does make a difference if they died between 18 months or 24 months or if they died between six and ten months.

DR. RUBIN: Most of the animals died around the 90-week level, between 18 and 24 months.

I took this, without knowing about this strain in particular, the CD Sprague-Dawley, I took this as the normative life span of these animals and perhaps there was something particularly morbid about their treatment, but I thought it was the normative life span. Many of them were dying around 90 weeks, 95 weeks, 98 weeks.

DR. WITSCHI: That's pretty far into the experiment.

DR. RUBIN: The experiment is 104 weeks long.

DR. FUCALORO: Can I ask a question? Is it indeed a fact that they only deal with different types of rats and you have no controlled experiments on them, but this would imply that in the lifetime of this particular rat 50 percent of them experienced tumors?

DR. RUBIN: That's right. Spontaneous fibroadenomas.

DR. FUCALORO: And that's not surprising results to people who know --

DR. RUBIN: That is not surprising at all. Leslie Folts in his book "Neoplastic Development," mentions the Sprague-Dawley rat in particular, and says 50 percent of Sprague -- as much as 50 percent of Sprague-Dawley rats develop fibroadenomas.

It is my personal position, given the way this pathology is done in this experiment, just by taking lumps and then slicing the lump and doing the histology that way, I think that it's quite possible that every animal in this study that survived had fibroadenomas.

The ones that are counted, the ones that are counted are the ones that grew big enough to make lumps. If you actually look at the mammary histopathology, you occasionally -- and the way they do it in a study like this is just take some normal mammary gland and do a section, boom. They don't -- these are not step sectioned, they are not quantitative histopathology. And occasionally you see a normal appearing piece of mammary gland showing a fibroadenoma. If you took -- how many mammary glands do rats have, eight or ten or something? If you did quantitative sectioning, my guess is you would see

fibroadenomas in every one of them.

CHAIRMAN FROINES: Let me make --

DR. FRIEDMAN: It's not a very good control group then, because hundred percent are going to get it. What chemical would make a difference --

DR. BYUS: If they live along enough.

CHAIRMAN FROINES: Here's the thing. You end up with 6 out of 26 and can you combine multiple fibroadenomas and carcinomas, you get 6 out of 26, 9 out of 20, 16 out of 32, and 15 out of 32, and clearly there's going to be some statistical significance at those higher values.

Now, everybody agrees this is a lousy study. I think no matter what your point of view we can all agree to that, this was not as well conducted as one would like.

But we have to be careful to reward the industry for doing a lousy study. I mean if somebody is going to do a poor study and they have a vested interest, one, it doesn't necessarily test their integrity, but one has to say we don't want to reward that poor study.

So it seems to me that you have to take the data at some level on its face value, and say we don't know whether there is a problem, but there could be.

It seems to me that it's clearly not black and white. It's clearly gray. It seems to me there may be something here and but we don't really know.

But it doesn't mean that we conclude the opposite, that there isn't something. I think that would be an under-interpretation of the study.

DR. FUCALORO: Yeah. But also an interpretation is that MITC extends the life of the rats, if you look at some of these. So one has to wonder.

CHAIRMAN FROINES: But there are people, lot of people who do studies like this, like Maltoni, who doesn't sacrifice the animals at 104 weeks, but actually carries the studies out until a later date when the animals are dying, and actually that's where you actually tend to find more tumors when you go beyond the 104 week, two-year period. So one could argue that the danger of a shortened study, of course, is that you don't see the cancers, because cancer is a late-stage event. You pick 104 weeks because that's when they're old. It's like picking -- it's like waiting until we're 65 and seeing if we have cancer cells. We might have. We will have more by the time we're 80. So we do need to be careful about our interpretations.

DR. FRIEDMAN: Can I add one?

Stan probably could figure this better than I can, but when I look at this Fisher test you did on the very bottom line that gave you .007.

DR. RUBIN: Yeah.

DR. FRIEDMAN: 36 over 60, compared to --

DR. RUBIN: No. The way I took the very highest incident rate, the one that's underlined there, 30 over 60 versus 44 over 60.

DR. FRIEDMAN: I don't think that's quite cricket to look at the data and then pick the one you wanted to test.

DR. RUBIN: I wanted to give it the most possibility of seeing something.

DR. GLANTZ: I think, I'm just sitting here doing a lot of arithmetic, if you take the -- if you look at the top at the terminal survivors and you add the multiple -- the thing John said, you add the multiple plus single fibroadenoma with the carcinomas, and you just looked at exposure, versus unexposed, which I think makes more sense when you look at these numbers, that is probably statistically significant. And, I mean, I think that if you look at the multiple fibroadenoma and you just looked at exposed versus unexposed, that's going to be significant.

DR. FRIEDMAN: Again, you're doing that after you see the data.

DR. GLANTZ: Well, that's true but, you know, hey. That doesn't bother me.

DR. FUCALORO: You've got to make a point.

DR. GLANTZ: I agree, picking out the highest incident rate, you don't want to go do that, but I think

that if you look at the data and you do a test of the trends, the test of the trends aren't significant, but if you look at the numbers, the reason it's not significant it looks like there's a threshold effect that you get exposed and something happens and if you got even more exposure, you don't seem to be getting a larger effect.

Now, whether that's because there was some enzyme that saturates and whether that's because the rats won't drink the water, you don't know. But if you just divide it, if you collapse the categories, then the first one will be much more significant, I think.

I don't have a statistical table here and this doesn't take a square root, so I was sort of having to guess a little bit.

I think if you look at the multiple plus single fibroadenomas, that probably doesn't reach significance, but you'd get a smaller P value than you have there, but if you add the carcinomas with the fibroadenomas, that gives you a Z of like 1.9, which is right on the border.

And probably if you do a Fisher exact test it would be significant.

So, you know, the interpretation I would put on this stuff is that it looks like you're showing that exposure is associated with an increased tumor rate.

DR. FRIEDMAN: And having seen that in this study

it would be really nice to do another study with that hypothesis in mind. If that were at all possible, that would be wonderful.

DR. RUBIN: $1.5 million.

DR. FRIEDMAN: I'm in the wrong business.

DR. RUBIN: Can I move on?

CHAIRMAN FROINES: I want to ask --

DR. GLANTZ: This is turning into a seminar here. Is this your thesis you're defending here?

CHAIRMAN FROINES: But this is important.

Although I don't think that the determination of these compounds as TACs rests on oncogenicity issue.

I think this is something that clearly requires follow-up, something that for which there are hints, but for which there is no defined --

DR. GLANTZ: But I think the data here are strong enough to say that's there's, at the very least, a strong suggestion of an effect.

DR. BYUS: I wouldn't say that at all.

DR. GLANTZ: You don't?

DR. BYUS: No. I would say you cannot say -- I would not say it indicates a strong --

DR. GLANTZ: No, I would say --

DR. BYUS: I would say there is maybe an effect.

DR. GLANTZ: Okay.

DR. BYUS: It's definitely not a strong effect from this data.

DR. GLANTZ: No, no. I said --

DR. BYUS: You said strong effect.

DR. GLANTZ: No, no. I said strong suggestion.

DR. FRIEDMAN: I would take out the word strong.

DR. GLANTZ: Okay.

DR. FRIEDMAN: It's suggestion of an effect, it should be followed up.

CHAIRMAN FROINES: If you want, we'll work on this in terms of our findings and we'll have to resolve this strong suggestion versus the suggestion.

DR. GLANTZ: How about a somewhat moderate --

CHAIRMAN FROINES: Somebody in this room, who is very articulate, start thinking of the term between strong suggestion and suggestion.

DR. BYUS: Stan and I can go out of the room.

DR. GLANTZ: No, no.

DR. KENNEDY: Real suggestion.

DR. GLANTZ: A moderate suggestion.

CHAIRMAN FROINES: All right. We'll come back to that.

DR. GLANTZ: Somewhat stronger suggestion, perhaps, an apparently somewhat strong suggestion.

CHAIRMAN FROINES: Bang, bang, bang, bang, bang.

DR. BYUS: Where is your gavel?

DR. GLANTZ: We're not allowed to joke.

CHAIRMAN FROINES: I have a question. I want to get back to science.

The second study, the mouse study, the reason I want to ask a question about the mouse study is that the principal findings of angiosarcoma in the metam-sodium is in the mouse, not in the rat.

DR. RUBIN: Right.

CHAIRMAN FROINES: Now, in the mouse study here I didn't understand this paragraph. You said in a two-year oncogenicity, 70 mice, blah-blah-blah, blah-blah, but I couldn't tell what was the size of each group, it looked to me like the size of each group was six.

DR. RUBIN: 70 mice per group.

CHAIRMAN FROINES: This says 70 mice per sex, per group, but then on the back you're seeing things like ovarian cysts were increased in 10 of 21 versus 2 of 21, so that without having a table --

DR. RUBIN: That's the death problem.

CHAIRMAN FROINES: I don't know what the size -- I have no idea how to interpret this study, because there's no data. I see six mice from each group were sacrificed at 26 and 52 weeks. So was the study terminated at 52 weeks? No?

DR. RUBIN: No.

CHAIRMAN FROINES: It was terminated at 104 weeks. These are mice, so how long, 18 months?

DR. RUBIN: Usually run an 18-month study with mice. I suspect the animals were dying and what you're seeing are the ones that are left.

CHAIRMAN FROINES: There's really not enough information in this section to interpret this study, and it's important precisely because you want to look at this. Again, the strains are different, conditions are different from the metam-sodium study, but if you want to look at mouse-to-mouse findings, you need to have the information to better understand what was done.

You see what I'm saying?

DR. KENNEDY: I see. I don't think it's going to change the oncogenic --

CHAIRMAN FROINES: I don't think so either.

DR. KENNEDY: -- endpoint. In terms of animals, I think many strains of mice, if they live long enough they all die eventually.

DR. WITSCHI: No. I think the question about the mice is very important, because Andy has taken a positive mouse study to ascertain the data which are as weak perhaps as metam-sodium as they are from MITC. But this was your -- made your decision swing. And he calls metam-sodium a carcinogen with lousy rat data and the positive mouse study.

And he calls the MITC not a carcinogen with lousy rat data and not positive mouse data. So they have a good --

DR. RUBIN: We're whistling a slightly different tune on the next slide. I think some of the language I've heard here is reflected in the next slide as to what the conclusion of the onco study is.

Here I just list some of the arguments for and against considering a MITC -- an oncogen based on this one study. I don't know if you want me to go through these, but I'll read the conclusion first.

There is weak evidence of a possible treatment effect. However, the data are not sufficiently strong to trigger a quantitative oncogenic risk evaluation. That is what I mean by that is plugging data like 50 percent versus 70 percent into a multistage linear extrapolation program because the data won't mean anything.

However, I think we have come to the conclusion in our branch that these data, particularly on fibroadenoma, are possibly consistent with the treatment effect. And that's all I think you can say at this point.

So I am going -- I'm changing the language, because the language in the document, as you have it now, is there's no clear effect of oncogenicity. I'm going -- I think the language really should be something like what I have here or some other language that you would suggest.

DR. WITSCHI: I think that's reasonable. We're talking about, I mean the data are so expensive, something seems to be there, but nobody in his right mind should use this study to a quantitative risk assessment.

CHAIRMAN FROINES: We just gave Craig his piece of this action, so it's okay.

DR. RUBIN: We've discussed everything on this slide. I think we can move on.

DR. WITSCHI: I might remind Craig that absence of evidence is never evidence for absence.

DR. BYUS: Absolutely.

DR. GLANTZ: It's noon, if you expect Blanc to show up at 12:30, maybe we should take lunch.

CHAIRMAN FROINES: 1:00.

DR. GLANTZ: 1:00, okay. I'm sorry.

CHAIRMAN FROINES: Why don't we stop about 12:15 and we will come back at 1:15.

And, you know, I don't want to make too much of having one person, because this discussion has been quite good. Everybody has participated.

DR. GLANTZ: Yeah, since Paul is going to show up, it would be good not to have him watch us eat lunch.

But, anyway, go on.

CHAIRMAN FROINES: I think there's a general consensus, there might be slight wording differences, but I

think there's a consensus here that there is a suggestion that something is happening. The data is not sufficient to use for risk assessment purposes. And that we all, I think, agree further work should be done.

So go ahead. Why don't we proceed.

DR. RUBIN: Next slide.

Now we'll get to shift gears and come to the risk characterization part of this document.

Just to refresh your memory, we have split this, these exposure and risk calculations, into acute and subchronic or seasonal exposures and then each of those categories are split into ambient exposures and that would be defined as exposures of the general public in the general area where metam is being applied, so that would be exposures in town, small townships and so forth, versus off-site, or perhaps a better term now, application site exposures, these would be people that are standing right off the field in a particular exposure scenario.

And I want to just give you the MOE values, the margins of exposure. A margin of exposure is defined as the NOEL, in this case for acute we're setting the NOEL at 220 ppb, divided by the measured air concentration. So the MOE is a value which expresses just how close to the NOEL a particular air concentration is. The lower the MOE, the more reason for concern.

What we have here are the high acute MITC exposure levels for these various townships and houses and outside of houses and in the general environment, four or five different townships.

We get MITC levels. I think Tom Thongsinthusak can comment better on this, but we get MITC levels ranging from .08 ppb all the way up to almost 9 ppb with a corresponding MOE values ranging from 25 to 2,750.

Since these MOEs are based on human data, the benchmark of concern is an MOE of ten. So for at least at this point, ambient exposures, that is exposure in town, in a season of metam application, is not ringing a bell, not raising a flag.

However, next slide, for the off-site or application site measurements, you get much higher MITC levels if you're standing five to 500 meters from a field where metam is being applied. Using the same NOEL value of 220 ppb, we're getting MOE values less than one in many cases, and certainly all ten or less.

These are --

CHAIRMAN FROINES: In the previous slide, the Kern County, I take the '97, '98, that's Jim Seiber's work; correct?

DR. RUBIN: Right.

CHAIRMAN FROINES: Okay. When he did that, did he

look -- did he estimate the MIC or carbon disulfide or any other breakdown products?

DR. RUBIN: I don't think MIC was estimated in that study, but there might be others.

Our exposure people are saying no.

CHAIRMAN FROINES: So that we may have half a loaf here or a ten percent or 90 percent of a loaf.

DR. RUBIN: We need monitoring data on these breakdown products.

What I'm going to give you here are just MOEs for MITC.

CHAIRMAN FROINES: And the MITC on page nine that you're at now, that also doesn't include MIC?

DR. RUBIN: Apparently not.

But even not considering MIC, we're dealing with MOE values that almost certainly indicate that a person standing next to a field when there's spraying going or where there's chem irrigation that is adding metam into the irrigation water or shank injection, that there's going to be at least eye irritation going on out there, and that's what these MOE calculations are telling us.

And there could well be pulmonary effects.

Next.

These are, I'm flooding you with numbers. You don't of course have to read every number in this chart.

CHAIRMAN FROINES: When was the previous slide collected?

DR. RUBIN: Excuse me?

CHAIRMAN FROINES: The previous slide, when was that was data collected?

DR. RUBIN: These are the off-site acute measurements. I have them in the document.

CHAIRMAN FROINES: I don't want -- I'm trying to avoid flipping back.

FROM THE AUDIENCE: 1993, '94 and '95 --

DR. RUBIN: That's right. '93, '93, '95, '93, '92.

CHAIRMAN FROINES: And use of metam-sodium has gone up since that time?

DR. RUBIN: It's about doubled.

CHAIRMAN FROINES: About doubled?

DR. RUBIN: Yeah.

MR. GOSSELIN: Also that kind of changes, the use has gone up, but in '94 we started a series of changing use practices, so how this data fits with what's going on now is something we're taking a look at.

DR. FRIEDMAN: Question about similar to my questions about your P values, when you show the MOE, why do you say less than one, why don't you pick the actual value, because .9 would be a lot different than .1.

DR. RUBIN: Yeah, I can do that. You're right. These already when you're dealing with MOE values of one or less, you're dealing with almost certainly seeing adverse effects. So to me it simplified it just to say they were less than one. You can do the division right out here. I mean, the numbers are, for instance, for site A, injection, 220 divided by 618, so it would be .3, approximately.

Would you suggest that I do that?

DR. FRIEDMAN: I would think that it would be good. Shouldn't require the reader to have to do it.

DR. RUBIN: Okay.

DR. FUCALORO: You can also put in the range too.

DR. RUBIN: Yeah, right.

CHAIRMAN FROINES: I think we should break now. This probably is a reasonable time, because it might be good for Paul to see some of this too.

It's going very well.

(Thereupon the lunch recess was taken.)

A F T E R N O O N S E S S I O N

CHAIRMAN FROINES: Go ahead.

DR. RUBIN: Dr. Froines asked me to go back to page nine, start up there.

This was the exposure in the MOE calculations for the application site or off-site measurements, five different studies, three of them injection studies or injection applications, and two of them sprinkler applications.

And the point of this slide was to show that when you're standing right off of a field in which metam is being applied, you're very high likelihood of sustaining some of the irritation effects. The MOEs are less than one. It was mentioned in the last session that I should perhaps express the exact MOE instead of just less than one. We'll probably do that.

Are there any more questions on this slide?

One issue came up, I was told site C, there was MIC monitoring in the site C study. That's the one study in which there is --

DR. ATKINSON: This was the '95 Kern County one, I assume?

DR. RUBIN: Yes.

Okay. Next slide.

Now we move on to the risk characterization for

seasonal exposures. The NOEL value used here for these MOE calculations is derived from the 12-, 13-week rat inhalation toxicity study. The endpoints were in that study, just to refresh you, were decrements in weight gain, increased water consumption and decreased serum protein.

And here these are the ambient MOE levels. And you can see that they're not tripping any red flags. They're all quite fairly high, ranging from low of 708 calculated for children at Lamont, to as high as 17,000 at Arvin, calculated for females. The Lompoc measurement there, the 3.4 million, I was told that maybe I shouldn't emphasize that. We're not so keen on the reliability of that data, so I'm going to cut back on that.

The next slide finally is the -- are the MOE calculations for off-site exposures for seasonal exposure. And here we get MOEs as low as two, ranging as high as a mean MOE of 236.

Now, for MOEs calculated based on animal studies, the benchmark or the convention for tripping a health concern is a MOE of a hundred. These are clearly coming in below a hundred.

DR. BLANC: Therefore, even if you had overestimated exposure by a factor of five to ten, you would still be triggering --

DR. RUBIN: That's right.

DR. BLANC: Do you think that is significant? Does that reassure you that even if there was some error in the field measurements that even so you would have such a high margin here in terms of your MOEs that even if you had overestimated field exposure by a factor of five to ten --

DR. RUBIN: I would still be concerned, yes.

DR. BLANC: Right.

DR. RUBIN: However, I'll just remind you that there is significant concern about the endpoints in the particular study. I would love to see this study done again in a properly characterized analytical procedures, the analytical chamber concentrations, all the individual animal data expressed. We're forced into a corner on this study. We have to go with it. We don't have anything better at this point.

So it is possible that a well-characterized study will come up with a higher NOEL value, in which case these MOE values are going to be higher.

DR. BLANC: Of course, it's also possible a well-characterized study would come up with an even lower --

DR. RUBIN: Yes, certainly is.

CHAIRMAN FROINES: There is some indication that based on George's paper and the Dunsmuir that you might find exposures over time of relatively low levels according to your document.

DR. RUBIN: Yeah. There is uncertainty in all of these calculations and some major uncertainties.

Next slide.

We have calculated reference exposure levels. These are as --

CHAIRMAN FROINES: Just one comment. I think, Paul, that the other thing that's missing here that you missed in earlier discussion is none of this includes MIC carbon disulfide, H2S.

DR. BLANC: That was the case.

CHAIRMAN FROINES: This is only MITC.

DR. BLANC: Yeah.

CHAIRMAN FROINES: So depending upon how much of that would be produced, MOE, however one would calculate it, would be different.

DR. RUBIN: Okay. Just we have calculated reference exposure levels for acute toxicity since we have -- we're dependent on a human study, eye irritation study, the reference exposure level is calculated by dividing the NOEL by ten.

And when you do that, when you divide 220 by 10, you get 22 for a reference exposure level. And it's quite instructive now to compare that reference exposure level to the actual measurements of MITC both in ambient and off-site studies.

The ambient does not appear to go above the reference exposure level. Those, say, in town around in a season of application. However, the off-site, the mean values never go below the REL, so that is an area for concern.

Okay. Next slide.

Reference exposure levels for the subchronic is equal to the NOEL divided by a hundred and that's because the subchronic NOEL comes from an animal study.

CHAIRMAN FROINES: What happens if you were to calculate in a REL for children?

DR. RUBIN: For acute or subchronic?

CHAIRMAN FROINES: I'm using acute.

DR. RUBIN: What we have made, I don't know whether to call it an assumption, but an irritation -- we've made the assumption that irritation in children, female adults and male adults is going to be the same. In other words it's not being -- it's not being metabolized, there's no breathing rate considerations here. So we have assumed that the effect on children of this irritation endpoint is going to be similar to that on adults.

DR. BLANC: Although to the extent that children would be more symptomatic or more sensitive, you're taking that much into account with a factor of ten, even with the human data.

DR. RUBIN: Right.

DR. BLANC: It does assume that there are sensitive subpopulations within the whole population. Otherwise, you'd have to assume that children were a separate population and then do another division for sensitive children. So that would be an unusual -- it would not be a standard approach. The factor of ten is taking into account that children may be somewhat more responsive as a subpopulation.

DR. RUBIN: If there are any literature out there that would indicate that children are more sensitive with respect to irritation endpoints, I'd certainly be interested in it.

CHAIRMAN FROINES: There may be to the degree that one thinks about micro-environmental monitoring, there may be some potential to dermal absorption in children that might be different.

Go ahead.

DR. RUBIN: Okay. The reference exposure for subchronic toxicity is the NOEL divided by a hundred. This is because the NOEL was determined in an animal study, so we have uncertainties of ten for both the human range of sensitivities and going from animals to humans.

The way we do this is to calculate from the rat NOEL what I would call a human equivalent NOEL, which takes

into account the different breathing rate of humans, in this case human children, compared to rats, and amortizes the data. This particular experiment the exposures were done only five out of seven days, and only four hours out of every 24 hours.

All these modifying factors changed the NOEL, the rat NOEL, which was one ppm in the rat to a NOEL of 0.1 ppm in humans, and dividing that further by a hundred gives us a REL of 1.5 ppb. This is subchronic REL.

And in the document you'll notice that I've also calculated a chronic REL by dividing further the subchronic REL by another factor of ten. I don't think OEHHA does that, and that I'm very open to comment. Perhaps a factor of ten is not appropriate.

DR. BLANC: Where did that ten come in again? I'm sorry.

DR. RUBIN: Because we want to generate a chronic REL value, but we only have a subchronic study.

DR. BLANC: Right.

DR. RUBIN: So there's another factor of ten uncertainty.

DR. BLANC: I see. I see. Okay.

DR. RUBIN: So we get a chronic REL of 0.1 ppb.

Okay. I'll finish the talk with just a couple of slides on the alternate or the other breakdown products.

Methyl isocyanate is an extremely toxic compound. I don't think I need to say that. It killed on the order of, say, anywhere from 2500 to 5,000 people at Bhopal in two or three days, maybe five days.

So this compound has a real good track record for toxicity.

We have up to this point only one monitoring study which tracks MIC. In that study there was one spike of MIC as high as 2.5 parts per billion, which was about four percent of the MITC that was there.

Now, that, I suspect, may be a high estimate of the amount of MIC around, but we definitely need, in my opinion, to have more data on the amount of MIC around when there are metam applications going on.

MIC, I've just listed here are the LC 50s in animals 6, 12 and 5 in rats, mice and guinea pigs. These LC 50s are quite a bit lower than MITC. This is a more acutely toxic compound --

DR. BLANC: By a factor of ten?

DR. RUBIN: Ten to hundred.

DR. BLANC: It's not in here, the LD 50, in this little handout

DR. RUBIN: For MITC, no, it's not in there, no.

DR. BLANC: But it's one to two orders of magnitude?

DR. RUBIN Yeah.

DR. BLANC: Like two orders of magnitude.

DR. RUBIN: Yeah.

CHAIRMAN FROINES: Can I ask you a question? You have the acute LOEL of one part per million.

DR. RUBIN: Yeah.

CHAIRMAN FROINES: But in the document, for example, you have a ten-minute study at .5 part per million found eye irritation, tearing, nose and throat irritation, and so that would seem to indicate that you have a LOEL at .5 part per million and then down here below that in the Allory studies you have certainly a LOEL of 1.3 part per million, increase in respiratory rate, and I didn't look at the paper, but I don't know whether he saw anything in lower dose than 1.3 part per million.

But it seems like given this ACGIH information, one could suggest a lower LOEL than one part per million, based on what you have in your document.

DR. RUBIN: I'll definitely go back and look at that.

CHAIRMAN FROINES: I'm just reading what you wrote.

DR. RUBIN: You're absolutely right.

DR. BLANC: Well, another way of asking the same question, I think why John is a little taken aback is

because typically the lethal concentration was six parts per million, and in five parts per million you wouldn't expect the LOEL to be one part per million. It's very steep -- it's possible, but --

DR. RUBIN: It could be that -- I have to go back and look. It could be that those are air concentrations, in which case they're very different.

DR. BLANC: That would be more relevant to our concerns.

DR. RUBIN: Exactly.

DR. BLANC: Do you remember the lethality studies well enough to have a sense of what the curve looked like in terms of mortality?

DR. RUBIN: I couldn't comment on that.

CHAIRMAN FROINES: The document has a LC 50 at 6.1 ppm.

DR. BLANC: He's got at the top here 6.1 ppm in rats and 5.4 ppm in guinea pigs.

And I don't know whether that's because they saw no lethality at .5 parts per million or -- in other words, if they saw 15 percent mortality at one part per million, you hardly call that a no effect level.

So maybe there's some information in the LC 50 studies that would be -- would take your LOEL lower than just by looking at it from that point of view. I don't know

what the studies were.

CHAIRMAN FROINES: But the ACGIH study did find, according to this, ten minutes at .5 ppm eye irritation, and so you may find when you look at that, that data you described may be awfully limited, would be my guess.

DR. RUBIN: Yes.

DR. BLANC: Wasn't there also some modeling data from Bhopal?

DR. RUBIN: What the concentrations were?

DR. BLANC: Yeah. From the various plume radiuses and when they no longer saw any symptoms.

DR. RUBIN: There was modeling data from Bhopal. There are estimates of the concentrations, that the max concentrations that would have been experienced around the factory, but I don't know how sophisticated it was. I have some of those estimates in this document.

DR. BLANC: Because you want us to make sure that you were being consistent, that it seemed consistent, and you didn't have an estimate that at two miles there's a concentration of .5 ppm and that's where people were having just eye irritation and all that stuff, and then we're sort of arguing against the LOEL.

CHAIRMAN FROINES: The other point I would make here is, and I don't know what you can do with it, if anything, but this data on pregnant mice --

DR. RUBIN: Yeah.

CHAIRMAN FROINES: -- where you say that exposure of pregnant mice for six hours per day on gestation days, but increased mortalities over control and fetuses at one and three parts per million.

So you're seeing more lethality, embryo lethality, at one part per million, but that's an interesting question about whether you would use a safety factor of ten to get you to a NOEL, when you have such a profound effect.

What would you use?

Anyway, let's let it go, because that's a LOEL of one part per million, but that seems pretty high.

DR. RUBIN: Yeah. That's what I used as the LOEL.

CHAIRMAN FROINES: But to take a factor of ten below that for your NOEL, with that endpoint I'd be nervous about it, frankly.

DR. RUBIN: So you would --

CHAIRMAN FROINES: I think you'd see more lethality -- well, I don't know, it's hard to say. Again, it's Paul's point about the shape of the dose response curves.

DR. RUBIN: Okay. Well, using a LOEL of one ppm, I calculated some conditional acute RELs for a one-hour, six-hour, 24-hour exposure, coming up with the numbers you see on the screen, 14.2, 2.4 and .6.

There's a mistake in the document. I had made the calculation in the document based on rat breathing rates, and these are actually mice in the experiment. So that's why the numbers look a little different than they do in the document.

DR. FUCALORO: These are just purely proportionate?

DR. RUBIN: Yes. These are based on a Haber's Law proportionality.

DR. FUCALORO: With a exponent of one?

DR. RUBIN: N equals one, yeah. I used N equals one. OEHHA in their acute hot spots document lists a number of end values for MIC irritation values. They range from .5 to 1.1. And I thought just to use one, it will be just a straight proportion, Haber's Law proportionality, and in extrapolating from six to 24 hours and from six to one hour.

As I said before, the MIC level, the high MIC level, measured after one metam -- after an metam application i one study, was 2.5 ppb. Clearly we're in that range just for the acute, for these conditional acute REL values.

I just listed some of the NIOSH values here. The TLV, the eight-hour PEL, based on corrosivity and reactivity of 20 ppb, which is somewhat higher than the values that I've calculated here.

DR. BLANC: They shouldn't be, because they intentionally don't take into account any susceptible populations.

DR. RUBIN: Right. These are workers.

DR. BLANC: If it were any lower than that, you'd really worry since you will --

DR. RUBIN: About child labor laws?

DR. BLANC: You should at least be ten times lower than that, at least, depending on how it's done, quite a bit lower than that, but at a minimum.

DR. RUBIN: Right. I don't have any eight-hour type of value here, because -- well, no, take it back. I do have a six-hour value here and it's getting down toward one-tenth that of the NIOSH value.

The other byproduct or degradation product of great concern is hydrogen sulfide. This we have -- you can fill this room with books written on toxicology of hydrogen sulfide. It's one of the most, if not the most, toxic industrial gas out there.

There's a fair amount known about the levels of sensitivity in human populations, getting respiratory irritation at 100 ppm up to cardiovascular arrest and death at 700 ppm.

For these values, I pretty much relied on the ATSDR values that for a minimum -- what's MRL stand for?

Minimal risk level. An acute minimal risk level of 70 ppb and subchronic minimal risk level of 30 ppb.

In the monitoring that we've -- that we have so far, we do see levels rising above those MRLs at one to four hours, 76 ppb, and then going down with hydrogen sulfide.

I suppose one always has to be worried that there are other sources, plenty of other sources of hydrogen sulfide in the atmosphere, so while it does appear to be going down, perhaps the reason it's coming back up into detectability ranges is that there's some other source there. I really don't know.

The real problem that we're up against here, in my opinion, is how would we go about doing a combined assessment, in other words MITC plus some average or some level, some high level of hydrogen sulfide or MIC, and that I think is quite a cutting-edge issue in risk assessment.

I don't have any answers for that right now. I've based this whole assessment on MITC alone, recognizing that hydrogen sulfide levels are high enough to be of concern and MIC levels are certainly high enough to be of concern in their own right, totally apart from whether they're appearing in conjunction with MITC.

There are a few other degradation products, including carbon disulfide, which are monitoring in the one study that I know of, our monitoring has not indicated

detectable levels. Also carbonyl sulfide and methylamine, which I don't think we have any monitoring data on.

DR. WITSCHI: I have a question or a suggestion to your question about different things being present. As far as MITC is concerned, some of the ambient levels of it were closer about the RELs, right?

DR. RUBIN: Yes.

DR. WITSCHI: So these were levels which presumably, accordingly to our business should have done something, and they can also be assumed that people at this time are exposed not only to MITC, but to MIC and sulfur.

Do we have any complaints or do we have any data on people getting sick?

DR. RUBIN: We do have a -- we have a program called PISP, Pesticide Illness Surveillance Program. And I've got some of that data in the risk assessment as recently as we have it, and there are indeed injuries in the field with metam applications.

DR. WITSCHI: Those data be complete enough at least to give you some clues as to what multiple exposure would mean?

DR. RUBIN: I would say there's probably not enough there to make any conclusions about response --

DR. WITSCHI: Not so much conclusion as hypotheses.

DR. RUBIN: I'm a good speculator. Sure. There's certainly a possibility here that some of the other degradation products could be responsible.

DR. WITSCHI: To say that really strikes me. This whole thing is we often construct some hazards or risk assessments from animal toxicology, but we do not very often have a chance to verify what the animal tells us about human data. And maybe this might be one of those situations.

MR. GOSSELIN: Maybe this might answer your question. Is your question have we been seeing incidents from metam-sodium applications where people have been complaining for exposure to -- we're not going to know exactly what they were exposed to.

DR. WITSCHI: Well, yes, my question really was this seems to me, given exposure data and the possibilities of exposure where there seems to be a real possibility that human data are out there which would reinforce what we conclude from the animal studies, and, if so, that could be very very closely looked at.

MR. GOSSELIN: Actually, that's been one of the things we've been chasing for a number of years is incidence from workers and also incidence from off-site ambient air samples. And it's caused over the years, most specifically since '93-94, alterations to what practices be allowed to happen. Some of these are occurring from legal applications

and then some are misused, but sort of the effects of the exposures, what we have the evidence on.

DR. BLANC: In fact over half of the cases reported to the pesticide and surveillance network have been nonoccupational ambient cases; right?

So that's a ratio which I would imagine is higher than the ratio of ambient to -- or drift, let's say, because I don't want to say occupation, because a lot of other pesticides it's not optional, but it is application driven, but that's fairly high ratio it would seem to me, other than the ratio by standard complaints, because of petroleum distillate smells or something. But that's sort of very strongly supportive of what Hans was saying, the fact you have a lot of evidence that there is a toxic air problem with this, at least in the acute arena.

DR. FUCALORO: Can I follow up on what Hanspeter was saying?

When you get something reported in your surveillance program, how much information is reported? How much are you trying to get? Do you get, for example, the length of time of exposure, estimated concentrations and the illness or the effect? In other words, is there something quantifiable, is it possible to get aggregate data and do something quantifiable? I don't know.

MR. GOSSELIN: There's a wide range of data that

comes through the illness surveillance program. Some of it lags a long time because we get what's called doctor's first reports. Some of you may deal with that. If you suspect it's a pesticide illness or exposure, you're required to report that in to the Department of Industrial Relations and we get that and we'll have staff review that and try to categorize what went on.

Other times there are incidents that are directly reported to us and we conduct an immediate investigation with the counties to, one, not only categorize what the exposures were and what occurred, but also to determine if there were violations that occurred under our normal enforcement and surveillance program.

DR. FUCALORO: I understand all those things.

MR. GOSSELIN: Here's kind of what you are asking about, looking at sort of trends and issues, what we've found oftentimes, particularly with agricultural workers reentering fields, sometimes there's trends that occur about from a variety of effects that are illustrated in the data showing a certain crop using a certain material and the time that's elapsed before people go in that causes us to go in and have to extend that time to allow the degradation of the material to occur. That data, that illness data, has also been used to fix some of those problems.

DR. BLANC: In fact, if we go back to the usage

data that we discussed at a previous meeting, where there was a sharp upswing in pounds applied in 1994, 1995, is that right? Do I have the year right?

DR. RUBIN: My recollection of the data was that from '91 to '98 the -- well, from '91 to '95 the use rate doubled, and so that's what we know.

DR. BLANC: In fact, beginning in 1995 you have a two- to fourfold increase in the number of reports of drift-related events?

DR. RUBIN: Right. And that's directly --

DR. BLANC: Wouldn't that support the -- wouldn't those observations of ecological data support the hypothesis that metam-sodium and its breakdown products are causing ambient air problems in California?

DR. RUBIN: I would definitely agree with that. The use went up and the ambient incidence went up.

DR. BLANC: If you only had the pesticide surveillance program data and none of the elaborate animal data that you have, would that alone be enough to support considering this material toxic as an air contaminant?

MR. GOSSELIN: It --

DR. BLANC: I don't mean from a strictly regulatory point of view, but from a sort of common sense, public health regulatory point of view.

MR. GOSSELIN: I think so. And I think the way

that a lot of the counties that have been facing incidents that are occurring, that's the way they have reacted. You know, there's been a lot of issues about the eye irritation, eye blink. This a traditional toxic effect.

The fact of the matter is regulators are going to do we need to solve that problem so that the phone calls don't come in and people don't complain. I think back in '97, beyond what things we had put out, '94 Kern County, I think, moved on their own, any application outside of the city limits, because they went through and started seeing where they were getting complaints historically, it was all within city boundaries, and on their own made a policy, I think, to move everything outside.

DR. BLANC: Is that historical event documented in your human health assessment section?

MR. GOSSELIN: I don't think a lot of --

DR. BLANC: Is that too anecdotal?

MR. GOSSELIN: It gets into, I think, some of the risk management things that have been done out in the field that's probably not captured to a great extent out here, I mean in this document.

DR. RUBIN: I just have a conclusion slide.

CHAIRMAN FROINES: Going back to Bob Spear's presentation about the variability of exposure estimation, it's interesting, because this data here for '95 and '96 is

so striking, recognizing that variability it again goes to this issue of whether or not MOEs is the way to determine whether something should be clarified a toxic air contaminant.

This compound, metam-sodium and its multiple products, are so toxic that to sort of rely on whether it's above this value of MOE or this value of MOE is going back to what Paul said. Questions one's common sense.

DR. ALEXEEFF: George Alexeeff with OEHHA.

I just wanted to get back to Dr. Fucaloro's earlier question, and actually it's OEHHA that designs the pesticide illness reporting form that's filled out in these cases and then it goes to DPR and to DIR.

And we're thinking about trying to improve this reporting form to get more information to help us in this situation.

Another responsibility we have is also training physicians on pesticide illness detection and reporting. And one is of course we change the form, we'd have to also train the physicians so they could use it properly. So we're also thinking of doing that. We haven't done much in the area of improving the form or in training physicians in the last several years, but at this point we are planning on doing so or actually we started this year.

So it's also the other thing we found, for

example, in the metam-sodium incident where we did go to the field and trained the physicians at that point on detecting it and trying to report as much information as possible so we can do retrospective analyses, it's just a hard thing to do in terms of the exposure concentration for getting those samplers there. That's pretty much the hardest thing is to get the exposure information.

DR. FUCALORO: I was thinking you'd have certainly a large uncertainty in exposure, but of course you could get the information about when it was applied and you have some historical understanding of what the concentration does as a function of timing and distance from point of application. I mean, I don't know that that's true. I hate to say it's fortuitous when someone gets sick from one of these things, but as Hanspeter was pointing out, you have so little information on human subjects that this is a rare opportunity.

DR. KENNEDY: I think your comments about professional education for physicians are fascinating. It's never ending in my particular practice. Our primary inhalent is cordite.

CHAIRMAN FROINES: I think that this raises a very important question, Elinor, that we may want to come back to at some point, which is the one thing it's true about pesticides, which we all agree, is that they're toxic. You

then debate whether they should be toxic air contaminants.

But what we don't have is an -- and we know that pesticides drift, people have occupational exposure and so on and so forth, we need to develop a good surveillance system for addressing pesticide-related health effects.

There is no good surveillance system except for what you have in terms of your pesticide injury reports, but the question is is there a way to improve upon that so we can actually develop more information, because you don't have the kinds of interventions that occur in industrial America out there in the field. It's a different ballgame.

DR. BLANC: Okay.

DR. RUBIN: Okay.

CHAIRMAN FROINES: Peter's point is really important.

DR. RUBIN: Just to wrap up of some of the things we've talked about.

MITC exposure was associated with both short- and long-term effects following the Cantara Loop spill. That we talked about in detail back in November.

The acute MOEs for ambient exposure range from, and these are mean values, range from 25 to 2,750. The off-sites from less than one to ten. By our conventional way of thinking, anyway, those off-site MOEs would trigger health concerns because they're based on human data and

they're less than ten and even less than one.

Subchronic MOEs, again, the ambient from 189 to 17,000, the off-site from 2 to 236. The convention is that when based on animal studies an MOE less than a hundred trips a concern.

The acute REL value, this is for children and adults, is 22 ppb.

The range of acute exposures for ambient is less than 22 ppb, but if the off-site exposures can be way more than 22 ppb, that would indicate again health concerns.

Subchronic REL value of 1.5 ppb for the ambient range of exposure from .13 to 4.09, so that value the REL falls right in the middle of that range.

The off-site values are quite far above that REL value. That would indicate perhaps some concern.

We also discussed in great length the oncogenicity study, and I think we probably agree that some change in language from the original draft that you have is in order.

And that's all I have today.

CHAIRMAN FROINES: That's very good. Very good. Thank you very much.

DR. WITSCHI: I would like to really say it's been pleasant to work with Andrew Rubin on this document and I would like to in the name of the panel thank you very much for the really big big effort you put into that.

DR. RUBIN: Thank you.

DR. BLANC: Here here.

DR. RUBIN: I have the feeling we have not heard the last from MITC, though.

CHAIRMAN FROINES: I had one question for OEHHA, George.

OEHHA also had comments that were submitted. Do you want to follow up and make any subsequent comments to Andy's remarks?

DR. ALEXEEFF: Yes.

CHAIRMAN FROINES: Paul and George --

DR. ALEXEEFF: We have somebody from OEHHA that can speak to it.

CHAIRMAN FROINES: Just one comment, due to the high-level policy operatives, in the future, if we could, it would be nice if we could have integration of your points of view, so we don't see this as an agency war, but rather as a collaborative effort. If that's possible. I'm joking obviously, but --

DR. ALEXEEFF: We're not really warring at all.

CHAIRMAN FROINES: The point is that we would like to see -- as you bring us comments, we like to see the OEHHA comments, but to the degree they can end up looking similar, because you've come to some common agreement, it's better from our standpoint.

DR. WITSCHI: What about the public comments? We talked about that one.

CHAIRMAN FROINES: We don't have any public comments.

DR. WITSCHI: Yes.

DR. KENNEDY: Request for delay.

DR. WITSCHI: I would ask Paul that one. When we reviewed the OEHHA documents in the halcyon days, which are past, whenever the SRP or even the lead person got the finished document he also got what many of us considered the most important volumes, these were the public comments, because the public comments sometimes alert you to things you wouldn't spot yourself.

I do not recall having seen a document in this case of the MITC, which might have alerted by comments made by interested parties to give a few things a closer look, studies or whatever it was.

So my question really is it possible, is it not in your process, that the time being the combined document just OEHHA and from you department and also at this time we get what usually be Part C, the public comments.

Because as Stan pointed out if you can get one of those documents, first thing you do is you look at what other people have to say to get your own thinking into gear.

MR. GOSSELIN: Yeah. We agree. And I think one

of the things, and actually staff has got together yesterday, ARB, OEHHA and DPR, to kind of go over what we have on the plate and we tried to scheduled out in a far better way so we get the ARB, OEHHA consultation done earlier on, the public comment period and public comments and then our response to those is one package, so when you get it it's not a piecemeal event so this thing can go a little smoother.

DR. WITSCHI: Yes. I really would like to emphasize that. I would like to see the public comments.

MR. GOSSELIN: I agree. It should be, as you said, part of the document with our sort of response or acceptance or rebuttal of that, so it's all there for everyone to see.

DR. FUCALORO: We just received one comment that was copied us by a group called the Metam-Sodium Task Force. Did you see that?

DR. WITSCHI: I saw that.

DR. FUCALORO: That's the only thing I received.

DR. WITSCHI: The way I understand the process, the DPR document has to be open for public comments for a certain period of time and people write and I would like to see those letters.

DR. FUCALORO: And the practice here that I've understood, and I see what you're getting at, was that there

would be a response from OEHHA to the public comments. For example, this document received from Metam-Sodium Task Force, some response to what they say. It's probably a group of three or four chemical companies that obviously have an interest.

CHAIRMAN FROINES: But there is one point that is very very important and I guess Stan is probably going to say it. Go ahead. If you don't say it, I will.

DR. GLANTZ: You can say it, whatever it is.

Well, no, I'll say what I was going to say and then you --

DR. FUCALORO: You go, Alphonse. No, Gaston.

DR. GLANTZ: But anyway, we have no sense of humor here.

I had a couple things.

On the point about the OEHHA comments and getting DPR and OEHHA together, I mean, I think, again, we don't want to have an adversarial relationship.

And I also want to second what the other people said. I think we've really come a long way in what DPR has been doing vis-a-vis this panel.

But I think I wouldn't want to like inhibit OEHHA's comments on the draft, but I think the best -- because I think it's helpful, but I think the way it would be nice to handle that is sort of this with the public

comments, so that we would get something like the old Part C document.

The other thing with regard to this Metam-Sodium Task Force letter, I don't know if this is what you thought I was going to say, I get real irritated with things like this. There is a process and there was public comments on this document sometime in the infinite past. And I think that it's not appropriate for these agencies to send stuff directly to us. It should go to DPR or OEHHA, as appropriate, and then be factored into the public comment process, you know, rather than having people come in at the last second and throwing stuff in front of this panel. This happens from time to time.

CHAIRMAN FROINES: But some time ago, years and years ago --

DR. GLANTZ: Is that what I was supposed to say?

CHAIRMAN FROINES: Yeah.

The panel established very clear guidelines about when something would go to the panel. And I don't remember the dates, Bill Lockett may, but it was something like if somebody is going to submit something and they want the panel to review it, it must be at least two weeks before the SRP meeting, and it may have been even longer than that.

Do you remember?

MR. LOCKETT: Not the exact time, but this was

done back in the mid '80s.

CHAIRMAN FROINES: Yeah.

We set up guidelines and Tom Mack and I sat down and wrote these way back when, and the idea was that we would love to see all the comments that people have to provide us, but it must be within a reasonable time frame so the panel can read it, consider it and then take it up at the meeting.

So I would argue that we should -- nothing should be sent to us closer than at least two weeks before the meeting, and if they get it within two weeks -- and because then we were getting Federal Express packages the night before the meeting, which is really insulting.

So whatever the date may be, whatever the date the panel wants to have, it seems to me we want to have a window of time between the time we receive a document and the time we consider it at a meeting.

And I think otherwise anybody gets to us after that, we don't take it up, period.

DR. GLANTZ: And the other thing I recall is that stuff shouldn't be sent by these people to us. It should go to the agency and then come to us through the appropriate channels.

And, I mean, I don't -- we didn't do that to be bureaucratic, we did it to be fair and have some control

over the process and not get sandbagged.

And but, yeah, that's a related point.

But I think that the point about bringing -- I mean, I think we did have public comment on the MITC document, it's just this has been going on a long time. And I think that as things speed up, I just think part of the, you know, when you were talking earlier about batching chemicals and things like that, and I think as part of the process you want to have a Part C document.

I think that the OEHHA comments on the draft could be handled along with the public comments. And in fact I think in one or two of the things we've seen that's how you did it and I thought that was completely appropriate.

Because, again, the way I use these like everyone else is I read the executive summary to kind of figure out what's going on, and then I read the public comments to see what issues are being raised, and then go read the document itself.

So anyway, but I think this other thing in this last-minute letter, that's just not appropriate.

CHAIRMAN FROINES: Can I stop?

I think Stan's finished.

But I want to stop because I think Paul has to leave in the next 10, 15 minutes.

DR. BLANC: Yes.

CHAIRMAN FROINES: Before OEHHA makes any comments, what I'd like to do is get Paul's comments before he has to leave.

DR. BLANC: Well, in general what I think I would say is that although the documents as prepared by the DPR may not have everything in exactly the form that we would want in the best of all possible worlds, and there may be some areas of discussion that could be clarified or expanded, this is not a doctoral dissertation and we're not the doctoral review committee.

I think the way I would recommend as a matter of process the way we handle clarifications and issues of emphasis would be in our written findings.

I think the scientific record is sufficient in the material that we've been provided to make reasonable comments on the indications for metam-sodium and its breakdown products to be treated as toxic air contaminants, and that's what we're required to do.

And I would say that we approach it that way rather than trying to seek further editorial modifications in the document.

I don't think that there's any question that the fundamental information as provided would support its designation as a TAC, and I think that we simply can serve to better clarify the record by emphasizing the key points

as we see them.

For example, the pesticides surveillance data that's in the document, for example, and data that is present in the document on the breakdown products and the distribution and the assumptions in the modeling, which are essentially conservative, and for every assumption where you can argue that it could go one way, it could as easily go the other way. So either way you would cut it you would still be saying that it certainly reaches a red flag level consistent with policy for TAC designation.

So that's how I would pragmatically approach the problem.

DR. GLANTZ: Are you saying, just to be clear, you think the report is okay?

DR. BLANC: I think we can come to the conclusions we need to come to based on this report.

DR. GLANTZ: So you don't think there's any additional changes they need to make to the document itself?

DR. BLANC: I don't think that that's required. I think that we can handle the gaps that we have based on clarifications that we can make in our finding. We can't make a finding based on something that's not even alluded to here. I suppose, although it's possible, that we could comment on the fact that what Paul was alluding to about Kern County having to ban it in the notes, but even that I

don't know that that's so germane that we'd be forced to do that.

So I recommend that we just move forward.

CHAIRMAN FROINES: And Andy has some changes he wants to make.

MR. GOSSELIN: Yeah. Actually Tom was going to come up and kind of go over some of the exposure numbers he was looking at in the newer study that will just be an addition to the report and maybe another look at some of the subchronic.

DR. BLANC: I don't think we need to meet and review your document again. If you want to give us your final report in the next three weeks or something, in the meantime we could draft our findings.

MR. GOSSELIN: And we've done that, I think, in the past on a couple and make sure the numbers that are in there match up with additional data and everything else.

CHAIRMAN FROINES: Yeah. And that would mean that we would be basically voting on the document.

DR. BLANC: Pending the stated revisions.

CHAIRMAN FROINES: Pending the stated revisions.

DR. BLANC: Minor revisions.

That would be my --

DR. WITSCHI: I would agree. I would second that one.

DR. GLANTZ: Then why don't you make a motion.

DR. BLANC: I move --

DR. FRIEDMAN: Can I just ask, is that setting a precedent? Haven't we always been really careful about approving every other document to the last detail before we come up with findings?

CHAIRMAN FROINES: No. The DEF document went through an enormous number of changes to bring consistency to the numbers and small errors.

DR. GLANTZ: We've never --

CHAIRMAN FROINES: We've never -- we have always made small changes that weren't fundamental changes. In fact, the closest thing to actually letting OEHHA or DPR or ARB go was DEF where we actually argued right at the end about NOAEL versus NOEL, and God forbid we ever go back to that argument.

And there were some major number errors between OEHHA's numbers and DPR's numbers and so I worked with, I forget who, but we worked it all out to make those changes.

But by and large we've generally accepted small changes without necessarily going back.

DR. BLANC: I make a two-part motion.

CHAIRMAN FROINES: But we could. Whatever you want.

DR. FRIEDMAN: I just wanted to raise that

question, because this sounded sort of new to me, even though we've always been so careful.

DR. GLANTZ: I think what we're talking -- I agree that we've always been very careful, but I think at this point we're talking about small changes to bring consistency within the report, based on the discussion at the meeting and correct some errors that have been identified. I don't think it's anything fundamental.

CHAIRMAN FROINES: I think we'll actually -- I think Paul can make a motion and we can second and vote and if something comes up as we discuss it for the rest of the day we can go back and revisit that motion. It's not cast in stone.

MR. GOSSELIN: I will say there is the -- I think one of the subjects of the letter you got in about the study in December that we are going to incorporate in the document, that Tom is going to talk about, some new information.

CHAIRMAN FROINES: Why don't Paul make the motion and we can go and then if we want to reconsider we can do that.

DR. BLANC: Move that the Scientific Review Panel accept the draft document for -- accept the draft document pending minor revisions.

DR. WITSCHI: I second.

DR. GLANTZ: Can I have one point of clarification? The final acceptance of the document on behalf of the panel would be the chair --

DR. BLANC: I want to make a second motion, so let me do that.

DR. GLANTZ: Make your second motion.

DR. BLANC: First, let's do this one. You have to do one at a time.

DR. KENNEDY: Call the vote.

DR. GLANTZ: Call the question.

CHAIRMAN FROINES: There's no further discussion, then all in favor of that motion.

(Show of hands.)

DR. GLANTZ: It's unanimous.

DR. BLANC: My second motion is that the chair of the panel review the revisions and in light of the draft and its revisions, draft findings for the panel to be circulated to its members.

CHAIRMAN FROINES: Well, I would, if I can add to that, I would say if the review indicates significant changes --

DR. BLANC: Certainly.

CHAIRMAN FROINES: -- then I would bring it back to the panel for --

DR. BLANC: Fine.

CHAIRMAN FROINES: -- reconsideration.

DR. BLANC: I accept your friendly amendment.

So let me read it to you so you have it, or state it to you.

The chair will review the revised draft document --

CHAIRMAN FROINES: I have a second friendly amendment. Sorry. Sorry.

I'm concerned about meeting Gary's question. I think it's important.

That the chair and the lead person --

DR. BLANC: Who is the lead person?

CHAIRMAN FROINES: Peter.

DR. BLANC: So that resolve then the chair and the lead reviewer will evaluate the revised document and either request further review by the whole panel or draft findings to be circulated for review by the panel.

DR. KENNEDY: Second.

DR. WITSCHI: Thank you.

CHAIRMAN FROINES: I just don't want anybody to say --

DR. GLANTZ: Just a point of clarification, though. I mean, I think it's clear if there's any substantive changes to the document, then it would come back to the panel.

CHAIRMAN FROINES: Absolutely.

DR. GLANTZ: That the review by the chair is to simply make sure that any changes that are made are consistent with the views expressed by the panel.

DR. FUCALORO: I understood it that way.

DR. GLANTZ: Just for the record.

Call the question.

CHAIRMAN FROINES: All in favor.

(Show of hands.)

DR. GLANTZ: It's unanimous for the record.

You're supposed to say that.

DR. FUCALORO: Since he never does, you always do.

DR. GLANTZ: I know. It's because I am so meticulous.

CHAIRMAN FROINES: It's always so much fun when you add in your little pieces and everybody enjoys it, so why would I take that away?

Okay. Can we take a five-minute break? I mean a five-minute break. We can finish with this fairly quickly.

DR. GLANTZ: We don't have draft findings already, do you?

CHAIRMAN FROINES: No. I wish we did.

Five-minute break and we're going to hear from OEHHA and then the other.

MR. GOSSELIN: We have a short presentation that's

going to be changes to the document and then OEHHA.

(Thereupon a short recess was taken.)

MR. GOSSELIN: We have ten-minute presentation, or shorter than that, and then OEHHA is going to wrap up. This is just on the exposure monitoring and one new study that came in that's going to be added to the document.

If we can go right to the overheads.

CHAIRMAN FROINES: Yeah. I have a question. How long is OEHHA -- does OEHHA want to make any presentation and, if so, how long would it take?

DR. ALEXEEFF: Two minutes.

CHAIRMAN FROINES: Two minutes.

You're considering how long?

DR. THONGSINTHUSAK: Ten minutes.

CHAIRMAN FROINES: Ten minutes. That's 12 minutes. I'm only asking because Peter just said that there's some panel members who can make a 3:45 plane if we finish in time.

DR. FUCALORO: Make that 3:40. I have to get a car back to the rental.

CHAIRMAN FROINES: If we were to move in that direction, we haven't had a discussion -- the trouble with Paul making his motion is that we have nobody on the panel has had a chance to give comments to DPR on their reading of the document. So I think --

DR. GLANTZ: Our reading of which document?

MR. GOSSELIN: Which document?

CHAIRMAN FROINES: The documents.

DR. GLANTZ: I thought we were --

DR. BYUS: We just voted for it.

CHAIRMAN FROINES: I'm still saying that we did vote for it, but nobody has had an opportunity, besides Paul, we have had a lot of discussion, enormous discussion during the day, so the question is are there any members of the panel who still would like to raise questions with DPR, so that they get their positions stated?

And, if not, we'll go with the -- try to make the airplanes. I don't mean to create a Hobson's choice.

DR. GLANTZ: I thought that's what we spent the whole morning doing.

CHAIRMAN FROINES: Your plane or your freedom.

DR. GLANTZ: I thought, John, that's what we spent half the morning doing.

CHAIRMAN FROINES: Okay. I'm just --

DR. GLANTZ: I don't want to shut anybody else down, but I thought --

DR. FUCALORO: Shut us down.

CHAIRMAN FROINES: All I'm --

DR. GLANTZ: Don't say things like that on the record. We're all going to be arrested and sued.

CHAIRMAN FROINES: Stan, you don't get it. He may have said it, nobody would have noticed. You just reinforced it.

DR. GLANTZ: And you just reinforced me. It's been a long meeting.

CHAIRMAN FROINES: Okay. A very good meeting.

DR. GLANTZ: It has been a very good meeting.

CHAIRMAN FROINES: As long as everybody feels fine about this process of doing -- excuse me, let me finish my talking.

We will go to a final presentation by DPR, a short presentation by OEHHA, and then we will essentially adjourn, unless somebody asks for a reconsideration and wants to have more comments.

Is that acceptable?

DR. GLANTZ: Can I just say one thing to clarify the record?

I would say the question you should have asked is, Mr. Chairman, does anyone have any additional comments about the document.

CHAIRMAN FROINES: Okay.

DR. GLANTZ: To guide DPR beyond what we've already discussed so far in the meeting.

CHAIRMAN FROINES: Tony?

DR. FUCALORO: No.

CHAIRMAN FROINES: Peter?

I think he's already voting with his head.

Roger said no.

Craig, I think, is saying no. He's trying to reach his coffee.

So let's go ahead.

DR. THONGSINTHUSAK: I'm Tom Thongsinthusak.

I would like to present the data from the letter submission from the Metam-Sodium Task Force. It's an off-site and monitoring studies conducted in 1999. The area is in Bakersfield, California.

Table 1, summary of the air concentrations of MITC from the application of metam-sodium through sprinkle irrigation. I present the table in two sections. The middle section is for ADD. This is for short-term exposure. And the last part is on the right-hand for SADD or seasonal daily doses. This is for subchronic exposure.

For this study, there were four to five sampling stations located 150, 300, 700 and 9700 meters, in the east and the west areas of the treated field.

This treated field consists of about four plots of 20 acres each.

And the maximum application of metam-sodium was applied, and the application was in accordance with the technical information bulletin. In other words, the

procedure in the application including pre-application irrigation and after the application it was a water tap to retain metam-sodium or MITC.

I group them into day one, day two, day three and day four for short-term exposure. Start on day one for the highest, down the road and then for the subchronic, the average of the four-day concentration, so they can be used for the subchronic exposure estimates.

Next, please.

The second table is similar to the first one, but this is the metam-sodium was applied through shank injection. The total area is about 79 acres of land.

Also there were four sampling stations located in the east and the west of the field. Also, air concentrations include four different days. That's for ADD and SADD.

CHAIRMAN FROINES: How do we know -- I'm sorry, I missed something. How do we know what the wind patterns were for these determinations?

DR. THONGSINTHUSAK: Yes, I will show them on the next table.

CHAIRMAN FROINES: Okay.

DR. THONGSINTHUSAK: This is summary, and the study assume that the sampling station was in the downwind areas, but according to the data I revealed it's not exactly

the way they wanted to see. Like this stand 150, 300 and 700 sampling stations A, C and A. Let's suppose that A, station A, should be in downwind direction, but because of the wind shifted, the C showed the highest air concentration in that direction.

So for the short-term exposure I pick the highest air concentration, I mean the daily air concentration, to represent the daily exposure for acute risk assessment.

And for the SADD, the sampling station is pretty consistent, when I take the average of the four sampling days, the high always in the A sampling station for 150, 300 and 700 meter stations.

For the acute exposure at 150 meters from the treated field, the air concentration is 101 parts per million. For the 300 it's 52. 700 meters it is 31.

And air concentration daily dosage represents ADD in term of micrograms per kilogram and per day. I would not repeat those numbers.

For the SADD or the subchronic exposure, the mean I showed the air concentrations as mean, low and high for all three sampling stations.

For example at 150 meters, mean value for the air concentration is 55 parts per billion.

And for the low, 50, and the high 63, and so on and so forth.

And then I calculate the subchronic exposure in terms of SADD. This is for adult female exposures.

For the 150 represents 100, for 486 the low is 5.5 and the high 6.9.

Next, please.

DR. FRIEDMAN: Can you explain why it's lower for SADD than ADD?

DR. THONGSINTHUSAK: Because I take the average of those four daily exposures. The first day will be higher than most of the time, the second day, third day and so on and so forth.

DR. FRIEDMAN: So this is one -- there is an application --

DR. THONGSINTHUSAK: Yes.

DR. FRIEDMAN: And then the A is right after the application and then it gradually disperses?

DR. THONGSINTHUSAK: That's right. That's correct.

The format is similar to Table 3 on the previous table, but this is for the shank injection method.

Presentation of the data is the same. The mean for a short-term exposure and the moderate-term exposure at 150, 300, and 486 meter sampling stations.

I would cite one example for the ADD run from 175 parts per billion for sampling at 150; for 300, 106; and 486

meters, 84 parts per billion.

Overall for two different methods, I mean sprinkler injection and shank injection, the air concentrations at similar distance from the treated field were similar.

And in my previous presentation, probably in November, there's a question about a retention of the silica gel tubes. This study has or used similar methods to that one. The previous one was conducted by ICI, and they use a silica gel dry tube, but they did not add residues of MITC from the tube to the total MITC residues.

I did not have any good answer for that. But this study can replace the previous one and the air concentrations at the same distance from the treated field was very similar.

So I propose that this study be used to replace the previous one, which was conducted by ICI, and there was so many questions about a retention of silica gel drying tubes, and the study did not include the residue in those tubes.

DR. FUCALORO: Are the results of this study significantly different from the one, the one that was in question? I don't remember.

DR. THONGSINTHUSAK: Very similar.

DR. FUCALORO: Very similar?

DR. THONGSINTHUSAK: Yes.

DR. FUCALORO: Okay.

DR. THONGSINTHUSAK: But we still have some work to do for this study, because the downwind direction did not stay put in the same direction all the time, and some MITC residues at relatively high amount was observed in the upwind area.

So I assume there was the wind shift, the direction did not go to the same direction during that four days of study.

Since the letter representative the metam-sodium application methods that currently used in California, I assume that in general the study should be more representative than the previous study.

CHAIRMAN FROINES: Where was this study conducted?

DR. THONGSINTHUSAK: Pardon me?

CHAIRMAN FROINES: Where was it conducted?

DR. THONGSINTHUSAK: Where was it conducted? In Bakersfield.

CHAIRMAN FROINES: Bakersfield.

DR. THONGSINTHUSAK: Yes. In 1999.

This is the last slide.

CHAIRMAN FROINES: How do we know about how much metam-sodium was actually used relative to other studies that have been conducted?

MR. GOSSELIN: You mean the rates of application? That should be part of the whole study report is to -- the method, injection depth or the sprinkler or how long it took to put the application on and how much material was actually put out.

And to kind of put that study and these other studies into context, all those variables, including the specific weather data and the residues that were found and everything else were used by staff in a similar way that Melanie described to us taking and doing some modeling to calculate out on either a regional, statewide basis what the air levels would be and make sure that we don't exceed an REL.

CHAIRMAN FROINES: Exceed an REL as opposed to MOE?

MR. GOSSELIN: Depends on --

CHAIRMAN FROINES: All this continues to reinforce this problem and that is that exposures are highly variable.

MR. GOSSELIN: Right.

CHAIRMAN FROINES: And defining decision criteria on highly variable parameters is a problem.

DR. THONGSINTHUSAK: This is the last overhead.

The last time I did not show chronic exposure estimates, and this one I estimated chronic exposure from three ambient air monitoring studies. The first one

conducted in Kern County and the second Bakersfield by Seiber and his colleague.

And number of potential exposure days, which is at the bottom as a footnote, it was estimated to be 188 days per year and the range is 79 to 328 days.

So I only estimated the exposure for these three because the ambient air concentrations should be more representative than the application site and monitoring study.

In the last column I represent annual exposure SADD, annual average daily dosage.

For example at a Shafter site the range is .001 to .32 and the median is .05. For B7, Bakersfield, Lamont, in the houses it showed AADD is .32, the range from .02 to 1.76, so on and so forth.

CHAIRMAN FROINES: I have a question. I don't want to hold it up.

Why do you have parts per million on one side and ADD in micrograms per kilogram on the other?

DR. THONGSINTHUSAK: The ppb represent the airborne concentrations of MITC. The AADD represents the absorbed dose.

So the risk assessor can use either values.

CHAIRMAN FROINES: The reader will generally find things in similar units to be better, if you can do it.

DR. GLANTZ: It's fine. Depends on what you're trying to do with it.

CHAIRMAN FROINES: Okay.

DR. THONGSINTHUSAK: That's all I have, unless you have questions.

It's been a little bit over ten minutes.

CHAIRMAN FROINES: That's all right.

DR. KENNEDY: Thank you.

DR. WITSCHI: What was the difference between those data and what you showed earlier, summer 1997 to winter 1998?

DR. THONGSINTHUSAK: Sorry?

DR. WITSCHI: In an earlier slide, very similar data for Lamont and Shafter and Seiber identified those Kern County in summer 1997 for Kern County winter 1998. Is this the same study or is this a different study?

DR. THONGSINTHUSAK: The same study.

DR. WITSCHI: Same study.

DR. THONGSINTHUSAK: It's the ambient air monitoring study.

DR. WITSCHI: Same study?

DR. THONGSINTHUSAK: Yeah. from Lamont.

DR. WITSCHI: The numbers are not the same.

DR. THONGSINTHUSAK: The second one by Seiber, that's a different one.

DR. GLANTZ: I think rather than replacing what's in the report with this study, you should just add it.

MR. GOSSELIN: That's what we're going to do.

DR. THONGSINTHUSAK: That's right.

DR. GLANTZ: That's a suggestion.

DR. FUCALORO: The explanation.

DR. GLANTZ: Just add it. Don't take what you've got in there out.

DR. THONGSINTHUSAK: Yes.

DR. FUCALORO: Validate the other.

DR. GLANTZ: Yeah. It's the results are so similar, it actually tends to affirm it.

DR. THONGSINTHUSAK: Okay. Thank you.

CHAIRMAN FROINES: Further comments?

George.

DR. ALEXEEFF: George Alexeeff with OEHHA.

I just want to say right off the bat our findings are very consistent with the report, with the DPR report.

And we've actually worked very closely with this one, and the major difficulty we had was just keeping up with their revised versions of it and it's something that we're working on to actually improve that so that sometimes our findings are not -- are in sync with the current version that they have as opposed to an older version.

But that's pretty much the biggest difference, the

difficulty we had.

We will revise our finding on oncogenicity so it's consistent with what the panel discussed here today, and it's more similar to what their older version or their current document says.

The other thing is that we did a little bit differently is emphasized a couple things differently in here, concerns that we had about uncertainties.

One was the concern about RADS, reactive airway dysfunction syndrome. We kind of emphasized that, that we're concerned about that as an outcome of an extensive exposure.

The other one is, and you talked --

DR. KENNEDY: In what regard?

DR. ALEXEEFF: In that spill that occurred of metam-sodium in the Cantara Loop, we think that it would be very likely to -- the health department, we did a study with the health department, Department of Health Services, excuse me, and we think that many of the individuals, about 20 or so, developed reactive airway dysfunction syndrome, as a result of the exposure, which I think is one of the first times an environmental exposure has resulted in that syndrome.

DR. KENNEDY: Sensitization syndrome?

DR. ALEXEEFF: Yeah.

So we think that's something that was important to us and it could be the MITC, it could be the MIC. We don't know. But we thought it was an important finding.

DR. KENNEDY: Has there been any -- is there an ongoing long-term follow-up with those patients for scar cancers?

DR. ALEXEEFF: I don't know. I can ask the lead physician.

DR. KENNEDY: Interesting to do over, say, 15 years.

DR. ALEXEEFF: Dr. Jim Cohn was the lead on that and he's with Department of Health Services.

CHAIRMAN FROINES: George, I don't see in here something about discussion of RADS.

DR. ALEXEEFF: Yeah, it's in there.

CHAIRMAN FROINES: Where?

DR. ALEXEEFF: It is in our findings. It's actually the last findings, I think, that mentions it and then the last word of our findings is RADs.

CHAIRMAN FROINES: I saw that.

DR. ALEXEEFF: And there's another finding.

CHAIRMAN FROINES: Where is it?

DR. ALEXEEFF: Finding No. 10. Our finding No. 10.

So this was simply a measure of emphasis, and then

also although we agreed with their choice for that human exposure study, you know, when you look at the -- weigh everything together, we also just felt it was important to look at the pros and cons of the animal study and the human study, because we sort of felt that neither of them are exactly what we'd like, so we kind of made a big deal about that in our findings, but just so that everybody understood the uncertainties of both studies or the pros and cons.

CHAIRMAN FROINES: There's no harm in using developing numbers from both studies. It doesn't have to be a bright line. It can say there are problems with this study, but this gives us these results, there's a problem with this study, this gives us these results and then you have covered your bases.

DR. ALEXEEFF: Yeah.

And I guess the last point, and this is not really directly related to the findings, but in response to Dr. Rubin's comments on how to address the multi-chemical situation, we can talk with their staff regarding the hazard index approach, which is what we are developing in the hot spots guidelines, of course the guidance isn't out yet, but we can explain to them what the approach is, the US EPA based approach is, and to see if that sheds any light.

CHAIRMAN FROINES: You say on your finding 24, OEHHA does not include a RAD on human breathing adjustment.

DR. ALEXEEFF: Correct.

CHAIRMAN FROINES: And you all need to work that out.

DR. ALEXEEFF: Yeah.

CHAIRMAN FROINES: And come back to us on that.

DR. ALEXEEFF: I agree. Paul and I talked about that one earlier today, and that is something we do want to try to work out. It has to do with simply the way staff have done their work in the different departments, and we need to work a couple of those things out.

CHAIRMAN FROINES: I want to emphasize one thing quickly. I think the RADS issue is really a major issue. It also goes to the question of chronic disease versus acute disorders. So it's something I think we should try and follow up on, because I think if we can -- if there's an issue of MITC or MIC producing RADS, that's a major health, potentially important health problem.

I think that's what Peter was --

DR. ALEXEEFF: Okay. That's all.

CHAIRMAN FROINES: Well, I was just going to say --

DR. KENNEDY: You better say it fast.

CHAIRMAN FROINES: Does anybody else on the panel, while you're still within the room, have any further comments?

DR. FUCALORO: I need to make a few comments with slides.

DR. GLANTZ: I'd like to make a comment that we adjourn.

CHAIRMAN FROINES: Move that we adjourn?

DR. GLANTZ: I move that we adjourn.

DR. ATKINSON: Second.

DR. GLANTZ: Call the question.

CHAIRMAN FROINES: The question, all in favor, was unanimous.

(Thereupon the meeting was adjourned at 2:45 p.m.)

CERTIFICATE OF SHORTHAND REPORTER

I, JANET H. NICOL, a Certified Shorthand Reporter of the State of California, do hereby certify that I am a disinterested person herein; that I reported the foregoing meeting in shorthand writing; that I thereafter caused my shorthand writing to be transcribed into typewriting.

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

IN WITNESS WHEREOF, I have hereunto set my hand this 8th day of February 2000.

Janet H. Nicol
Certified Shorthand Reporter
License Number 9764