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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WEDNESDAY, DECEMBER 6, 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. Gary Friedman
Dr. Anthony Fucaloro
Dr. Stanton Glantz
Dr. Hanspeter Witschi

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD:

Mr. Jim Behrmann
Mr. Bill Lockett
Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Joseph Brown, Staff Toxicologist
Dr. James Collins, Staff Toxicologist
Dr. Melanie Marty, Senior Toxicologist
Dr. Andy Salmon, Chief, Air Toxicology and Risk Assessment

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Mr. Paul Gosselin, Acting Chief Deputy Director
Dr. Robert Howd, Chief, Water Toxicology Unit
Dr. Keith Pfeifer, Senior Toxicologist

OTHERS:

Mr. Bruce Reeves, Attorney General's Office

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P R O C E E D I N G S

CHAIRMAN FROINES: So we shall officially call the meeting to order.

And the first item on the agenda is a discussion of substances to be included in the Air Toxic Hot Spots Program risk assessment.

So why don't we begin with Melanie Marty.

DR. COLLINS: Good morning, Dr. Froines. I'm James Collins, and I'm the chief -- I'm lead staff person on the chronic REL document here with Melanie Marty, chief of the Air Toxics Section, Epidemiology Section.

Today we're going to talk about three chemicals remaining from batch 2 A of the chronic RELs, and those three chemicals are chlorine dioxide, glutaraldehyde and 1,3-butadiene.

In regard to chlorine dioxide, we used a French study. There were actually three separate studies on chlorine dioxide, and we came up with a value of .6 micrograms per cubic meter.

During discussions, a member of the panel expressed concern that we had not used a human study published by Scandinavian workers in 1957.

And the reason we did not the use that study, because the authors themselves ascribed the adverse effects of chlorine dioxide to exposure excursions above the

reported mean level of .1 part per million. They did not specify how high the excursions were, but they were excursions.

So because of that, we decided it was safer to use the animal study at which several levels had been studied over a period of years.

If there are any -- and we added that statement from the workers into our summary of the adults, of the human studies.

If there are any questions about that.

DR. FUCALORO: I think it's fine.

I mean, just another small thing. Although right, the vapor pressure is 760 torr at the boiling point, it's superfluous. I mean I would just lose that.

DR. MARTY: So take out the "at."

DR. FUCALORO: No. I would just take it out completely, the vapor pressure, unless you do it at another temperature.

DR. MARTY: I see what you're saying. I'm sorry. Okay.

DR. FUCALORO: All that tells you is that vapor -- the atmospheric pressure is 760.

DR. COLLINS: If there are any questions about -- or any more comments about chlorine dioxide?

CHAIRMAN FROINES: I just have a quickie.

I assumed that the study that you quote, Ferris, 1967, is a study at Harvard by Ben Ferris, and in which they looked at trace levels up to .25 parts per million, and I don't know what they then concluded with respect to average or the distribution of exposures, but you didn't use that study either. Can you just say a couple words about it?

DR. COLLINS: The problem with that study is they really looked at chlorine, more than chlorine dioxide. And some of the workers weren't even exposed at all to chlorine dioxide. So there was some exposure, but not enough that we thought you could make -- you could reasonably develop a REL from.

I have that study here with me.

CHAIRMAN FROINES: They're very solid investigators.

DR. COLLINS: I have that study. That's the problem. There was actually probably less exposure in that study than there was in the Gloemme and Lundgren study.

CHAIRMAN FROINES: Unless there are other questions, we should proceed.

DR. COLLINS: The next chemical is glutaraldehyde. In that study we used an NTP study. And the most sensitive sex and species was female mice. We developed a value of .08 micrograms per cubic meter using a LOAEL, UF approach.

And one of the panel members suggested or

requested us to evaluate data using the benchmark concentration approach.

We did use that approach, and we ended up with a revised value of .08 micrograms per cubic meter. So we ended up with the same number, but we ended up using an uncertainty factor of 30, rather than a hundred, and there is probably an improved estimate in using more of the data by using the benchmark concentration, so we ended up with the same result, but hopefully by a better method.

CHAIRMAN FROINES: Do you have any information -- Mike Poor would be the person to ask, I guess, but has anybody looked at glutaraldehyde in the air?

DR. ATKINSON: Not that I know of. That's not an easy thing to see.

By the way, the vapor pressure that's given at 20 degrees C looks awfully high to me, given that high volume point of 188. You might want to check that it's not 1.7.

DR. MARTY: Okay.

DR. ATKINSON: It could be 0.17

DR. MARTY: In regards to the air concentrations issue, we don't have concentrations available, but we do have from the air toxic hot spots California database on inventories the estimated emissions from stationary facilities is 29,600 pounds per year.

DR. ATKINSON: It's also formed in the atmosphere.

It's an atmospheric reaction product of cyclohexene.

DR. MARTY: That might actually be a larger contributor.

DR. ATKINSON: I don't know.

CHAIRMAN FROINES: This is one of the reasons that we want to have a session with Peter Venturini and other people to talk about priority setting, because this is a classic secondary pollutant in that sense of being formed in the atmosphere. And so at this level of .02 parts per billion, it's an interesting issue given that the squamous metaplasia, the respiratory epithelium -- what's the data on the carcinogenesis?

DR. COLLINS: I'm not aware that it's considered carcinogenic. I don't know whether I have that data with me. I could check it. I doubt that it's carcinogenic. It's certainly not something we have on our list as a carcinogen yet.

CHAIRMAN FROINES: I think the word "yet" may be the operative term. It's going to be fairly reactive. And the fact that you do see metaplasia suggests that you're a little bit on the way down the path of that.

This is -- these aldehydes are really important, I think, and it's something that hopefully we can take up as a class at some point, because I think they are so important. And we tend to focus on formaldehyde or acetaldehyde, and we

have a large range of other compounds, ranging from acrolein to glutaraldehyde and so on and so forth.

DR. COLLINS: The study, the summary I have here of NTP does not mention carcinogenesis, but they are concerned about the metaplasia and hyperplasia as possible, but it did not, from what I can tell, extend into carcinogenicity.

It's also true that the chemical was positive in several genotoxic tests including salmonella typhimurium. So that may also be a concern, cause for concern.

Is there any other question about glutaraldehyde?

Finally, I'd like to come to butadiene.

For the development of the chronic REL for butadiene, we also used a NTP study, and mouse was the species we used. We had an original value of 8 micrograms per cubic meter based on a LOAEL, UF approach with ovarian atrophy.

CHAIRMAN FROINES: What was the strain?

DR. COLLINS: I assume it's B6C3F1.

The original value was 8 micrograms per cubic meter. By using a benchmark concentration approach with the data, we ended up with a BMC 05 of 20 micrograms per cubic meter.

Based on Dr. Glantz's suggestion, we incorporated some information about arteriosclerosis in cockerels, due to

butadiene.

Today we want to address the panel's concerns about the kinetics of butadiene, especially how it might relate to an uncertainty factor.

So with the chairman's permission I'd like to yield ten minutes of my time to the honorable pharmacokineticist from OEHHA, Dr. Joseph Brown.

DR. MARTY: The issue that was raised was can we have a smaller uncertainty factor for interspecies extrapolation from the mouse to the human, because it's felt that the mouse probably makes more epoxide metabolite, which is the proximate toxicant to the ovary.

So we have actually an interspecies uncertainty factor of three, so we already lowered it from the guideline of ten, but we were asked by Dr. Witschi could we even lower it further, or do you even need one.

So we felt that we would like to stick to our interspecies uncertainty factor of three, and Dr. Brown is going to provide some description of the work he's done on looking at the kinetics of the epoxide formation.

DR. BROWN: Morning.

The main question here raised at the last meeting was why are we using the uncertainty -- interspecies uncertainty factor that we are, aren't mice a lot more sensitive than rats --

CHAIRMAN FROINES: Can you hear him in the back?

DR. BROWN: -- than rats or humans to the toxicity of butadiene.

This idea of this I think largely comes from the cancer bioassays that have been done. In the cancer bioassays mice have shown much higher tumor yields for a number of sites, particularly the lung and lymphoma in rats. In fact, the main study that's used has not even established an effect level for tumors, particularly lung tumor.

Rats showed tumors at different sites, testes, uterus, pancreas and mammary, so in some respects while it's clear that these tumors in the rats were observed in much higher concentrations, the fact that you're looking at different sites makes this comparison a little bit more complicated.

For example, in the mammary there is a fairly high background, but the incidence at the high dose is very high, and there's a very high multiplicity of tumors in the mammary gland of the rat.

So I think I've heard some people talk or in some papers that butadiene is almost noncarcinogenic in the rat. Well, it isn't.

There's also some data recently from a human occupational epidemiology study. The data are sort of weak, but they actually suggest a supralinear dose response.

The next slide shows --

CHAIRMAN FROINES: When you say the data are weak, are you talking about that specific study, because I don't think it's fair to say that the epidemiology data on butadiene is weak.

Genevieve Matinowski and Carl Santos Brugoa in work, and others that have published over the years, was then -- much of the work was reanalyzed by Phil Cole, who duplicated the earlier work, and I think that there's greater, if you go through Bradford Hill's postulates, butadiene looks pretty reasonable carcinogen in human studies.

DR. BROWN: Perhaps this is a toxicologist speaking about epidemiology data.

If you look at the -- this is from the Delzell report, not the publication, the actual report to EPA, they fit a number of dose response models to their data, and the authors concluded that this square root model, which gives sort of a supralinear response that has a higher slope at the lower cumulative butadiene exposure levels was the one that fit the data best.

Now, EPA in their 1998 draft report actually fit a linear model to those points.

So I guess I meant in the sense that the study, this study here, was done on males only in an occupational

setting and was weak from that point of view.

But as far as the epidemiology studies go, it's probably stronger than many other ones.

DR. MARTY: The relative risk would not be characterized as a weak effect.

CHAIRMAN FROINES: Yeah. I think that overall the epidemiology has grown considerably stronger over the last five years.

DR. BROWN: The next slide shows sort of a, I hope you can see this, this is sort of barred from -- if you turn it around the right way. You can see in the upper left-hand corner we have butadiene.

And just I wanted to point out here that a lot of metabolites have been detected in butadiene metabolism, but the ones that have been studied in most detail and are of most use and from the point of view of pharmacokinetic modeling, are the 1,2-epoxy-3-butene, what I call butadiene monoepoxide, that one in sort of the center of the screen there, with one epoxide group, and further on down the diepoxybutane, the DEB.

Also the glutathione conjugates have been studied in some detail, certainly in vitro preparations.

But there are a number of further downstream metabolites that have not been studied as well, and I'll talk about one of these later, later in the presentation.

But as you can see, there are three main types of metabolism, oxidation, conjugation, and hydrolysis, which lead to this plethora of metabolites.

The one in circles are the ones that are thought to be reactive in the point of view of possibly forming adducts with biological macromolecules.

Next slide, please.

Now, pharmacokinetic chamber studies and physiologically based pharmacokinetic modeling studies have shown that mice have much higher internal doses of butadiene monoxide, or BMO, for short, either as a peak mixed venous concentration, or as an area under the blood concentration times time curve, the AC, than is found in rats.

The difference is about 1.6 fold at butadiene exposure concentrations below 1000 parts per million, and two- to three-fold higher at higher concentrations, and there is evidence of glutathione depletion in the rats, which could lead to this explanation, partially explain this difference.

Medinsky in 1994 also did some modeling and metabolism, and they suggest a greater role for the lung metabolism at lower butadiene exposure concentrations.

In this case, the mouse BMO lung concentration was 15-fold that of the rat after ten parts per million exposure to butadiene for six hours.

There's been a lot of elegant pharmacokinetic modeling done on butadiene over the years, but the bottom line here is there has really not led to an improved elucidation of the target tissue dosimetry, and more importantly the response, or the pharmacodynamic component here for the various endpoints in the rat, the lung, heart and malignant lymphoma.

Next slide, please.

A recent study, this time not with butadiene, the parent compound, but with the diepoxy metabolite, the DEB, showed upper respiratory cancer in rats, but not in mice, despite a twofold higher tissue dose to the mice. This is recently published by Henderson et al.

One conclusion here is that the butadiene pharmacokinetic models may not be sufficiently sophisticated and need to incorporate possibly more metabolites and certainly some sort of pharmacodynamic components, for example DNA repair.

The roles of other metabolites such as the diepoxybutene, diepoxybutane, the dihydroxybutene, the epoxybutanediol, and possibly even the conjugates of butadiene or even a minor metabolite such as crotonaldehyde or even the butene butenal, shown in the earlier slide, need to be defined, especially for other toxic endpoints.

Next slide, please.

This is a quote from the EPA's 1998 draft document, which is currently under revision. I looked on their Web side yesterday and I couldn't find any new information. I assume they are still revising this.

This refers to the carcinogenic endpoint that they're evaluating, and in the middle of that quote you can see that they say that any attempt to extrapolate the risk in rodents to humans, given the dramatic and unresolved interspecies differences between the mouse and the rat, would involve far greater uncertainties than basing the risk assessment on the occupational data of the Delzell et al study.

I'm not sure I would go that far, but this is their feeling, that they have actually in this draft assessment thrown out the animal data and basically based everything on this human study.

Next slide.

Okay. Basically the butadiene cancer dose response has been studied in more detail than any of the noncancer endpoints and to date we're not aware of any regulatory agency that's determined that humans are less or even equally sensitive than rodents for cancer or even other toxic endpoints.

Now, more pertinent to today's consideration, a variety of developmental and reproductive toxic effects, or

DART effects, have been seen in mice and rats exposed to butadiene by inhalation, testicular atrophy, ovarian atrophy and uterine atrophy.

In our current document or current draft document the chronic REL is based, as stated earlier, on a benchmark concentration at the five percent level of 1.4 parts per million for ovarian atrophy in mice.

We have calculated from this a human equivalent concentration of 0.25 parts per million, giving a CREL of the human equivalent concentration divided by these two uncertainty factors. The one that's in question, the threefold for interspecies and a tenfold for interindividual variation, giving eight parts per billion.

I want to point out here that the critical study is the same one used in the cancer data that had no NOEL determined at 6.25 parts per million. So we're actually extrapolating here to a value that's about five times lower for a NOEL based on benchmark dose methodology.

There are no human DART data on butadiene as far as I'm aware. So we're putting a lot of faith on this benchmark dose procedure.

Next slide.

Now, EPA in that same draft analysis that I mentioned earlier actually analyzed the same data set. They derived a human equivalent concentration of 0.38 parts per

million. As far as I can tell, the difference between the two values is that we corrected for the weekend off, the five over seven, and they didn't, I guess, and that's what looks like that's the difference between the two numbers.

Since the adverse effect has been linked largely to the amount of diepoxybutene metabolite in the target tissue, and this is in a separate study published by Doerr et all, where they exposed mice to DEB and also butadiene monoxide for 30 days, and since humans are expected to produce less DEB than mice overall, the agency concluded that they could use a smaller or less productive interspecies uncertainty factor of 1.5, allowing for some increased human sensitivity to DEB.

Doerr also found that BMO was ovotoxic to mice, but at higher concentrations, five- to tenfold higher doses.

So in this case there's sort of a disconnect here between, I guess, different people were doing the cancer assessment than the noncancer part, but the agency felt at least in the draft that they could live with a 1.5 uncertainty factor.

Next slide, please.

Now, what about the DEB? Csanady et al in 1992 found no BMO oxidation to DEB in human liver samples. These were surgical samples, 12 samples, or in five lung samples or in Sprague-Dawley rats. And they also found that the

mouse activity for the oxidation of BMO to DEB was relatively low, compared to the other metabolic steps that weren't analyzed.

More recently, Perez in 1997 found adducts of trihydroxybutyl valine, it's formed from the reaction of the epoxybutanediol with the internal valine of hemoglobin. This was found in in vitro preparations first and then in rats and also in humans exposed to butadiene by inhalation and also in the rats by intraperineal injection.

There also were a much lower level of monohydroxy adducts formed from butadiene -- excuse me, yes, from butadiene monoxide, but the major adduct formed was from the epoxybutanediol.

There's presently no adequate pharmacokinetic model to compare ovarian or uterine internal DEB or BMO dosimetry in mice versus humans, and there are no human data addressing this particular dosimetry issue.

I think the next slide shows -- this is a simplified metabolic scheme showing that you can get to the epoxybutanediol either through diepoxybutane or through the butenediol.

So just finding this adduct does not mean that it was formed from diepoxybutane, but at least there's sort of a 50/50 chance.

There's also some stereo isomerism in the products

formed, which can give you a hint about which side they might be coming from, but at least there's some indication that it's the DEB is formed in humans, or at least could be.

Next slide, please.

Now, we didn't have a lot of information on this, but despite this lack of pertinent information, we attempted to evaluate the ovotoxicity data of Doerr et al in mouse and human pharmacokinetic models. These are research models based on a number of published studies.

Although there are extensions of those studies that are published or validated in a proper sense, these are sort of research models to answer what-if questions.

There's a description, sort of a nonmathematical description, that I've attached to the handout.

What we did, we tried to simulate the ovotoxic intraperitoneal epoxide doses that were published from the Doerr study, and these doses were determined by Doerr were 39.2 micromoles of butadiene monoxide per day, times 30 days, and 3.9 micromoles of the DEB for 30 days.

And then what we did, we chose the metric of the area under the curve, the blood concentration, times time curved as the appropriate metric to use. So determined from the model now what metrics those doses would give, and we found that they would give metrics of 624 micromoles per liter times hours for BMO, and 36.9 micromoles per liter

times hours for DEB.

Then we asked, well, what sort of inhalation concentrations in these models would give those doses, and this is now in the mouse and human pharmacokinetic models.

And the results basically were for the mouse, 210 parts per million times eight hours of exposure, would give a metric for butadiene monoxide equal to the 624 figure, and 150 parts per million times eight hours will give a value in the human model for the DEB metric.

Now, I don't want to make too much out of these results. These are based on essentially taking the mouse kinetics and scaling them to humans.

And also it doesn't say anything about the response. We don't know anything about the response in humans.

But anyway you can see that the numbers are similar.

Next slide, please.

Essentially we view these various studies as indicating that there are still outstanding uncertainties in the interspecies dosimetry and response and that we think we ought to keep the threefold interspecies uncertainty factor for the ovarian atrophy.

My view is that you know this is already in our guidelines and we would need sort of very strong evidence to

the contrary for the toxic endpoint question to move away from that.

But I put these slides together to sort of frame a discussion so that the panel members would have a chance to check it out.

CHAIRMAN FROINES: Thank you.

Peter, I think you raised this issue originally, and so we should turn to you, in case you have further comments.

DR. WITSCHI: No, I don't have any further comments.

It's more on a real general basis, I think. You don't assume that people are more sensitive than the most sensitive animal species, but the data show this overall are really virtually nonexistent.

And so in the case of butadiene, I raised it because if people always do the default, even if you have data to the contrary, and then do all kind of things to still justify the default, to me that's not the very productive approach.

CHAIRMAN FROINES: I have a couple of comments.

Everything that Joe looked at, it's what I would call the front end of the process, and I think the part we're missing and we're going to need to think about it and talk about it in the future is how do we view this problem

when we consider GST polymorphism, because we know that humans have GST polymorphisms.

We know that -- I was at a meeting yesterday in which people were looking at the risk of lung cancer in males and females from an environmental tobacco smoke and the GST variation was really quite striking.

And so that when you have the so-called null allele of GST, the risk goes dramatically up with environmental tobacco smoke.

And so the heterogeneity of humans is really quite important to consider, and we tend to look at the issue from more classic toxicokinetic approaches rather than gene environment interaction.

And maybe some time in the future we can have a session and talk about how can we try and explore data that's in the literature that looks at the back end, at the lack of ability to conjugate these epoxides, so that they have a lot longer, a greater AUC and a longer residence time.

And that's why I would keep -- see, I would keep the risk factor of three, the uncertainty factor of three, precisely because I know that there are susceptible populations out that there that do have GST markers that we aren't taking into consideration.

DR. BROWN: We did include in our modeling a

somewhat susceptible population. We used some data on obese young women, and we tried to model that, because we thought the higher body fat content would prolong this process of butadiene uptake and slow elimination, more chance for the area under the curve of the critical metabolites to be bigger, so we did include that in the analysis.

DR. MARTY: Joe, you guys didn't include the detoxification kinetics?

DR. BROWN: No.

DR. MARTY: And I think that's the point.

CHAIRMAN FROINES: And with work that we've done on looking at the interaction between MEK and hexane, we find that the interaction primarily occurs at the conjugation step, not at the bioactivation.

And so if one doesn't take into account the conjugation step, you actually miss the dominant competition between those two molecules, so it's -- let me just ask one more question and then I would go forward.

You said here in the document that the statewide mean outdoor monitored concentration of 1,3-butadiene was approximately .2 part per billion. And then you talk about the air toxic hot spots.

But I'd be curious to know what you know about hot spots or ambient levels in Southern California where the monitored concentrations are clearly not going to be as low

as .2 parts per billion, and so where does your eight part per billion, how does it relate to what we find in Los Angeles?

DR. MARTY: That's actually --

CHAIRMAN FROINES: Maybe Roger knows.

DR. ATKINSON: I don't know, but I would guess that it's less than eight, possibly more.

DR. MARTY: We can look that up and put that information in here.

CHAIRMAN FROINES: Does Lynn know?

FROM THE AUDIENCE: No.

CHAIRMAN FROINES: This is going to become one of these Froines litanies, right, that every time I see a document I'm going to ask what's in the air in LA.

So but it's obviously a relevant issue. It doesn't -- the statewide average concentration doesn't tell us what we need to know, I think.

DR. MARTY: The other issue is it's emitted from the tail pipe of vehicles and that's not included in the hot spots database, which is strictly stationary source.

CHAIRMAN FROINES: If you look at the Mates 2 document, and look at the risk numbers at the LA airport from butadiene, they're quite high. So there's something about LAX that was -- caught AQMD's attention, so that there are obviously some hot spots that are not just vehicular

related.

So go ahead, Melanie.

DR. COLLINS: That completes our consideration of batch 2 A.

And I don't know whether the panel wants to -- has any other comments about the 20 chemicals in that batch.

DR. MARTY: We had some other small comments given to us that we haven't gone over, but we're making a few other small changes to the document total and then of course will go in as an addendum to part 3, our chronic reference exposure levels document.

CHAIRMAN FROINES: Okay.

DR. MARTY: So we need the panel's endorsement.

CHAIRMAN FROINES: We have endorsed the document, so unless -- we don't need to re-endorse these chemicals, do we?

DR. MARTY: This batch you haven't yet officially endorsed.

CHAIRMAN FROINES: No. I mean the ones that were dealt with today, I thought we'd already --

DR. COLLINS: It was continued for various reasons. It had been to be continued because of the organophosphate thing last time. You had to -- you didn't finalize it.

CHAIRMAN FROINES: So you need a vote from the

panel on the entire document and the issue we talked about with -- we're going to withdraw for this moment, methyl ethyl --

DR. MARTY: That's actually one that had already gone through the process, and we're going to talk about that in a second, but it's separate from this batch.

CHAIRMAN FROINES: Okay. So we need a motion to adopt these, the second batch of the chronic RELs.

DR. GLANTZ: So moved.

DR. WITSCHI: Second.

CHAIRMAN FROINES: Discussion?

All those in favor please say aye.

(Ayes.)

CHAIRMAN FROINES: Opposed.

(No response.)

CHAIRMAN FROINES: So the second batch is now approved by the Scientific Review Panel.

DR. COLLINS: Thank you.

CHAIRMAN FROINES: And thanks for the effort on this. I think that these were good questions that were raised.

And Peter particularly raised, I think, a very fundamental question that gets us out of the kind of lockstep approach to some of these things, and so that was a useful exercise. Don't you think?

DR. WITSCHI: Yes.

CHAIRMAN FROINES: Okay.

DR. MARTY: The next thing we wanted to talk about was we had a chronic exposure level developed for methyl ethyl ketone, which the panel had approved last February, and subsequent to the approval we received information from the Ketones Panel of the Chemical Manufacturers Association objecting to the use of the primary study that was the basis of the reference exposure level.

We met with the Ketones Panel in March, and we agreed to release the chronic REL for further comment.

The basis of that agreement was that the prior public draft was actually quite a bit different than the draft we ended up presenting to the panel, and which got approved, and so we felt that they were correct in being concerned that that draft had really not undergone public comment.

We then received comments from the Ketones Panel and from Dr. Graham Doyle from Vanderbilt, and we responded to those comments, and then presented the package to you several weeks ago, and are now bringing methyl ethyl ketone reference exposure level back to the panel.

So, Dr. Froines, I know you had some comment.

CHAIRMAN FROINES: Are you going to go further?

I had some agreements with the ketone folks.

I don't think that -- I don't think that one needs to -- historically, the toxicity of methyl butyl ketone and hexane have been characterized by their pathology, which Peter Spencer and Herbert Shamburg have called central peripheral distal axonopathy. And it's characterized by changes, particularly changes at the node of Ranvier and long nerves and degeneration distal to that.

And so that there was in the '70s and '80s, a whole series of compounds ranging from hexane to MBK to carbon disulfide to acrylomide and some organophosphates and others that fit into this pathologic pattern of central peripheral distal axonopathy.

And so that for a period of time, that type of neurotoxicity was considered relatively unique and people put a lot of time into studying the mechanisms of that particular neurotoxicity.

And Dr. Graham Doyle, Graham, was one of the leaders in that area of research.

And so there is some of the comments that were received, I fully concur with.

I think, however, that it's a mistake to in a sense say that neurotoxicity is limited to the kinds of changes that you see from hexane or MBK or some of these other compounds that have been so carefully studied.

So I think that one has to have a broader

definition of neurotoxicity than perhaps was used by the Ketone Panel.

So I would agree with OEHHA on that particular issue.

At the same time, I think the study that was used, the Mitran study, is extremely weak. It's weak statistically, it's weak in terms of the nerve conduction velocity measurements, and in general I think it's a study that as it sits out there by itself is very difficult to accept as a means to identify a REL for methyl ethyl ketone.

And so I personally feel that the current REL, based on the Mitran study, should be rethought, reconsidered by OEHHA, and then come back at a later time.

And I can go into more detail if you want, but I think that that's

DR. MARTY: We actually have an alternative REL based on animal studies. In fact, our original REL was based on animal studies.

So we can look at it now if you'd like, or bring it back to the panel at a later date.

It's based on Cavender study and Fischer rats and the critical effect is hepatotoxicity.

Andy, if you want to show the rest of it.

DR. GLANTZ: Wait, wait. Go back. Some of us

aren't good at speed reading.

DR. MARTY: There was not a NOAEL observed. The LOAEL was 1254 parts per million, six hours per day, five days per week for 90 days.

If you do a time-weighted extrapolation, that's equivalent to an average experimental exposure of 224 parts per million.

For a chemical with systemic effects, the human equivalent concentration is essentially the same.

DR. GLANTZ: What is RGDR, again?

DR. MARTY: Regional gas dose ratio.

DR. GLANTZ: What does that mean?

DR. MARTY: It's meant to account for differences in the rodent versus the human dosimetry in the lung.

DR. GLANTZ: That's once it gets there?

DR. MARTY: Yeah.

DR. GLANTZ: What's the number? Is it one? What you're saying here --

DR. MARTY: Because it's a systemic effect and not an impact on the lung or the respiratory tract.

DR. WITSCHI: What's the -- is the increased liver weight the only thing that was found?

DR. COLLINS: There were some other changes. There was increased liver weight in females at the three doses. There was an increased liver weight in males at the

highest dose. I think there was some increased brain weight in something. But it's not the only thing.

DR. WITSCHI: Was there any pathology?

DR. COLLINS: I'd have to check the thing. I have the paper.

DR. WITSCHI: That's been, on the other hand, that's been a very old bone of contention with increased liver weight as a toxic effect or an adaptive effect.

DR. COLLINS: I don't know. It's also dose related.

CHAIRMAN FROINES: Probably a reversible effect too.

DR. COLLINS: This is a 13-week study and they just did the animals then, so whether that was --

DR. MARTY: We applied a LOAEL uncertainty factor of three because it was considered a mild effect.

We have a subchronic uncertainty factor because it was only a 90-day study of three.

We have an interspecies uncertainty factor of three and an intraspecies uncertainty factor of ten with a total cumulative uncertainty factor of 300. This gives you a chronic inhalation REL of 2000 micrograms per cubic meter or .7 PPM.

DR. GLANTZ: How does that compare with the one you had before?

CHAIRMAN FROINES: 200 versus 700.

DR. GLANTZ: Pardon me?

CHAIRMAN FROINES: 200 versus 700.

DR. MARTY: Right. 200 parts per billion versus 700 parts per billion.

The study basically states that they didn't attribute any histopathology of the liver to MEK, but that the pathology was normal age-related pathology for Fischer rats.

So it is just increased liver weight.

I think if we had seen pathology, we would not have considered it a mild effect.

CHAIRMAN FROINES: I would suggest that we go back to the drawing board on this one.

DR. MARTY: That's fine.

CHAIRMAN FROINES: And consider it further, because I don't think anybody is going to be very happy with the pathology that you just described.

DR. MARTY: Okay. Why don't we roll it into our next batch.

CHAIRMAN FROINES: Peter, do you agree with that?

DR. WITSCHI: Yeah.

DR. MARTY: Why don't we roll MEK back into our next batch and we'll officially withdraw the existing REL.

Actually OEHHA never adopted that REL because of

the concerns brought up by the Ketones Panel.

CHAIRMAN FROINES: This isn't a criticism, it's really an honest question. There must be a lot of studies on neurobehavioral effects of MEK over the years, I would assume. And I gather that you haven't found much. I just would assume that people who look at neurobehavioral effects of solvents would have looked at MEK, because, you know, the one thing that's true about it is that it's very widely used in industry, so that there is a lot of exposure to MEK. It's just not a very toxic compound. It has air pollution implications that are different than its own inherent toxicity.

DR. SALMON: I think one of the problems is that because it is known to be a relatively nontoxic chemical, people have not paid a great deal of attention to it. It's certainly one problem.

Certainly there are neurobehavioral or neuralsensory effects reported after a fashion in the Mitran study, for instance, which was probably a better endpoint to look at, other than nerve conduction results from some standpoints.

But nonetheless I think we have to look very hard to find a good basis for a REL for this compound because the data on it isn't as good as you would hope.

DR. MARTY: Most of the studies that were done

looked at potentiation of the neurotoxicity of other chemicals.

CHAIRMAN FROINES: Well, I think it's also good if we can get Stan to look at the Mitran study, because I think the statistics are almost nonexistent, and so it's very hard to trust the comparisons that they report.

DR. MARTY: Right. They did statistics only on the nerve conduction velocity data, but not on their other data.

We did some statistics on their other data and found significant impacts, but again it's -- those are difficult to interpret that data, symptomatic type thing.

CHAIRMAN FROINES: I think in terms of the -- accepting a document that's in the peer reviewed literature, I think the panel would prefer to have documents in which the authors had done some statistics that was then peer reviewed.

It's great that you folks come in and do your own statistics, but it seems that the research papers should have had that within it to be considered. In fact --

DR. MARTY: I agree.

CHAIRMAN FROINES: -- one can honestly ask the question how did it ever get through a peer review process, given the quality of this paper.

It's Environmental Research, so it's a reasonable

journal.

DR. COLLINS: One of the reasons was it appeared in a symposium several years ago, and I think the journal relied on the people in the symposium to send them something credible.

CHAIRMAN FROINES: Oh, so it may end up being not really peer reviewed.

Because I would urge, since some of the panel members probably haven't looked at the paper very carefully, I'd urge you to look at it and make sure that you agree with what I'm saying.

But, to your credit, you didn't claim it to be the end-all be-all when you wrote your response to the ketone committee.

So let's go back and see what we can come up with.

And I think Andy is right, the problem is that this is nontoxic and nobody -- but you would have assumed that the Swedes would have at some point or the Finns would have looked into it. They've looked at all these solvents.

Okay.

DR. MARTY: Okay. I think that concludes our REL agenda item.

DR. COLLINS: Thank you.

CHAIRMAN FROINES: We're altering the agenda.

We have a problem that Paul Blanc can't be here

until about noon, and so what we're going to do is -- and the closed session we consider to be a very important meeting for the panel, since there are two suits pending and a third administrative procedure, so we want to take that up as soon as we can.

But we wanted Paul to be here for that, since it does concern him.

So we hate to have a legal discussion about a suit or two suits without one of the key players able to hear and participate in the discussion.

But so at this point I'd like to move on to the overview of Senate Bill 25, which I think is more informative for information purposes than having any major decisions on the part of the panel.

Has everybody on the panel been sent this summary document, Peter?

DR. GLANTZ: Which summary document?

CHAIRMAN FROINES: This SB 25.

DR. GLANTZ: No.

CHAIRMAN FROINES: It wasn't? That's an oversight. I'm sorry. Hopefully we'll cover it and then we can get you the document.

DR. MARTY: Okay. This is Melanie Marty from Office of Environmental Health Hazard Assessment.

I'm just going to give a fairly brief overview of

Senate Bill 25, which was written by Martha Escutia last year in the past. It's called the Children's Environmental Health Protection Act.

And I'm going to go through -- the first slide will be just a very brief overview just to give you an idea of the breadth of the act, and then mostly talking about the role of the OEHHA and the panel for the remainder of the slides.

The requirements of the act include -- the basis of the act is to get people to look specifically at infants and children when setting ambient air quality standards for the criteria air pollutants when evaluating health effects of the toxic air contaminants, but it also includes trying to look at our air monitoring network that the Air Resources Board already has set up and evaluating whether that's adequate to really measure exposure of children, and it requires monitoring at specific areas where there are children.

There's also provisions in there for the South Coast Air Quality Management District to notify day care centers when standards are exceeded.

And it also created a children's environmental health center that is in Cal EPA.

I did mention already that we are reviewing all existing health-based ambient air quality standards to

determine whether they adequately protect the health of the public, including infants and children. There isn't any SRP involvement, but I did want you to know that was going on. It's a big deal.

We actually already have gone through a prioritization process to prioritize for re-review that underwent public comment and peer review by the Air Quality Advisory Committee, and tomorrow will be an item at the Air Resources Board just to adopt the order in which the chemicals will be reevaluated.

So that's all I'm going to say about the criteria pollutants.

The statute requires OEHHA to list up to five toxic air contaminants that may cause infants and children to be especially susceptible to illness and we have to create this list by July 1st, 2001, and the SRP is responsible for reviewing the report containing the justification for the chemicals on the list.

DR. GLANTZ: When you say up to five toxic air contaminants, does that mean of the ones that are already identified?

DR. MARTY: Yes.

CHAIRMAN FROINES: Can I ask a question about that?

DR. MARTY: Sure.

CHAIRMAN FROINES: When you're making up -- when you're making this determination that children are especially susceptible to illness, at some point are you going to describe for us what the criteria for that determination is going to be?

DR. MARTY: Yes. It will be in the report that you folks review.

CHAIRMAN FROINES: So that the actual methodologic approach will be reviewed by the panel as well?

DR. MARTY: Yes.

CHAIRMAN FROINES: Gary.

DR. FRIEDMAN: One thing I'm not clear about is whether the illness must occur during infancy and childhood or whether if the person when they're exposed at a very young age is especially susceptible to getting something 30 years later, is that also --

DR. MARTY: That's included, yes.

DR. FRIEDMAN: Are both of those?

DR. MARTY: Both those concepts are included in the way we're looking at it.

DR. FRIEDMAN: Okay.

CHAIRMAN FROINES: My question is actually different than that.

My question is when you look at that, are you going to consider different routes of exposure as well as

the toxicologic side of it?

DR. MARTY: Yes. Actually the next slide might clarify some of that.

It actually states in the statute that when we're evaluating chemicals we have to look at exposure patterns that might result in disproportionate exposure of infants and children. For example, kids have much -- toddlers have must greater mouthing behavior than an adult, so oral exposures can be much greater in a child than in an adult.

Likewise for chemicals that are heavier than air, the exposures closer to the ground, the concentrations closer to the ground are heavier, and you can get very large differences in the inhalation exposure to an adult versus the inhalation exposure to a toddler standing in the same room.

So those kinds of things need to be accounted for.

The statute requires us to account for special susceptibility of infants and children, and this gets at the idea of windows of susceptibility during development of organs.

And effects of exposure to pollutants with common mechanisms of action, we do do that right now with our hazard index approach, so we'll be looking at the hazard index approach again.

And finally the statute requires us to not -- they

didn't want us to look at criteria air pollutant in a vacuum, and toxic air contaminants in a second vacuum, so is there interactions between the two.

DR. FRIEDMAN: What's the difference between the two?

DR. MARTY: The criteria pollutant are those chemicals which have actual levels which are standards not to be exceeded, and they are generally the major components of what we think of as smog. So particulate matter, carbon monoxide, ozone, nitrogen oxide, sulfur oxides.

And then I think there's a couple more. Hydrogen sulfide is one.

We actually have a criteria for lead, but lead is also dealt with in the toxic air contaminant program, and we intend to deal with it in the toxic air contaminant program for this process, rather than reevaluating a lead ambient air quality standard.

It was a little more important when there was lead in gasoline. It's more of a hot spot issue now rather than a general ambient issue.

The ramifications of developing this, creating this list, is that within two years of the creation of the list, the Air Board has to reevaluate their airborne toxic control measures for any of the chemicals that make the list.

So in other words, by July 1st, 2003, if a chemical makes the list which does not have an airborne toxic air control measure, or an ATCM, then the Air Board must develop one within three years of the listing of that chemical.

CHAIRMAN FROINES: Would that mean that the Air Board would actually reconsider controls on point sources as well as ambient?

DR. MARTY: Yes.

CHAIRMAN FROINES: For lead, say?

DR. MARTY: Yes.

DR. FRIEDMAN: Was the reason to limit this to five so as not to overburden you, or what?

DR. MARTY: Exactly.

DR. FRIEDMAN: Maybe you can go through and find -- if you found like six really important ones you just don't -- you can't do the sixth?

DR. MARTY: Well, we can, because we're allowed to update the list.

But the initial statute required up to five, and I think ARB would really appreciate it that it be no more than five the first time around, because of this measure that they have to deal with looking at the airborne toxic control measures.

Okay. Jim.

The progress to date, we started out with all of the TACs that are already identified, and we went through a prioritization process based on amount of emissions, the toxicological data availability and the toxic endpoints. In other words, for the toxic endpoints if it was something like an eye irritant, we would be less concerned than if it was a neurotoxicant, because children are likely to be more sensitive to most neurotoxicants than adults, so we considered that.

We ended up skinnying down the list to 33, so we made a cut at 33 TACs, which we selected for focused literature reviews of the toxicology and epidemiology literature to see if there are any indication whether infants and children might be more susceptible to that compound than adults.

DR. GLANTZ: Do you have the list of the 33?

DR. MARTY: We do, but it hasn't been released.

The literature reviews are currently being conducted. Some of them are in house, but most of them are by contract by UC, various UC people.

CHAIRMAN FROINES: So that Kent Pinkerton at Davis is doing a lot of work on animal models that look at developmental changes associated with particulate matter exposure, so PM could be one of the --

DR. MARTY: PM actually we're dealing with a

criteria air pollutant, so we did have Kent involved in that part of the process.

The next steps are to collect literature reviews of all 33 chemicals and study those reviews, and then further winnow down the list and select ten, based on the likelihood of having potentially differential impacts on children relative to adults.

Then we will prepare the report providing the criterion and the justification for the listing choices and release that for public comment.

OEHHA then will respond to public comment and bring the report and the comments and the responses to the panel.

And SRP will review this report, provide comments to us, and input to the selection of the first five TACs.

Then we will revise our report based on the panel comments and submit it to the Air Resources Board. This has to be done by July 1st.

CHAIRMAN FROINES: We'll get ten?

DR. MARTY: You'll get ten. You'll get ten.

Actually it may be a little more than ten, so there's some wiggle room in there, depending on what we see in the reports that we get back, which is -- we've gotten three back. We're getting 30 more this month.

So what the panel will see from OEHHA, I broke it

down between 2001 and 2004, and then 2004 and beyond.

Initially the report describing the criteria for identifying which chemicals may differentially impact children, you will see that hopefully by March, the beginning of March. This will include the list of the ten candidates or maybe a little more, and also our responses to public comment.

As part of this process we are actually being required to go back and look at the health evaluations we've done for the toxic air contaminants and decide whether they adequately protect children.

DR. GLANTZ: What is the CPF?

DR. MARTY: Just a second. I'll get there.

DR. GLANTZ: I'm sorry.

DR. MARTY: So as part of that process we are evaluating our existing methodologies that we use to develop cancer potency factors, CPF, or unit risk factors, and reference exposure levels for adequacy in protecting children.

We have to do this before July 1st, 2004.

The panel is going to review any proposed revisions to our health risk assessment methodology that we think we need to make in order to adequately protect infants and children.

And so that will be happening more like 2002

through 2003.

Then beginning July 1st, 2004, OEHHA needs to annually evaluate at least 15 TACs and provide threshold exposure levels. That's the legal term. We just call those reference exposure levels.

And non-threshold health values as for the carcinogens, e.g., the cancer potency factors, if that's appropriate, for each of the 15 toxics.

And then the panel has to review our evaluations of the health effects of those toxics.

CHAIRMAN FROINES: Is there a time table? Is that 15 per year?

DR. MARTY: Per year. It's 15 per year.

CHAIRMAN FROINES: 15 per year?

DR. MARTY: He's laughing now.

CHAIRMAN FROINES: We want a raise.

DR. MARTY: The activities are scheduled to continue until all the TACs have been evaluated.

And also I wanted to add that OEHHA shall update the list by July 1st, 2005, so they have a provision in there to update the list. They've given us a few years to work out methodologies and the list update follows the review of the health evaluations by the panel.

This is just a time line. I can provide copies of the time line to the panel. Actually we should have

attached them to the handouts.

Just gives you an idea for this first set of five, what we're doing and where we are. We started out with all of the TACs and then I mentioned we eliminated certain ones based on really lack of data on toxicity or exposure, got down to 90. Skinnied that down to 33. The literature reviews are ongoing.

We are developing the document as I speak.

And we will be preparing then a summary of at least ten, possibly up to 20, chemicals for public input and then review by the panel to decide which five chemicals should make the first cut.

So it's a lot of work in the next six months, basically.

DR. WITSCHI: Have you already developed some criteria how you're going to identify those five? I mean, is it going, for example is it is going to be very toxic to just a few, or something that's not really that toxic but might effect many? All those kinds of things.

DR. MARTY: All of that comes into play. If it's very toxic, but there are hardly any emissions, then it would rank lower than something that is fairly toxic with lots of emissions and exposure.

And we actually did that first when we did that first cut of the TACs. We based it on emissions, times

toxicity. So we used the same method that ARB uses to prioritize their candidates for TAC.

DR. WITSCHI: Yes. What is the first thing we are going to see, because I would like to see all 90 to begin with and then the 33 and then your five.

I'm not saying I would like to do the work in ranking them, but I would like to see everything that you have considered, simply because once in a while one of us might have additional opinion on where something belongs.

DR. MARTY: We're going to describe everything we've done in the report that you get.

So if you disagree with our -- and the reason we're providing not just five for you to look at, but ten to 20 is because we know that there's going to be people who think one of these is more important than another, and we need to hear that.

But we probably will actually end up if we gave the panel the same chemicals and told them to do the same thing, we'd probably end up with about the same top 20 or 30 anyhow. That's my guess.

DR. WITSCHI: Have you looked at this report that was issued, it was about five or -- five or eight years ago. I think it was called comparative risk or relative risk, where it was a huge committee which tried to rank all the agents which are around us, and I was on that one. I was

actually on two of them.

DR. MARTY: The comparative risk report?

DR. WITSCHI: Yes.

DR. MARTY: The comparative risk?

DR. WITSCHI: Yes.

DR. MARTY: Yes. We have that.

DR. WITSCHI: That should give you some idea of what you might get into.

DR. MARTY: We have that.

There are also actually a number of publications that have come out looking at children as susceptible subpopulations, and the reasons why that might be. So we're looking at all that information also.

DR. WITSCHI: I wasn't referring to the relative risk report with regard to children. I was referring to it, how incredibly complex and difficult and next to impossible it is to rank any of those things.

DR. MARTY: Yes. Yes. That report had nothing to do with kids actually. It was just is this thing more risky than that thing.

DR. WITSCHI: The other one is this was about ten years ago, the US EPA came up with unfinished business, and the Health Effects Panel, of which I was a member, couldn't come up with any intelligent ranking.

And the most interesting thing which came out of

the unfinished business report is that the people really had something to say what was bad and what was not so bad, were people who dealt with the environment, but not with the health effects.

The health effects were stymied because we couldn't say what's more important, ozone or maybe lead or a cancer agent where we know there's only very little around, as opposed to an air pollutant which might not cause that much, but there's a lot around.

DR. MARTY: We're obviously not in as envious a position as people who work on criteria air pollutants, because they have lots of epi data and they have lots of data on kids, but there are certain compounds where there have been a lot of data. Lead is one of them. And in fact the basis of our TAC document, as you'll recall, impacts on children.

So the first five are likely to be chemicals where there is a reasonable amount of actual hard data that indicate kids are differentially impacted relative to adults.

DR. WITSCHI: You said for children. I think if I get that one, you said the concentrations are lower where they breathe? The breathing zone of toddlers.

DR. MARTY: If a chemical is heavier than air, it tends to be more concentrated in if you're in a room, the

lower down you are --

DR. FUCALORO: Like a solid.

DR. WITSCHI: I know that.

Is it really established that there's a breathing zone for toddlers which is --

DR. ATKINSON: I wouldn't have thought you would find that unless it's in an enclosed area with almost no air movement.

DR. MARTY: Yes. It's generally been found in a closed area.

For example, there's a somewhat famous report of a house being painted with latex paint that had mercury as a fungicide and a three-year-old in the house came up with signs of mercury toxicity, where the adults and an older sibling were unaffected.

DR. WITSCHI: There's actually one spectacular incident about this thing being heavier than air, and this was about when 15, 20 years ago, this lake in Africa, which blew up, and the carbon dioxide spilled over and about 1500 people died.

DR. FRIEDMAN: I'm just curious, when you get a new major responsibility like this from the Legislature, do they also give you added resources to carry it out or will this cut into your other work and we can expect slower production of other reports that you had planned in the

past?

DR. MARTY: Well, when we get another responsibility from the Legislature, we are given the opportunity to what they'd call a bill analysis, and part of the bill analysis is an estimation on our part of how much we think it's going to cost to do that.

And then we have to go through the channels to get the money approved. Very rarely do they actually put the appropriations in the bill anymore, because it won't pass if they do that.

So you go through another set of processes to get the money from the Department of Finance.

But I can tell you that we got I think less than half what we asked for.

So it does impact on other things that we're doing.

At the same time this is an amendment to the statute that set up the toxic air contaminant process to begin with. So it just adds it to the TAC process, but we're already looking at that stuff anyway. We're just going to be doing more efforts to focus on children, both from the exposure standpoint.

And we did do some of that in our exposure document for the hot spots, where we had for chronic exposure we had separated out children from adults and when

we developed our distributions and our point estimates.

So we have done a little bit of that already.

DR. FRIEDMAN: This panel I know is always putting pressure on the agencies to produce reports in a timely fashion. As a result of this new assignment, should we expect that other reports will be coming more slowly or that they should be coming at the same rate of speed?

DR. MARTY: I think they will be coming a little more slowly.

So, for example, if we're asked to do a toxic air contaminant report on a new unidentified TAC, it's going to be difficult to fold that into this process, time wise.

CHAIRMAN FROINES: Well, it's following up on what Gary is saying, having been here since the beginning of this process, in the beginning, you know, we took benzene and we did benzene, and that was a major effort.

And then we did ethylene dibromide and that was an effort.

But since that time, since we've been doing chemical by chemical, we've added pesticides that we now are putting enormous effort in. We've developed a certain number of workshops that we hadn't done before. We had your acute and chronic RELs. We have added the methodology for risk assessment. And now we're adding SB 25.

So that one of the problems is that we've added an

enormous number of responsibilities to this panel, and there is a question about how do we function as an advisory panel within that particular context, because clearly one of the good things is people respect this panel, so they give us work to do. But as long as they keep respecting us and keep giving us work, we're still the same group of nine people who meet on average once every couple of months.

So we don't get the same actual improvement in resources that you all do.

So it's -- I'm a little concerned about, which I think is your implication too, of that we become, you know, what's that tunnel in going into Walnut Creek, we become the --

DR. MARTY: Caldecott.

CHAIRMAN FROINES: -- the Caldecott Tunnel.

DR. WITSCHI: There's a light at the end of it.

CHAIRMAN FROINES: I think your implication was that the light will seem very far away, though.

DR. WITSCHI: Well, you don't know if it's a light or a train coming there.

DR. GLANTZ: Could I -- so the chairman thinks we deserve a raise, I think.

CHAIRMAN FROINES: No. I'm not saying that.

DR. GLANTZ: No, I know --

CHAIRMAN FROINES: I do think that it raises a

question, for example, Elinor Fanning has played a very important role as a consultant to this panel, and so I think that we have to consider how can we best do our job within the time constraints that everybody on the panel has. That's all I'm raising.

DR. GLANTZ: Can I just get back and add, I actually agree with that. And I think she's done a great job, actually. That summary, which I reread, which you sent around to us with bad memories, was very excellent actually.

I just want to clarify a couple of points.

One, what you're doing is you're going back over the existing list and looking for areas in which kids have special susceptibilities; is that right?

DR. MARTY: Yes.

DR. GLANTZ: So if the kids are sort of like everybody else, or we already -- in a few cases, as you mentioned, already looked at kids, and that in the report that was done, those don't have to be revisited?

DR. MARTY: Exactly.

DR. GLANTZ: So this is just looking for places where they may have been overlooked?

DR. MARTY: Right. For the vast majority of toxics, we're not going to have information specific to kids. We might have for a handful some information where they exposed animals young or even in utero, and we actually

if it's a developmental endpoint for a reference exposure level, we've actually already looked at the developmental endpoints.

So the bigger issue is our general, in my mind, are our general methodologies adequate to protect kids. For example, we have the tenfold uncertainty factor intraspecies variability, is that adequate to protect a kid versus an adult?

So those are the kinds of questions that we're going to address when we look at our risk assessment methodologies.

CHAIRMAN FROINES: But you also have to look at mechanistic issues, because if you know that certain enzyme systems develop slowly and certain chemicals require biotransformation to be activated, then you have a potential enhanced risk because of the pace at which developmental processes occur.

DR. MARTY: Correct.

It also works in the other direction, where a chemical has to be activated. There's a very nice article by Cristay, Tia Cristay, and he looked at the development of cytochrome P 450 isoforms starting mid-gestation through age 25.

And you can clearly see that the isoforms are different neonatally and develop slowly into adults, and in

many cases in the pharmaceutical literature you can see that kids can't activate a chemical to a proximate toxicant. Likewise they can't detoxify either, if that's the step that's --

CHAIRMAN FROINES: We're going to have to work out a way in which some of the important articles that you identify end up getting sent to the panel, so that our level of knowledge can grow with yours, because a lot of people don't necessarily work on some of these.

DR. MARTY: I'd be happy to set up some presentations to the panel too, prior to you getting the document for review, that go over some of these main issues.

CHAIRMAN FROINES: I think, keep in mind with Peter's request is that he would like to see the 90 and the 30 and the, you know, whenever you can release that I think people would be interested to see how the process is going forward.

DR. GLANTZ: My understanding was that we should be able to look at that stuff prior to public release. I mean, we're certainly in the reports that have been developed, we've seen prerelease drafts.

DR. MARTY: Yes.

DR. GLANTZ: And I actually had the same thought. I kind of like to see what the lists were too.

So I think it would be helpful if those could be

circulated.

The other thing, and I'm not trying to make more work for you when you've already got a lot of work, but you may have already done this, if you had it, it would be interesting to see which things on the list have sort of already been taken care of for the reasons that you outlined before. I think that would be a useful thing to just know.

DR. MARTY: Okay.

DR. GLANTZ: There may be a few.

DR. MARTY: Why don't I put together a packet for the panel then and send it to -- describes what we've already done and where our thoughts have been on this issue.

DR. FUCALORO: Because it's not clear to me exactly how you get this list down, and I think that's what Peter is saying, and I'd like to see --

CHAIRMAN FROINES: There's all this data that's developing on children being born, and I don't remember the details very well, low birth weight or obese or various things, that then make them susceptible to hypertension later in life, to cardiovascular disease, and one of the questions that we really have no knowledge of is to what degree do environmental chemicals impact that process as they go through their maturation, given that they start with certain characteristics that put them at risk.

And I don't know if there's any literature

whatsoever on that.

DR. MARTY: There's some literature. For example, Ira Taeger and John Baums and Kent Pinkerton and others have looked at lung development and they actually have some studies where they looked at impacts of prototype toxins on lung development and how that affected lung function later on.

There are some human studies that have been done.

A lot of people have focused on premature births and how that impacts function later on.

But there are studies that have looked at toxicant exposure and how that impacts function later on.

So there is a certain amount of literature that we're looking at.

DR. FRIEDMAN: I don't know if this is premature to ask, but just to get a feel for your thinking, I'm just thinking of two hypothetical toxic air contaminants, one of which would cause a rash in a child, but not in an adult. Say one out of every hundred children exposed to it would get a rash, but adults are not affected for some reason. Whereas another chemical would cause both the children and adults to get, say, one in 10,000 exposed would get leukemia. Which would you say is the more important?

DR. MARTY: It's hard to answer that question, but I can assure you that one of the things we're looking at is

not just a quantitative difference in response, but a qualitative difference in response.

And the one thing that pops into my mind, which everybody is familiar with, is Minamata disease. You had moms exposed to the same amount of methyl mercury within a bounds, as the babies either in utero or just post-natally, and it's the babies that had profound neurologic impacts and the moms had nothing measurable.

So that's an example of both a qualitative and quantitative. You couldn't even measure the effect in an adult.

And we see that a lot in development studies where --

DR. FRIEDMAN: I'd be much more worried about something that causes leukemia in one out of every 10,000 kids exposed to it, even though they're not more susceptible than adults, than I would in something that causes a transient skin rash in one out of a hundred, even though adults don't get it at all.

DR. MARTY: Yeah. Oh, yeah, most definitely. So the severity of effect, that's something that considered.

DR. FRIEDMAN: That will definitely enter into --

DR. MARTY: Yes.

CHAIRMAN FROINES: Question about one of the things that triggered concerns about children, of course,

was the -- I think it was a 1993 National Academy of Sciences report on pesticides in children, and the question is where do pesticides fit into this equation and is there any relationship with DPR within that context.

DR. MARTY: Right now the statute only addresses already identified TACs. So insofar as there are pesticides that are identified as TACs, they're subject to this whole process.

DPR has talked to me about what we're going to do with kids. We're trying to get everybody included, especially when we start looking at our risk assessment methodologies and revising those, because they are well aware that that's going to impact them as well.

DR. GLANTZ: Now, what happens if something gets added as a TAC, does that just automatically get rolled into this process?

DR. MARTY: It's rolled right in and in fact if there's a candidate TAC from the get-go we're going to be looking at whether or not there's differential impacts on children.

CHAIRMAN FROINES: So if we were to get styrene for just as an example, and I think we are going to get styrene -- I'm looking at Janette Brooks.

FROM THE AUDIENCE: It's already a toxic air contaminant.

CHAIRMAN FROINES: But I thought we were still going to get it.

My point is that I guess this is the same question as Stan, will every TAC hence forth have a section that deals with children's susceptibility?

DR. MARTY: Yes. Yes.

CHAIRMAN FROINES: So that's an ongoing requirement forever?

DR. MARTY: Yes.

DR. GLANTZ: Well, you know, this brings up the issue of ETS, which we took right up -- I can't resist this. We took right up to the point of recommending listing as a TAC, and there are huge differential effects on kids. Huge huge differential effects on kids, and they are the most susceptible subpopulation.

And it seems to me that we ought to finish the process that we started with ETS, and it ought to be rolled into this, because it's just the elephant sitting in the middle of the room, you know, when you talk about effects of air toxics on children.

I don't know how the rest of the panel feels about that.

DR. WITSCHI: I would say that's the most important one there is.

DR. GLANTZ: How can we get the process, you know,

we took it right up to the end, and I think all that's left to be done, and I don't know what's involved, would be for the ARB to list it. And I mean is there anybody here who could speak to that?

CHAIRMAN FROINES: First time Janette's opened her book all morning, to write something down. It was, is now. So that she may be making a note --

FROM THE AUDIENCE: I'm being watched.

CHAIRMAN FROINES: I actually have no idea whether you opened your book earlier but --

DR. FUCALORO: It was a good guess.

DR. GLANTZ: That's why you're the chair.

I mean, I think that -- I mean, with what Dr. Witschi said, I mean, I think we should -- we're just about there with that. It got sort of put aside largely because of political pressures at the time and I think we ought to just finish it and it ought to be part of this process. The basic work is all done, including there's a whole chapter too on kids in the report.

DR. WITSCHI: I'm not so sure it was the political pressures. I thought one of the reasons was that it's unenforceable.

DR. GLANTZ: No, I think it was political pressure from the Governor's office. I was told that in those words by several sources. But we have a new Governor now.

CHAIRMAN FROINES: So this is an action item. This is an action item, and so I think that the action item would be that the panel request consideration from ARB about taking up ETS, and that that would imply that the panel is suggesting that ARB take up the ETS.

DR. FRIEDMAN: I just didn't realize that there was this -- that process didn't get completed because we got this big book, beautiful report. I thought it was all done.

Could you just for the record tell us what happened? I didn't know that it wasn't a toxic air contaminant.

DR. GLANTZ: What happened is -- were you at the meeting? I forget who was at the ARB meeting.

What happened was there was a huge amount of political pressure put on by the Governor's office, and as a result the ARB, I forget technically what they did, maybe someone can -- Bill Lockett maybe can tell us.

I think they took notice of it or received it, but they didn't act to list it.

And in fact one of the members, there was a Dr. Friedman, I think, also on the ARB and he said why aren't we listing this, and there was some mumbo jumbo response provided.

And I sat quietly because at the time we were embroiled in the controversy over diesel and I thought --

but I think now is just time to go back to them and say you have a perfectly good report. It went through the whole process. There was all the public comment, et cetera, et cetera.

The only thing that's changed since then is the evidence has gotten stronger and we should ask them to simply do what -- finish the process, whatever that, I don't know exactly what would be involved.

And then I think we should ask them to do that expeditiously, and I think it should be rolled into this, what's the bill?

DR. FUCALORO: Stan, when you say we should ask them --

DR. GLANTZ: The SRP. I think the SRP should request --

DR. FUCALORO: Should actually do something? That's not generally with our purview. I don't mind doing it, I'm just saying let's understand -- what we do is -- we did our job.

DR. GLANTZ: Yeah.

DR. FUCALORO: We had the findings on it.

And I was like you, Gary, I didn't realize --

DR. GLANTZ: Yeah. Well, there was -- I think we should -- I don't think we can direct them to do anything, but I think we should request that they take it up

expeditiously.

And then once that's done, that it be rolled into this process Melanie is talking about.

CHAIRMAN FROINES: Well, I think Tony is raising an important point, because without going into all the detail, the two suits that have been brought against the panel allege that our -- let's take diesel, that our unit risk factor is a regulation and agencies are using it as a regulation.

Now, we never intended it that that be the case, but that's what's being alleged.

And there has always been a very important historical separation philosophically, intellectually between the risk assessment process and the risk management process and that we have stayed out of the risk management process to preserve the scientific integrity of the panel.

And I think the two that agree that we start to make a recommendation about a process that in essence sets in motion a regulatory process, and then we have, although we do recommend compounds be listed as toxic air contaminants.

So on the one hand we recommend they be listed as toxic air contaminants and so it seems to me that that's what we should do at this point, because that's within our historical purview.

If we went beyond that in any way to recommend that all of sudden now ARB should start to regulate ETS, then I think that's dangerous.

DR. GLANTZ: No, no. I agree. I was not proposing that we recommend that they regulate anything.

But I think it may be that the appropriate thing to do would be to go back and get the findings, because there was a lot of negotiating about that wording, because of this issue, and simply move forward a recommendation that it be listed as toxic air contaminant, which isn't, I think isn't exactly -- I think the findings sort of side stepped that issue, because of all the politics, and so it may be that that's all we should do is just recommend that this list this.

DR. FUCALORO: I'd like to see our document again. I don't have a copy.

DR. GLANTZ: I can run upstairs to get it.

DR. WITSCHI: I personally -- I was given those final list of compounds and ETS wasn't one of them. It just was lost, because the most important public health problem would not be there.

And I think it's the panel's, I wouldn't say obligation, but we can certainly point this out.

CHAIRMAN FROINES: Bill, do you have any -- Bill or Janette, and I don't know who is the most appropriate,

but Bill was involved in this historically. If we go back and look at our findings --

DR. GLANTZ: I notice he's staying back in the back.

CHAIRMAN FROINES: I notice that. I wasn't going to comment.

MR. LOCKETT: My apologies, Mr. Chairman.

DR. FUCALORO: State your name and position, please.

MR. LOCKETT: Bill Lockett with the Air Resources Board.

I've only heard portions of this discussion, so I'm happy to respond.

CHAIRMAN FROINES: I think that the question that Stan is raising is, and I don't even know if we need an answer from you, I think it's really up to the panel. I think that if you have any clarifying comments, I think that would be what we would seek.

I think what Stan is suggesting is that we take the findings that we developed on ETS, review them and perhaps send a new version, if you will, that recommends that ETS be listed as a toxic air contaminant.

MR. LOCKETT: I gather from that you're thinking about updating the findings that the panel did before?

CHAIRMAN FROINES: That's right. I think that's

right. Does everybody agree?

DR. GLANTZ: Well, there's two things you could do. You could update them, which would require collecting, probably going through and adding to the literature. And what that would do, because it's the literature I follow, is it would further strengthen them.

Or what I was just thinking of is to just take the findings as they existed, and given that I don't think anything has come forward that would lead us to -- lead to less strong findings, and simply forward those to the board and say we recommend this be listed as a toxic air contaminant. Probably we could --

DR. FUCALORO: Do the findings say that?

DR. GLANTZ: Maybe what we should do in the interest of time is table this discussion, and at lunch I can go get that stuff out of my office or we can look.

But I think the clear intent of my suggestion is that we -- that the board, that we do what we can to get the Air Resources Board to finish the process of listing ETS as a toxic air contaminant, which didn't happen when it was presented to the panel -- or to the board, rather.

CHAIRMAN FROINES: I think that the way to say -- let me just say it a little differently. I think because I am concerned about the risk assessment, risk management process, and I think that what we can say is that based on

new scientific evidence has accumulated, and, secondly, based on the concern with children's health that we think the panel would like to review its recommendations with respect to recommending ETS as a toxic air contaminant, period. And send any augmented findings that we consider relevant.

DR. GLANTZ: The one thing I would add to that, I mean, I think that we probably shouldn't -- we probably can't act on that at this meeting, because it's not on the agenda, but I would hope that we could do this expeditiously, given the deadlines that are established in the bill that Melanie was talking -- was it SB 25 -- in SB 25, so that this can be taken into account in those deliberations, which are operating on a pretty short time frame.

CHAIRMAN FROINES: It's particularly interesting, because, as I said earlier, there's a lot of work coming out now on polymorphisms, genetic polymorphisms, in relation to ETS, and so there's a very strong database, very sophisticated database emerging with respect to ETS.

DR. GLANTZ: You know, the other thing, and then I think we should probably move on, but one of the areas that's gotten very hot lately is the issue of breast cancer, ETS and breast cancer, and it's beginning to look like exposures during puberty are particularly important.

So this is an area where another very important endpoint that may -- I mean, it's looking like there aren't big effects in older women, but in women during puberty and first pregnancy, that exposure seems to be the riskiest.

So I mean I think it's very -- that isn't in the document that we approved, because that research was, I think, was published after it was written, but I think it's very important that that get into these SB 25 discussions.

DR. MARTY: That's primarily studies with active smokers?

DR. GLANTZ: No, no. Passive smokers.

CHAIRMAN FROINES: Does the panel have any other comments about the SB 25 discussion?

Thank you, Melanie.

Let's take a ten-minute break and then go on.

(Thereupon a short recess was taken.)

CHAIRMAN FROINES: We're going to go to the follow-up discussion, item 4, follow-up discussion of the October 4th panel workshop.

Because that's going to be a progress report, rather than them coming in with firm risk assessment guidelines for our consideration, and I thought that since it is an updating about their activities since they -- since the workshop, that that again was something that we could do without Paul being here.

So Gary is back, so we do have a quorum.

So we are going to move on to item 4, and it appears as though Melanie and Paul Gosselin are going to be the participants.

DR. FUCALORO: Or two victims.

MR. GOSSELIN: I wouldn't say that.

Thank you.

At the last meeting's workshop on OPs, we left that workshop and went back to go back and take a look at our OP, the policy we have for OPs, and one of the things in consultation with OEHHA to come back and present to the panel what our policy guidelines are regarding OPs, and we have, as you know, a number of OPs that have already come before the panel and we have a number of them coming up, and we wanted to make sure that the criteria we used and the issues are well articulated, and we have a standard process of dealing with them.

When we went back and looked at some of the draft papers that we've been using over the years, and I think in light of the lengthy discussion over how EPA went through and crafted their policy, we actually -- and OEHHA came across the same lines, that there needed to be a, I think, a major rewrite and almost a new document that would much more clearly articulate, without any vagueness, what sort of issues we deal with with risk assessment and OPs and to try

to clarify how we view some of those scientific issues.

What we wanted to do today, and staff has spent the last couple weeks spending a considerable amount of time working through these issues that have come to the point, at least today, is a status of the outline and presentation of some of the issues that will go into the policy. It's going to take some more time to actually go through some of those issues and put pen to paper and make sure they're articulated in a way that it's far more definitive and clear than some other policies that are out there.

At this point I'll turn it over to Melanie to give the progress to date on this, and what you'll also find is we're going to have a staff joint presentation.

CHAIRMAN FROINES: Paul, just before we move ahead, when do you anticipate that you would be coming back to the panel with the final document for review?

MR. GOSSELIN: We're actually considering a status in January, but some of the issues, as we heard in the workshop, are fairly detailed and complex, so I would say five, five, six months.

CHAIRMAN FROINES: Five or six months?

MR. GOSSELIN: I think one of the things that as staff started to take a look at this, we wanted to make sure -- and that was kind of the point from the workshop, to make sure that what guidelines and policies we come out with

are going to be fairly solid, that it's not going to be vague, and articulate some of the points you'll hear in a moment.

We're trying to expedite this as quickly as possible and maybe get it done sooner than that, but I think in January we'll have a better idea on the status.

CHAIRMAN FROINES: Why don't we -- let's assume six months from the time of the workshop, so that workshop was held, what was the date? October. So if you figure November, December, January, February, March, so you would -- so shoot for a final document in at an April meeting.

Is everybody comfortable with that?

That wasn't just a question to the panel, and I heard some comments in the back of the room there.

DR. GLANTZ: I'm comfortable. I think that would be quite reasonable. I mean, we do want to move this along.

DR. FUCALORO: On the other hand, we don't want to push too hard. That's why we're asking. So I guess your response --

DR. GLANTZ: I think six months from the workshop is reasonable.

DR. FUCALORO: I guess I'm looking for a response from staff.

DR. GLANTZ: I want to push. Six months after the

workshop. I was expecting something back in a month or two.

MR. GOSSELIN: Well, we can give you item number 4, question 3. And honestly I think it is -- I'll have to go back and talk to staff about exactly what, because some of these issues are complicated.

And I think you heard a lot of groans about the six-month time frame on getting this together, and they have spent the last couple of weeks looking at these issues critically, and wanting to get a policy that when it comes back here we're not going to exchange a lot of questions and have us sit here and say, well, we really don't know, or it's a case-by-case basis, and get into a real vague exchange.

What I could do is go back after this, confer with staff and get a better time line at the next meeting as to exactly how soon a draft can be put together.

CHAIRMAN FROINES: All right. I don't know if anybody else wants to comment, but the comment about fair amount of effort in the past couple of weeks, remember, it has been seven weeks since the workshop, so the danger is that these things -- if the endpoint becomes very open ended, people treat it like a gas, it fills any volume you give it, you know. And we want to avoid that at some level.

So I think Stan is right to push, but I think you have to push and make it also -- make it reasonable so we

get the best product possible.

It also means that the panel has this also, and one of the points is that --

DR. GLANTZ: What did you hold up there?

CHAIRMAN FROINES: This is the transcript plus all the overheads.

DR. GLANTZ: That's the stuff that came in that binder.

CHAIRMAN FROINES: That came with the workshop.

So the panel needs a certain amount of time to review this as well.

But so I would still argue that an April date would be good, but then the burden then becomes on you to tell us why that can't be met.

Because we are developing a risk assessment guideline document. We're not doing the science. We're doing the interpretation of the science.

DR. GLANTZ: Just for my information, when you held up the material from the workshop and said review it, you just meant review that for our edification. There's no action item in there, is there?

CHAIRMAN FROINES: Well, yeah, because they're going to be coming with presumably a relatively sophisticated document when they actually make their final presentation, so we just want to make sure -- there was a

lot of really good information at that workshop.

DR. GLANTZ: Right. But, again, there's nothing in the workshop training materials that are action items for us. That's for our -- that's to educate us.

CHAIRMAN FROINES: Yeah.

DR. GLANTZ: I just wanted to be sure I didn't miss something.

CHAIRMAN FROINES: Is everybody comfortable with where we are?

Tony?

DR. FUCALORO: Yeah.

DR. MARTY: This is Melanie Marty from OEHHA. I'm acting as George Alexeeff today because he could not be here today.

I have a little slide -- Laurie, could you move that down just a little bit.

This just describes the progress to date on coming up with a policy on cholinesterase inhibition and the use of that type of data.

CHAIRMAN FROINES: I'm sorry. There is one more question that relates to this.

For example, we have azinphos methyl before us at this point, and between now and April do you anticipate any other OPs coming before this panel? Because obviously we have a chicken-egg problem. If you've got a risk assessment

process that you're working through, but you're sending documents to us, we want to ensure that the documents that come to us have the most up-to-date policy with respect to risk assessment.

MR. GOSSELIN: Yeah.

CHAIRMAN FROINES: I don't want to review azinphos methyl and then three months from now go back and have to re-review it again.

MR. GOSSELIN: Yeah. And I don't think we want to do that either, but we have had OPs that have come through the panel. We have azinphos and potentially chlorpyrifos that might come before the panel in April.

I think as -- I think what I would like to seek to try, because I wouldn't like to see all the documents be totally ground to a halt, but I think there needs to be some understanding that the documents that whether it's azinphos or chlorpyrifos, are done in concert with the development of the guidance, that shouldn't be any different than the issues that were raised and discussed on the previous OPs that went through.

So I don't think the issues are going to be totally unrelated, but in the end it should be consistent with what that policy document looks like.

CHAIRMAN FROINES: We just don't want to have to do too many bites on the apple.

MR. GOSSELIN: No. I agree, but I think probably proceeding with those documents going forward, but keeping one foot in a real conscious effort as to where this other process is going, so we're not too far off.

CHAIRMAN FROINES: Okay. Go ahead.

DR. FUCALORO: The apple may have very many organophosphates on it. We want to minimize those bites on those apples.

DR. MARTY: Okay. I just have one slide on our progress to date.

In looking at data on cholinesterase inhibition and how to use that to assess health impacts, staff are reviewing current policies, slash, thoughts. Some of these are really informal policies or proposed positions, including the US EPA dated the year 2000, which you heard about at the workshop, CDPR's policy that was dated 1997, we're reviewing that.

Also the UN's, FAO and World Health Organization had a paper, a formal paper in 1998 on pesticides in food where they have a section on the use of cholinesterase inhibition data.

And we're also evaluating a 1999 position paper from an industry panel that states their position on the use of cholinesterase inhibition data.

We conducted really a preliminary literature

review updating the literature, particularly since CDPR did their 1997 document, and what is new out there with regard to cholinesterase inhibition and types of data and conclusions you can make from that.

We've had a planning meeting between OEHHA and DPR, and we have agreed to collaborate to get work together to establish a common policy on cholinesterase inhibition and use of that data, both in public health risk assessment and in more general context.

In the presentation that you'll be hearing from staff will cover issues, goals and our future work plan.

So now if we can have staff from OEHHA, Keith Pfeifer from DPR, and Bob Howd from OEHHA, will provide you with some more information.

CHAIRMAN FROINES: Presumably that policy will attempt also to include children's considerations as well?

DR. MARTY: Yes.

DR. PFEIFER: Good morning. My name is Keith Pfeifer. I'm one of the senior toxicologists with the Department of Pesticide Regulation and today

Dr. Howd and I are going to share in the initial presentation of the panel, and primarily we're going to be looking at some of the key issues in the interpretation of cholinesterase inhibition.

And I just wanted to make the point up front here,

that because the organophosphates and carbamates primarily act through this mechanism, this is why we're initially looking at cholinesterase.

However, we will not ignore any other systemic toxic effects and certainly also focus in on developmental effects.

What we tried to do is phrase some of the issues in the forms of questions.

So the first question, what are the physiological functions and toxicological significance of cholinesterases. And primarily here we're interested in the acetylcholinesterase and butyrylcholinesterase, sometimes call pseudocholinesterase.

However, there are other esterases that interact with organophosphate compounds.

But again we're primarily interested in these two, since these two are the ones that are most commonly measured and looked at for toxicological significance.

The tissues that are generally looked at for these cholinesterases are the brain, in some cases peripheral tissues, commonly erythrocyte and commonly also in plasma and/or whole blood.

The reason that we put up with the brain, the whole versus regions, is that occasionally we've reviewed studies where there is some differential or preferential

inhibition depending on which region of the brain is sampled, and this may be due to differential metabolism or binding site, so that raises a question as to whether whole brain or specific critical regions of the brain might be more appropriate.

With regard to peripheral, and we have the diaphragm there as an important organ that can be regulated by acetylcholinesterase, EPA recently has suggested that as part of their general protocol, that peripheral cholinesterase be routinely sampled to get an idea of impact on organ effects. So this is one reason that that's up there.

Occasionally you'll hear that measurements of erythrocyte or RBC acetylcholinesterase may serve as a surrogate with that regard.

And this isn't just for the diaphragm. It might be a heart, spleen or skeletal muscle also.

Again, moving down to enzyme speciation, we're primarily talking about acetylcholinesterase and butyrylcholinesterase. And butyrylcholinesterase is found in the central nervous system and in other tissues.

However, a clear function for this enzyme has not always been clearly delineated. There is some evidence that it may be important in certain drug metabolism and certainly some evidence that it may be important in the early

development of the nervous system.

Butyrylcholinesterase is a predominant form of cholinesterase in human plasma, and on the next slide I'll be contrasting that with some of the rat information that we have.

Acetylcholinesterase, the function is well characterized, both in the central and in the peripheral nervous system both.

And also there's some recent evidence of acetylcholinesterase in lymphocytes, which may imply a certain immune function, and erythrocytes, red blood cells, the predominant form is acetylcholinesterase, but again the function not clearly delineated.

The second question we phrased is what is the extent of intra and interspecies variability.

Now, under intra we're primarily concerned about the variability in humans. With regard to gender, for example, males usually have higher plasma cholinesterase level. With regard to age, there is evidence in neonatal rats that they have lower cholinesterase activity, thereby maybe rendering them potentially more susceptible to organophosphate compound.

And again the area of enzyme polymorphism, for example, there are five known genotypes for plasma cholinesterase in humans.

In the area of interspecies variability, again primarily comparing laboratory animals with humans, one area that's interesting is the ratio of acetylcholinesterase to butyrylcholinesterase.

In the human plasma, the ratio is one to a thousand.

In rat plasma, female rat plasma, the ratio is one to two.

In the male rat plasma the ratio is three to one.

So we have some normal type of variability already in these values.

Also, as far as interspecies differences, looking at anatomical differences, such as the blood brain and placental membranes.

And I guess the bottom line question comes out as to what would be the appropriate default uncertainty factors to consider under both inter and intraspecies variability.

Another question that we pose is how are structure activity relationships useful in looking at cholinesterase inhibitors.

And maybe rephrasing this, are there other factors or any factors that can help characterize the pharmacokinetics and subsequent correlations between cholinesterase inhibition and clinical signs.

As far as a physical chemical property, one

example is octanol water partition coefficient, which generally is an indicator of the ability of a chemical to partition more into lipid soluble compartment or in some cases the ability to cross, say, the blood-brain barrier.

Structure activity might be useful in grouping of organophosphates with possible correlations. You could use the ring structures, the phenyl, heterocyclic or aliphatic, or you can get into more detailed areas, grouping them into the moieties that are on the site change. Some of the examples are on this slide.

Certainly, structure activity relationships give you some idea of differences in biotransformation, both activation potential and potential detoxification characteristics.

And then also primarily in vitro you can have different binding affinities to characterize these inhibitors.

The area of laboratory variability in the measurement of cholinesterase inhibition, as you know, is a favorite topic of Dr. Barry Wilson. And I think it is an important area that is sometimes overlooked, and I think it's something that should be at least considered and addressed in any policy development for how to interpret cholinesterase inhibition.

Certainly, you want uniform sampling and handling

of both tissues, and with humans and blood and plasma sampling he'd like to see standardization of methodology. I know Dr. Wilson is a proponent of that.

And even so, with standardization of methodologies you still can have intra and a great deal of inter laboratory variability.

Both Dr. Wilson and Dr. Padilla several years ago did a study, a published study, where several laboratories measured cholinesterase inhibition using a standard methodology, and they still came up with variability in the double digit percent area.

So this leads to the final point up there, what is the impact of this type of variability on the interpretation of cholinesterase inhibition, and a more pointed question might be is cholinesterase inhibition below a specific percent within the variability of an analytical method and what would be the toxicological significance then of that.

With that, I'll turn the rest over to Dr. Howd.

DR. HOWD: I'm Bob Howd of the Pesticide and Environmental Toxicology Section of OEHHA, and have worked in that context with DPR over a number of years on interpretation of cholinesterase inhibition data and other kinds of data for pesticides.

When we start to develop a consistent methodology for pesticides, we have to think about dose response

assessment for the cholinesterase inhibitors, and among those things the endpoint selection is very important, because sometimes, although we think of these chemicals as cholinesterase inhibitors, cholinesterase inhibition, per se, is not the endpoint of most sensitivities. So we have to agree on when it is or is not the endpoint that we should be considering.

A neurological endpoint, for example, would be a good endpoint, but often the neurological tests that are available for cholinesterase inhibitors are very poor.

So this is one of the items in which there are not good guidelines in how you develop or select what you're going to use for the critical factor.

In short-term versus long-term exposures, it meshes with the next point there on tolerance that when you get tolerance to the chemicals that are as significant as we have for cholinesterase inhibitors, you have to try to figure out how you're going to evaluate cholinesterase inhibition when the same level of inhibition in a long-term exposure would actually have less effect after the longer term exposure.

So how do you take that into consideration in interpretation of this kind of data?

And my opinion, some of the chronic cholinesterase inhibition data is virtually useless, and one really should

be looking at different kind of exposure for those different kinds of endpoints for that kind of data, because of the question of homeostatic mechanisms coming into play in these chemicals.

Also, we have to look at central versus peripheral nervous system responses, and that isn't well delineated in many of the studies coming down from the manufacturers.

And in that regard, have to say that the basic guidelines on how you do the studies for cholinesterase inhibitors called the FIFRA guidelines are really not very good to address many of these points that we're bringing up, and that's the basic problem with interpretation of cholinesterase data.

If you have to do this basic set of studies concentrating, for example, on cholinesterase inhibition and have very very little data on what the actual effect is on the animal, how are you going to produce safe estimates, estimates at safe level in humans?

Laurie, could you go up to the next one.

The benchmark dose measures are something that we've been talking about at OEHHA for quite a long while, because it can help possibly solve some of the problems with the traditional LOEL NOEL approach.

Cholinesterase data tends to be fairly variable, as Keith was just pointing out.

You can look at data across many studies at many doses and incorporate that all into a benchmark model. You can get a better estimate of the true potency for, than doing risk assessment from.

The interpretation of that will still probably involve an uncertainty factor, and that's one thing that we have to discuss between our groups if we're going to attempt to use that for evaluating cholinesterase inhibitors.

I might say in this regard that US EPA does not yet use this approach for cholinesterase inhibitor evaluation, although they've been pioneers in the use of benchmark doses. It hasn't yet been applied here.

So there's a lot of work that needs to be done there.

DR. GLANTZ: Can I just ask a question -- this is just exhibiting my ignorance again. But could you go over again the difference between the benchmark dose approach and the NOEL approach?

DR. HOWD: Well, with the NOEL approach, if you study a chemical at one, ten and a hundred milligram per kilogram, and so you have this differences in doses by a factor of ten, and you have zero percent inhibition in one and five percent inhibition, which is not statistically significant at ten, and 80 percent of inhibition at a hundred milligrams per kilogram, how do you interpret that

data.

You have to say that the LOEL is in that case is a hundred, and the ten is NOEL.

Well, if you can use that in a modeling approach to determine what is some consistent amount of inhibition that you will assume to be a benchmark, and let's call it 20 percent inhibition, drawn between those points, and then do your risk assessment extrapolation from that theoretical 20 percent, you have a better idea of the absolute potency of the chemical, than in that more broader base approach from that three-dose experiment.

DR. GLANTZ: So what you're saying in the benchmark approach is you establish some specified effect level?

DR. HOWD: That's correct.

DR. GLANTZ: And then you try to estimate --

DR. HOWD: So you're more consistent.

DR. GLANTZ: Okay. Is there any standard effect level that you use?

DR. HOWD: That would be one of the things that we're trying to decide on which we use -- would what we would use for this evaluation to achieve a consistent response.

Now, one of the reasons why I back there was groaning when the six months was date was mentioned, was

because one of the things that we'd like to do is actually look at enough of the data from different chemicals to know what is a value neutral approach to use.

If you use 20 percent, what does it do to the risk assessment. Does it imply -- and uncertainty factors. Does it mean that we're less health protective than before, more health protective than before? What actually happens if you were to evaluate data that way?

Maybe in order to achieve a consistent approach that we could agree on, we wouldn't even be able to use benchmark approach, and use the standard approach of NOEL LOEL in what we'd bring to the committee in April.

That was what the problem is with a specific deadline and trying to resolve some issues like this.

CHAIRMAN FROINES: I think the problem you're going to find, which you already know, is that the quality and quantity of data that you can use for the benchmark approach is very limited, and so you're going to be trying to find things that you may have trouble finding.

And, of course, I'd love to get into a thing about how inadequate the FIFRA guidelines are, but there's no sense doing that here and now.

DR. HOWD: No.

CHAIRMAN FROINES: But I think that -- I wouldn't -- I think given the limitations of the data for

doing -- and we've been through it with Melanie in terms of what the chronic and acute RELs, where the number of compounds for which the benchmark dose could be used was vanishingly small, and so one has to be careful not to try to find that which may not exist.

And for Stan's points, I think you understood it, but basically the benchmark dose just allows you to make the better -- use the dose response data better than the safety factor.

DR. HOWD: Yes. For pesticides, of course, there's more data than from any other chemicals, because of the FIFRA guidelines require a relatively large number of studies compared to other chemicals.

But still it is a problem with data quality and interpretation of it for all of the reasons that we have been discussing.

To go on here, among the things that we would wish to discuss is to whether to use a statistical significance measure versus a percent inhibition measure. That's the -- that's been a hassle with regard to the use of the determination of a LOEL, would be avoided if we used a benchmark approach.

With regard to evaluation --

CHAIRMAN FROINES: I don't want -- I don't want to interrupt you a lot. I just want to make one comment.

It seems to me that one of the things you might do on that kind of issue is interact with the panel during the course of your deliberations, because Stan may have some ideas that you can run by him that you might save him not agreeing with you when you got here in April.

DR. PFEIFER: Dr. Froines, we're thinking along the same liens.

You were asking when we might have a final product, and that date is kind of up for discussion, I guess.

However, in our discussions with OEHHA we thought it would be a good idea maybe to come before the panel with periodic updates on some of the key issues, maybe not just everything, but certainly some statistical type information or approaches.

DR. GLANTZ: Yeah. We're also available to discuss these things with you informally too, because I mean I don't want to take time now, but I would actually have dealt with the issues you just put forward differently, because I don't think you need to require -- look at statistical significance in each dose.

I think you can look at the dose response relationship as part of overall, and even when you're talking about trying to establish NOEL levels, we don't need to get into that.

DR. HOWD: That would be a break with present practice, but I agree with you that we shouldn't make that break.

Anyway, that's the kind of thing that we need to discuss, and it will require some time to make the decisions on what -- how we should be going forward on this.

CHAIRMAN FROINES: I think that California may find itself breaking a bit with EPA and the quality -- and that discussion that went on at the workshop with the fellow from EPA suggests that there's a need to break, I think.

DR. HOWD: To move forward to use the methods suggested in fact by US EPA for this purpose.

But as you heard also from Stephanie Padilla, they're well aware of these issues and would like to have some prodding of their own regulatory organization, I would think, to move forward.

CHAIRMAN FROINES: I think she's terrific, and the more input you got from people like Stephanie Padilla, I think the better off we'd all be.

DR. HOWD: Yes.

DR. PFEIFER: We interact with her quite a bit on our risk assessments on organophosphates.

DR. HOWD: To go on here, the use of the concurrent control versus baseline values is a question often with both animal and human data where cholinesterase

values normally change over time a moderate amount, and given the variability of the data, there will often be many different ways to do the evaluation, and you have to consider different approaches for different kinds of data sets.

With a root-to-root extrapolation, issues here include the extent to which you can use different exposure assumptions of estimates of amount of inhalation uptake, estimates of amount of dermal uptake.

There's actually relatively poor data, for example, on dermal uptake of pesticides, and often that's the major exposure route.

When there's this unanswered questions about the amount of metabolism that might occur with slow absorption through the skin, for example, this is a major factor in interpretation of the data. The slower a pesticide gets into the body, also the less net effect it has for a number of pharmacokinetic and toxicodynamic reasons that have to be interpreted when you make root-to-root extrapolations. This is not a small factor.

What weight should be given to the human versus animal data in risk assessment is another important issue.

I have to bring up in that context that US EPA has vowed in certain context not to use human studies anymore, and we in the State of California tend to disagree with

that. We think that if you got data available, you should use it.

And we might want to point out the inadequacy of some of the kinds of human data that is available in a single exposure, defined condition, a study by Inveress in Scotland, which is one of the laboratories that does this, there's a real problem with overinterpreting some of those studies.

Clinical symptoms versus clinical signs are different. This is an important issue with regard to how you evaluate animal versus human data with subjective measures that you can get in people, which often are much more sensitive than the more objective measures in animals.

If you have the ability to quantify nausea as a symptom of a cholinesterase inhibitor in a human, whereas we can't measure that in a rat or mouse, it gives you a better perspective on what the threshold dose is. And we should use that data. We should make full use of that which we can in our interpretation of what's really going on.

The number of treatment groups is a big problem often with interpretation of the data.

The number of subject and animals per group, one of the big problems is that some of the best data is in dogs, and the FIFRA guidelines only specify that four or six dogs be used, and you have to get an effect in three out of

four in order to have statistical significance.

So often we're saying, well, but there were only one animal affected, but, you know, we shouldn't ignore that. This makes another argument for using benchmark.

DR. GLANTZ: FIFRA says you should only use four animals?

DR. PFEIFER: Generally the dose group.

DR. HOWD: Where it's in dogs.

DR. PFEIFER: Four or five.

DR. HOWD: Rats and mice, rabbits, guinea pigs, use greater.

DR. FUCALORO: For any measure?

DR. GLANTZ: That's crazy.

DR. FUCALORO: That's not a statistical pool.

DR. GLANTZ: You have to like having them all drop dead for it -- in fact it might not even be if they all drop dead that might not be statistically significant.

DR. HOWD: That's what I'm getting at.

DR. GLANTZ: That's crazy.

DR. HOWD: This is a problem.

Of course, in the human studies they're often low numbers of subjects also.

Now, the adequacy of the clinical observations is also often a problem, and again with the small number of human subjects, how do you interpret that data.

We want to use it, but it's problematic data.

So there aren't consistent guidelines on how you do the studies that would answer all the questions we have about cholinesterase inhibitors, and there aren't adequate ways on how you interpret the data once you get it.

That's part of the reason why you got what may have seemed like double talk from the guy from EPA in your earlier meeting. It really is a difficult question.

CHAIRMAN FROINES: I think the word seemed, may be a euphemism, but that's okay.

I think it would be useful as we go forward is to let the panel know some sort of -- that because most of us don't know what the FIFRA guidelines say, and you guys do, so as you go forward, I think it's educational when you say, well, this is what we have to live with versus what we think what should be done. In other words, the compare and contrast.

DR. HOWD: We can't rewrite the FIFRA guidelines.

CHAIRMAN FROINES: I understand. I'm just suggesting just for the panel's -- this issue just right now about the number of animals is at least worth the panel knowing about, so we understand when we're reviewing data what the limitations that we're going to come up against as we look at these documents.

DR. HOWD: Right. I agree.

And we will attempt to delineate some of those problems.

We want to develop uniform policies to evaluate and interpret the CHE inhibition and of course that's what you've asked us to do.

And uniform methodologies and defaults to interpret the data, and in this regard of course it has to be more than just the cholinesterase inhibition, per se, but the effects of cholinesterase inhibitors, which is a larger context there, because there will often be endpoints, as we've pointed out, that are not cholinesterase inhibition at all, and we have to figure out how we're going to use some of that data.

And the big deal with regard to the use of pseudocholinesterase has always been a kicker where how to treat that as a surrogate for other effects or not.

We want to prioritize the steps that we need to achieve these goals, and keep you apprised of our progress, and to the extent that we need to do that, have different problems and problem areas put together by different subgroups of people so that we can keep different parts of this moving forward and assigning tasks to OEHHA and DPR representatives, keep it moving forward, because it is such a considerable task to evaluate these different data.

For example, if we were to work on some benchmark

modeling approaches to evaluate the real data that is there to assess the strength of that, strength and weaknesses of that approach to see if we could use that for developing a uniform policy, that would be a different group as opposed to one which is evaluating some of the use of the human data, for example.

We also want to keep track of the policy development at US EPA. We're not saying that they will solve all of our problems for us, because actually historically speaking we have moved forward faster on many of these issues than the US EPA. In fact it's been our actions that have prodded them to move in some cases.

So one of the things that they have provided for us most recently is a very nice piece of software for evaluation of benchmark methods that's available free and its a wonderful statistical tool. We'd like to make use of that and anything else that they can provide, including work with Stephanie's group at US EPA, to see if she can help answer questions that need to be addressed.

So that's the full presentation, what we are planning to do.

And that was again why you had a bit of a groan. There's a lot of different problems that need to be addressed here.

DR. FUCALORO: Yeah. This issue comes up. It's

the old journalism thing, do you want it good or do you want it Tuesday. In some ways we're asking you to have it soon, but then there is also a concern that somehow that this will float off into some time indefinite, and we want a time definite, of course, obviously.

So I suppose we can program some times in which you report on progress, and I'm just suggesting this, and we can assess whether or not we think real progress is being made and getting to the end of this, because it seems like you've convinced me you have a very ambitious program here that you're engaged in, and that's good. And I think it would be beneficial.

So I'm prepared to wait a little longer, but I also take note of what other people have said to make sure that things are moving at pace, and so that's what I would suggest for this spot.

DR. PFEIFER: I'd just like to comment.

Dr. Froines mentioned earlier in the meeting today that you've been here from the beginning. And I, too, have been here from the beginning, both under SB 950 and 1807.

And the area of cholinesterase inhibition has been like an albatross. It's something that we know we need to address and we've tried to, but we've always fallen short of coming up with some definitive statements and policies.

And so over the last 15 years we've dealt with it

on a case-by-case basis.

Now, if you look at what EPA has done, I don't know if even though they have looked at it more systematically if they've come up with any better conclusions than we have so far.

But I can assure you that I think that this start of a more systematic approach and more unified approach, I think, is going to get us a lot farther down the road.

And I agree with Dr. Fucaloro that if we can come up with some milestones, some times where we can present to you our progress and get feedback and suggestions on where we're going and if we're going -- if we're addressing the most appropriate issues first, then that would be useful also.

CHAIRMAN FROINES: I assume the panel generally agrees with Tony's suggestion.

So we can -- I would suggest that where you have areas of specific interest, for example, some statistical questions, Gary Friedman and Stan Glantz might be the people to talk to, so that what you want to do is try and, yes, give us progress reports, but try and resolve certain issues outside of the scope of the meeting like this, so we're not -- so we use the time at the meetings as efficiently as possible, and get as much input as you can external to the meetings, and just as a matter of efficiency, more than

anything else.

But other than that, I think it seems like it's a great undertaking.

Stan.

DR. GLANTZ: Well, I just like -- obviously, we don't want it not done right, but I sort of think they can have it done right by Tuesday.

DR. FUCALORO: You're a hard man, Glantz.

DR. PFEIFER: You have to understand at least in my group the same people that will be working on this are the same people that are doing the risk assessments for the candidates coming through.

DR. GLANTZ: We're the same panel that has to deal with it. You know, I just know that -- this isn't a comment on you, but with lots of people it always gets done at the last minute, so it's just a question of when the last minute is.

But we're reasonable people here.

DR. PFEIFER: I know.

DR. GLANTZ: If we see progress --

DR. ATKINSON: We are?

DR. GLANTZ: Some of us are.

DR. FUCALORO: Where did we go wrong?

DR. GLANTZ: And well dressed, too.

CHAIRMAN FROINES: Well, but I think you've -- I

think one thing that might be helpful is you've raised a series of generic questions and general questions.

And it seems to me that the next step that you could undertake is to define specific questions that you need to answer, and then tell us what they are, and then tell us the progress with respect to the specifics, not the general questions, because then we really know whether you're making progress or not.

DR. HOWD: We had a set of 25 slides on the technical details that we thought would be inappropriate to present at this time, I mean, because they're all questions.

CHAIRMAN FROINES: Sure.

And the workshop was successful insofar as it actually demonstrated the wide rage of issues that we have before us and will have implications beyond organophosphates.

DR. HOWD: Yes.

CHAIRMAN FROINES: So Dr. Blanc is here. Welcome.

DR. BLANC: Thank you. Sorry.

CHAIRMAN FROINES: He's yawning. He's ready to take a nap.

DR. FUCALORO: Ready for lunch.

CHAIRMAN FROINES: Thanks very much. That was very helpful and I think it's a good first step.

So we're just as a scheduling issue, the plans

were to break for lunch now, the panel will take a 45-minute lunch. After lunch the first thing we'll take up will be an executive session to discuss the legal suits.

I think then after the discussion with the attorneys is over, we'll go back and finish the items 3 and 4 with time permitting, so that the members of the representatives --

DR. FUCALORO: Items 2 and 3.

CHAIRMAN FROINES: 2 and 3, sorry.

So that I suspect that other representatives from the various agencies probably are going to have an hour and 45-minute lunch.

DR. FUCALORO: Life is wonderful.

CHAIRMAN FROINES: So why don't we break at this point, and then so for everyone else we should be back here -- you should be back here about -- I'm not smart enough to do that.

DR. FUCALORO: We should be back at 1:00.

CHAIRMAN FROINES: About 1:00, and the rest come back about 2:00.

(Thereupon the lunch recess was taken.)

CHAIRMAN FROINES: If I can break into the post-lunch levity, I have to make a statement, which I've forgotten the actual details on, but I think it says that the panel is meeting with legal representatives from the

attorney general's office and from the Air Resources Board to discuss litigation involving the panel, and no one is here in the room with the exception of our legal representation, the legal representatives and the panel.

Thank you.

(Pause in proceedings.)

CHAIRMAN FROINES: The cases are, one, metam sodium task force versus John R. Froines, et al, Superior Court, Sacramento, case number 00AS04636.

Two, request for determination concerning the Office of Environmental Health Hazard Assessment and the Scientific Review Panel, range of unit risk values for particulate emissions from diesel-fueled engines established by OEHHA, specific unit risk factor for diesel-fueled engines adopted by SRP, file number 99-026.

The panel -- that's it.

The panel will hold a closed session as authorized by Government Code 11126, subdivisions (e)(1) and (e)(2)(A) to confer with or receive legal advice -- advice from legal counsel regarding this litigation.

(Pause in proceedings.)

MR. REEVES: Bruce Reeves, from the State of California Attorney General's office.

The request for determination concerning the OEHHA and SRP unit risk factors will also extend to the judicial

litigation over that same issue, entitled Apodaca versus California Air Resources Board, et al.

(Thereupon the panel went into closed session at 1:17 p.m.)

CHAIRMAN FROINES: The executive session to discuss the litigation -- do I have to go through all the -- the executive session discussing the litigation pending with the Scientific Review Panel came to a close at 3:52 p.m.

DR. WITSCHI: I make a motion the meeting be adjourned.

DR. FRIEDMAN: I second it.

CHAIRMAN FROINES: All in favor.

We don't have a quorum -- yes, we do. Pardon me.

Meeting is officially adjourned.

(Thereupon the meeting was adjourned at 3:53 p.m.)

CERTIFICATE OF SHORTHAND REPORTER

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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 19th day of December 2000.

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