MEETING

OF THE

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

CALIFORNIA AIR RESOURCES BOARD

SOUTH SAN FRANCISCO CONFERENCE CENTER

255 SOUTH AIRPORT BOULEVARD

SOUTH SAN FRANCISCO, CALIFORNIA

MONDAY, MAY 14, 2001

9:00 A.M.

JAMES F. PETERS, CSR, RPR
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APPEARANCES

MEMBERS PRESENT

Dr. John Froines, Chairperson
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. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HAZARD ASSESSMENT

Dr. George V. Alexeef, Deputy Director for Scientific Affairs

Ms. Colleen Heck, Chief Counsel

Dr. Michael Lipsett, MD, Air Pollution Epidemiology Unit

Dr. Melanie Marty, Chief, Air Toxicology and Epidemiology Section

Dr. Mark Miller, MD, MPH, Air Toxicology and Risk Assessment Unit

Dr. David Morry, Air Pollution Epidemiology Unit

Dr. Bart Ostro, Chief, Air Pollution Epidemiology Unit

Dr. Andy Salmon, Chief, Air Toxicology and Risk Assessment Unit

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PROCEEDINGS

CHAIRPERSON FROINES: So we are missing, as everyone can see, two members of the panel who are anticipated.

But I think since it's 9:15, we should go ahead, so we will officially call the meeting to order for May 14th, 2001. And we will continue the discussion of the SB 25 listing of the Priority Top 5 substances. So, Melanie, I think you're on the lead.

SUPERVISING TOXICOLOGIST MARTY: Okay. What I wanted to do to begin with was to go back to some of the issues that the panel asked us to come back with more information on, including changes to the introduction of the document, which we made and sent to the panel last week.

(Thereupon an overhead presentation was presented as follows.)

SUPERVISING TOXICOLOGIST MARTY: So I just have about nine slides, going over the changes made to the intro. We have more examples of information that we put together that is related to the prioritization process. We have a comparison of formaldehyde and acrolein which the panel asked us to bring more of the guinea-pig data forward, so we have a few slides on that. And then there was an issue about exposures to mercury in lead, so we

have a little more exposure information on those two compounds.

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SUPERVISING TOXICOLOGIST MARTY: In terms of the introduction, which is basically Section 2 of the document, we added text on our prioritization process to clearly indicate that the selection of the 35 or 36, depending on how you count them, TACs for focused literature review was based not only on the quantitative ranking, we did based on reference exposure levels or unit risk factors in air concentrations, but also on other evidence of the exposure including the hotspots stationary source emissions database, and also importantly the nature of the toxic effects.

We had certain end points, toxicological endpoints, that we considered a flag for concern, including neurotoxicity, immunotoxicity, endocrine toxicity, impacts on the respiratory system and developmental toxicity. So those chemicals -- if there was evidence that chemicals induced those particular end points, then we had a little more concern for those than for some of the others.

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SUPERVISING TOXICOLOGIST MARTY: We also added in additional explanation of the source of the ambient air

data. Dr. Atkinson asked us to do that.

CHAIRPERSON FROINES: Let me interrupt you just for a second. This new table this is the new table that you just referred to, am I correct?

SUPERVISING TOXICOLOGIST MARTY: It's one of the tables, yes.

CHAIRPERSON FROINES: That you just referred to?

SUPERVISING TOXICOLOGIST MARTY: That I just referred to.

CHAIRPERSON FROINES: So why don't you go ahead and then we'll come back to it because I know that Dr. Blanc had some comments about the evidentiary bases for some of the compounds in here. So why don't we go through the presentation and then come back to that issue.

SUPERVISING TOXICOLOGIST MARTY: Okay. I added a new Table 1 in the document, which is a table of the rankings and the reasons for selecting the TAC for focused literature review or deferring that literature search. We also added a table of the TACs that we chose for a literature search, which I'm calling on this slide New Table 2, which we could replace with the table that Dr. Froines just referred to, which has more information about each one of those.

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CHAIRPERSON FROINES: That's Table B?

SUPERVISING TOXICOLOGIST MARTY: Table XX is the one that has all the information on the 35 TACs, the evidence for potential differential effects and reasons for lower or higher priority. So that's the one I think that Dr. Blanc has comments on.

PANEL MEMBER BLANC: But the current table that you're saying that would replace the Table 2, which currently exists?

SUPERVISING TOXICOLOGIST MARTY: Right, Table 2 in the document is just a list of these 35 substances. It doesn't --

PANEL MEMBER BLANC: That's the one on page 14?

SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: But, Melanie, then there's this Table B?

SUPERVISING TOXICOLOGIST MARTY: Right. That's an additional piece of information that the panel requested. I think it was Dr. Glantz wanted us to take all of those chemicals that didn't make the initial ranking and say what was missing, ambient air data, chronic reference exposure levels, unit risk factors. So that is what Table B is that Peter is handing out, so I was going to get to that, too, in a minute.

We also, in the text of the document, added a little more clarification on developmental toxicants and

listings. We added a small section on asthma in children. And I did want to point out that we didn't make all of the changes that we wanted to make pursuant to the comments from the panel from the meeting of the 27th. And we will be making more of those changes.

So if you see something that you asked for and it's missing, we didn't forget about it. We're just still working on it.

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SUPERVISING TOXICOLOGIST MARTY: Okay. Then back to Table XX, which is the table that was sent to the panel along with the revised introduction. The panel asked for more information on the 35 TACs that were chosen for literature search and in particular how come we picked 11 out of those, what was our thought process in doing so.

So we created this table to describe the reasons for higher or lower priority in deciding on the 11 candidates for listing. The table has evidence of -- has a column for Evidence Potential for Differential Effects or reason for concern in the first place. And then it was a table listing Noncancer Ranking, another column listing Cancer Ranking and then the final column Reasons for Lower Priority.

We did go ahead and bin the quantitative rankings for both cancer and noncancer into high, moderately high,

medium and low. And that's noted in the footnote. And essentially that is what we did when we went through these chemicals to begin with, to try to see if the ranking could tell us anything about the importance of those chemicals for listing under SB 25.

I do want to reiterate that the ranking is not the only thing that went into the decision to look at it, that the toxicity was an important consideration.

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SUPERVISING TOXICOLOGIST MARTY: So we can go through that table if you want to now. I have overheads of that table if you want me to put the overheads up or if you just -- or if Dr. Blanc just wants to start with chemicals that he has concerns about, however, you want to do it.

CHAIRPERSON FROINES: Well, I think one problem that I had, and I don't know if it's shared by other panel members, but we got a lot of new information in a short period of time and it's very difficult, having spent a lot of time on the first two documents, that is your document and then the comments, hopefully people have had a chance to go through the additional materials.

But I think we've got an awful lot going on especially in terms of this pretty thick new document. So my sense would be that, at least for the moment, it would

be better to go to some -- if Paul has some specific comments rather than try and spend a lot of time going over the entire document.

PANEL MEMBER BLANC: Well, before we do that, because I think, unless we get into the specific chemicals, we may lose site of the forest for the trees a little bit, the purpose of the revisions of the main document was to try to make the document more transparent?

SUPERVISING TOXICOLOGIST MARTY: Correct.

PANEL MEMBER BLANC: And I think that the thrust of what you were trying to do was consistent with the feedback that you got from the panel in terms of doing that. So I think, first, it would be useful to hit on general issues of transparency and where that still needs to be addressed, and then we can get some of the specific arguments about the various chemicals.

One part that I think you were committed to make more transparent and which I didn't see in my read of this, and maybe I just missed it, was the part where you were going to be very specific about how you had farmed out the literature reviews to outsources and who those outsources were and how that has done.

SUPERVISING TOXICOLOGIST MARTY: We didn't get it into this draft, so I actually have it in my head if you want me to --

PANEL MEMBER BLANC: Well, I mean, what I want to understand is the implication is not that you don't plan to do that?

SUPERVISING TOXICOLOGIST MARTY: Exactly, we are doing it.

PANEL MEMBER BLANC: Okay. So one thing that would have been useful for this kind of revision, and would have been helpful for me, is to say, okay, here's where this will go, but we didn't have time to do it, because reading it, it's hard for me to know whether your intent is not to do that or it is.

SUPERVISING TOXICOLOGIST MARTY: Yeah, we're going to do it. I couldn't figure out, actually, or I hadn't thought about where exactly to put that.

PANEL MEMBER BLANC: I think it goes in the part where it says you then decided to do literature reviews of 35 chemicals, because you didn't. Your basis of choosing the 35 substances or whatever that list was, was not based on any outside consultancy.

SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER BLANC: As far as I understand it.

SUPERVISING TOXICOLOGIST MARTY: That's right.

PANEL MEMBER BLANC: The second thing is that the step of going from the 35 chemicals, and I may have the number wrong, but the chemicals that are essentially on

Table XX now and then some number of those will be decided as being lower priority, and therefore won't be included in the final group for consideration of choosing the five. That still remains rather vague in terms of what your target number was, if there was a target number, for how many you were going to winnow away.

For example, could all 35 have remained if they had all had enough information or was there an a priori decision that of these 35 would probably be reasonable to prioritize the top ten, and then there just happened to be 11, or the top, you know -- some going into it, can you expand on that a little bit just verbally?

SUPERVISING TOXICOLOGIST MARTY: Sure. We actually did have an a priori number set that we wanted to bring to the panel. As we read through the literature and as staff wrote up information on each chemical, we made decisions whether we thought that evidence was strong or not, and also with input on information on exposure to decide whether to go forward.

So we thought we should probably have about ten or so, but we didn't really say we will have ten and the rest of them fall away.

PANEL MEMBER BLANC: Well, I think the document needs to be more transparent. First of all, in saying that you did have an intent to get somewhere around ten,

although, you weren't wedded to that. And, secondly, some sense of what your methodology was. And I will come back to that when I come to some of the specific chemicals that seemed to have dropped off. But it's not transparent to me reading it how one got from 35 to the 11, even if I were to accept at face value the comments on Table XX.

SUPERVISING TOXICOLOGIST MARTY: Okay. We can add a little more verbiage to the actual text, just to describe our process.

PANEL MEMBER BLANC: So those would be some general comments about -- the other thing that you haven't responded to here and perhaps you're prepared to talk about that a little bit later is how you are going is handle is the use of developmental affects. You've allude to it in your introductory comments by -- and also to state in here as being the reason why you would choose something, but you haven't come back to the question of the policy and potential legal implication of interpreting the legislative act to apply to the teratogenic effects, for example.

CHAIRPERSON FROINES: They have, in their revised document, they do address on one page, 15, developmental toxicants as a special -- as a new item, and I assume you're going to speak to that? Are you going --

PANEL MEMBER BLANC: Yeah, I saw that, but that

didn't seem to --

SUPERVISING TOXICOLOGIST MARTY: I think Paul is concerned that you guys asked us to come back with a legal opinion and we actually have a legal opinion. We didn't write it into here --

PANEL MEMBER BLANC: But you're going to be presenting that today?

SUPERVISING TOXICOLOGIST MARTY: Yes, we could do that now. We could do that later.

CHAIRPERSON FROINES: Well, I think before going to specifics, why don't we address two questions now. One is the developmental question that Paul and I just raised, and the second is after that you can go over the general views on asthma and children as being two particularly important new areas that you've put in the document.

SUPERVISING TOXICOLOGIST MARTY: OEHHA's Legal counsel is here today, Colleen Heck.

OEHHA COUNSEL HECK: Good morning, Mr. Chair and Members. My name is Colleen Heck. And as Dr. Marty has indicated, we are prepared to offer a legal opinion today that developmental toxicants that cause adverse effects on infants and children are within the scope of SB 25. It is the legal opinion of both OEHHA and the Air Resources Board that toxic air contaminants that cause developmental or other problems for infants and children's -- excuse me,

children as a result of prenatal exposure to those TACs are within the scope of the statute.

The opinion is based on a comprehensive reading of the statute, both its spirit as well as the letter of the law. The legislative history is quite informative as well.

It's also consistent with good public health principles, which is a relevant consideration in looking at how to interpret a statute of this sort.

It's clear from reading SB 25 that its principal purpose is to protect, in quotes or underlined, infants and children from the deleterious effects of air pollution. In order to protect infants and children, one must take into account those factors that affect them. Prenatal exposures is certainly one such factor.

The statute is replete with references to protecting infants and children from the effects or impacts of air pollution. There is no focus on the type of exposure in this statute, unlike perhaps other statutory schemes one can think of.

Rather, the focus of the statute is on what is the effect of exposures regardless of time of exposure. There is references throughout the statute to those things to which infants and children have a special susceptibility. From both the rules of statutory

construction and the understanding in the scientific community of what that means, infants and children exposed prenatally to certain air pollutants are especially susceptible to the harmful effects of those pollutants.

And lastly in terms of the principles of how to interpret this statue, when interpreting a public health statute, unlike say a criminal or penal or punitive statute, one must interpret broadly when there is doubt, ambiguity how to interpret a statute to be inclusive or less inclusive.

So unlike those criminal provisions, when we have a public health statute of this sort, doubt, if you will, is to be resolved in the favor of being more inclusive, more protective. So all of these principles align nicely, the science and the law and the policy and the legislative history to tell us that prenatal exposures which can differentially affect infants and children are within the scope of this statute. And I'd be happy to answer any questions.

PANEL MEMBER BLANC: Well, I have a few questions. Did you find anywhere in the legislative history reference to birth defects?

OEHHA COUNSEL HECK: Per se, no. There's strong statements from the author's office about getting a -- getting at protecting infants and children and her long

held view that the current statutory approaches are not protective of infants and children. The words birth defects as a distinct phrase do not appear.

PANEL MEMBER BLANC: Did the word fetus or fetal exposure ever appear, since it doesn't appear in the law itself in the legislative discussion?

OEHHA COUNSEL HECK: No. Again, these discussions are far more generalized at getting at the fact that these beings have different biological functions than adults that the current regulatory regimen is not protective, does not get at the effects of the pollution. They don't use all of the various terminologies about why that may or may not be true.

PANEL MEMBER BLANC: Is it your legal opinion that an infant born with cerebral palsy who then throughout life, both in childhood and as an adult, would manifest the effects of cerebral palsy but wouldn't manifest an effect that was preferentially detrimental to the childhood period of life of that human being?

OEHHA COUNSEL HECK: Well --

SUPERVISING TOXICOLOGIST MARTY: Let me jump in here for that one. I think it's -- we talked to our reproductive toxicologist, including Dr. Gollup who works at UCD in the center and has been doing teratological research for quite some time. She says that you need to

consider that a child born with a birth defect has impacts on their development from the get-go.

So if you are born with no legs as an infant, then you have -- you don't develop the way a kid would develop who had legs. If you lose your legs as an adult, you've already made those neuron connections that are associated with crawling and walking and so forth.

Also, she brought up the point that most teratogens don't just result in an anatomically distinct abnormality, that they're most associated with a syndrome that includes other toxic effects.

And so, in her view, those -- it's too limiting to say well, if you're born with no legs as a kid, and you have no legs as an adult, there's not a differential susceptibility.

CHAIRPERSON FROINES: Let me ask a question about that. One of the things that the public wants to know and this panel needs to know in making a decision is what is the evidentiary basis for a decision? In other words, we want to know what was the scientific basis to underlay a particular decision?

To appear before the panel and to say that one of your toxicologists gave the opinion that children who have no legs will be forever impacted because there are other developmental factors that may occur, this panel -- that's

not a scientific statement. That's a speculation, in my view.

It may have a scientific underpinning. But if we're going to have a document that we use for decision making, then we should have the scientific basis of that statement laid out. Otherwise, it's somebody's point of view, it's not a -- there is no evidentiary basis for it.

SUPERVISING TOXICOLOGIST MARTY: Well, we did in our --

CHAIRPERSON FROINES: There may be an evidentiary basis for it, but none that we have seen, so we can't accept her position. One, she's not even here, but, secondly, we can't just simply let people say our toxicologists says the following is true and then we all bow and say thank you very much, we accept that. That's simply not a process that we can accept.

SUPERVISING TOXICOLOGIST MARTY: Okay. Let me just say that there is a lot of literature that backs that statement up. We can put in the citations.

CHAIRPERSON FROINES: Well, then we should see it. Well, that's what we judge the literature. We don't judge the comments. That's all we can do is judge the scientific basis of which you give us. That's our job. Our job is not to judge the speculation of an interested party to a circumstance.

SUPERVISING TOXICOLOGIST MARTY: We can bring in some citations, but I think we need to make sure that --

PANEL MEMBER BLANC: First, you need to make sure that you're going down the road that's consistent with what you're going to be -- that you're going to receive an appropriate response, if you're going down that road -- that you're headed down the right track, is that what you were about to say?

SUPERVISING TOXICOLOGIST MARTY: No, I just wanted to say that we were looking at chemicals on a case-by-case basis. And we do make the point that just because something is a developmental toxicant doesn't mean it automatically gets listed or is subject to listing under SB 25.

CHAIRPERSON FROINES: Well, when we get to glycol ethers today, then we will expect to have a presentation of what was the underlying basis that shows effects, not simply in terms of birth defects, but long-term impact of glycol ethers on the child and subsequently the adult.

PANEL MEMBER BLANC: Well, let me come at it from a different way, because I think, Melanie, if I understand what you're saying and what legal counsel is saying that hypothetically there certainly could be a chemical that would make it all the way down the list, even into the top five, if it were a developmental toxin with exposure

concerns that was high level of exposure and there was no direct evidence that you had no evidence either in animal or epidemiologic human studies showing an effect on children when exposed as children. And so the entire extrapolation was based on -- or the entire finding was based on the known and well-established developmental effects in utero.

And what you're saying is that from a legal point of view, were a chemical to have those aspects, would be, potentially could be, listed. We're not saying that one of the ones would be. What Dr. Froines is saying, and what I would echo, is that to do that one thing is that your section on developmental toxicity should be a bit more explicit about the scenario, wherein a child would be deferentially affected by coming into childhood with a series of impairments and citing the literature to support that.

The second thing that I think is very important would be for us to hear a legal opinion and for somehow this document to take account of that, that this in no way is meant to imply that a fetus is a child, that the interpretation of this act is that a fetus is a child or that the ARB's interpretation is.

And that's what really concerns me, that someone could take your document and then say well the Air

Resources Board has, through its findings, declared that --

OEHHA COUNSEL HECK: We'd be happy to make it clear that that's the basis for the legal opinion that prenatal exposures leading to differential outcomes in infants and children is the basis for our opinion.

PANEL MEMBER BLANC: I'd like to see that stated explicitly in the document as well.

PANEL MEMBER FUCALORO: And, Paul, the reason for that is because it's inconsistent with California law? I mean, what's the reason you would want a legal statement on that?

PANEL MEMBER BLANC: The fetus is not a child, and the --

PANEL MEMBER FUCALORO: The law.

PANEL MEMBER BLANC: -- the law says, which this law is based, is talking about children. It never once mentions fetus. And then to turn around and declare a chemical under the statutes because it only affects a fetus without then saying -- but it's not because of its fetal effects, because if that fetus did not survive the birth, this is not the issue. The issue is fetuses that survive to birth and then have these problems including childhood.

PANEL MEMBER FUCALORO: You're more sophisticated

legally than I am, but isn't it true that -- I mean, this takes us far afield and that's why I was a little worried about this line of questioning, although I think it may be necessary. Isn't it true, and I could be wrong, this is just from reading the newspapers, that people can be charged with murder for killing a fetus? I mean, saying that -- and the crime or something like that?

OEHHA COUNSEL HECK: Yeah. The penal code was amended about 35 years ago. There was an individual charged with homicide for assaulting his late-term pregnancy wife. The fetus did not survive the birth. He was charged with homicide. He was convicted. The Court of Appeals overturns it saying the fetus is not a human being within the meaning of the historic common law which underlies our homicide statute. The statute was amended, Penal Code Section 187, to say homicide is unlawful killing a human being or a fetus.

So it was named as a distinct entity that could be the basis for murder as opposed to being within the subset of the term human being.

PANEL MEMBER FUCALORO: So we're going to have it both ways. Good, I see.

(Laughter.)

OEHHA COUNSEL HECK: That's the way the Legislature saw fit to solve that dilemma.

PANEL MEMBER BLANC: And, finally a long the same lines, I think, Melanie, it would be useful in your discussion on developmental toxicants to emphasize perhaps a bit more than is there in a couple of sentences why for all of those reasons toxins, which would tend to manifest their effects in later gestation, would be even more of concern perhaps, under this approach, since they would be more likely to affect the developing nervous system and ways in which a fetus would then survive to childhood or however you want to phrase that.

DR. MARTY: Yeah, then, again, it's a case by case issue.

PANEL MEMBER BLANC: I understand that, but you just do lay out general principles it seems to me.

SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: Are there any chronic RELs or acute RELs based on birth defects?

SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: Based solely on birth defects?

SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: So does that mean that you now need to go back and use another basis for your input for that risk assessment, because the law seeks to develop new risk assessments, as I understand it, based on the

differential risk; isn't that correct? Doesn't the law ask you to look at how a new risk assessment might be developed based on the notion of a differential effect?

DR. ALEXEEFF: Well, at a later stage we'll go back and look at the reference exposure levels, but it's simply to see if they're protective of infants and children. Maybe the numbers don't have to change at all. We haven't developed a new methodology that would say you have to add an additional factor or an additional sort of formula in order to protect infants and children, mathematic -- or quantitatively.

So, at this point, we don't -- you know, if it's already based on birth defects, we wouldn't change it at this time. But we're planning on developing methodology or looking at methodologies that we will bring to the panel on how we would handle understanding differential treatment.

So what I'm saying is there's no a priori reason we're going to go and change any chronic REL right now because the chemical is on the list, but at some point, we will look at methodologies to see if infants and children are protected with the current methodologies, and they may be.

PANEL MEMBER BYUS: It is confusing. It's just not you guys have been talking, but it is confusing. On

first reading this, I would not have thought that teratogens and developmental toxicants would have been included in this. And it's okay that it is, but, I mean, my reading was the same as the rest of the panel's. And then to this chronic REL issue is even more confusing to me as you said, John, because the chronic REL was based on developmental toxicity, then that chemical shouldn't be on the list, because it was developed already for children and there's no reason to consider it -- I mean, the child was the driving force behind it.

SUPERVISING TOXICOLOGIST MARTY: The list triggers risk management, that's what it does. And so if there's -- the effect that a chemical has a reference exposure level based on developmental toxicity is not connected to whether or not risk management actions have been taken against that chemical.

CHAIRPERSON FROINES: Yeah, but I think that the Legislature believes that some chemicals differentially impact children's health more profoundly than the same exposures to the adult. I mean, that's what they're trying to get at. They think that kids are more susceptible, in many cases, than adults. And so to the degree that we're saying we have those chronic RELs based on birth defects, there is a contradiction. There is a logical contradiction between what the Legislature thought

they were doing and what we're actually doing.

I think it --

OEHHA COUNSEL HECK: I think there's a consistency that in both cases we're saying these are chemicals that may have differential outcomes on kids. The fact that the REL was based on the birth defects is confirmative or consistent with saying, yeah, the chemical that we need to look at to make sure the risk management levels, when set, are protective of all those people of the infants and children, that could be differentially impacted.

CHAIRPERSON FROINES: Except for -- I understand what you're saying. Except that this law was new. It was an attempt to seek out new science around differential susceptibility. To the degree that we focus on what we already know, then we don't go to the new science that the Legislature was looking for. We already know about thalidomide. We don't need to build a State law to address it. And you're saying it fits. And, of course, you're right, of course it fits, nobody is arguing that.

But it's not really new. Thalidomide we understand its teratogenicity. Martha Escutia, Senator Escutia did not push that bill to develop legislation to address thalidomide. She did it to address new science of differential susceptibility. That's what she's trying to

get at. And to the degree that we go back and tell her what we already know, it doesn't meet the goal of the legislation, that's the problem.

PANEL MEMBER FRIEDMAN: I don't agree with you. I think their approach is very reasonable. I think that if, you know, given that children or infants are more susceptible, if the standard that has been developed protects them, okay fine. I don't see that we have to come up with something new in a case like that, and I think that their approach is very reasonable. So I don't want you to think the whole panel disagrees with that.

DR. ALEXEEF: This is George Alexeeff, I didn't introduce myself, with OEHHA, for the court reporter.

There's a couple of different factors. There's three sort of areas that's happening with this new law that has to do with toxic contaminants. One is the listing process, this list we're developing. The other one is the ATCM process, the toxic control measure process, which is Air Board's responsibility. The third area is us reevaluating our chronic RELs or Reference Exposure Levels or cancer potency factor. There's three different things that are happening. The way this list is set up is that we identify chemicals where children are differentially impacted and put them on this list.

The next step is for the Air Resources Board to

look at their ATCM, if they have one, and to reevaluate it, look at the current information to see if their ATCM is proper.

If they don't have one, they have to develop one. So that's what the list actually --

SUPERVISING TOXICOLOGIST MARTY: If they don't have one, they have to do a needs assessment to see whether they need to develop one.

DR. ALEXEEF: Oh, that's right Excuse me. There's a whole process, the whole ATCM process, so it triggers the ATCM process, if they don't have it which starts the needs assessment, check for exposure and all those sort of issues. And then a later stage in a couple of years, there's a time line in the law, several years we'll be coming back and looking at reference exposure levels, either updating ones we've presented the panel or providing even new ones based upon, you know, the information we've developed over the next couple of years.

So there's sort of three different things, they don't necessarily, you know, play off one another. I think the key factor is chemicals that do go on this list then require the Air Resources Board to consider the control measure process and to see if their control measures are adequate.

CHAIRPERSON FROINES: I think we should go on,

because we've gotten a sound legal opinion, and Paul's asked for some specific language and now we're talking about our views of the issue. And I think we should go to the substantive things that we need to pursue.

DR. ALEXEEF: That's fine, but I think the key is the legal opinion stated, that Melanie stated, was that developmental toxins are an area that we can consider. It doesn't mean they're on the list, but we're not excluding them all. They can be a factor in this process.

CHAIRPERSON FROINES: But keep in mind, the importance of developing the evidence when you're going to be making an argument so that we avoid this kind of speculative argument.

So we're back to Paul now.

PANEL MEMBER BLANC: Well, no, I think your request was that consistent with the general principles that we also address the asthma section.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER BLANC: Well, that was your last request.

SUPERVISING TOXICOLOGIST MARTY: We added a small section on asthma in children to the introduction. Basically, we make the point that the prevalence rates statistics indicate that kids have more asthma than adults as a percentage of the population. And we make the point

that because they have smaller airways, we're concerned, and it seems that they get into trouble faster when they have an asthma attack than someone with a larger airway like an adult.

And we also bring forth the use of hospitalization rates for children being much higher than adults and realize and state that while hospitalization is influenced by a number of factors, that we believe this information supports the concern that asthma impacts children more than it does adults. Therefore, TACs that exacerbate asthma should be considered for listing under SB 25.

Any questions about that information?

PANEL MEMBER BLANC: Well, one of the things that -- since you put in a section on asthma, one of the things that seems to be missing from it is that clearly you would also be concerned about things which induce asthma and not only things which exacerbate asthma.

SUPERVISING TOXICOLOGIST MARTY: Yes, did I -- it's not in there.

PANEL MEMBER BLANC: No. We have included exacerbation of asthma, so it should definitely be induction or exacerbation.

SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER FUCALORO: That was mentioned at the

last meeting.

PANEL MEMBER BLANC: So therefore things, which -- such as diesel, hypothetically, which might act as adjuvants to sensitization might be an issue, if you we were concerned about asthma in childhood specifically.

DR. MARTY: Yeah.

PANEL MEMBER BLANC: Now, another question I would have about, since you have a section on asthma in childhood, you have a section on developmental toxicants. It's fairly early on, and these are both separate from the section factors influence in why infants and children might be more susceptible than adults, wherein you have the inhalation issues -- it's, you know, unchanged from previous ones, food intake, the sort of roots of exposure issues, behavioral factors that influence -- all things that influence exposure, thermal exposure, metabolic differences, distribution difference. Those all sort of pharmicokinetic, pharmicodynamic things, inexcretion, obviously.

Then later on, page 43, the central nervous system, the endocrine system, the immune system, lung development, children's cancer risk. There's a little question about asymmetry, since you have, sort of, upfront as an outgrowth of the, you know, of the questions that were raised, you have these sort of isolated sections

about developmental and asthma as particular issues.

And I don't know how you want to handle this, but I think you should go back and take a look at the document and make sure that you're putting things in the right order, that something isn't sort of hanging things out there, illogically.

SUPERVISING TOXICOLOGIST MARTY: Yeah, I think, actually you have a good point. We should probably take that whole section 3D and move it in front of all the physiological and pharmicokinetic --

PANEL MEMBER BLANC: Because it implies that other things, you know, aren't going to be something you can take into account. For example, you're talking about developmental lung, but things that affect -- and cancer, you have those three things. And then it says if hematological effects wouldn't matter.

There's another issue I would make about asthma that you could use as an argument as to why it might matter and also why cancer wouldn't matter differentially for children, because I understand you have a bit of a problem with the cancer issue again as to the logic as to why children are more at risk unless you're going to generically invoke the shelf-life issue.

And one issue you could make is that children who had to undergo chemotherapy would probably differentially

have long-lasting effects as compared to adults who underwent chemotherapy. And the same thing would actually be true of asthma, you could make the argument that children who needed steroids for asthma are more likely to experience deleterious effects of systemic corticosteroids than adults who got corticosteroids at a similar dose, so that the treatment for the disease would make children more at risk. I don't know whether that's something you want to throw in there.

SUPERVISING TOXICOLOGIST MARTY: We actually allude to it in the section on cancer, because kids who, for example, receive --

PANEL MEMBER BLANC: You say, that they're more at risk, later malignancies, but just in terms of developmental impacts of --

SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER BLANC: From our pediatrician, from a pediatrician.

DR. MILLER: Mark Miller, with the OEHHA. A good example might be pediatric brain tumors for which radiation is often the treatment of choice, and you can't really radiate a child under three years of age, because of the developmental impacts on the brain. And it puts oncologists in a dilemma.

SUPERVISING TOXICOLOGIST MARTY: We can add that

information.

CHAIRPERSON FROINES: I just want to go back and reraise an old issue, that I'm still slightly uncomfortable with, and I don't want to take much time on it. I think it's -- the inclusion of a section on asthma in children is very important. And so I commend you for that. I also agree with the prevalence statistics that you have developed. And I agree with the differences in the physiologic characteristics.

Where I still have a problem with your argument is with this hospitalization rate question. And I readily admit that I had it backwards last time between blacks and whites. And so I was wrong. I remembered my own slide incorrectly. The argument is still, as far as I'm concerned, the same. I still think that at some level from an epidemiologic standpoint that what influences hospitalization or seeking of health care has a lot to do with social and behavioral factors that we've all -- I think we all would agree that those are important.

But in the document you have two sentences on hospitalization, two or three sentences on hospitalization. And so you're making hospitalization rates as an argument for differential impacts of asthma in children. And I just want to be clear on what you're really trying to say with that argument, because I think

there's a very clear reason why blacks or whites seek hospitalization differently. And I think that that has to do a lot with socioeconomic factors as well as behavioral factors.

But I think it's important to put on the record and put in the document what is it that you're really saying about the differences between childhood asthma and adult asthma, for example, in terms of the hospitalization argument.

PANEL MEMBER BLANC: John, can I -- maybe, I'll just save them some time here. I think that --

CHAIRPERSON FROINES: Well, Michael just came to the table. We'll miss the opportunity here.

PANEL MEMBER BLANC: I want to hear what Mike says, but, you know, there's --

PANEL MEMBER BYUS: Not that much.

(Laughter.)

PANEL MEMBER BLANC: Hospitalization, I just don't want you to get yourself out on a limb. Hospitalization is considered, in general, a nondiscretionary marker of severity in asthma. So that although visits to the emergency department are considered discretionary, because one could go to their doctor if they had good access, getting admitted to the hospital is not considered discretionary and therefore is considered a

true marker of severity as good as we have such markers.

Mike.

CHAIRPERSON FROINES: I think next time you should let Mike say it first.

DR. LIPSETT: This is Michael Lipsett, OEHHA. And that's exactly what I was going to say.

(Laughter.)

DR. LIPSETT: And I just wanted to add also that just -- you don't necessarily even need to look at that in terms of a severity marker, but if you're also looking at issues related to prevalence as well, that's not necessarily something that has to do with, say, the behavior types of factors, if you're looking at it.

As for the hospitalization of -- I won't take anymore time. That's exactly what I was going to say.

CHAIRPERSON FROINES: Well, my point here is going back to something I said much earlier about the evidentiary basis for things. I think what Paul just said and what you followed up with is very useful, and I don't want to be out on a limb, because then I get eaten up by Gary or Paul or a whole bunch of people.

But the point I'm trying to make is that the document should have those kinds of arguments, because that really clarifies the issue. That's the issue here.

PANEL MEMBER FUCALORO: It's in one sentence.

CHAIRPERSON FROINES: Proving that I'm wrong is not the issue, it's what's in the document.

SUPERVISING TOXICOLOGIST MARTY: I'll put that in. Also, I did want to add that I was going to take some of the prevalence rate data and make a table for that, and I thought I had done that, but it's not in here.

CHAIRPERSON FROINES: Well, this issue is so important because it comes up with Phs, with diesel, with acrolein, with formaldehyde and so on and so forth, and it may come up again in the future. So having this laid out as clearly as possible is really important.

SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER FRIEDMAN: I'd like to just reemphasize what Stan said, I think, a few meetings ago about the absence of environmental tobacco smoke from this list, because we all know that it has harmful effects on children. And I contacted Melanie and she informed me that the reason it wasn't being considered is because it's not officially labeled as a toxic air contaminant.

And I think, you know, that we should be explicit that, you know, that I gather that was a political not a scientific decision, because the report that came through said -- it recommended that it be listed as a toxic air contaminant. So I think, you know, there's something funny the fact that's totally missing from this

consideration, and I wonder if it could be brought up in someway in connection with SB 25. Maybe that would take a legal opinion, but I'm bothered by its absence, and instead we're looking at chemicals which are much less prevalent.

CHAIRPERSON FROINES: I don't know who wants to speak to this issue from ARB, but --

OEHHA COUNSEL HECK: Colleen Heck, again. Dr. Friedman's exactly right in that the reason for its -- the simple reason for its noninclusion is it has not yet been identified as a TAC and the statute is very clear that we're only to look at those things that are, in fact, listed as toxic air contaminants. We would have no authority noted as discretion at all to exercise here to look at ETS unless and until such time as it is identified as a toxic air contaminant.

So the only quibble I would have with your description is the use of the word political. It's a legal problem, if you will, or barrier for OEHHA. We have no authority here to delve into this. So if Senator Escutia could amend her bill to name ETS by name or ETS could get listed. Until either of those things happen, we're handcuffed.

CHAIRPERSON FROINES: Well, the question that I had is, it is my impression that the Air Resources Board

and OEHHA are going to consider moving ETS forward as a toxic air contaminant. And so I was hoping to get some clarification on that issue from somebody from ARB and OEHHA, because that, I think, would respond to Dr. Friedman's question directly.

MS. BROOKS: My name is Jeanette Brooks and I'm with the Air Resources Board and our management has seriously considered entering environmental tobacco smoke into the process. And I don't have a final decision for you today, but very soon I will.

PANEL MEMBER FUCALORO: What is very soon?

MS. BROOKS: I'm hoping within the next week or two.

PANEL MEMBER FRIEDMAN: What's the process? I just don't know what you say by when you say entering -- what process are you talking about?

The formal identification of the substance as a toxic air contaminant. Since it's a hazardous air pollutant it's not an automatic listing as a toxic air contaminant, so it would be a process similar to the one we went through with diesel exhaust. But there is a report that we can use as a basis there, but there will need to be some updating.

There was no quantitative risk assessment in that report, and Melanie can speak to that. And then SB 25 did

amend our identification process in the law where you do have to take into account the impacts on children. So more work needs to be done on that report, but there is a good basis to start with.

PANEL MEMBER FRIEDMAN: So we've gone through, you know, the process and gone through the OEHHA beautiful report on environmental tobacco smoke. We reviewed it, approved it, and then it goes to ARB. And could you explain a little more what that process that ARB goes through before it labels something as a toxic air contaminant?

MS. BROOKS: Well, what we do normally is we have a public -- before we start the process, we have a public information request that goes out on exposure and health effects. We get that information back, and we make a formal request to OEHHA in a memo asking them to begin work on their Part B report, and then they start their work on their side of the report and then we start our work on the exposure part, and it involves public workshops and a panel review of the report.

PANEL MEMBER FRIEDMAN: But hasn't that all been done already?

MS. BROOKS: Not everything that's in that previous report will meet the requirements in the law now for identifying a substance. So we need to build upon

what's been done and bring it back to the panel for review. There will be some new information in that report.

PANEL MEMBER GLANTZ: Well, we've been hearing for several months this was going to start in two weeks.

MS. BROOKS: The best I can do right now.

PANEL MEMBER GLANTZ: Where's the hang up?

MS. BROOKS: We're waiting for our Executive Officer to approve a letter to the panel.

PANEL MEMBER BLANC: Can I ask a legal opinion again? There would be nothing in -- there would be nothing that would legally preclude OEHHA from, in their document, in the introductory part of their document, from being explicit as to why environmental tobacco smoke will not be addressed, --

OEHHA COUNSEL HECK: That's correct.

PANEL MEMBER BLANC: -- even though on a biological basis it would otherwise meet criteria?

OEHHA COUNSEL HECK: Right. We may have a little bit of a semantic disconnect. We'd be saying that the inclusion doesn't mean that other things were ruled in or out purely on a science basis, but what was the scope of SB 25 and anything not attacked was clearly outside of that.

PANEL MEMBER BLANC: Right, because it was our

specific request at the last meeting and it's exactly parallel that there be a similar paragraph addressing the obvious reasons why pesticides would otherwise be of grave concern, but could not be included here because of statutory reasons, and that was not yet in this version.

SUPERVISING TOXICOLOGIST MARTY: It's not in there yet. It's coming.

PANEL MEMBER BLANC: And I think that in the same section, an explicit comment on ETS would be appropriate as long as you don't believe there's a legal reason why they can't do that.

OEHHA COUNSEL HECK: No, I think it would be clear to point out though that we'd be stating not that we delved into the merits of ETS, but that we could not because of a legal bar. So I don't know how that would exactly read, but let me just answer your question, we're not legally precluded from making such a statement. We could do so if we --

PANEL MEMBER FUCALORO: I think that would make us feel a lot bet on this panel, if both of those, the pesticides and the ETSs were in there.

OEHHA COUNSEL HECK: Since you've brought up the pesticides, let me just quickly add that not only was it not within the scope of the existing law about what the TAC program could get at, it was reiterated quite clearly

in SB 25 that pesticides and their pesticidal use were outside the ambit of SB 25. So we can clarify both of those points.

PANEL MEMBER BLANC: I think the panel is trying to make clear that we want to see accompanying that a comment in the report which says, of course on biological grounds, these would have been a priori substances that would have gotten a great deal of attention other wise.

SUPERVISING TOXICOLOGIST MARTY: I don't think there's a problem saying that.

PANEL MEMBER BYUS: Certainly, given the laws suggesting that we consider additivity of exposure by common mechanisms, which clearly the pesticides probably fall into as a group more than any other compounds, series of compounds.

CHAIRPERSON FROINES: Can I go back to Stan's question and Gary's point. I think the Chair would entertain a resolution from the panel that I write a letter to the Executive Officer of the Air Resources Board and stating the opinion of the panel with respect to the ETS issue in terms of its being considered as a TAC.

In other words, we should send a letter to -- I think we should send a letter to Mike Kenny requesting that this issue be moved forward as expeditiously as possible. So I think we need a resolution, Stan, to that

effect.

PANEL MEMBER GLANTZ: Gary brought it.

PANEL MEMBER FRIEDMAN: So moved. I move what you just said that you write the letter asking about this.

PANEL MEMBER GLANTZ: I'll second it.

CHAIRPERSON FROINES: Any discussion?

PANEL MEMBER FUCALORO: Yeah, just a question. I've said this before and I'll say it again, I was very impressed with the presentation you made a couple years ago regarding how you set priorities for those chemicals that came up as TACs. Do you know what I'm referring to?

SUPERVISING TOXICOLOGIST MARTY: The ARB's prioritization process?

PANEL MEMBER FUCALORO: Yes, it was ARB's right. Does ETS show up on the radar map on that particular one? I don't know the answer to that.

DR. MARTY: Jeanette, do you know the answer to that?

MS. BROOKS: I'm sorry, I don't know the answer to that question.

CHAIRPERSON FROINES: Can she come up and speak into the microphone for the court reporter.

DR. ALEXEEFF: This is George Alexeeff. Jeanette, I think the question was, if you can recall the prioritization procedure the ARB has for prioritizing

potential toxic contaminants, if you recall where ETS is on that prioritization list or if it has been prioritized.

MS. BROOKS: I can't remember the exact ranking, but I know that it wasn't in the top 40 ranks.

CHAIRPERSON FROINES: Was it the list?

MS. BROOKS: And we were looking in our last update a couple years ago we were looking at the top 40 ranks, so it must have been somewhat lower.

PANEL MEMBER FUCALORO: Now, does the top 40 include those who have already been considered TACs?

MS. BROOKS: Yes, it would be -- once we go through our prioritization scheme, then they just, you know, they just fall out in terms of the information.

PANEL MEMBER FUCALORO: You don't recall where it is?

MS. BROOKS: I don't recall the exact score.

CHAIRPERSON FROINES: But Jeanette, are you sure it would have been on the list --

MS. BROOKS: It's a candidate.

CHAIRPERSON FROINES: -- because I think you're going to talk about getting out on a limb, if it's not in your top 40, somebody is going to be out on a limb. And so I would be careful on that. I suspect it wasn't on the list.

MS. BROOKS: Well, at one point, in our last

update, we just picked the rank of 40 to stop at, because there was just, you know, so many.

PANEL MEMBER BLANC: But, you know, it's very hard to believe given the level of toxicity that you're dealing with. I think you better go check your list, but I'll tell you --

MS. BROOKS: We'll do that. We're going through that process this year.

PANEL MEMBER GLANTZ: -- It's very, very troubling. I mean, this issue has come up at this panel now for the last half a dozen meetings, and we have been told over and over again by ARB that this was going to be dealt with expeditiously. And every meeting we hear that in two weeks there will be a letter, you know. I mean, it's just ridiculous.

CHAIRPERSON FROINES: But I think the reason I suggested sending a letter to the Executive Officer is it -- I don't want to pick on Jeanette, because it's not within her --

PANEL MEMBER GLANTZ: No, I agree.

CHAIRPERSON FROINES: She has to. She's caught between --

PANEL MEMBER GLANTZ: No, I understand.

MS. BROOKS: I'm used to being caught. That's all right.

PANEL MEMBER GLANTZ: I understand, but I think it's important, though, to state for the record that I think, in terms of this specific issue, the ARB has not been responsive to the suggestions of this panel. And to bring forward a report on exposure of children to toxics that ignores ETSs from a -- I mean, I understand what the legal issues are, but from a scientific point of view it's really embarrassing.

You know, and if you read your own report, which was approved by this panel, there are, in fact, one or two chapters in there that deal with effects on children. And, in fact, the evidence on health effects of ETS, the oldest and best established evidence going all the way back into the fifties, sixties and seventies is affects the children, asthma and other issues like that. So, I mean, I think we need to get this resolved.

CHAIRPERSON FROINES: I think we should move ahead. The point has been made and made and made. And the frustration is the fact that it's been made and made and made, but we shouldn't -- I feel a need to redo it again.

MS. BROOKS: We understand the panel's concern.

PANEL MEMBER FRIEDMAN: Can we vote on your letter on this motion.

CHAIRPERSON FROINES: Oh, I'm sorry. You're

right, we didn't vote.

All in favor?

(Ayes.)

CHAIRPERSON FROINES: Did you want to comment or leave it as stated?

DR. PRASAD: Leave it as stated.

CHAIRPERSON FROINES: I saw you move forward at one point and thought you were going to come to the table and I wanted to give you the opportunity.

DR. PRASAD: Shankar Prasad from ARB Chairman's office.

DR. PRASAD: Basically, I would add hear is that there is an interest from the Chair's office and the Executive Office to move forward on that, but certainly it's been held up because of the reasons. There has been a constant dialogue going on between the two agencies OEHHA and the ARB. And I'll carry the message about the panel's interest and certainly you will hear from us.

CHAIRPERSON FROINES: Thank you.

Melanie, I think we are now, unless I'm mistaken -- Paul, did you want to pose some specific questions?

PANEL MEMBER BLANC: Well, first I'd ask do you want to take a short break before we do that, because it's 10:30 and this is going to be a --

CHAIRPERSON FROINES: Take awhile?

PANEL MEMBER BLANC: Take awhile.

CHAIRPERSON FROINES: Let's take a ten-minute break.

(Thereupon a brief recess was taken.)

CHAIRPERSON FROINES: Back to work. Can we begin, please.

PANEL MEMBER FUCALORO: Can we have the lights on, please. Is that a problem for anyone seeing that screen without the lights on?

CHAIRPERSON FROINES: Jim, Bill, we're going to start.

SUPERVISING TOXICOLOGIST MARTY: I don't know if anybody had comments on Table 1, which was the big ranking table that we put actually into the document with reasons for conducting the literature search and reasons for deferring?

It starts on page 8.

PANEL MEMBER GLANTZ: Yes. I had one. First, this is a great help in the report, but I think that it's very confusing to have several compounds appear on several of these lists. And so I think that the -- what I would suggest doing is having nonintersecting lists, where you would have your -- one table would be the five final compounds and another table would be your Tier 2 or what

we end with up as Tier 2, another one would be the, I think it was, the list of 35 this table here, table 20, but excluding the 11.

And then this table one would be the low priority ones, which would exclude the 35, because I just think right now it's a bit confusing to have things keep reappearing, but other than that, I thought it was much clearer than before.

SUPERVISING TOXICOLOGIST MARTY: The purposes of the tables are a little different, too. This is the initial ranking where we used ambient data and so forth not what's on your screen, but Table 1 in the document, the preliminary ranking and initial prioritization, so those are the chemicals -- I think we need to have the 11 and 35 in this table also, because you need to know what the rankings were and what our reasons were for conducting a literature search, but we can create these other tables that we talked about before.

PANEL MEMBER GLANTZ: Well, so what --

DR. MARTY: We actually have created a table which you have in front of you as Table B. This was the list of the chemicals that fell out, because they didn't either have ambient data or we didn't have a quantitative handle on the toxicity. And then you folks asked us to add why, what was the reason for each one of those, so we

created this Table B, which you have in front of you.

PANEL MEMBER GLANTZ: Where is Table B?

PANEL MEMBER BLANC: It starts on -- it was handed out.

SUPERVISING TOXICOLOGIST MARTY: It was just handed out separately.

PANEL MEMBER FUCALORO: It looks like this.

PANEL MEMBER GLANTZ: Oh, okay.

SUPERVISING TOXICOLOGIST MARTY: So that's another table that, I think, Stan, actually you asked us to put that together.

PANEL MEMBER GLANTZ: Right.

SUPERVISING TOXICOLOGIST MARTY: I'm not sure that we want that in the document or not.

CHAIRPERSON FROINES: Which one is that, XX?

SUPERVISING TOXICOLOGIST MARTY: It's Table B.

PANEL MEMBER GLANTZ: Well, no, I think that should be in the document, because I just think it needs to be very clear as to what was considered and why of all the potential TACs that there were, you know, everything that could potentially be considered should be listed somewhere in the document so people can see that it was, in fact, thought about even if it was decided that it wasn't worth the Table B ones. So I would like to see this in the document.

So Table 1 includes all the stuff in Table B, too, no.

SUPERVISING TOXICOLOGIST MARTY: Table 1 includes the ranking of the chemicals that had ambient air data and the either RELs or potency factors or both. And also we added other chemicals that didn't have ambient air data because we were worried about the toxicity. The Table B is basically the 200 plus TACs minus all of those that ranked, so it's the ones that fell away in the very first --

PANEL MEMBER GLANTZ: So if you take Table 1 and Table B and put them together, that's all however many TACs there are?

SUPERVISING TOXICOLOGIST MARTY: That's right.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER FUCALORO: Yeah, I have a question about Table 1, there's almost a correlation of one, not exactly for those substances that have ambient air concentrations that are printed in unbold type, that is to say it's typed -- it's obviously data from other than California, but some of them have very high ambient concentrations.

And in your reasons for deferred search -- deferring the search, sometimes you just say low emissions, and yet there's a number that's pretty large in

the ambient air concentration. That's somewhat confusing, I think, and somehow that would have to be explained.

For example, Acrylonitril, number nine on your Table 1, has a. -- by my lights and I'm not an expert on this, it has .66 micrograms per cubic meter. And say low emissions, but yet it's a pretty high number.

SUPERVISING TOXICOLOGIST MARTY: It's low emissions in the California Air Toxics Hotspots Database. And those numbers came from a compilation that US EPA did of the measurements around the country.

PANEL MEMBER FUCALORO: No, that's understood. I gathered as much from the one footnote you have based on other numbers are from various sources as compiled by US EPA in 1993, which is old data, of course.

SUPERVISING TOXICOLOGIST MARTY: Right, and actually a lot of their compiled data are even much older than that.

PANEL MEMBER FUCALORO: Well, maybe a few words, I don't know, in the text, that explains why some of those things were eliminated.

You see, one of the problems I have in trying to understand how this priority list was developed is things like that, for example, you look at 1-2 dibromo, DBCP, 3-chloropropane is eliminated, but yet arsenic and formaldehyde -- and you look at the ambient air

concentration is high, but really it's because it's not really high in California. Maybe that's the reason, and I think that ought to be made clear I think at least in the text, so that one can get a better handle on how you've actually compiled the list.

CHAIRPERSON FROINES: Tony, I'd almost argue that the Acrylonitril is a good example of a number that should not be even listed. Why list it? What's the purpose of it, because it's in --

PANEL MEMBER FUCALORO: You may be right.

CHAIRPERSON FROINES: You know, if we were in Delaware and we were near the Dupont Chamber Works that would be one thing, but we're not. And so the point is why list values that are nationally based data rather than California based data, which may have zero relevance to California?

PANEL MEMBER FUCALORO: I think you've cut it to the heart much quicker than I have. I think that's exactly right.

PANEL MEMBER BLANC: I think the solution to both of your comments would be to change the word "low emissions" to "low California emissions." If you just put that on the table, because, you know, in terms of transparency, I think it's good to include the numbers as long as you're making sure why it's not driving the

decision.

CHAIRPERSON FROINES: Well, I think there's one other issue that if Roger were here he would raise, which is there are compounds that come out of sources, say acrylonitrile from Dupont, but there are also atmospheric transformation products that may have relevance in California, even though the numbers come from outside of California, so that if that were the case, then you might want that in.

SUPERVISING TOXICOLOGIST MARTY: I think, you know, we have to keep going back to this is a prioritization process and we use data that we had that were available to us.

PANEL MEMBER FUCALORO: Yeah, but just be clear, that's all we're saying. And what Paul suggested "low California emissions" or even better "low California concentrations."

SUPERVISING TOXICOLOGIST MARTY: Well, I would hate to say that, because we don't know what the California concentrations are, so I don't want to --

PANEL MEMBER FUCALORO: Fair enough.

CHAIRPERSON FROINES: The point I think everybody is making it goes back to the transparency issue, is that any number that's in any table one should be able to understand it and not have to interpret it.

SUPERVISING TOXICOLOGIST MARTY: I can pull in more information from the compilation, which describes what they did, but even then it's hard to know how good that data is. We definitely weighted the California Air Resources Board's data more --

PANEL MEMBER FUCALORO: Sure, rightfully so.

SUPERVISING TOXICOLOGIST MARTY: -- because it's more representative of chronic exposures for one.

PANEL MEMBER FUCALORO: But, again, I'm not asking for me. I'm not asking for anything extensive, just make some little indication that these are -- that it's not "low California emissions" I understand that.

SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: Melanie, can I make one specific request? And it's really on behalf of Roger Atkinson. At the last meeting, Roger raised a number of questions about the ambient concentrations of acrolein in California and argued that the numbers were much lower than what had been previously estimated. I would appreciate you folks talking with Mike Port at ARB and try and come up with some reasonable estimate of what ARB thinks the acrolein concentrations, because this is an extremely important issue.

Acrolein is an extremely toxic chemical as we all know. And having some sense of what, to the degree that

we can, of what the realistic airborne concentrations would be, I think, is particularly useful.

SUPERVISING TOXICOLOGIST MARTY: Sure.

PANEL MEMBER BLANC: So we're still on Table 1. Are there any chemicals that appear on Table 1 which were deferred for literature search, which are capable of inducing methemoglobinemia.

CHAIRPERSON FROINES: Are capable of what?

PANEL MEMBER BLANC: Inducing Methemoglobinemia.

SUPERVISING TOXICOLOGIST MARTY: If we knew that they were capable of doing that, we would have flagged them, since that's an issue for us.

PANEL MEMBER BLANC: Even with low ambient levels?

SUPERVISING TOXICOLOGIST MARTY: Well, it would depend on what data we had, how good the data were, but we would be concerned about something that induced methemoglobinemia.

PANEL MEMBER BLANC: So can I make a special request that you have your toxicologist go back over that list and double check, because I'm not going to have the time to do that?

SUPERVISING TOXICOLOGIST MARTY: Sure, that's fine.

PANEL MEMBER FRIEDMAN: Why is that important?

PANEL MEMBER BLANC: Because infants are particularly susceptible to not being able to cope with methemoglobinemia, because they don't have developed Methemoglobin.

PANEL MEMBER FRIEDMAN: And what is the result to them of not being able to cope with it very well?

PANEL MEMBER BLANC: They could have hipoxic injury or hemolysis. The main issue for infants is in drinking water exposure to fertilizer runoff, but since the statute requires consideration of concomitant exposure with other routes of exposure.

PANEL MEMBER BYUS: Contaminated well water, too.

PANEL MEMBER BLANC: But usually from runoff, I suppose.

PANEL MEMBER BYUS: Coli makes the nitrates that also cause it.

CHAIRPERSON FROINES: What did you say?

PANEL MEMBER BLANC: Ecoli.

PANEL MEMBER BYUS: Is contaminated well water.

PANEL MEMBER BLANC: Then could you clarify something else, I know we discussed this at the last meeting, but I don't remember the answer for Methyl Bromide?

CHAIRPERSON FROINES: What number is it, Paul?

PANEL MEMBER BLANC: Number 78, which then makes

it into the literature review, although other things don't make it into the literature review because they're pesticides. So was there a nonpesticidal use of Methyl Bromide that was why?

SUPERVISING TOXICOLOGIST MARTY: Yes, that's why.

PANEL MEMBER BLANC: What is the nonpesticidal use?

DR. ALEXEEFF: George Alexeeff. It's a pesticidal use, but Methyl Bromide falls under a different -- there's another law which requires the air districts to permit or did require the air districts to permit fumigation chambers. So it fell under the Air Board's jurisdiction.

PANEL MEMBER BLANC: And is that other wise then excluded by the specific statutory language of this law which said that pesticides -- which reiterates? Could legal counsel comment?

OEHHA COUNSEL HECK: As I mentioned briefly before, it is clear that pesticides and their pesticidal use are excluded from the ranking process and the related processes that happen after that under SB 25. So if Methyl Bromide were to be examined, it would have to be in other than its pesticidal uses.

SUPERVISING TOXICOLOGIST MARTY: I think it's because it's emitted from a stationary source that it can

be evaluated, rather than its use on a farm or in a field.

OEHHA COUNSEL HECK: Well, to follow up on that, I think, Melanie is correct, there is -- one of the clarifying statements in the law is that the manufacturer of the pesticide is not the pesticidal use of that pesticide. In other words, it's fair game in this statute. So if that were the source of the emissions, that could be evaluated.

DR. ALEXEEFF: Actually, if you look at the statute states toxic air contaminants evaluated and listed pursuant to the section shall not include substances in those uses that are not subject to regulation by the State Board to this chapter.

It doesn't actually use the word pesticides, and Methyl Bromide as this unusual fumigation chamber, which are subject to regulation by the air districts, and that's why it falls under this. But general pesticidal use of most pesticides is not subject to the Air Boards. This is one exemption because of the fumigation chambers. We can look at that. Why don't we look at that. That's my understand. Why don't we look at that one and have the Air Board double check on that one.

PANEL MEMBER BLANC: It's certainly going to confuse -- it confuses me, so I suppose anybody reading this document who says okay, well I see pesticides are

dropping out in Table 2, and then there's Methyl Bromide, so there needs to be a footnote perhaps.

But then in light of the other statement, since there was not one single astacolon esterase inhibitor included in the literature review certainly. And actually I don't know if there are any in Table 2, which then drop out. There may be some that fall in the column of pesticides. Are none of those pesticides manufactured in California for which there might be hotspot releases?

SUPERVISING TOXICOLOGIST MARTY: I don't know. We don't have that information from the Air Board.

CHAIRPERSON FROINES: There is a company in southern California that does manufacturer pesticides or did because we used to take students to it to show them pesticide manufacture. So I can give you the name of the company. I don't remember it off the top of my head, but there was not too many years ago.

PANEL MEMBER BLANC: Well, I think it would be useful to have some sentences somewhere in the document, perhaps, which say the following organophosphate pesticides are manufactured in California and we may have to return to hotspot emissions for them even though they're not included in this document. Perhaps in the same paragraph wherein you say, in general, we have not looked at pesticides because we're prohibited in their

pesticidal use. However, their manufacturing would be covered, but we haven't addressed it, but we will address it. And in that same paragraph perhaps you can then talk about Methyl Bromide.

SUPERVISING TOXICOLOGIST MARTY: Sure.

CHAIRPERSON FROINES: This issue raises a question, which is if Methyl Bromide is one of the compounds that can be considered because of this special fumigation chamber issue, does that mean that by your evaluation it ranked 78th? Because Methyl Bromide talks -- I mean if I had to choose between glycol ethers and Methyl Bromide, I think I'd choose Methyl Bromide in some respects.

SUPERVISING TOXICOLOGIST MARTY: We couldn't rank it, because we didn't have concentration data. But, you know, I would ignore that -- I wish we could -- their ranking numbers are not as meaningful as you would like them to be. Because of all of the data gaps, is issue of bringing in other information on emissions from stationary sources and the toxicological considerations, it's difficult to just say this chemical is number 80 and that chemical is number 59.

CHAIRPERSON FROINES: But one of the things that we keep pressing you on is this notion of transparency. And when you end up with up with statements like that,

means that anybody who's reading the document, it obviously leads to some level of confusion. If you have something that says 78, but you say it doesn't matter, then how do we understand it?

SUPERVISING TOXICOLOGIST MARTY: It matters only if you had the information to rank the chemical to begin with and only if there is no other reason to be concerned about that chemical, i.e. from stationary source emissions or because you know it's a developmental toxicant.

CHAIRPERSON FROINES: Well, then would it be better just to have an alphabetical list rather than put it with a ranked number?

SUPERVISING TOXICOLOGIST MARTY: We can do that. We can alphabetize it.

PANEL MEMBER GLANTZ: Yeah, I think that would make a lot more sense given the way the process went. And see if you did that, then, I mean, what you could do -- I keep wanting to break -- have things not appear in multiple tables, see then you've got your -- as I figured it out, finally, the Table 20 your XX is all of the stuff in Table 1, which has an entry under reasons for conducting literature search. I finally figured that out.

And so then what you could do is you could have one table, which is all the stuff that you've deferred in alphabetical order, and then Table 20 would be all of the

things where you have conducted a focus literature search. And what you could do, at that point, is maybe even combine the information that's in Table 1 and the information that's in table 20 for those compounds, and I think that would also be less confusing.

PANEL MEMBER FUCALORO: Well --

PANEL MEMBER GLANTZ: And then it becomes clear as to why you did what you did, because you didn't -- you know, as I've come to understand the process, you didn't really much use these numerical rankings in the end. And so, I mean, you sort of use them a little bit, but in the end what happened was you identified those things where there was a reasonable justification for doing the literature search. And, you know, and not a good reason not to do it, you know, like no emissions in California or something and so that separates them, I think, much more clearly.

DR. MARTY: Okay.

PANEL MEMBER GLANTZ: And then the 11 that you ended up with in your Tier 1 and Tier 2, those things really came out of the more focused literature reviews rather than this arithmetic ranking.

SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER GLANTZ: So given that that's the case, I just think it would be much clearer to get rid of

the numerical rankings.

CHAIRPERSON FROINES: I'm getting nervous about time, because we have six chemicals to go through today, and we're spending -- all of this the highly relevant, but it also is something that, I think, we should get passed.

So I think Paul had some specific questions to raise, but then I think we should move as quickly as we can to the actual substances of concern.

SUPERVISING TOXICOLOGIST MARTY: Okay. Paul, had questions on table 20, that's the information that we developed for the panel in response to their request four of the 35, why did some end up in the 11 and some didn't, so that's why we developed this table. And it is alphabetical, and we took away the numerical noncancer and cancer rankings and put them into bins of low, medium moderate. I should say not medium, low, moderate, moderately high and high.

PANEL MEMBER BLANC: Okay. So let me first say that I think it is important to have a table like this, and I don't have a fundamental problem with the structure of the table, but I have to say that the content of the table, to the extent that I was able to cross check information, I found deeply disturbing, and suggested to me strongly that your literature reviews were either two possibilities, one is that your literature reviews were,

in certain cases, terribly flawed or else the interpretation of the literatures reviews by OEHHA somehow short-circuited. I don't think the latter the probably the case and you have admitted the understandable challenges of the time crunch.

So I'm going to take some examples. They were things that I was most suspicious of and most concerned with. So they may be the worst case scenarios, but nonetheless they're so disturbing, that I think there has to be some real content addressed here on the part of OEHHA and senior staff.

So let's start with carbon disulfide. What it says here is the evidence for concern is a transient delay in behavioral development among young animals siting in 1980 study, that I'm going the leave aside the cancer ratings. That's not the issue.

Inadequate data. "No studies directly addressing age-related susceptibility."

Here's a study from 1987, Metabolism and Distribution of Label Carbon Disulfide in Immature Rats at Different Ages.

This study demonstrates clearly that young rats metabolize the material differently and more slowly, therefore have higher or more persistent levels. Last sentence of the abstract, "The rats showed that

elimination of the biotransformation products of SC2, in particular, the covalent binding of sulfur metabolize was prolonged in new-born rats in comparison the 40-day old rats."

Now, it may be that you didn't feel that this study, you know, rose to the level of supporting concern, but given the fact that most of the time you were saying there was no study at all. I mean, this ipso facto is enough to make you want it included among the 11, I would say, or in your final group.

SUPERVISING TOXICOLOGIST MARTY: Well, it certainly made us want to include it the 35.

PANEL MEMBER BLANC: Well, it's not cited in the table in either place and yet this the -- and in the table it says, "No studies directly addressing age-related susceptibility." This the a study which directly addresses age-related susceptibility, and, in fact, confirms that there is likely to be age-related susceptibility.

And if you're asking me as a scientist to review your document and approve it, when, in fact, there's something which is so scientifically inadequate and inaccurate, it's extremely concerning to me, because I don't know where else there are similar errors. So on the one hand the demand of making the table, puts you in a

certain vulnerability because it means that you're going to have to say things that you can stick by.

But I have no way of knowing that you looked at this and this the not what you mean by that statement or did you never see this study?

SUPERVISING TOXICOLOGIST MARTY: Okay, I would have to ask the staff people that looked at CS2, but yeah, I didn't realize we said no studies. I don't if they meant no studies in humans or no studies looking at the toxicity where you had young animals versus older animals.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think the entry in the table specifically addresses the or is designed specifically to address the toxicological endpoints, rather than the metabolism or the biomarkers for that effect, but I agree that perhaps in this case there may have been less detail than this finding deserved. I don't know.

PANEL MEMBER BLANC: Well, given the level of evidence that you lack for most things, which was your rationale for not moving them into the final category, which I think is reasonable, this kind of evidence which is, you know, sort of as clear cut as you can get that there is a preferential susceptibility on a biokinetic basis, which you spend a great deal of time in your general introduction saying it's the reason that the, you

know, a difference between younger versus older animals, since we don't have it generally in humans.

And then you have a study where this chemical has been tested and it has been shown. I'm really at a loss as to then why it wouldn't be in your final group. You know, it's a very widespread ambient chemical. You know that it has neurotoxic. I mean it's a, b, c, d, e. It's met everyone of your criteria.

SUPERVISING TOXICOLOGIST MARTY: Let's go back to the fact that we can only pick five.

PANEL MEMBER BLANC: I'm talking about the 11. We're going to get to the five later on. I'm talking about --

SUPERVISING TOXICOLOGIST MARTY: Even the 11 we had --

PANEL MEMBER BLANC: Who said?

SUPERVISING TOXICOLOGIST MARTY: -- heavily weighted to toxicology information. So if you look at CS2, what kinds of data do you have on developmental effects? It really isn't very much, even though as you're pointing out there's a good mechanistic reason why you would expect that compound to be worse in young animals.

So it's not that we ignored it or that we don't think it's important, it's that we think that for these other compounds we actually have stronger and more

studies.

PANEL MEMBER BLANC: But we don't see, as a panel, your literature reviews on anything except for the 11. So you're asking us to accept, and that's why we asked for Table XX. And then you give us Table XX, which is fatally flawed, what am I supposed to do as a scientist in my role as a reviewer of the scientific validity of your document?

PANEL MEMBER FUCALORO: Let me ask a question, just for a minute and it's related to this.

The paper he cited seemed to be relevant to me.

DR. MARTY: Yes.

PANEL MEMBER FUCALORO: And my question simply is were you aware of this paper?

SUPERVISING TOXICOLOGIST MARTY: I was not personally aware of this paper.

PANEL MEMBER FUCALORO: Was the reviewer aware of this paper, I mean isn't that what you're getting at?

MR. LEWIS: Which paper was that you were saying?

PANEL MEMBER BLANC: It is Drug Metabolism Debt Disposition 1987?

PANEL MEMBER GLANTZ: I think the reporter wants your name.

MR. LEWIS: David Lewis, OEHHA.

PANEL MEMBER BLANC: Was that in your list?

MR. LEWIS: I don't believe -- you know, I don't believe it was.

PANEL MEMBER BLANC: Okay. How about Zhaosf, Z-h-a-o-s-f, et al, The Evaluation of Developmental Toxicity of Chemicals Exposed Occupationally Using Whole Embryo Cultures, International Journal of Developmental Biology, 1997. Is that a reference that sounds familiar for carbon disulfide?

CHAIRPERSON FROINES: Why don't you say what it shows, Paul?

BOARD MEMBER BLANC: Also, it's not as, you know, convincing a study, but it also does show some invitro evidence that there were developmental effects from carbon disulfide. Invitro studies showed that, blah, blah, blah while carbon disulfide, 1-2 dichloroethane and vinyl chloride mainly induced embryo growth retardation.

SUPERVISING TOXICOLOGIST MARTY: Well, we could get those studies and take another look, but you have to realize it's going to have to overshadow the data that are available for the other chemicals.

PANEL MEMBER BLANC: I'm raising a fundamental question about the quality of the hired out literature reviews that you had for certain chemicals. If I can go on to MedLine and in, you know, an hour or two of work of things that I'm particular suspicious of, I grant you,

find a series of citations which are inconsistent with your table, and which also make me wonder, well, how did this chemical not make it to the final group, and I don't have the documents to then cross check against, because we're not supplied because they dropped out, it puts me in an incredible double bind.

MR. LEWIS: Well, I think my overall impression of the human and animal data, as a whole was that effects were seen at approximately similar levels. You know, You're raising these metabolic studies that seem are interesting and I --

PANEL MEMBER BLANC: Well, I'd be happy to give them to you.

PANEL MEMBER BYUS: Just a general comment. It addresses the same point. I mean, I was struck by kind of a very significant review of the pharmicokinetic, toxicokinetic differences, and then also the differential. And neither exposure parameters or any toxicokinetic differences are listed in your table at all. I just look it over again.

None of those two criteria, which speak to the relative amount of exposure and/or internal dose are mentioned in this table. You steal almost exclusively with the toxicology endpoints, which is, I suppose -- well I don't know whether it is okay. But you don't mention

any of those other two parameters whatsoever.

I mean, I would have -- when I got this table, my thinking was, I think it is much better that we have this table than when we didn't have the table, but I would have divided it up into the three different areas of exposure differences, toxicokinetic differences and then, what I would call, farmico dynamic or toxico dynamic differences that address susceptibility either developmental or neurological or whatever.

So, I mean, what he's saying is he just happened to pick out now a difference at the level of metabolism or toxicokinetics, but there's no references to any of those two parameters in the table.

SUPERVISING TOXICOLOGIST MARTY: Well, we did weight direct toxicology studies heavily, especially in this first iteration, where we have to come up with up to 5. I mean, it's not to say that we're ignoring all the other information or that we're not going to consider it when we update the list, which we are allowed the do under law and actually required to do under law.

But for this first go round, we heavily weighted studied where there was direct toxicology information.

PANEL MEMBER FUCALORO: But you see the problem that now I have, that Dr. Blanc had before, but now he's an expert in this area. And we all rely on each other's

expertise on these sorts of things. And he's cited now two papers that have been overlooked. And this causes him some concern and I must admit it spills over to me quite a bit. We want to be confident that when it says a literature search has been done, it's relatively exhaustive and inclusive. And now I'm feeling less confident that that's happened. And I think that's the point he's making.

And the other issue is how much do you include in the little box. I understand that, and that we can argue about, but that's not as fundamental as the question or the issue presented to us by Dr. Blanc.

SUPERVISING TOXICOLOGIST MARTY: Yes, I would agree that that is disconcerting that our lit reviewers did not pick those studies out. However, I still think that people need to realize we focused heavily on where we actually had toxicology studies that looked at either young animals or humans.

PANEL MEMBER BLANC: Well, if you did, then isn't all the more an indictment that your literature review didn't meet -- I mean, we're not talking about when you do a focused literature review, in fact, you're really not talk about that many papers.

SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER BLANC: So therefore why weren't

these two included, out of, you know, I don't know how many papers the person who you hired to do the literature review actually found that were on point 5, 3.

You know, I mean I'm not talking about general review of carbon disulfide toxicity.

Now, I'm going to go on to another example manganese. What your table says is, "Neonate may be more at risk because intestinal absorption is higher excretion mechanism is absent, causing manganese to accumulate in brain tissue." Then it says reason for lower and this is why it didn't make it into the next cut. "Adult workers exposed to manganese showed neurologic effects, but there are no studies in children." Of course there are no studies in children.

"Children with learning disabilities have been shown to have higher manganese levels in their hair. The weak evidence, hard to interpret."

Okay, so here's a paper from the Journal of Applied Toxicology 2000. Neurotoxicity of manganese chloride in neonatal, on adult CD rats following subchronic 21 high dose oral exposure. Now that would seem to be a paper that would be pretty much on point. The purpose of this study was to evaluate the relative sensitivity of neonatal adult CD rats to manganese induced neurotoxicity.

Now, there's a series of different findings. That's not a slam dunk study, but I will read you the final line of the abstract. "The results of our experiment suggest that neonates may be at greater risk for manganese induced neurotoxicity when compared to adults receiving similar high or oral levels of manganese." Is that a paper which you reviewed?

SUPERVISING TOXICOLOGIST MARTY: It would depend when in 2000 it came out, because now we're a year past when we started to get the literature searches done.

DR. MORRY: David Morry, OEHHA. I didn't bring all the manganese papers with me, but that sounds familiar so I think we did see that paper.

PANEL MEMBER BLANC: Well, I think in fairness to the committee, If you did I would certainly put it ahead of the 1997 sort of weak inferential paper that you -- the '87 paper. Here you have a very recent animal study, you know, by established criteria, which is very strongly indicative of a preferential effect.

SUPERVISING TOXICOLOGIST MARTY: We can add that to the table. That's not a problem.

PANEL MEMBER BLANC: That's at a minimum. We're going to come back to what needs to be in the final cut or not, but I'm saying at a minimum. I mean, I'll really angry about this. I'm not happy at all, because you're

asking me to put my name on the scientific approval of something which is inappropriate, from what I can tell.

DR. MORRY: We also wrote summaries for each of these chemicals. And the information you're talking about is probably in the summary.

PANEL MEMBER BLANC: Which is where?

SUPERVISING TOXICOLOGIST MARTY: Well, we didn't provide summaries of all 35. We only provided summaries of the 11.

PANEL MEMBER BLANC: Well, that's what I'm saying, and I have been saying.

Now, there's another study, which is not quite as strong, but nonetheless is relevant. It's a 1997 publication, so it's also more recent than anything cited in the table, which is by Papas.

And that study shows portical thinning in young rats. I believe it's young rats right from -- well, actually, it's a fetal exposure, because it's from conception to post-natal day 30, so it includes both in utero and then young rats. And it shows some negative findings, but it does show portical thinning, which the authors interpret as being an important marker of exposure. Now that's not a head on versus adults, but it certainly is a study of neonates.

SUPERVISING TOXICOLOGIST MARTY: We apparently

didn't look at that study.

PANEL MEMBER BLANC: Okay. Then let's go on. I have to answer, sorry, a page that I got.

Well, actually let me take a break and let other people talk and let me answer a page.

CHAIRPERSON FROINES: Well, I think --

PANEL MEMBER BLANC: Because I have another chemical to go on. I'll be right back.

CHAIRPERSON FROINES: The problem with Paul walking out At this point is I think we're ready to go on to the other chemicals unless others have comments at this point?

Oh, melanie, why don't --

PANEL MEMBER FUCALORO: Why don't we -- I don't -- he can go and continue this what he's doing and point out some papers that maybe we missed. How are we going to feel confident that the literature search was complete? Are we going to get something like this, again, with a list of references for each chemical? I mean, I don't know. What the mechanism --

CHAIRPERSON FROINES: I think there's a question. Well, there's a very difficult question that this raises, because we know we have a July 1st deadline for this list of five. And I think that, at this point, I may be wrong to say this, but at this point I think this panel is going

to have trouble signing off on where we reach, wherever that may be given the level of uncertainty.

So we have a problem that's actually related to OEHHA's problem and they're obviously connected. But we're going to have some questions about how we proceed because, as Paul says, I don't, at this point, I don't know how comfortable people will be signing off on some document that says I'm comfortable with the materials that have been developed. I don't know how you feel at this point.

PANEL MEMBER WITSCHI: Lousy.

PANEL MEMBER GLANTZ: Well, I mean, I think that the issues that are being raised are -- I mean, they are not insoluble. And it may be -- I don't want to be stoned for saying this, but I mean we may have to have another meeting, you know, to -- I mean, I think that the issues that are being raised are pretty concrete. I think that the document is getting better fairly quickly, but I also think there are still these unresolved issues. And it may be that we'll have to finish this and, you know, give OEHHA a chance to drink more coffee and stay up late at night some more and hopefully these issues can be resolved.

I mean July is like -- it's you know, it's a while. It's soon, but it's not tomorrow.

CHAIRPERSON FROINES: Well, I think the problem we have is we're going to have a discussion at some point, this afternoon hopefully, about the list of chemicals on the 11. And people are going to judge the level of information that they have provided. What Paul's point is bringing up is the question is, are there things in the list of 11 that were missing? But we can have a discussion about the list of 11, recognizing what we have here.

PANEL MEMBER GLANTZ: Right, and we could also have a -- we're not limited to only talking about those 11. I mean I think if there are others which ought to be, you know, seriously discussed, then we can discuss those too. And it may just be -- I mean, one other question that we might want to think about is what the law requires is five. And may be we should have a list of five and then other.

You know, we have basically, we've gone through this iterative process, and there's the list. There doesn't seem to be a lot of controversy between the list of 35 and the rest, that people seem reasonably comfortable with.

And so the so-called list of 11 is drawn from the list of 35. And maybe what we ought to be doing is come up with a list of five and then the other 30 and leave out

the Tier 2, because I think that there's nothing that requires us to have a Tier 2 right now. The law explicitly says that they'll be a continuing review, and then some of these issues become less sharp, you know.

And then we don't have to argue about whether they're in the list of 11 or not 11. I mean the law says there have to be five, and we can have those five and the other ones which seem to be of reasonably high priority for further discussion later. And that maybe one way.

Then the argument is what should the five be, that's really the important question.

CHAIRPERSON FROINES: Were you going to say something, Gary?

PANEL MEMBER FRIEDMAN: No.

CHAIRPERSON FROINES: I think that I basically agree with everything you said. I think that the question will be will we feel comfortable signing off on a transmittal letter that says that the reviews that we've received of the five we ultimately select that we're comfortable with, so that's just a decision what we'll have to make.

PANEL MEMBER GLANTZ: Yeah, and we may or may not be able to do that at the end of today, but I still think we could -- I think that it will be possible to do it by July.

DR. ALEXEEFF: Just one comment, you know the July 1 deadline is a deadline for OEHHA, okay. And your responsibility is to make sure you're comfortable with the list that we've come up with, so if you're not comfortable with it, you don't sign off on it, whether it's July or August or whatever month it is.

So we have to wait until you feel that we've brought all the scientific information before you. And the fact that the list is not adopted pretty much falls on us, our department, and, you know, it's our fault or whatever, so that's --

CHAIRPERSON FROINES: But your.

DR. ALEXEEFF: Sure we'd like to meet the July 1 goal.

CHAIRPERSON FROINES: I mean, I think that this panel will be very uncomfortable when July 1 comes up with a list of five.

DR. ALEXEEFF: I can assure you the Director will not adopt the list if you haven't signed off on it yet.

PANEL MEMBER GLANTZ: Well, I think Paul has now returned and we should return the floor back to him.

DR. ALEXEEFF: So all I'm saying is if you are not ready, let's say, by the next meeting to sign off, then we wait until the following meeting to sign off.

I mean that's --

CHAIRPERSON FROINES: I think --

DR. ALEXEEFF: And the Director won't adopt it until the panel feels that they've had sufficient review.

CHAIRPERSON FROINES: We hear that. I'm simply trying to make clear what are the procedural questions that we have to think about. Paul, can go back to the specifics, but we're going to have -- I want to make sure what issues we need to be thinking about as we go forward.

Paul, go ahead.

PANEL MEMBER BLANC: Well, I'm going to bring up one more example. And, again, this is meant to be exhaustive, but these are the ones that I thought were the most --

CHAIRPERSON FROINES: Paul, can I interrupt you, there is one question that I don't know quite how we're going to resolve it. But, for example, is the use of whether manganese should now move up to the list of 11 and becomes a list of 12 from which five are chosen, that's a separate and important issue we've haven't talked about yet.

So go ahead.

PANEL MEMBER BLANC: Stan, made a suggestion and I think we should come back to that discussion. But let me just take one more example and then may be out of that. In terms of methylene chloride, which is on page nine, the

Evidence of differential effects decide it is a Marginal effect on spontaneous abortions and occupationally exposed women."

So, again, presenting sort of very -- we're only looking at this to because there's sort of this very marginal reason. But then the reason for giving it a lower priority, there is no data on developmental effects in children. By that I guess you mean there's no data in human children, which there isn't for anything virtually that you have, so that's not really an issue.

Negative studies. Now this would be a lot more convincing. There's a series of negative studies, you're saying. It's been looked at. We have negative studies. "No effect on birth weights, Bell et al. While exposure to pregnant rats to CO results in higher CO in the fetal blood, exposure to methylene chloride results in equivalent CO in maternal and fetal blood."

So I thought that was interesting, okay, here's a study of, you know, fetal transplascental exposure, so I pulled the paper to look at it. Now, what the paper -- it's a very brief paper, but still it's on point. So what it shows is in its two-line table that when the maternal animals were given 500 parts per million of dichloro methane. They had 8 parts per million of dichloro methane of 176. And the fetal levels we dichloro methane were

115. So there were lower levels of dichloro methane in the fetus.

But, in fact, the carbon monoxide levels were the same 167 and 160, virtually the same statistically not differentiable, although there was a wider variability, which is of interest in the fetus, so some of the fetuses clearly Got up to much higher levels in fact than the maternal. So we don't have all the data, but the Standard deviation for maternal is 12 and the Standard deviation for the fetal is 31. So that it means that even within the 95 percent confidence interval some of the fetal animals had levels that were considerably higher.

This is in parts per million of carbon monoxide not as a percent of carboxy hemoglobin. So it's a little tricky to fully get, but I'm assuming that it would parallel carboxy hemoglobin. I would have sort of a completely opposite interpretation then of these findings, because we know the fetal hemoglobin binds carboxy hemoglobin more tightly than adult hemoglobin. So therefore having -- even if they were the same level, it would be worse for the fetus, and, therefore, be it the developmental toxicity.

So my interpretation of the study is quite different than OEHHA's apparent interpretation of the study which may simply be OEHHA swallowing whatever the

hired gun said.

The second study that I thought was relevant, you know, was a study which showed behavioral toxicity in the offspring of rats while in the maternal exposure to dichloro methane, which is from Toxicology and Applied Pharmacology from 1980, so it's an old study, was coupled with a publication from the same group in the same Journal issue where they showed that it wasn't a teratogen, but they did show this behavioral toxicity, which they felt was probably related to carboxy hemoglobin production. So I thought it was quite relevant. I don't know whether it was included in your literature review.

By the way, the last paragraph of the first paper reads, "The finding of elevated fetal carbon monoxide concentrations in pregnant rats exposed to dichloro methane argues that pregnant women should avoid exposure to dichloro methane, which is used industrially in various processes and in the home as a pain remover is because maternal carbon monoxide exposure decreased oxygenation of the fetus and chronic low level maternal exposure to carbon monoxide may adversely affect fetal growth and development."

So those were the three that I, you know, spent time going through, you know, the major medical computer database. But I don't know what would have happened if

I'd spent another couple of days going through the rest of the things on this list. And it leaves me in a quandary as to how to proceed, you know, appropriately with the data on Table XX.

I mean, there are other things that I think -- but, in general, there seems to be a tendency to either stack the deck with very weak evidence of the things that you want to make the argument for discarding in the first column and then having sort of a different standard for what, you know, the lower priority reasons are in the last column.

SUPERVISING TOXICOLOGIST MARTY: Well I can assure you we weren't trying to stack anybody's decks. You know, all I can say is I'll take the papers and bring them back to staff and we can rediscuss these three chemicals and take another look at the data for the other 30 something.

PANEL MEMBER BLANC: Well, without naming names, can you tell me were these three reviews done by the same consultant?

SUPERVISING TOXICOLOGIST MARTY: I'd have to look it up.

I don't think so actually.

CHAIRPERSON FROINES: I'd actually think that these comments are reflective of a larger problem, which

is that the document that we had had literature reviews of the toxicity of the compounds. And I felt for a long time not sufficient attention to the differential issue. And I think this is like another example of that, so I think that, in a sense, your consultants sort of wrote literature reviews, but didn't give adequate attention to the specific question, because the literature reviews that we thought all were of the whole toxicity of the compounds.

So, for example, on diesel we get to see the TAC process over again and the industry comments. And so, in a sense -- the point's made.

Gary.

PANEL MEMBER FRIEDMAN: I think you in view of what Paul was brought up, we're going to need some kind of evidence of quality control on the literature review, either the staff, you know, sampled and for each of the vendors that did this, you know, and did some of the stuff that Paul did with going back to MedLine and looking for other papers or some kind of duplication or validation of what was done. I won't feel comfortable unless I see some evidence of that.

SUPERVISING TOXICOLOGIST MARTY: Well, how about if we just come back to the panel, and we can't do this in two weeks obviously, with a summary on all 35 of the ones

that we chose for literature reviews? It shoots the deadline, but --

CHAIRPERSON FROINES: Paul, how much time did you put in would you say?

PANEL MEMBER BLANC: Four hours.

PANEL MEMBER FRIEDMAN: But, I mean, I still won't know whether the literature review was complete.

SUPERVISING TOXICOLOGIST MARTY: Well, we can update the literature reviews ourselves, and staff were doing some double checking. And we actually added in stuff that we found that the reviewers had not found, but we can just start again and come back with the summaries of 35.

PANEL MEMBER BYUS: Did you provide your people -- I mean, I had the same feeling that you just said the reviews are more of the general toxicology and didn't focus on the differential issues. I mean, it's all through here rambles around. And you have to try and extract the differential issues out of it. And that's really -- did you give them very specific query, do this, do that, don't do this, do the next thing, because I think I'm sure you did --

SUPERVISING TOXICOLOGIST MARTY: We told them what we were trying to do. We didn't go as far as saying use these key words please.

PANEL MEMBER GLANTZ: Well, I think one question is do we want to see all 35 of the reviews or would -- because I worry that that's going to just drag on interminably and in the end not really address the point. I mean, is there a way to, you know, further wonderfulize Table XX, you know, focusing narrowly on the questions, you know, of differential susceptibility, you know, to go back through your -- the 35 reviews and maybe do some checking of the nature that Paul did?

SUPERVISING TOXICOLOGIST MARTY: It would be a pretty big table.

PANEL MEMBER GLANTZ: Well, that's okay.

CHAIRPERSON FROINES: But let's focus the question better than that, because it seems to me that one question has to do with -- Paul has raised questions about three very important chemicals. This is dimethyl sulfate or something. These are three -- methylene chloride, for example, is really very widely use, as we all know, and we've been through a TAC process on it.

And I would argue that we're going to get a presentation today on non-coplanar PCB's. And I can give you my impression very quickly as to whether or not I want to spend any time on that if there is sufficient evidence on manganese or methylene chloride that they should be in the list, because non-coplanar PCB simply is not a major

public health issue in California, as far as I know anyway.

And so part of the problem, Stan, comes not just about whether or not we have 35 better literature reviews, but what should be on the list.

PANEL MEMBER GLANTZ: Well, no, but obviously the purpose of doing this is to make that decision.

CHAIRPERSON FROINES: Well, somehow, I don't know how to proceed on this. This is really quite very difficult.

PANEL MEMBER BLANC: Well, I mean, I think that one -- Melanie, I think that one middle ground would be, and this is a direction I was headed at our last meeting, and it was not clear to me from the revised -- from this revision that, in fact, it was a direction that you were going to go. It seems like perhaps not, and that Table XX was an attempt to temporize that.

I think that there probably are things among the 35 that I would be comfortable seeing a table such as XX and sort of briefed, you know, this the why we didn't proceed with this, even though it made it into this 35. That I think that there clearly needs to be a bigger group than the 11, and I think that four of those 11 we do need to have literature reviews, summaries just like you do for the other 11.

I think at an absolute minimum, I've raised enough doubt about these three chemicals that they need to be among the final group for which we have summaries. And I think that it would be useful to take some time with this panel at this session today, other wise you're going to be too far behind in time to highlight some other substances, which just on a generic basis that would seem to be enough suspicion despite what you have here on Table 20, and coming at Table 20 with some skepticism that, you know, it's going to have to be sort of show me why they're not, show me more as to why they're not in the final 15.

Whereas, there are other things for which I'm willing to take -- you know, I don't want to have more discussion on asbestos, I don't need to see that more. So, you know, that's okay. And I think carbon tetrachloride given, you know, what exposures are like in the ambient air, I don't need the see more about that. I think chlorine I did raise an issue just in terms of the consistency before, so maybe that would be something that needs to be there.

And we could go around the table, but maybe that would be the middle ground. I think clearly there's stuff -- and then we can have the more substantive discussion about, if I'm going the compare methylene chloride with, you know, planar PCBs what makes it -- and

formaldehyde, what do I think should be in the top five, which is a separate discussion.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: Yeah, I think that getting back the Stan's point, the goal is to get five and give the point about the time pressure, I would think, you know, that if we can go around the table and see if there are other chemicals that people think should be considered for the top five and not so much worry, at this point, about the top 11, that that would be more useful given the time pressures.

And, you know, I can't contribute to that, because I'm not a toxicologist. I don't really know subject matter much about some of these chemicals, but others like Paul probably could.

PANEL MEMBER GLANTZ: Yeah. I mean, I'd like to, you know, we're sort of agreeing with each other, but I think that's what the -- the think I said while you were out answering the page, was that this top 11 is really kind of artificial, I mean, in a way. And I think what we ought to be doing is going through and identifying anything that they didn't do to focus -- that aren't in the 11 that you think ought to be Seriously considered.

And, again, like Gary I'm not a toxicologist, and then make sure they get thoroughly considered. And it may

be there's -- you don't need all 35, there may be five more or three. You mentioned, what, three. I mean what are the other ones that people think ought to be seriously considered for being in the top five?

PANEL MEMBER FUCALORO: That's pretty much what we suggested. That's what Paul suggested. And --

PANEL MEMBER GLANTZ: Okay, well then let's just hear what people have to say.

CHAIRPERSON FROINES: The problem is that Paul went and did a literature search. And so starting from zero he found some compounds. For us now the go through a list is a little difficult because we don't have any information that suggests there's something missing, so we're in a sense --

PANEL MEMBER GLANTZ: Well, I think those are two different problems. I mean one of them is reassuring ourselves that the literature searches are reasonably complete. And I think that Gary suggested a protocol that OEHHA could use to double check what they've got. I think that needs to be done.

But then the other question is from based on what we know, from what's presented here and just where people know, I mean, which of these compounds that aren't on the list of 11 ought to be getting a fuller treatment, so that we can then participate in a sensible discussion about

what the top five are?

PANEL MEMBER FRIEDMAN: Do you think Paul that of the three that you mentioned any of them are candidates for the top five?

PANEL MEMBER BLANC: Yes, I do.

CHAIRPERSON FROINES: I would argue manganese and methylene chloride are --

PANEL MEMBER BLANC: Well, let's take a stab at this then shall we. George, I mean do you think that's -- Melanie, do you think that would be --

DR. ALEXEEFF: We'd be happy to do that.

SUPERVISING TOXICOLOGIST MARTY: The other thing that might help is that --

PANEL MEMBER FUCALORO: The alternative the do 36, so this is a half-way house.

DR. ALEXEEFF: I think it's important to focus on the ultimate purpose of this, and, in part, by maybe raising this group of 11, you know, in one sense it's what Stan was indicating that we've added information that wasn't necessary. At the same time, it did raise the issue the your attention that possibly some of our literature reviews weren't on point, in part, because this was a difficult subject for us to do literature reviews.

But regardless of all that, we'd be happy to add additional information or bring to the panel any

additional information, any of the chemicals that you feel you need the look at before you can decide on which five should be recommended.

CHAIRPERSON FROINES: Let's take up the suggestion that basically Gary, Paul and Stan are making. I just want to make -- ask one question, before we do it. With arsenic and cadmium, under your reasons for lower priority, you say lower ranking and less concern than lead or mercury for neurotoxicity. That's a little problematic, I think, because it's a comparative statement. And I think we should be looking at the evidence on an absolute basis. And that is, is there evidence -- what the strength of the evidence with cadmium for differential effects?

I don't know how to draw a conclusion from a comparative statement like that. Does that mean to say that I don't need the worry about cadmium for kids or what does it mean?

SUPERVISING TOXICOLOGIST MARTY: No, that does not mean that at all. It means that for the five, we have loads of evidence in humans that lead and Mercury are a problem for develop neurotoxicity. When you compare that database to what you have for cadmium, you don't have near the weight that you do for lead and Mercury in humans.

So when you're just considering that you're

trying to skinny this down to five, we wouldn't put cadmium up there. We would put lead up there. And we suggested that possibly even mercury should go up there. And also if you look at the emissions from stationary sources, there really is a difference. And, actually, I have a table -- I don't think I gave it to anybody, because I just put it together yesterday of the top 35, and, you know, cadmium, and this is again -- you know, there's holes in the data, because this is emissions inventory from just those facilities reporting out of the hotspots program. But for cadmium we have 3,600 pounds, for lead you have 233,000 pounds and for mercury you have about 10,000 pounds. Arsenic is about 11,000 pounds.

Now that doesn't represent your total exposure, but it gives you an indication that lead is still being emitted from stationary sources in considerable quantities. So that would then tie into why you would be more worried about lead, the human data, plus you know you have leading poisoned kids out there. We already know that. I don't know if we have arsenic poisoned kids and I don't know if we have cadmium poisoned kids, but I sure know we have lead poisoned kids and there's no reason to put anymore lead out into the environment.

PANEL MEMBER BLANC: And the coplanar PCB poisoned kids?

SUPERVISING TOXICOLOGIST MARTY: There are actually human data on developmental neurotoxicity for coplanar PCBs.

PANEL MEMBER BLANC: But see what I'm saying, the implication here is well we can only put two metals on the five, so therefore, you know --

SUPERVISING TOXICOLOGIST MARTY: Well, it's true. I mean we had the balance -- are you going the put all neurotoxins are or are you going to ignore all the carcinogens, are you going To ignore all the other points. And that just points to some of the difficulty in trying the pick five.

PANEL MEMBER BLANC: Yeah, but it's part of the difficulty of when you -- you set up for yourself a hierarchical process, where first there were 35, which sort of -- you were going to throw a broad net, 35 -- we're going the take in this group anybody for whom we either think on toxicologic grounds could be a problem, just, you know, based generically or there is a lot of exposure, or the ratio of the exposure to the REL, et cetera. You had a bunch of different criteria that ones could have immediate it.

So you're going the throw a broad net, appropriate. We've all been satisfied with that, especially now that it's been explained. And you take the

35. These 35, they have made it to this threshold, we're going the do literature reviews. We're going to have these literature reviews. Okay, you have literature reviews done.

Now, we're read the literature reviews. Some of these, okay, we had concern going in, but now seeing the literature review, it's so skimpy that we really don't need to give it further consideration. Not, there's stuff there, but boy compared to lead, it's not so bad. That was going the next step.

So you're using as an argument for not going from this group to the sort of core group from which you're going to choose the five as the reason to not get -- that it's really because it couldn't make it into the five, that it's not getting into that group. Do you see --

SUPERVISING TOXICOLOGIST MARTY: Well, it couldn't make it into the 11.

PANEL MEMBER BLANC: That's right, but the REL -- but what John was saying was, you know, the statement lower ranking and less concern of lead or mercury for neurotoxicity is not a rationale for not being in the group of 11 or the group of 15. Saying there's no human data, and we're requiring some human data at least the get into that next step, or there's --

PANEL MEMBER GLANTZ: Okay, but wait. I think

what we should do to try the move on is we should -- I mean I haven't heard -- I mean the 11 that they did those are there. And I think the real question is the there anything where there is enough evidence and concern, for whatever reason, that they deserve more thorough discussion about being in the five. And so I think we should just -- I'd like the hear what the people who know about toxicology think of anything in the list of 35 that ought to be elevated up to the list of however many, that then ought to be seriously discussed, compound by compound and then we can talk about all these.

PANEL MEMBER BLANC: Well, I would say that in follow up to John's comment then, if I had to think about arsenic and cadmium, although I don't think the cadmium data -- there may be some intriguing data, but I don't think there's as much there. I do Think that for arsenic it could be discussed in terms of the top five.

PANEL MEMBER FUCALORO: And the others you gave?

PANEL MEMBER BLANC: The others I gave for sure.

PANEL MEMBER FUCALORO: I'm counting four more.

DR. MARTY: I've got five.

PANEL MEMBER FUCALORO: Okay, five.

SUPERVISING TOXICOLOGIST MARTY: I've got chlorine also.

PANEL MEMBER BLANC: And then chlorine I would

add to that because of issues of consistency. I would say methyl bromide, just based on what I see in the table.

CHAIRPERSON FROINES: It's a problem.

PANEL MEMBER GLANTZ: Let's just let, any others?

PANEL MEMBER BLANC: I think that those are the ones I would say. But can I also say a few for which I would be particularly concerned about quality control, just to make sure, because I'm taking on face value to a certain extent. And I haven't gone the pull the articles. So I don't have another reason to say it, but I'm just -- one, is methanol, you know, for all the reasons. I think --

SUPERVISING TOXICOLOGIST MARTY: We were just discussing that.

PANEL MEMBER BLANC: You need a very careful literature search for methanol, because I could easily see it being a candidate for one of the top five.

And I'm going to also take as fairly convincing on face value, and John maybe you have some comments on that, I think the study that, since it was specifically studied, n-Hexane. And young animals were relatively resistant to it. And then on top of that there seems to be well done negative teratogenic studies. That would seem to be fairly convincing negative data. And I'm assuming that there aren't positive studies that you're

overly discounting for some reason.

And this was something I did look at briefly, and I didn't find anything else on it, so I think the Hexane doesn't need to be considered for the top five.

CHAIRPERSON FROINES: Yeah, I agree, it does not.

PANEL MEMBER BLANC: So, but, you know, it's obviously something you want to double check.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It was a compound which we gave very consideration to.

PANEL MEMBER BLANC: Right. And then I want to raise again is the use that I had raise earlier, which had to do with oxidants, with things that could cause methemoglobinemia, just make sure that we haven't missed something there, either something that was in your 35 that does cause -- for example, dichloro benzene, negative study, "A woman who ate dichloro benzene throughout pregnancy showed hemotoxic effects, but the infants showed no toxic effects upon delivery."

And I don't remember if dichloro benzene induces methemoglobinemia. But obviously if it did, then -- and if you believe that there's ambient -- if it's an ambient pollutant, because it could be an additive with other, you know.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Some of the aromatic amino compounds certainly would produce that effect, but I don't think that we have uncovered any which have sufficient exposure in terms of hot spot emissions or ambient levels to draw our further attention to.

PANEL MEMBER BLANC: Right. Again, can I just say one other thing about it. I understand that the two things that you're trying to get a list of five, and that just because something is on the list of five doesn't mean that it won't be looked at later, but I also realize that if something doesn't make it into the sort of, smaller group, that there are going to be regulatory ramifications of that. I mean, in terms, of how far up -- yeah, it's true if something theoretically didn't even make it into your list of the 35 and then later on some, you know, evidence could emerge.

But, in fact, given the facts and all of the things that are looked at, you know, things are going to fall. This prioritization is going to have impacts.

CHAIRPERSON FROINES: But I think there's an important point here. I think that this is not just a regulatory process. And we're tending to think about it as a bureaucratic regulatory process. I think having a list of five, but also having confidence in a subsequent list of 10 to 15 tells the world that the State of

California thinks there is some evidence for say perhaps a total of 15 to 20 chemicals, and that that is an important message to go out beyond the narrow regulatory context. And so this is a very important discussion, well beyond the relatively narrow decision we have to make.

PANEL MEMBER FUCALORO: Clearly, the number five is arbitrary when it comes from the Legislature. I mean, the difference between five and six may be negligible. And, in fact, it may run out to 12, 15 or something like that. I mean, I think that's implicit, but maybe it ought to be explicit. I think that's what you're getting at, John. I would agree with that.

CHAIRPERSON FROINES: I think it shows to our credit to have come up with a list of 15. That doesn't necessarily have regulatory significance, but it certainly has public health significance, and it tells researchers out there to go study the problem and ARB to monitor and so on and so forth. It has wider implications than simply the designation of the five.

Peter, additional chemicals?

PANEL MEMBER WITSCHI: No.

CHAIRPERSON FROINES: I wanted to raise a couple of questions. I agree with Paul that we shouldn't consider hexane. I think we have two aldehydes already, but I wanted to raise this and then I don't want -- let's

not get into a discussion for time purposes. The emissions for acid aldehyde certainly are dwarfed by formaldehyde, for example. And acrolein emissions are not the relevant questions anyway.

But for the issue of acid aldehyde is an interesting one, because of a point that you actually raise, which is fetal alcohol syndrome. I mean acid aldehyde is a metabolite a ethanol. And I got a request yesterday to review an ethanol document for the New England states on the use of ethanol in place of MTBE. And so as we replace -- if we do replace MTBE with ethanol and we then clearly have to worry about acid aldehyde, now there are different studies that some show that there may be importance and there may not be importance. It's not really clear as of this point.

But I think that given the considerations about the potential use of ethanol in California, acid aldehyde is one that we should at least be able to say something about what we think vis a vis fetal alcohol syndrome and that which is presumably a neurologic dimension. So I would say acid aldehyde is something that we need to consider as being on some list.

The other three chemicals that I would add to it, I would add not because I know the literature on differential effects. I would suggest them precisely

because I don't know the literature, but perchloroethylene has a total of 4,500,000 pounds per year. That's a lot. You compare that to formaldehyde which is one and a half million. So that PCE, as we all know, is extremely widely used in California and there is an awful lot of people, exposed to it.

And we did a study of levels we PCE in my son's -- coming from son's bedroom, and they were quite high. We were at the parts per million level, so that there are kids who are exposed to dry-cleaning, and so it's an issue.

Toluene we have five million pounds, and zylenes we have three and a half million pounds. So simply on the basis of the fact that you have a few million pounds of those, we better make sure that we've looked at the literature on those. And you may be fine. I'm not suggesting you not. But I'm saying that given the quantities we have here the fact that I think toluene and zylenes are listed under Prop 65 as developmental toxins, we just better be sure --

SUPERVISING TOXICOLOGIST MARTY: Toluene but not zylenes.

CHAIRPERSON FROINES: -- that we've adequately covered those areas.

PANEL MEMBER FUCALORO: What's the asterisk mean?

SUPERVISING TOXICOLOGIST MARTY: Those were chemicals that we think are underreported. CS2 I don't believe that number that it's only 1,500 pounds. And PCBV and PC dioxins, I know for a fact that the refineries were not -- there was one refinery out of seven in the bay area that reported emissions of dioxins and I don't believe that either.

I do want to make a comment on the aldehydes, formaldehyde especially. The vast majority of formaldehyde in ambient air is a secondary formation, so this emission rate of a million and a half or so pounds from stationary sources, that is really a drop in the bucket probably compared to what's actually out there from mobile sources in secondary formation.

CHAIRPERSON FROINES: Which is why acrolein is -- it's irrelevant this number here.

SUPERVISING TOXICOLOGIST MARTY: Right. And Roger is not here, but I'm guessing that acid aldehyde there is also secondary formation of that. Andy is telling me that about 85 percent in the air is secondary formation.

CHAIRPERSON FROINES: Right. And there are studies that suggest if go to ethanol there won't be an acid aldehyde problem, but it's not entirely clear yet. And one of the interesting chemicals that isn't on the

list, which it will be worth looking at, I don't if you did, was PAN.

SUPERVISING TOXICOLOGIST MARTY: It's not a TAC.

MR. SALMON: We'd love it to be one, but it's not.

CHAIRPERSON FROINES: What?

DR. MARTY: We'd love it to be one, but it's not.

CHAIRPERSON FROINES: Well, we should consider taking it up. That's quite important.

PANEL MEMBER FUCALORO: What is that?

CHAIRPERSON FROINES: Peroxyacetil of --

DR. MARTY: Nitrate.

CHAIRPERSON FROINES: -- nitrate.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The report which we did on the ethanol versus MTBE comparison in addition to pointing out what we were just saying about the important role of secondary sources in generating aldehydes like formaldehyde, acid aldehyde and acrolein also showed an important hazard index for irritants of which PAN obviously figured very largely. The only good thing one can say about the situation is that levels have, in fact, declined dramatically over the years as a result of improved engine technology, but it's still a considerable amount of it. And it appears to be an important contributor to respiratory irritants and eye

irritants.

CHAIRPERSON FROINES: Well, it's also -- if we use ethanol, we'll have to worry about it again, but also there's enough toxicologic data to make you worried about it, but it's also defined by how little toxicologic data as you know there is.

PANEL MEMBER BLANC: So, John, the ones that you mentioned, for example, tetrachloroethylene, you were using those examples where you just wanted a real double check of the -- they weren't things you were elevating?

CHAIRPERSON FROINES: I wasn't suggesting they get elevated, but I think that they are of sufficient exposure that it's worth, given what you've found, that we do a double check.

CHAIRPERSON FROINES: I don't agree about this notion a carbon disulfide. I think it's an important Paul has raised, but I'm not convinced there's very much of it in the air.

PANEL MEMBER BLANC: I think that there's a lot -- EPA data suggests there's an awful lot of it.

CHAIRPERSON FROINES: What's the source?

DR. MARTY: The reason I put an asterisk on that is there was a source in the bay area that had reported under EPA's reporting program, but for some reason did not report under the California program, so we were going to

look into that, and it was 200,000 pounds per year was my recollection from a single facility in the bay area.

Now, I can double check that and make sure that that was a real number. We did contact the bay area district about that.

CHAIRPERSON FROINES: We could give the panel a test and ask them what chemical we've dealt with produces carbon disulfide, but it is metam sodium. We can't take it out.

PANEL MEMBER BLANC: It's proved because carbon disulfide is not used as a pesticide.

CHAIRPERSON FROINES: I know.

(Laughter.)

PANEL MEMBER BLANC: Actually, it is used as a pesticide, but is'a byproduct, but anyway.

SUPERVISING TOXICOLOGIST MARTY: So can I clarify, John, that the chemicals you mentioned did you want a summary like we had for the 11 for those or just you wanted to double check?

CHAIRPERSON FROINES: No, on those I'm not suggesting a summary necessarily, whoever said it. I was just asking for a double check given the amounts that are used, because trichloroethylene is a very important chemical, and -- I mean, pardon me perchloroethylene, and so we just need to make sure that we're comfortable with

the literature that we have. That's all I'm saying.

PANEL MEMBER BLANC: And, John, you had mentioned I think at our last meeting some concern over butadiene. That would also be something that you would just have a double check of the literature but not beyond that.

CHAIRPERSON FROINES: I suspect that they've given a lot of attention to butadiene at this point. And I'd be surprised if they didn't have all the information. I don't think butadiene is one to worry about, given its toxicity carcinogenicity.

It's 12:15. Can we take a 45-minute break and start at 1:00 o'clock and go directly to PAHs and then diesel?

SUPERVISING TOXICOLOGIST MARTY: Yes.

(Thereupon a lunch recess was taken.)

CHAIRPERSON FROINES: I think we should begin.

SUPERVISING TOXICOLOGIST MARTY: Andy Salmon is going to make the presentation on PAHs and why we included them in Tier 1.

(Thereupon an overhead presentation was presented as follows.)

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. Well, I'd like to start by summarizing the situation.

Can you hear me all right now?

I'll start by summarizing a summary of Benzo[a]pyrene and other polycyclic aromatic hydrocarbons. We included the proposed Tier 1, because of the concern over the toxicity of various types, and also about ambient and indoor air levels and mobile and point source emissions.

The effects which we were concerned about in this specific context of differential impacts on infants and children are both carcinogenicity and various types of developmental toxicity. And also that we found evidence that there is greater exposure to children than to adults in the same environment.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'll start by summarizing the toxicological effects that we found. Obviously, there's an enormous literature here which I won't even pretend to be covering in any detail. I've selected a few key studies illustrating the points I want to make. The carcinogenicity, of course, is well known.

The regular kind of developmental toxicity, there is evidence of fetotoxicity, growth retardation and the induction of teratogenesis. There is quite a lot of animal data on all those, but also specifically human data, particularly on the growth retardation issue.

There are also some other developmental effects, which, in some cases, would have shown off the transplascental or paternal exposure even. In this case, the obviously transplascental carcinogenesis is a known phenomenon.

But also, I think the adult toxicity of PAHs, the immunotoxicity, suppression of hematopoiesis and reproductive toxicity, those are well known effects in adults. They have counter parts in the developmental area when exposure occurs in utero or presumably has necessarily been well tested, postnatally at a young age.

The effects are often significantly different in and significantly more severe and/or occurring at significantly lower doses. I'll now go into the next issue. This a very brief summary of what we know about mechanism of action.

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MR. SALMON: Polycyclic aromatic hydrocarbons are metabolized by reactive intermediates. This is, of course, well known as the mechanism underlying the carcinogenic effect. But it appears that the same mechanism is also involved in the developmental end points.

In the case of adverse birth outcomes in humans exposed to PAHs, it's been shown that PAH-DNA adducts

appear in the white blood cells in cord blood. And DNA adducts have also been shown in the fetus.

This formation of adducts from the reactive intermediates is mediated by various citochrome P450 enzymes. There's been some considerable amount of work on exactly how these so-called Phase 1 enzyme activities varied at different developmental stages, both pre- and postnatally.

And it's been generally argued that, in fact, the Phase 1 activities may be lower at the younger ages, but they're not zero. It does appear that, at least, if you have a fetus or young animal which caries the responsive, the AHG, that the enzyme activities are inducible. And the other important issue is that it seems that the amount of toxicity, the amount of adducts formed depends not necessarily on the absolute amount of Phase 1 enzyme you might happen to have around at the time, but also, most importantly, on how the Phase II enzymes are developing.

It would appear that the balance between deactivation and activation are very important in determining the final impact. And there are some indications that the fetus and/or the young animal are, in fact, more sensitive to these effects than the adults, in particular, the fetus is more sensitive to adduct formation than the other under some circumstances.

--o0o--polycyclic aromatic hydrocarbons, it's been shown that there is extensive exposure of children to polycyclic aromatic hydrocarbons from various sources indoor air being one of them where house dust and smoking by adults in the family is important. And we have some evidence that the child receives a higher dose in terms of the impacts of those PAHs than the adults in the same environment.

This obviously excludes the primary smoker, but the impacts is greater on the child exposed to secondhand smoke than a nonsmoking adult exposed to same level of second-hand smoke.

Various other indications that this exposure occurs, that it is specifically the PAH component of the exposure, which seems to correlate with the various adverse outcomes. It's also interesting to note that polycyclic aromatic hydrocarbons are transferred in breast milk, which is another source of special exposure for infants.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm going to now turn to a few detailed descriptions of studies in the hope of illustrating some of these considerations. It's somewhat difficult to provide a satisfactory comparison of the sensitivity of

adults and children to polycyclic aromatic hydrocarbons carcinogenesis.

Basically, the studies either haven't been done or perhaps even can't be done to do the kind of, for instance, I think when we're discussing Vinyl chloride, you'll see a bioassay, where they actually have detailed differential exposure patterns at different ages and you can you see different carcinogenic potency at various points during the lifetime.

Those studies don't appear to be available to polycyclic aromatic hydrocarbons, but what is in the literature is a very general presumption that the younger animals are more sensitive and particularly the neonatal animals have been, in fact, used quite specifically as a rapid and highly sensitive bioassay for demonstrating carcinogenicity of polycyclic aromatic hydrocarbons.

The study which, I'm showing here, La Voie et al is typical of many such studies. Basically, they were surprised that the adult carcinogenicity studies which have been performed with fluoranthenes had not, in fact, identified fluoranthene itself as carcinogenic in spite of the fact that the genetic toxicology metabolic indications seem to imply that it would be.

The protocol used was newborn mice given three intraparitoneil injections of the hydrocarbon groups

included obviously dosed groups, control and the positive control Benzo[a]pyrene itself, and therefore long tumors were observed at one year of age.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The results show clearly that although the as perhaps is expected, the mouse, the neonatal mouse responds to the methyl fluoranthenes, which is consistent with the finding with the adult mouse, skin promotion, bioassay, which the initiation components of the standard mouse skin bioassay, which is probably the most sensitive assay, at least one of the most quietly used for the adult system, but we also see the neonatal mouse responding to fluoranthene quite strongly.

I mean, in terms of trying to interpret what this means, one is attempted to suspect that this represents a sensitivity rather than an absolute statement that the fluoranthene is not carcinogenic in the adult, but that it is in the --

CHAIRPERSON FROINES: Was the method of administration for the adults the same as the method --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No, it was not. These are basically -- that comparison has not been done, and it does appear, I mean, this is a generic problem that people have not done the

sort of, you know, standard administration across different life stages. This is comparing what is considered to be the most sensitive adult bioassay for hazard identification for PAHs.

CHAIRPERSON FROINES: The newborn what was the method of administration?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's the intraperitoneal injection. And I think it's fairly common to find that the adult rodent will respond to intraperitoneal injections of PAHs, but you would almost certainly not see the kind of sensitivity that you see with the neonatal mouse system or the neonatal rat. The other paper, which I cited in my introductory summary table is typical.

It was a study of Nitro-PAHs by my colleagues. And they specific say right at the beginning of the paper, we chose to use the neonatal mouse carcinogenicity assay on the expectation that it would be more sensitive and have a wider range of responding tumor sites than seen in the adults. And one keeps seeing statements like that in the literature.

CHAIRPERSON FROINES: Well, I think, again, a statement is not a scientific fact. It's a statement somebody made.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: This is why --

CHAIRPERSON FROINES: So really one has to be somewhat careful in considering these results since the newborn mouse data isn't coupled with an adult mouse assay. So what the results of the skin bioassay may be relevant, but they are not directly comparable.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This obviously requires careful interpretation, but unfortunately the State of the data is such that this is the best I can offer you on the spot.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Fortunately, the situations on the developmental toxicity is a little bit more straightforward, in so far as developmental toxicity every is straightforward. Benzo[a]pyrene causes a range of developmental effects, including fetal death and resorption. And also malformations and stillborn and those fetuses which are carried to term.

And in this particular case, it's interesting to note that where the fetus is carrying the gene for responsiveness to induction of the citochrome P450 by polycyclic aromatic hydrocarbons. The impact is greater. This is numerical results.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'd like to, if you don't mind, present this in graphical form. It's a little bit easier to see what's going on here, and draw your attention to the front row of columns here for the percentage carrying all effects. The B6 control versus the B6 treated there's obviously a large and statistically significant increase in the number of impacted fetuses in that group.

And similarly, although the AK mouse shows a lower overall rate of effects, there is an increase in that strain also. The proportional increase in effects is greater in the B6 mouse, which is the one which is responsive to the P450 induction. You see the same effect with the resorptions.

Malformations, in fact, in this particular experiment, the AK mouse, didn't show Malformations, but the B6 mouse did. The other thing which is notable is that the treated mice in both strains show a substantial impact on the number of successful implants, and the number of successful pregnancies relative to their controls.

PANEL MEMBER BLANC: Now, going back to our earlier discussion, however, the only, in fact, adverse impact that would be relevant would be the malformations, since the fetuses that don't survive to be born would not

be and effect that would be relevant to what we're looking; is that correct?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, there are actually a suite of different responses. The ones which were assayed in this particular experiment and not all the responses which PAHs have been shown to produce, but in terms of this particular group of effects, yes, it's the Malformations which are the most critical finding, because those are the ones which would provide a continuing impact on health of surviving infants.

PANEL MEMBER BLANC: But the document doesn't necessarily reflect that in its discussion. It doesn't say -- and, of course, although there are these other effects, what we're really focusing here on the malformations?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think the point that we would be trying to make and I'll bring this up, perhaps, if I may, by continuing some of the other discussions is that what you have actually is a continuum of effects, some of which result in -- some of the end points are things which obviously are not strictly relevant to the differential effect on children's health, but nonetheless, part of the overall toxicological response. And so where the --

PANEL MEMBER BLANC: Yeah, but you have to be careful, not to interrupt you, but I am interrupting, but you know you don't want to make an extrapolation of an extrapolation of an extrapolation.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah. All I'm hoping to do is to demonstrate there's a consistent experimental picture here.

CHAIRPERSON FROINES: But I think that you can't as much as you might like to argue that there's a continuum, there still needs to be some evidence to demonstrate that the continuum exists.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

SUPERVISING TOXICOLOGIST MARTY: The evidence is in the next two slides.

CHAIRPERSON FROINES: But the basic policy statement is that embryo lethality is not a criteria for defining differential effects.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No, but I think that the biological suggestion is that embryo lethality and anatomical terata often shown linked does response and they appear to do so in this case.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: My next slide, I have to apologize to you, this study actually wasn't in the toxicity review, which you received in the original packet, because it came out in December of 2000 and actually didn't make it into our initial review cut.

But we subsequently identified it and I wanted to include it in this presentation, because I think it clarifies and perhaps make a rather clearer case for what we think might be going on in this particular series of findings.

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CHAIRPERSON FROINES: The public hasn't had a chance to comment on this?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No, the public has -- let's see -- no, the public has not seen -- well, I'd assume the public has read Environmental Health Perspectives, but other than that, no.

PANEL MEMBER BLANC: The intent is that this will be in the next revision of your --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The intent is that this will go into the next revision, yes.

It also builds on several previous studies, which were referenced in the summary, which has been put out for

public review. This was a study of birth outcomes in two districts of Bohemia where air pollution is a known problem. And the difference in the two districts basically consists of a difference in the balance between the specifically polycyclic aromatic hydrocarbon pollution and the general pollution as measured by particulate matter, in this case PM 10.

And both districts showed substantial pollution problems. And associated with that higher level of pollution is an increase in the adjusted odds ratio for intrauterine growth retardation, which is a specific end point, which is being affected by the pollution.

PANEL MEMBER GLANTZ: What the control group?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The way this study was designed, they had the areas divided into areas where the pollution was measured to be low, medium or high. And they also used a temporal approach, whereby they would measure the pollution at different times over a period of several years. In fact, they were looking at all the registered births in these areas, so it's quite a large and complex study. So they were using both geographical and temporal differences to separates out the impacts of higher versus lower air pollution levels.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: To put this as simply as I can, what you see is that where the pollution level is low or lower, the ratio for the intrauterine growth retardation is consistently related to the level of PAH exposure, but if you look across the two areas, in fact, the relationship with PM 10 is inverted between the two areas.

The suggestion being that this constitutes evidence that the response is specifically associated with exposure to the PAH component of the pollution as opposed to the PM 10 in this case.

CHAIRPERSON FROINES: What are the PAHs that were measured?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The PAHs here were the, I think, it's 9. US EPA identified PAHs which are commonly used. They're the ones which were listed, I think, also in the beginning of the report as being commonly measure carcinogenic PAHs.

CHAIRPERSON FROINES: All particulate based?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: These would have been the particulate based ones. I don't think there were any measurements of the specifically volatile ones like naphthalene. Although, I will mention in passing that, you know, we've got naphthalene on the TAC list separately, but for the sort

of discussions that we're having here, it would probably be advisable to consider it along with the particulate bound PAHs.

PANEL MEMBER BLANC: ACtually, can we digress for a moment on the naphthalene front.

So naphthalene in your Table XX -- well, actually in Table 2 is listed as something which has reason to have a more thorough review, but then doesn't appear on Table XX because it's subsumed in --

SUPERVISING TOXICOLOGIST MARTY: In PAHs.

PANEL MEMBER BLANC: -- Supposedly subsumed in PAHs, but it's the only separately listed TAC from within that category, is that the only separately listed TAC for which that would apply, because it is on your list of, you know, pounds of exposure. Is it here? No, it's not actually. PAH is here.

But in the section, I guess, it seems to jump out as being something with a fairly --

SUPERVISING TOXICOLOGIST MARTY: Yeah, there is some history to that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's complicated, because, in effect, you have overlapping and somewhat redundant classifications in that we have naphthalene, if you like a free-standing agent, but it's also clearly included within the definition of

the federal hat, which is the basis of the TAC listing.

PANEL MEMBER BLANC: But you have 360,000 pounds per year emitted. Although it does not appear --

CHAIRPERSON FROINES: Where are you looking?

PANEL MEMBER BLANC: Well, I'm looking on page eight of the PAH summary, so it absolutely dwarfs all of the other --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, it's a very large emission.

PANEL MEMBER BLANC: But it doesn't appear on your stationary source. Is that because it's all mobile source emissions?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The vast majority is mobile, I believe.

SUPERVISING TOXICOLOGIST MARTY: It's a product of incomplete combustion, and it represents about half the PAH's, plus or minus of combustion sources. It may be --

CHAIRPERSON FROINES: I don't agree. I don't think it's half. I think it's much more.

SUPERVISING TOXICOLOGIST MARTY: Well, suffice it to say, the huge fraction -- so I think the reason that it's listed separately is because historically having to did with you -- they listed the chemicals that needed to be quantified under the air toxics hotspots regulations and that may be why it's listed separately.

PANEL MEMBER BLANC: But you have PAHs total -- so the answer is that it's -- most of these 360,000 pounds is from mobile sources, so it wouldn't appear in the hotspot?

SUPERVISING TOXICOLOGIST MARTY: Yes. And the other answer could be that it's not tallied into that, to that table that you're holding in your hand.

PANEL MEMBER BLANC: Okay, but on the other hand, it's the only individual substance for which you have it listed, and then falling out and then appearing within another group, as you note in a parenthetical comment, in Table 2 it says, "Treated as --

SUPERVISING TOXICOLOGIST MARTY: -- PAHs right. I actually think that it's hard to say. There's a lot of separate PAHs that are listed separately under the hotspots. And in going back to the original table that we started with, the prioritization table, for some reason it's pulled out and there's a notation that it's because it's under the federal half step initiative in its separate category than PAH, but it is a PAH.

So I don't -- you know, we knew when we saw that that we were going to just consider it, especially since the carcinogenicity data just became available showing it to be a carcinogen.

PANEL MEMBER BLANC: Well --

SUPERVISING TOXICOLOGIST MARTY: You know in terms of exposure, the exposure piece. If PAHs gets on the list, ARB has to do the footwork on figuring out what the exposure profiles are.

PANEL MEMBER BLANC: But do you think naphthalene is important enough individually to warrant some emphasized comment within your section or do you think it's going to be obvious to anybody who -- I'm talking not about five pages. I'm talking about does it deserve a paragraph where in you say something about it?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think we'd be prepared to take your direction on whether you thought some of the appropriate --

CHAIRPERSON FROINES: I think naphthalene should become one of the compounds that receives a careful analysis. I'm not even equivocal about this. I think --

PANEL MEMBER BLANC: Well, they're saying it already has, because it's been --

CHAIRPERSON FROINES: I understand that, but I don't accept it. I think that, in fact, there are lots of reasons why naphthalene needs to be considered on its own. I'll give you a couple of examples. One, when we did diesel, we ended up with diesel particulate. We didn't end up -- and so that when diesel was identified as a TAC the vapor phase compounds were not included.

So that with respect to diesel, obviously naphthalene is missing from that control strategy. When you look at the concentrations of naphthalene, at least where I live in southern California, You probably have 10,000 times more naphthalene in the air than you have Benzo[a]pyrene, which everybody goes out and studies about its carcinogenicity.

But if we have literally 10,000 times more naphthalene, it deserves considerable attention, because most people are breathing very large quantities of it.

And third, there is some very nice work at UC Davis looking at effects in the lung respiratory effects in the lung from naphthalene. And particularly in those regions of the lung, where there is active P450 metabolism, which suggests that the formation of 1-2 and 1-4 naphthoquinone are probably important pathways for its bioactivation.

And so that, I think naphthalene in and of itself is such an important compound that has been very much overlooked over the last few decades because of the general orientation for the larger ring PAHs that we've neglected. David Diaz-Sanchez's has worked, for example, on finantherene as another example of a compound that's a smaller ring compound that has effects.

So we tend to think this notion that everything

will get taken care of because we list PAHs isn't true. There is no control strategy with ARB for PAHs. And there's certainly not under the diesel rule. So that naphthalene, I think, is one that we're really missing, especially given the respiratory effects that David's people have identified.

SUPERVISING TOXICOLOGIST MARTY: Well, we can add something --

PANEL MEMBER WITSCHI: But there is quite a lot of information about it and the respiratory effects in neonates and young animals and they are more sensitive to naphthalene.

SUPERVISING TOXICOLOGIST MARTY: We can add a section on naphthalene, under the PAH, but I don't think it's necessary to list it separately.

CHAIRPERSON FROINES: Why can't it be listed separately?

SUPERVISING TOXICOLOGIST MARTY: Well, then you're taking up another slot, when you can consider it as a PAH, which is a general category of TACs.

PANEL MEMBER BLANC: But isn't it possible also that were you to focus on naphthalene -- I'm just asking the question. It's not a rhetorical question. If you were to focus on naphthalene, since almost any release or control strategy you could think of that would control

naphthalene would probably control polycyclic aromatic hydrocarbons as a group, is that true?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No. I don't that we're in a position to answer that. You'd have to go ask --

SUPERVISING TOXICOLOGIST MARTY: There are also significant naphthalene emissions from the air toxics emissions database for stationary sources, so they were not tallied into the number that I just pulled off this table yesterday. So there is 152,000 pounds per year from of naphthalene from stationary sources.

CHAIRPERSON FROINES: I don't accept the argument that if something takes up a slot, therefore we shouldn't do it.

SUPERVISING TOXICOLOGIST MARTY: No, no, that's not at all what I'm saying. What I'm saying is we can list it as one of the PAHs. We list PAHs. We can say including, within a whole, but not limited to, and list the ones that jump out at us including naphthalene.

CHAIRPERSON FROINES: Well, I think, for example, Paul raised is the use this morning of manganese from the standpoint of its toxicity, but also because of its potential public health implications. And I think naphthalene falls into that same kind of category that this may be a compound that we should focus on in order

for us to then take seriously whether something might need to be done about it.

SUPERVISING TOXICOLOGIST MARTY: We can do that.

CHAIRPERSON FROINES: Especially, if Peter is right, and I suspect that he is, that there is evidence of differential toxicity, and if it's strong, then in some ways, one could argue that you would rather, if you could -- if there is strong evidence, then something like that that you really focus should become the focus of attention, rather than just lumping it with every PAH known to human kind, because within the context of PAHs, we know there's big differences between pyrene and Benzo[a]pyrene and so on and so forth, so that the problem with the lumping is that we then lose the benefits of the splitting approach.

SUPERVISING TOXICOLOGIST MARTY: Well, if we provide the toxic data to ARB, you know, it gives them the information they need to do something about naphthalene. They're already concerned about it, and that's why they've asked us to look at PAHs again, under the TAC to add more potency factors, for example, to the list that we already have.

PANEL MEMBER BLANC: Well, let's take Table 2 on page five of this thing where naphthalene doesn't -- there's no potency factor for --

SUPERVISING TOXICOLOGIST MARTY: There is not a unit risk factor for naphthalene, because it used to be considered not a carcinogen until very recently. So that work has yet to be completed. But the ARB has asked us to come up with potency factors for additional PAHs and, of course, naphthalene is one of them.

PANEL MEMBER BLANC: So there is a paragraph here that will say that, let's say.

SUPERVISING TOXICOLOGIST MARTY: We can put that in there.

PANEL MEMBER FUCALORO: But from what you know where does it fall? Where does it fall in here? I mean, it is suggested that potency equivalency factors from one one-hundredth to twenty or so? I mean, my guess is it would be pretty small, because it's not been identified. It's certainly common. It's much more common than the rest of these.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I don't think we ought to come up with numerical pronouncements until we've done the work, but we are certainly of the opinion that it is carcinogenic as a result of the recent bioassay, which was published, but we are still at the stage where we're having to do --

PANEL MEMBER FUCALORO: But you see my -- just a point I'm trying to make, is that naphthalene is just a

common chemical compound, compared to all these others, that surely it's been studied and there must be some limit however.

SUPERVISING TOXICOLOGIST MARTY: We haven't done that calculation from the data that are recently available. But OEHHA is working on a potency factor; is that correct? Our Cancer Hazard Assessments Section is currently working on that.

The other issue, I think, to respond to your question is since the concentrations are higher and quite a bit higher than most of the other PAHs, that even if it was 10, or a hundred fold lower than Benzo[a]pyrene in potency --

PANEL MEMBER FUCALORO: I'm not using this as an argument to eliminate it. I'm just trying to get a feel for it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think it's reasonable to suppose that it might not be as potent as Benzo[a]pyrene. And we might, you know, as you say have know about it already, but beyond that that I think it would be improper to speculate.

SUPERVISING TOXICOLOGIST MARTY: But it doesn't mean it's not important.

CHAIRPERSON FROINES: Well, without being too critical, let's face it the NTP bioassay wasn't done

yesterday. We've had those results for about a year now. One can run it through a multi-stage model with the NTP bioassay and have a result in a couple days.

My concern about this notion of not having gotten to naphthalene, I think, is because of this notion that it becomes a PAH and doesn't get the kind of attention that it deserves. And I think that it's -- when the NTP bioassay results came out given what we know about how much is in the air, I would have made it a major priority to go to a risk assessment and see where we are.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It is a major -- my team are, in fact, working with the cancer hazard assessments section on this at the moment. And one of the things we've been looking at is the pharmicokinetics issues relating to that as to how one should best analyze the bioassay.

So the answer is, yes, it is something we've been asked to do. It's something which we are currently working on, and which we hope to be able to present the results of our efforts in due course. But this process amongst others, of course, is also, a separate one.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay, one other interesting piece of information, which we were able to extract from the data by looking at

the time series aspects of the data was the fact that the impacts of PAH pollution appear to be primarily in the first month of gestation. And this is consistent with some other reports and scientific literature that in fact this intrauterine growth retardation end point is a specific developmental event, probably impacting the placenta in fairly early stages of the pregnancy.

And so this particular end point is separate from some of the other things which might be classified as general sort of failure to thrive or interference with other specific developmental events.

PANEL MEMBER BLANC: So intrauterine growth retardation as used here does not imply lower birth weight. It simply implies --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No, it implies both lower birth weight and --

PANEL MEMBER BLANC: We didn't study lower birth weight. They studied --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: They studied birth weight and -- well birth weight was the primary index which they used.

PANEL MEMBER BLANC: Okay, so it was birth weight.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes. There's another study which is related to this, which is, in fact, this is Perera et al. 1998, which is looking at the similar findings.

CHAIRPERSON FROINES: Excuse me. I thought I'd made it clear to Melanie in a number of E-mails that I don't think one can use a review article as a primary science. And you have quoted the Perera article at least 20 times in your slides so far. That's a review article. And unless you have the primary data, you should present the primary data not as a review article.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Can I draw your attention to the difference between Perera 1998, which is a review article, and Perera et al. 1998 which is a presentation of a specific series of primary findings.

PANEL MEMBER BLANC: Probably, if you did 98(a) and 98(b), it would help clarify that, because it is a subtlety that is easy to overlook.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I will mend the text accordingly. But the point I wanted to make from this slide is that the outcomes actually reflected firstly in a reduction the birth weight. This similar study was in Poland rather than Czechoslovakia but in other respects they're fairly similar.

The other findings, which they measured here, were more for metric differences in birth, length and head circumference. And these are seen as differential impacts rather than just reduction in overall size, as you might say.

The other thing which Perera et al. 1998 indicated was that there was an association between these outcomes and high levels of PAH adducts detected in the leukocytes So this was tying this particular type of end point into specifically PAH exposure again.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The further study, again, with somewhat similar findings were leukocytes, PAH-DNA adducts in newborns were correlated with exposure to outdoor and indoor air pollution. And the finding here is that although one might perhaps consider that the fetus should be protected from these effects by the maternal system and the placenta and this has certainly been argued on a number of occasions by people reviewing the literature, it appears, in fact, that the levels in the fetus are typically comparable or at least the levels in the newborn I should say, are typically comparable.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: And in the particular case here in Whyatt et al. study in the medium group, it was actually higher in the newborns than in the mothers. And the index of exposure here obviously is somewhat indirect in that it is PM 10 rather than PAHs. But nonetheless, it was believed for this particular study that that was a reasonable index of exposure.

And the other interesting thing which they note was, again, that you saw a difference depending on the fetal metabolic capability. They compared the levels with the presence of particular polymorphisms and citochrome P454(a)1 gene.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next topic I wanted to draw your attention to is the study here.

CHAIRPERSON FROINES: How big is the population that was on the previous study?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The Whyatt et al. was --

SUPERVISING TOXICOLOGIST MARTY: Seventy mother and newborn pairs.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So it was quite a bit smaller than the Dajmek study, but nonetheless it was a significant size.

CHAIRPERSON FROINES: Those ends there are numbers of newborns?

PANEL MEMBER BLANC: There's only 19. Are you sure it wasn't 19? There seems to be only data there for 20.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think this particular graph might be a subset of all the data they looked at.

SUPERVISING TOXICOLOGIST MARTY: It is.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There were several classes depending on what other exposures were involved, coal stoves, smoking, and things of that sort.

For the exposure of children as opposed to fetuses to polycyclic aromatic hydrocarbons, this study actually looked total exposure from all sources and found that the total exposure and also inhalation exposure was somewhat higher in children. But one of the most important factors was what they described as nondietary ingestion, which obviously reflects significant amounts of hand to mouth transfer of house dust contaminating the PAHs and things of that sort.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: These are the actual data.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I just have this in form of the table. So in particular, the children have high nondietary ingestion, but they also have a substantial increase in inhalation exposure. And regardless of the perhaps hard-to-quantify contribution of airborne PAH pollution to the dietary PAHs, it's clear that the inhalation and nondietary ingestion, both of which have a fairly direct relationship to airborne PAHs, but air emissions of PAHs would have a significant input from to these children's differential exposure to PAH's.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: A final note. We mentioned environmental tobacco smoke on a number of occasions. This particular slide Tang et al. shows increase of the number of biomarkers for exposure to ETS components. And these were looking at African-American and Hispanic children.

And if you look at the levels comparing the no ETS versus ETS exposed children, there's a distinct increase in cotinine. There's approximately twice as much as the PAH albumin adduct. There's also a modest increase in the systichromatic exchange, an increase in the 4-aminobiphenyl/hemoglobin adduct. So this is

demonstrating that that particular exposure is a source of differential impacts on -- well, it's a source of exposure of children to PAHs, at least, that's the point of this slide.

PANEL MEMBER BLANC: Right. And can you tell me why this is relevant? I mean, you wouldn't have a hypothesis that children who were exposed to PAHs wouldn't absorb them, would you? I mean --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I wouldn't.

PANEL MEMBER BLANC: No, but I mean, part -- you know, again, it comes into -- this is a generic issue as you go through some of these documents, but in terms of -- yes, if I was going to have a review of exposure to children of PAH's, you know, this would appear in such a review. But if I was having a review you about preferential impact of PAHs on children compared to adults, this wouldn't be a relevant study, right, because this is not a study comparing the children to the adults in the same household with the same exposure showing that the children have a higher number of adducts or something.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think that the value of this is perhaps linked with the previous study, which was an exposure measurement showing that not only is there an increase in the exposure

term, but there is also an association between exposure and adducts, therefore -- so you can say A to B and B to C therefore C to E.

PANEL MEMBER BLANC: Well, except it's not. It's A to B and then Q to W or something. And because you've got a subject of PAHs where there's obviously a very, very large literature looking at a lot of different aspects, it tends to obfuscate more than clarify, I think, because what you really care about is what are the pertinent studies which show a preferential impact one way or the other in children. And listening -- I think this is fairly close to the last slide, isn't it?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER BLANC: Or is it the last slide?

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is actually the last one.

PANEL MEMBER BLANC: So if I had to summarize all of the data that you've shown us for Benzo[a]pyrenes as a group, there is one, vis a vis carcinogenicity preferentially, there is no direct evidence whatsoever? There is one indirect sub-example of one of the Benzo[a]pyrenes for which there is not a carcinogen in adult rats, but it is a carcinogen in neonatal mice.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I hoped I had explained that that was a selection of the --

PANEL MEMBER BLANC: Well, if that's the best example you could -- and there may be other examples where there also is not a head-on exposure. So there's sort of the very indirect suggestion of the possibility of preferential carcinogenicity of some Benzo[a]pyrenes perhaps and then in terms of an adverse reproductive outcome, you have some epidemiologic studies of air pollution showing adverse birth outcomes in eastern Europe, where one realizes that the Benzo[a]pyrenes are probably linked to a lot of other concomitant exposures.

In terms of supportive data in an animal study, you did show one study with Benzo[a]pyrene, I believe, where there was an increase in malformations although the more dramatic effects were increases in -- decreased stillbirths. And the implication that there might be some other similar teratogenic studies.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There are others, yes, other agents and mixtures.

PANEL MEMBER BLANC: Is that a safe summary of the data?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, the final one I wanted to show you was an

example of the developmental effects on fertility, Which I mentioned right at the beginning.

This was prenatal exposure to Benzo[a]pyrene. And in both males and females, there's a fairly clear dose-related decrease in fertility as a result of exposure so -- this is fertility of the offspring following prenatal exposure against to Benzo[a]pyrene.

So this, if you like, is an illustration of how, an effect, which is, perhaps, maybe possible to see in adults at some level, but is more dramatic and is also permanent when the exposure occurs in utero. And this --

PANEL MEMBER WITSCHI: The come back. The parent of ETS, there quite a few good studies, which show the ETS gives an increased risk of cancer in adults, but to the best of my knowledge, for children the evidence isn't there that strong, if at all.

So wouldn't this imply the opposite, that children are more resistant to the carcinogenic action?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think it implies that people haven't looked with the same power of study typically.

PANEL MEMBER WITSCHI: I'm NOT so sure about that one. The children and ETS has been looked at a long time in several studies. And, you know, I agree with you, the ETS adducts, that's the measure of exposure, but By this

talk, and then you could say the this case the kids more resistant than the adults are.

PANEL MEMBER BLANC: So is this study also one of a group studies that have -- or is this an isolated --

PANEL MEMBER GLANTZ: So this isn't a people move is it?

PANEL MEMBER BLANC: No, it's an animal study.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm sorry.

PANEL MEMBER BLANC: Was the fetal exposure having an adverse reproductive outcome -- or fertility outcome in adult animals?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah. Sorry, let me get -- I'm sorry, I've got the wrong button.

This is an animal study.

PANEL MEMBER BLANC: Right. Is this one of a group of animal studies?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There are other similar, yes.

PANEL MEMBER BLANC: With an adult impacted in utero exposure in terms of fertility?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah. I'm trying -- yes.

SUPERVISING TOXICOLOGIST MARTY: There is another

one, Kristensen et al 95 which looked at prenatally exposed female mice and then followed them.

PANEL MEMBER BLANC: Kristensen?

SUPERVISING TOXICOLOGIST MARTY: Kristensen. It's on page 29 of the summary.

PANEL MEMBER BLANC: Kristensen, how do you spell Kristensen?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: K.

PANEL MEMBER BLANC: With a K?

SUPERVISING TOXICOLOGIST MARTY: They measured fertility in mice following prenatal exposure and report that the group exposed prenatally to Benzo[a]pyrene showed more reduced fertility.

PANEL MEMBER BLANC: Because obviously one of the challenges I think with the Benzo[a]pyrene epidemiological literature is your per force limited to studies in which clearly Benzo[a]pyrene the but one exposure. And I think that despite the lengthy discussion of this recent paper, I don't think it completely suspends my disbelief in terms of what's linked to what in terms of, you know, the supposed difference between the PM 10 dose response and the Benzo[a]pyrene dose response.

So obviously for the epidemiologic data and this particular scenario, and ETS, of course, you're talking

about myriad of concomitant exposures. So obviously you would need fairly straightforward animal data with clear cut exposures in dose responses to support those.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, which, you know -- I mean, there are animal experiments which correspond in their findings to those in human.

PANEL MEMBER BLANC: So you're putting the weight then for polycyclic aromatic hydrocarbons is really the weight of your argument in terms of what's bringing it up to the four, would be its developmental toxicity.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think it's easier to point to specific experiments which demonstrate that as a concern. The problem with the carcinogenicity literature is that people, although they've done a huge amount of work and everybody who writes on the subject seems to cite this belief that the exposure is occurring early in life offer greater sensitivity.

Nonetheless, it's relatively hard to find a good clear cut experimental demonstration why they have that believe. I think the answer is because it's a belief which was established, you know, probably 50 or 75 years ago, in the early stages of the development of the carcinogenesis literature. And people didn't necessarily

bother to document the basis of their beliefs quite so thoroughly as they do now.

PANEL MEMBER BLANC: Now, let me ask you another question about the preferential sensitivity of children involved to our discussion this morning about developmental effects and why that would be relevant to the issue at hand.

If a toxin, let's say, were a fairly potent carcinogen in adults and that was its major effect, and didn't seem to -- let's say children were resistant to that affect, hypothetically, of course, you know substance A. And then that substance also had a developmental effect, which you made the argument is an effect on children, if they survive to be born, would that overall make that chemical a priority in your view, even though it's other toxic effects were really more important in adults.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think one of the reasons why I personally think that this -- some of these findings are worth looking at further is illustrated by this slide here of the time course. It's possible to -- I haven't done the arithmetic here, so I couldn't tell you how exactly this would work out. But I think looking at this kind of situation where you have a narrow sensitive window and looking at this as

a specific developmental interference rather than perhaps a more general adverse health impact kind of thing.

You could have a situation where on the one hand perhaps steady ambient levels of pollutants such as Benzo[a]pyrene and other PAHs would probably -- that would be impacted, you know, in terms of the adult carcinogenic potency as a regulation say on the average -- the annual average level.

But to protect against an effect like this, you would need to have perhaps a protection against the short-term peaks. And, in fact, Dejmek at al. show that time course of exposure as being very episodic So it's possible that you would want actually the know about both effects and to have regulations framed to deal with both episodic peaks in the exposure, which might impact infants and/or fetuses at the specific phase of development, versus the adult impact, which would be more concerned with the annual average.

That would be one. I mean, I'm not saying that that's -- you know, that that doesn't prove anything, but it's -- it's a reason for wanting to be concerned about both types of end point.

SUPERVISING TOXICOLOGIST MARTY: I think there's another issue that we need to look into a little more. There was a paper at the toxicology meetings last month

that looked at a mechanistic reason for intrauterine growth retardation by PAHs.

And they found that the PAH that they used inhibited vascularization of the placenta. So that, to me, would be a strong mechanistic reason why you would have intrauterine growth retardation.

Now, it's just an abstract and I want to go back and talk to this person and see if she's published other papers, but we can try to develop that line of evidence also.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There are things in the literature saying that this specific effect is related to placental development as it were, rather than anything else, but exactly I don't how much detail you want on that.

CHAIRPERSON FROINES: We have a history of focusing on PAHs, because they're products of incomplete combustion, so when you have one, you have others. And we develop -- there have been enough carcinogenicity worked on at least to indicate that at least a certain number are carcinogenic. And so we developed these relative potency scales.

Where we're looking at other effects, developmental or any other effects for that matter, it's not entirely clear to me that one can simply link quote

"PAHs", because for that abstract that she's talking about, do we know that that occurs across PAHs or do we know that it occurs in the PAH that they looked at and do we have evidence to indicate that it occurs in others?

So, for example, we look at pyrene as a noncarcinogen and we look at BAP as a carcinogen. We recognize that there are differences. So at some level this grouping everything under one umbrella has some potential dangers to, it seems so me, because on the one hand some of the data is with a specific PAH, but there's no evidence necessarily to indicate that it goes beyond that.

There is an assumption that it does, and, you know, from a control strategy, clearly it would be nice if everything was simple, but it's a bit of a problem.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's certainly not always easy to address that, but I think some of the evidence linking the various effects seen with the formation of DNA or protein adducts from PAHs at least tends to tie it together into a single mechanistic picture, which gives you some hope that the range of problems isn't too diverse.

CHAIRPERSON FROINES: Well, I think Peter also raised the question, if I understood it, that the formation of an adducts as we well know, does not indicate

a risk to cancer. It's a first step in what the long process.

PANEL MEMBER WITSCHI: Yeah, actually it's a good example as far as swapping adducts in liver, because it has been never been shown to be a liver carcinogen.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Clearly it's not the whole story.

PANEL MEMBER BLANC: Well, I guess maybe we should move on to the next chemical.

CHAIRPERSON FROINES: Is everyone satisfied with the discussion to this point on PAHs that we can move on?

PANEL MEMBER BLANC: I'm satisfied that I understand the basis upon which you've made the conclusion that you've made. I think that's the purpose of it, right, is for me the understand the thinking on it, right?

PANEL MEMBER FUCALORO: I think your summary was fine.

CHAIRPERSON FROINES: Obviously, we're not going from their presentation immediately into the discussion of what we think. I think it's important for the panel to be -- each panel member to be thinking about the criteria that we want to use in addressing the chemicals that we think are important. In other words, we need to think about the questions that we want to ask ourselves, what are our criteria, what are our questions, because it's

going to come back on us at some point.

PANEL MEMBER FUCALORO: It's somewhat fortuitous that the next item the diesel exhaust, because diesel exhaust was a substance, or actually a combination of about 200 substances, that we designated as a toxic -- at least a particulate matter, which still has roughly a couple hundred substances.

And the PAHs is a collection of compounds. And one has to ask the question why are they connected? Are they connected in their production in the environment. In other words naphthalene the produced separately, right, naphthalene the produced separately so therefore that seems reasonable to at least consider that separately, because it is produced separately.

Whereas, the others may always be produced at the same time in complete combustion, isn't that the primary source of the rest?

So, in that regard, I guess the PAHs could be lumped together with the exclusion of naphthalene. You see, I'm trying the get a consistent way of looking at it.

Here, the particulate matter comes out from the diesel engines. So therefore you lump it together, but PAHs. There's a natural break with naphthalene, at the very least. There may be others. I don't know the chemistry as well.

SUPERVISING TOXICOLOGIST MARTY: Naphthalene the form during incomplete combustion.

PANEL MEMBER FUCALORO: But where is it mostly formed?

SUPERVISING TOXICOLOGIST MARTY: That's a question for the Air Board.

CHAIRPERSON FROINES: From everybody's moth balls in their closets.

(Laughter.)

PANEL MEMBER FUCALORO: I mean, it's a commercial product, isn't it?

SUPERVISING TOXICOLOGIST MARTY: It is.

PANEL MEMBER BLANC: Isn't naphthalene -- I guess this may be offbase, but isn't naphthalene also an inducer of methemoglobinemia. Where's our pediatrician? I mean, wouldn't that actually be an incredible tip in the scales based on your criteria?

SUPERVISING TOXICOLOGIST MARTY: It would be.

CHAIRPERSON FROINES: Naphthalene has some very powerful evidence for cataract formation.

PANEL MEMBER BLANC: I'm almost sure that naphthalene can induce methomoglobinemia because the old moth ball preparations, which no longer contain naphthalene. But in the old days, it was a major source of childhood congestion. And were that -- unless I'm

confusing two different -- is it naphthalene we're talking about. Naphthalene was in moth balls, correct?

CHAIRPERSON FROINES: Um-hmm.

PANEL MEMBER BLANC: Melanie, if that, indeed, is correct, then I would say that that would be an overwhelming reason why you'd have to treat it separately.

PANEL MEMBER GLANTZ: This report is a real work in progress, isn't it?

PANEL MEMBER BLANC: I'm serious though, because that would just drive --

SUPERVISING TOXICOLOGIST MARTY: Yeah, I can see where you would need the look at the toxicity separately, but in terms of listing it, if you list PAHs, then ARB has the look at all the sources of PAHs and deal with all the sources when they do risk management, which would encompass everything.

PANEL MEMBER BLANC: All I'll saying is it would be a complete slam dunk in terms of naphthalene, if it induces -- on top of everything else, if it induces methomoglobinemia.

PANEL MEMBER BYUS: What dose though, that's the key?

PANEL MEMBER BLANC: I don't think that it's a threshold, it's just a question of --

PANEL MEMBER BYUS: I'd be surprised.

PANEL MEMBER GLANTZ: Why don't we go on to diesel. We've sort of pounded PAHs pretty well.

CHAIRPERSON FROINES: But there's nothing that requires us -- that says we cannot separate out a chemical if we think that it's relevant to do so.

(Thereupon an overhead presentation was presented as follows.)

SUPERVISING TOXICOLOGIST MARTY: Diesel Exhaust Particulate was placed in Tier 2 in our assessment. The evidence that we gathered about diesel exhaust particulate in terms of impacting children were that it contains PAHs so it's an important source of PAHs in the atmosphere, and you just heard our discussion of PAHs.

It is a component of PM 10. We are concerned about PM 10 effects on asthma, including exacerbation of asthma.

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SUPERVISING TOXICOLOGIST MARTY: And also there are studies which have associated PM with infant and child morbidity and mortality. There are a number of studies now showing evidence of enhanced allergenicity by diesel exhaust particulate. And, of course, this is a form of immunotoxicity, which is one of our flags for concern for kids.

And then there is evidence we respiratory health

impacts in traffic studies. And, of course, we consider it a carcinogen.

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SUPERVISING TOXICOLOGIST MARTY: Diesel exhaust particulate contains PAHs and nitro PAHs. We just heard a discussion on the developmental toxicity issue, including reduced birth weight and dysmorphogenesis. We're concerned that the fetus or neonate may be more susceptible to the genotoxic effects of PAHs.

PAHs undoubtedly contribute to the carcinogenicity of the diesel exhaust particulate, and they are bio available.

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SUPERVISING TOXICOLOGIST MARTY: Diesel exhaust is also a source of PM 10. Actually, it's very small PM, so it's PM 2.5 or lower. And there are a number of studies that have associated PM 10 with exacerbation of asthma and bronchitis and wheeze in kids.

There are several studies now which have demonstrated an association between neonatal, infant and child mortality with both short-term episodic exposures to PM 10 and also with longer-term exposures to PM 10. There are studies associating decreased lung function in children with PM 10 exposures. And, in addition, children experience higher particle loads per unit lung surface

area than adults breathing the same concentration.

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SUPERVISING TOXICOLOGIST MARTY: Immunotoxicity, as I mentioned earlier is a concern. It's one of our red flag toxic end points. And there are now a -- there's a growing database that's looking at enhancement of allergenicity by diesel exhaust particles. Intranasal installation studies have shown enhanced IgE response the aeroallergens, increased pro-inflammatory cytokines in the nasal lavage.

There's recent studies indicating that diesel exhaust particular enhances the development of new allergy in people who are atopic. And this has implications for a possible role in increasing asthma prevalence and implications in children in particular.

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SUPERVISING TOXICOLOGIST MARTY: I just wanted to have a little bit of information for just a few of the many studies that are looking at this is use of enhanced allergenicity.

Diaz-Sanchez and colleagues in '97 published a paper where they looked add intranasal challenge with ragweed. And then 60 days later challenged them intranasally with ragweed plus diesel exhaust particulate. In both cases, they looked at the nasal lavage fluid to

look at impacts on different IgEs. And ragweed specific, IgE was elevated in the nasal lavage with diesel exhaust particulate plus ragweed relative to just the ragweed along. And that was highly statistically significant. They also found elevated IgG4. And they found altered cytokine production towards the pro-inflammatory cytokines.

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SUPERVISING TOXICOLOGIST MARTY: Diaz-Sanchez et al in '99, the purpose of this paper was to look at whether you could induce a new allergy in atopic subjects and they used the keyhole Limpit hemocyanin in protein, which is a protein that you wouldn't normally be exposed to, certainly not by inhalation or intranasally, unless you're snorting Limpits.

They did a co-administration of diesel exhaust particulate with this KLH, and found IgE specific KLH, but they did not find that in the lavage fluid when they just used KLH alone without this co-administration in the diesel exhaust particulate intranasally.

They also found stimulated IgG4 production relative to just the keyhole Limpit hemocyanin alone. And then also increased allergy related cytokines in the presence of DEP relative to when the keyhole Limpit hemocyanin was given alone.

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SUPERVISING TOXICOLOGIST MARTY: And the same group in 2000 published a paper where they found that diesel exhaust particulate enhanced clinical symptoms of allergy in people who were sensitive to dust mites. So they instilled the diesel exhaust particulate and challenged them with dust mite also.

They measured the histamine release that was about three times higher when the installation included the diesel exhaust particular compared with just the allergen alone. They also looked at whether carbon black would have the same effect. And in this particular study it did not.

And they also looked at murine mast cell model to look at histamine release by a degranulation of the mast cells. And this was increased by dichloromethane extracts of the diesel exhaust particulate. And this implies a role of absorbed chemicals on the particulate in enhancing the allergenicity.

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SUPERVISING TOXICOLOGIST MARTY: I did want to touch on some of the traffic studies that have been done in Europe that we're trying to evaluate respiratory symptomatology in lung function in kids in association with proximity the dense traffic.

There were a number of studies. They looked at increased respiratory symptoms, allergic rhinitis, and decreased lung function, which correlated the truck traffic density black smoke measurements, which is a measurement of fine particles, it's primarily PM 2.5 and less, in several cross-sectional studies. Some of the studies used traffic density as the exposure metric, some of them used truck traffic density specifically and one measured black smoke.

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SUPERVISING TOXICOLOGIST MARTY: There were two publications in '97 by the same group. It's actually the same study, Brunekreef et al. published on the lung function Measurements and van Vliet et al. was the same study publishing the information on the respiratory symptoms.

And they evaluated current respiratory symptoms and lung function in boys and girls in six Netherlands communities. The traffic metrics used were distance from home and the school to a road coupled with traffic density and truck traffic density. They also measured NO2 and they measured black smoke. And they also measured PM 10 inside of the schools that the kids were attending.

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SUPERVISING TOXICOLOGIST MARTY: They found

increase cough bronchitis and wheeze, but not asthma, was associated with black smoke and truck traffic density, and is primarily for girls living within 100 meters of the roadway. They did find statistically significant decreased lung function associated with traffic and black smoke and truck traffic density were the stronger predictors of that effect.

The effect was stronger in girls. And relative to residents more than 1000 meters from a roadway, there was an increased effect for those kids living within 300 meters of the roadway.

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SUPERVISING TOXICOLOGIST MARTY: And this is just a little bit of the data from Brunekreef. This gives the percentage change with the 95 percent competence interval in lung function for kids, this is both genders now, living within 300 meters of the motorway. And FEV1 dropped 4.1 percent per 10,000 trucks or 3.7 percent per ten micrograms per cubic meter of black smoke. And peak expiratory flow rate dropped 7.7 percent per 10,000 trucks and about at about 5.8 percent Per 10,000 micrograms per cubic meter black smoke.

PANEL MEMBER FRIEDMAN: Were these cross-sectional studies comparing, you know, truck traffic in different areas or did they look at truck traffic over

time and find these differences as that changed?

SUPERVISING TOXICOLOGIST MARTY: It was cross-sectional looking one area to the next.

PANEL MEMBER FRIEDMAN: Did they control for exposure to environmental tobacco smoke?

SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER FRIEDMAN: Because you know, you might think that lower socioeconomic status would be living close to the roads maybe smoke more and so on.

SUPERVISING TOXICOLOGIST MARTY: They did adjust for the confounders on this slide, age, gender ethnicity, smoke, presence of pets in the home, dampness of the home, number of people living in the home, whether or not there was a gas stove or other gas appliance and parental education.

In this study, there is a clear dose response between FEV1 and truck traffic density across the six communities that they looked at.

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SUPERVISING TOXICOLOGIST MARTY: I did want the touch on Osterlee, another traffic study and done in '96 in the Netherlands. this is again a cross-sectional study using within neighborhood comparisons. They evaluated prevalence of respiratory symptoms either ever or current. And they evaluated it in children zero to 15 years old and

also in adults in the same household via respiratory health questionnaires.

They traffic metric was essentially they modeled nitrogen dioxide using CAR model, which predicts concentrations in urban areas on the basis of traffic density.

They're quote, "exposed group" were kids and adults that lived on busy streets with the predicted NO2 concentrations as seen in the slide. And this represented about 10,000 to 30,000 cars per day on those streets, the residential streets. And then they compare these to people living in less exposed, which were residences with low traffic density, but in the same neighborhood.

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SUPERVISING TOXICOLOGIST MARTY: There was a significant relationship between the traffic density and current asthma medication. It was significant for kids but not for the adults. And the odds ratio is as seen on the slide 2.2. There was a strong effect in girls than the odds ratios following for wheeze-ever, wheeze past year, dyspnea with wheeze-ever, dyspnea with wheeze in the past year and respiratory meds.

Those were OR specifically for the girls in this study. So many of those are significant. Those are all significant actually.

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SUPERVISING TOXICOLOGIST MARTY: When they combined the boys and girls and looked ever wheezing, the result was significant at the P.05 level, but it was not for adults. And the only significant effect they found in adults was occasional dyspnea while walking. So the investigators then conclude that children are more sensitive to the respiratory impacts of traffic related pollutants.

PANEL MEMBER FRIEDMAN: How were they able the narrow this down the diesel exhaust specifically?

SUPERVISING TOXICOLOGIST MARTY: They did not do that. The point that I wanted to make in Osterlee was that this is the one study that's actually looked at traffic and has looked at children and adults.

So you can't -- you can't say from this study that those impacts were all from truck traffic, but there was significant truck traffic in the mix of traffic, and there's significant diesel exhaust from automobiles in the mix of traffic in the Netherlands. And NO2 is also associated with emissions from diesel engines. So it's an arrow that's pointing in the direction, but you can't call it conclusive evidence.

PANEL MEMBER FRIEDMAN: Are most of the trucks there diesel trucks?

SUPERVISING TOXICOLOGIST MARTY: Yes. It's my understanding that most of the trucks are diesel. They actually use a fuel that's cleaner than in the US. It's clean in terms of much lower sulfur content, which leads the less particulate matter emission.

--o0o--

SUPERVISING TOXICOLOGIST MARTY: There were a number of other studies looking at self reported traffic exposures that are mentioned in our document, but I didn't think were particularly useful to bring up in this discussion.

PANEL MEMBER WITSCHI: In this study, there was a check for lead, because I think in Europe they still have the fuels.

SUPERVISING TOXICOLOGIST MARTY: I don't know if they checked.

AIR POLLUTION EPIDEMIOLOGY UNIT CHIEF OSTRO: This is Bart Ostro from OEHHA. But there's also been very little evidence relating lead to some of these respiratory outcomes. That might not -- there's very little evidence relating lead to these respiratory outcomes, but they didn't specifically measure lead.

SUPERVISING TOXICOLOGIST MARTY: I just wanted the mention that Michael Lipsett and Bart Ostro are here from OEHHA to address issues related to the particulate

studies.

PANEL MEMBER BLANC: I have a few questions then. First of all, the pieces that seems to be missing from the summary discussion on this section would be the explicit rationale for why something, which could act as an adjuvant in sensitization would be likely to differentially affect children.

So I think there needs to be some series of statements there with whatever supporting literature you can that probably would be referenced to the epidemiology of childhood asthma in terms A2PNIG sensitization and why something which could induce sensitization would likely -- that this would likely be a target population.

Secondly, I don't really understand some of the organizational aspects of the summaries, because you have on page five, six and seven, for example, of the section, you have summary of key -- so you start off with carcinogenicity.

Then you, B, other effects. And then the next page it's potential for differential effects. You have, A, carcinogenicity, B, general effects, and C immunological and respiratory effects. Now, in the immunologic and respiratory effects that where this discussion would happen, but in B which the general effects, you have a lot of stuff about asthma. And then,

again, in respiratory effects, you have stuff about asthma, so I don't really -- it was confusing the logic of that, it didn't parallel the other sections. So I would just do the noncarcinogenic or however you're going the do it be logical about it.

SUPERVISING TOXICOLOGIST MARTY: Sure.

PANEL MEMBER BLANC: You seem to -- I don't think that you can use the Thirsten citation 2000 as you have, since it refers to an internal document prepared for OEHHA, so it's not even is the use of citing a review article, it's even worse than that.

SUPERVISING TOXICOLOGIST MARTY: Where is that?

PANEL MEMBER BLANC: It's on page six, middle paragraph, "These effects are particular seen for asthmatics and those with other existing respiratory and cardiovascular diseases, especially the Elderly Thirsten 2000. And then Thirsten 2000 is particulate matter in sulfate evaluation of the current California air quality standards with respect to protection of children prepared for the California Air Resources Board.

DR. LIPSETT: You're concerned about that is that it hasn't been peer reviewed?

PANEL MEMBER BLANC: Yeah, how am I supposed to know what that is? Am I supposed to go to the library and find that?

DR. LIPSETT: Well, it is on our web site. It was part of a review that Dr. Thirsten did for us as part of the SB 25 process dealing with the criteria pollutant prioritization. And perhaps the web address for this ought to be included in here if it's not.

CHAIRPERSON FROINES: Unless I'm mistaken --

DR. LIPSETT: It was also included in the responses to some of the comments too.

SUPERVISING TOXICOLOGIST MARTY: Yes, it is. And this document was actually peer reviewed by a panel that included a large number of people.

PANEL MEMBER BLANC: Well, perhaps what you suggest as an option is putting this on the web address if it's been electronically published.

CHAIRPERSON FROINES: Is what's in here the full document?

SUPERVISING TOXICOLOGIST MARTY: No.

CHAIRPERSON FROINES: That looks like a much thicker document.

DR. LIPSETT: Yeah. Well, this document here which was done for the criteria pollutant process includes reviews for the other criteria pollutants as well. I think the only one that's included in the comments, Melanie, you can correct me if I'm wrong about this, is Dr. Thirsten's report, which is one of several that's in

here.

PANEL MEMBER BLANC: But, for example, in the methylene chloride discussion, you don't cite carbon monoxide Criteria review, I suppose?

Okay. The Diaz-Sanchez I mean you presented a lot of sides, and of course that's very important and relevant work. You might want the check the Diaz 2000 reference, the Diaz-Sanchez doesn't appear to be in the reference list in the back, although you do cite it.

SUPERVISING TOXICOLOGIST MARTY: Sorry. There's actually many more we could have put in here on that same issue.

PANEL MEMBER BLANC: Well, yeah, and of course obviously you want to cite other people's work too. And although you do have two of the -- or at least -- well, I believe two of the Japanese papers. There's essentially been a sort of flurry of these papers from Japan, and I think they should be cited.

SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER BLANC: And double check those to see that there isn't something, in fact, that would be age relevant, because there's been so much on this. I would wonder if by now somebody hasn't done something that would be -- so that you weren't completely relying on, you know, the logic of it. There was some direct evidence to the

extrapolation, but certainly a plausible argument, but it would be nice.

Now, let me ask you another question in terms of the contribution to nonpoint source PAHs from diesel, as the percentage?

SUPERVISING TOXICOLOGIST MARTY: I think we have something about that in our response the comments and I can't remember what we said off the top of my head.

PANEL MEMBER FUCALORO: You mean mobile sources?

PANEL MEMBER BLANC: Yeah. Is it five percent? Is it 20 percent.

PANEL MEMBER BYUS: It's eight percent or something in the letter that was sent in response.

PANEL MEMBER FUCALORO: EMA said eight percent?

PANEL MEMBER BYUS: Something like that. It's in their comments.

SUPERVISING TOXICOLOGIST MARTY: I think that was the percent contribution to PM, not the percent contribution the PAH.

PANEL MEMBER BYUS: Oh, that's right.

SUPERVISING TOXICOLOGIST MARTY: John is telling me that there is not a good estimate percent contribution to atmospheric PAH.

PANEL MEMBER BLANC: Well, my follow-up thought on that would be that let's assume that it was a

biologically meaningful proportion of the PAHs were from diesel particulate, included in diesel particulate, and then you were going to argue that -- so that it has all of the attributes that you've just made the arguments about PAH.

And then in addition to that it has all of this asthmagenic or allergenic potential, wouldn't the logic be there for that it would somehow have to outrank PAHs no matter how you did it?

PANEL MEMBER FUCALORO: PAH plus?

SUPERVISING TOXICOLOGIST MARTY: Well, we ended up putting it into Tier 2, primarily because the pieces of evidence we had were indirect. They were all pretty big arrows pointing to diesel exhaust particulate, but they --

PANEL MEMBER BLANC: Well, certainly the arguments in terms of PAHs are no less indirect than PAH. So anything that you have beyond a PAH effect would certainly be supplemental to that, wouldn't it?

SUPERVISING TOXICOLOGIST MARTY: For example, we didn't have good studies on teratogenicity of PAHs or developmental -- I'm sorry -- teratogenicity or developmental toxicity of diesel exhaust, but we did -- we had a few. We had two, but we had more studies on teratogenicity and development toxicity of PAH.

PANEL MEMBER GLANTZ: Yeah, but you know, if you

look at just the stuff that you presented today in terms of differential effects on kids, I think you showed stronger evidence here for diesel exhaust than PAHs. I mean that's the way it looks to me. Do you want to --

PANEL MEMBER FUCALORO: I mean think about it. It's a plausible statement I think.

SUPERVISING TOXICOLOGIST MARTY: Well, I guess then why would you want to remove PAH and not --

PANEL MEMBER BLANC: Well, that's a separate argument.

PANEL MEMBER GLANTZ: Yeah, that's a separate question.

PANEL MEMBER BLANC: That's a separate argument about whether or not they would both be in the top five or neither would be in the top five. I was asking the question, logically, how could PAHs be in the top five and diesel not be in the top five from your point of view, based on your --

SUPERVISING TOXICOLOGIST MARTY: Just the directness of the studies, that we had studies of PAH in humans. We have it in animals. We have it in developmental types.

PANEL MEMBER BLANC: But you don't have any doubt that PAHs aren't in diesel, do you?

SUPERVISING TOXICOLOGIST MARTY: I'm sorry.

PANEL MEMBER BLANC: You don't have any doubt that PAHs are in diesel particulate?

SUPERVISING TOXICOLOGIST MARTY: In diesel, no we don't have any doubt about that.

So you're saying that there's more than one end point relevant to children, so why doesn't that outweigh --

PANEL MEMBER BLANC: Right. And If I am to accept your argument for PAHs, then I have to apply all of that argument to diesel and then anything else in addition to that that you could come up with regarding diesel.

SUPERVISING TOXICOLOGIST MARTY: Well, there's actually an interesting twist to this whole discussion, and that is that there are some pieces of evidence showing that the enhanced allergenicity by diesel exhaust particulate might be from the PAH content of the particles.

PANEL MEMBER BLANC: Perhaps.

PANEL MEMBER FUCALORO: That doesn't vitiate the argument.

CHAIRPERSON FROINES: I think she means it supports it.

PANEL MEMBER BLANC: No, it doesn't.

SUPERVISING TOXICOLOGIST MARTY: Yeah. So it would support both. It would support diesel being listed,

and it would support PAH being listed.

CHAIRPERSON FROINES: But I think --

PANEL MEMBER FUCALORO: No, all it supports is a reordering. It doesn't know what comes in Tier 1. They both may be in Tier 2, but it orders it. Isn't that what you were saying?

PANEL MEMBER BLANC: I'm just saying that based on what you've presented and what --

PANEL MEMBER FUCALORO: Yeah, it would support a reordering.

PANEL MEMBER BLANC: At a minimum, one would have to go before the other. Now, maybe both of them would make it into the top five. Maybe neither of them would, you know, exceed, but I fail to see the logic of including PAHs in the top five and excluding diesel from the top five. If we accept the rationale for PAHs, don't we have to apply that rationale to diesel and then look at what else you have for diesel over and above that?

SUPERVISING TOXICOLOGIST MARTY: If that's what you folks want to us to do --

PANEL MEMBER FUCALORO: No, no, no that's not what --

CHAIRPERSON FROINES: Melanie, at this point, I think what you should do is say thank you --

SUPERVISING TOXICOLOGIST MARTY: Yes, I should

say thank you.

CHAIRPERSON FROINES: -- because what he's raising and what Stan is raising and what Tony is raising are basically issues that we're going to have to decide on the panel about how we think about this is use. And so for him to ask you the question is to help clarify it for the panel's benefit, but you're now in a position where it's reasonable to give it to us and say you folks decide how you think about this.

PANEL MEMBER GLANTZ: Can I ask a couple questions?

I got from Jim Bearum via E-mail the letter from the engine manufacturers association, where they did take exception to some of the arguments in the earlier report. And, you know, I know this came in late, and so there wasn't the usual kind of formal response, but I would be interested in hearing what you guys had to say about the specific objections that they make, particularly the stuff -- well, the pages aren't numbered.

But they have a sort of general introduction, but then they list, I think, five specific points, which differ pretty substantially from the argument you guys are making, you know, for. And I think it would be -- I'd be very interested in just hearing what are your responses to the specific criticisms that they've raised.

SUPERVISING TOXICOLOGIST MARTY: Okay. Actually, we read that letter and we've prepared some responses to those particular criticisms.

The first comment is basically that health effects associated with PM 10 or PM 2.5 cannot be specifically attributed to diesel particulate matter. And that we incorrectly attribute health impacts associated with PM 10 or PM 2.5 to diesel exhaust PM, and that the associations between PM and cardiovascular events, hospital visits and even deaths are tentative, and that diesel exhaust particulate only contributes a small portion of PM 10 and PM 2.5.

So, I mean, our response is first that there are dozens if not hundreds of studies linking PM 10 and PM 2.5 to cardiovascular and respiratory and morbidity and mortality. And we would not call that a tentative, association. Rather it's robust and many, many studies with statistically significant effects and it's consistent across studies. So we don't agree at all that there's tentative associations between PM 10 and health effects.

Secondly, we did not suggest that diesel exhaust particulate matter was the singular predominantly or unique cause of any health effects of PM as stated in the comment, but rather that diesel exhaust particulate matter is a component of PM that's been measured in the studies

associating PM with the health impacts.

We would also say that mechanistic data indicate that diesel exhaust particulate matter exerts specific affects on the immune system as noted in the last set of slides. That's not necessarily shared by other PM components like Crystalline silica. That was shown in a study by Z-i-j-b-e-r-d-e-n et al 2000 and that these enhance allergenic effects could lead to the exacerbation of allergic rhinitis and very possibly asthma.

And then, of course, since the prevalence of asthma the higher in kids that's a flag for concern for kids.

The second comment.

DR. LIPSETT: Melanie, could I interrupt --

SUPERVISING TOXICOLOGIST MARTY: Sure.

DR. LIPSETT: -- and amplify that comment a little bit. There are actually several cities where some of these PM studies have been done where the predominant contributor to PM is diesel. And London is one of those cities. Santiago is another where you might have as much as 80 plus percent of particulate during much of the year due to diesel exhaust. So there are at least certain instances where these PM studies have been done linking PM to mortality and morbidity, where the primary constituent really is diesel.

CHAIRPERSON FROINES: I think that that's important to document. I, frankly, have some trouble with the notion that PM diesel is a component of PM 10, therefore diesel fits this criteria. I actually don't buy it. And as everybody knows there are differences in particle size, distribution and particle number and a lot of different variables that need to be considered in this.

And we're all -- the people in this little round table here are all familiar with the various issues. And I think it's a stretch to say that because diesel the constituent of PM 10, therefore there is a differential susceptibility in children as demonstrated by various studies.

And I'll give you one reason I say that is at the last external advisory committee meeting to John Peters Children's Health Study, Jonathan Sammut, who we all know, said that John Peters after ten years of investigation has now demonstrated that air pollution has effects on children.

And that's good, showing chronic effects in children is important, but that did not -- what Jonathan was saying is that we don't know, in fact, what causes those chronic effects in children, so I don't think that we should say here anything that goes beyond that conclusion either.

PANEL MEMBER FRIEDMAN: Are you suggesting that if 80 percent of the PM 10 in a city that's causing these problems is the proportion from diesel exhaust that we have to raise a question as to whether the whole effect is due the other 20 percent from other sources?

CHAIRPERSON FROINES: No, but I'm also saying that there are studies in the east coast of the United States that have very high sulfate levels that one could make similar arguments to. So I think one has to be careful -- I mean, I think it's important for Michael to document the 80 percent, but there are a whole series of studies with very different characteristics of the particulate matter that shows these kinds of findings.

So it's very important not to overreach in terms of trying to identify that piece, and say okay in Philadelphia it's caused by sulfate, and in Boston it's caused by something else and in Chile it's caused by something else. I don't think you can draw a conclusion that the studies that we all are familiar with demonstrate that diesel is the culprit or plays a fundamental role.

I, basically, think it probably does, but I'm talking about what the level of proof that we have in this respect.

PANEL MEMBER FRIEDMAN: If it's 80 percent of the substance in question, then don't you think you can point

the finger at --

CHAIRPERSON FROINES: No, I think that you have a whole series of studies with very different amounts of diesel contributing to the particulate and you don't know. We don't -- I don't think we know.

PANEL MEMBER GLANTZ: I think Gary is making it, thank you for talking.

PANEL MEMBER FRIEDMAN: I always need Stan to explain what I'm saying. I bring him along.

PANEL MEMBER GLANTZ: Well, no, but I mean I agree with what he's saying though, as I understand it, if the diesel exhaust is contributing most of the PM 10, then -- or PM 2.5, then that's the problem.

CHAIRPERSON FROINES: It's a bit of a misstatement by Michael to emphasize the 80 percent in Chile. When you take all the data that have been developed in the six studies and other associated studies to pick out Chile and say 80 percent the leave aside an enormous database that we have to work with.

PANEL MEMBER GLANTZ: Well, what does Michael have to say about that.

DR. LIPSETT: I think that the only point I was trying the make was that if -- to the extent that particles seem to be associated with morbidity and mortality in a variety of different urban locations

throughout the entire world, that in areas where you see a high proportion of diesel, relative to the other kinds, you see basically similar kinds of effects, I think it's not unreasonable the attribute to the diesel particles, the same kinds of effects you would attribute to particles anywhere else.

SUPERVISING TOXICOLOGIST MARTY: That was the point of our discussion.

PANEL MEMBER BLANC: And I think it's reasonable -- I think both points are well taken, that is to say make sure in the revision of the section that that point the made. And, secondly, I think that based on your presentation and on the written section, I wouldn't say that the PM 10 component is overly emphasized. It's alluded to, and it's put in its place, but it's not driving your diesel section. It would appear, based on the information you have.

So I would take both strategies. One, I would make sure that it's not overlystated. I don't think it is particularly, but two to the extent that there is epidemiologic evidence that in areas where the PM 10 is dominated by diesel, those areas are not protected by that effect. Therefore, there's no reason to think that diesel acts any better or worse than any other generic polluted ambient source of binding, particularly to the extent that

if diesel were equal to all other particulates to the extent that it tends to be even more predominant a component 2.5 and to the extent that PM 2.5 maybe more important for certain outcomes, that it would relatively be more important not less important.

PANEL MEMBER FRIEDMAN: If I can draw an analogy. If we find, say, that cigarette smoke -- well let's forget about ETS but cigarette smoke to the smoker is causing a variety of harmful effects and in one city, you know, 80 percent of the smokers smoke Marlboros, where in another city 80 percent of smokers smoke Camels, you can't say well we have no evidence that it's really Marlboros that are harmful.

You know, I think if you think of that analogy, that's what I'm trying to say about diesel exhaust in some areas the main source of particulates. Well, I think we have to worry that diesel exhaust the harmful.

CHAIRPERSON FROINES: Well, I don't think there's any question about that. But the National Academy of Sciences has written three volumes in the past years that raise the question of the causal factors associated with all the cardio respiratory diseases that's being discussed today.

There are five centers in the United States that are studying the problem. There is a major, major

research effort trying to look at the underlying factors associated with cardio respiratory disease derived from particulate. And I think it's a bit glib to say that it is the diesel proportion of PM 10 that's causing all of those factors.

PANEL MEMBER FRIEDMAN: That's not what we're saying.

PANEL MEMBER FUCALORO: That's not what he's. He's saying that at the very least, there's certainly other sources of PM 10 that are dangerous, but at the very least, because of the Santiago data, that diesel contributes its share.

PANEL MEMBER BLANC: John, can I check in with you, as Chair. How many more of those are we going through, because somebody's going the need a break soon including me.

CHAIRPERSON FROINES: We are going to be able to go through maybe one more.

SUPERVISING TOXICOLOGIST MARTY: Should I finish the comments?

PANEL MEMBER GLANTZ: Why don't we take another three hours and finish the last couple of comments or however long it takes. That was a joke for the record.

(Laughter.)

PANEL MEMBER FUCALORO: I wasn't smiling, Stan.

(Laughter.)

PANEL MEMBER GLANTZ: Well, but I think these are important points that I think we need the hear about. Why don't we try the do of that and have a break. Is that okay?

There's only two more or three more.

PANEL MEMBER FUCALORO: Well, what are you suggesting, Stan?

PANEL MEMBER FUCALORO: I'm just suggesting to let Melanie and her people finish giving us their responses to this letter and then we can --

PANEL MEMBER FUCALORO: Prior to that, we really need the know the reporter when he needs a break, because there are some rules I know that regulate that.

CHAIRPERSON FROINES: Melanie, how long are you going to take to finish this?

SUPERVISING TOXICOLOGIST MARTY: Ten minutes.

CHAIRPERSON FROINES: Then let's take a break.

(THereupon a short recess was taken.)

CHAIRPERSON FROINES: Okay, melanie.

SUPERVISING TOXICOLOGIST MARTY: The second is the comments from EMA. The second comment indicated that the relationship between asthma and diesel exhaust particulate matter is not known and OEHHA's contention that diesel exhaust particulate matter demonstrates immune

system effects that uniquely result in exacerbation of asthma is not proven by scientific evidence, and it goes on to describe that asthma is a complicated disease with lots of different factors that influence it.

And although there is evidence in this current literature indicating that increased levels of air pollution may exacerbate asthma, much work needs to be done to determine which substances might be the more important or might play a role. An expression of asthma symptoms may be, at best, associated with a wide variety of air pollutants, and certainly have not been shown to be specific to diesel exhaust particulate matter.

And our response to that is we're not really Stating the document that asthma is caused by diesel exhaust, rather we're arguing that diesel exhaust exposure exacerbates immune system response to aeroallergens, this could, in fact, exacerbate asthma. And because it also causes new allergies in atopic people, it might, in fact, be a factor in increasing prevalence of asthma.

We're arguing with the respect to asthma more that we have many studies which show an association between PM 10 and PM 2.5 exposure and asthma exacerbation. So, as such, diesel exhaust particulate matter, which is a particle of the PM 10 and 2.5 can be associated with exacerbation of asthma.

And, yes, it is true that there are probably additive or interactive effects of hall these different pollutants, but the statute requires us to consider that in addressing which chemicals get on the list. So it's still important the consider exacerbation of asthma by diesel exhaust particulate matter.

CHAIRPERSON FROINES: Can I make one comment about that, and this reflects something that Paul said earlier. I actually think that there is a very large database on diesel and exacerbation of asthma and other immunologic effects. And just to reemphasize his point, what I'd like you to do if you would, would be to -- I brought about 30 papers with me today, and there's at least 50 that one could include.

Your document tends to emphasize David Diaz-Sanchez's work. There's the Japanese work. There's French work. There's Scandinavian work. There's British work and so on and so forth. So I would -- I think this is an extremely important argument, and so I think adding some of the literature to the document would be very helpful, precisely because it is often times diesel specific rather than PM 10 or PM 2.5.

SUPERVISING TOXICOLOGIST MARTY: Sure. We also have the truck traffic studies which measure respiratory impact in kids from -- that were correlated the black

smoke from truck traffic and correlated to truck traffic things so not just to general traffic, so that's another piece of evidence.

CHAIRPERSON FROINES: I think the Brunekreef work is important to emphasize and the adjuvant effects the second.

SUPERVISING TOXICOLOGIST MARTY: The third comment the that OEHHA incorrectly argues that diesel exhaust particulate matter uniquely demonstrates enhanced allergenicity. And that we cited a lot of David Diaz-Sanchez's work, but while he does demonstrated some response, there is little evidence to date to say that diesel exhaust particulate matter is unique in the regard.

And the comment goes on to point out other substances that enhance allergic end points such as environmental tobacco smoke, vliage, phenat 3, Benzo[a]pyrene and TCDD. And our response is that the comment implies that we state other PM models do not elicit immune modulatory responses, and, in fact, we make no such generalizations.

We do make the point that diesel exhaust particulate is not just a contributor to ambient PM 10 and PM 2.5 and therefore to PM health effects, but that it is also associated in this other body of literature with enhanced allergenicity and that there's a considerable

body of evidence in that regard.

And then we go the point out that in some studies neither carbon black nor Crystalline silica produced responses. Although, in one study carbon black had some immunomodulatory role, it was different than diesel exhaust particulate.

And also it's a mistake to attribute the same types of enhanced allergic end points to across the Board the other PAHs an to TCDD, so it's not necessarily globally attributable to all PAHs or to the AH receptor lag based on toxicity information on those compounds.

And, yes, other things have in PM may exacerbate asthma, but that doesn't mean that therefore diesel exhaust does not.

And then there was a comment on the fact that we didn't take into account the risk reduction plan to reduce particulate matter emissions from diesel fueled engines in vehicles. And in our view that's irrelevant to the process that we're doing of listing health impacts -- or listing TACs that have health Impacts on infants and children. That's basically the gist of it.

PANEL MEMBER BLANC: Do you want to go on to the next substance.

SUPERVISING TOXICOLOGIST MARTY: We can go on to the next substance.

CHAIRPERSON FROINES: I was just waiting, because I thought Michael was going the make a comment.

DR. LIPSETT: Okay. Well, this if the panel wants the hear anything more. I was prepared to say a little bit more about the adjuvants effects of diesel exhaust on expression of allergy and these series of studies that have been done. I don't know if you're convinced already by the presentation and would rather just, in the interests of time, move on or if you'd like to take a few minutes to go over some of this.

PANEL MEMBER GLANTZ: I wouldn't mind hearing some of it.

DR. LIPSETT: You would or would not.

PANEL MEMBER GLANTZ: I think it would be helpful.

PANEL MEMBER FRIEDMAN: Excuse me. John has already said he has got multiple studies. I would tend to prefer moving on given the lateness of the hour. I don't know, maybe we should vote on it.

PANEL MEMBER BLANC: Well, let me ask the same question a different way. The material that you would be prepared to present now will be included in the modified version of the section that's the intent.

DR. LIPSETT: Yes.

PANEL MEMBER BLANC: And it expands on other

studies beyond the Diaz study?

DR. LIPSETT: Yes.

PANEL MEMBER BLANC: Are there any studies in what you're going to present which would have looked at adjuvants effects preferentially in younger versus older test animals or humans?

DR. LIPSETT: Not in humans. And actually in the test animals that would be for one of the toxicologists to address. I'm not aware of any specifically that address that.

CHAIRPERSON FROINES: My only question in terms of resolving this is use the quickly as possible is are we going the get something new between now and the next meeting for the panel to look at? And if not, I'd like Michael just to give us your point of view the panel has some sense of what the issue is about. If we're going to get something in writing then we can go ahead, but if not, I think it might be useful to take less than five minutes hopefully.

SUPERVISING TOXICOLOGIST MARTY: Why don't we just have Michael five a five-minute overview.

CHAIRPERSON FROINES: Gary, do you mind?

PANEL MEMBER FRIEDMAN: That's fine, if it's short like that.

CHAIRPERSON FROINES: I'm just worried that

between now and the next meeting if there's nothing that we received, we'll be left with what we already have.

DR. LIPSETT: Okay, Melanie has already mentioned this series of cross-sectional studies that suggest increases in allergic rhinitis, wheeze, asthma in children living near busy roads, particularly in instances where there's self-reported high truck traffic.

In addition, in Japan there is a study that suggests that people living on bear busy roads in urban areas have a higher rate of allergy to cedar than in people who live further way or in more rural areas. Now as Gary and Stan and Paul and others recognize, these are not necessarily causal because of their cross-sectional nature you can't necessarily draw a causal inference, but they're suggestive of relationships certainly between diesel exhaust and the expression of allergy.

Now, with respect to childhood asthma, about 85 to 90 percent of it is related to allergy. And this whole series of studies, not only the UCLA studies, but the ones in Japan and the UK have shown a variety of effects on the expression of allergy with diesel exhaust alone acting to increase the expression much IgE, which is the allergy specific antibody as well as IgG4. In both humans and animals, you see a dose response kind of relationship, with intranasal installation in humans and for a variety

of different methods of administration in animals.

Now, there's a very clear synergy also when diesel exhaust is administered with allergen that you get up to 16-fold greater expression of the allergen specific IgE over that produced by exposure just to the allergen alone. In addition to which, you see a, within say a nasal lavage fluid, skewing of the cytokine profile that's expressed to one that's very typical of allergy and away from the sort of nonallergic cytokine profile that you see either just with the expression -- or with administration of allergen alone.

Now, in addition, diesel exhaust particles have been administered in a controlled exposure study to human volunteers in England and with some Scandinavian investigators and show a very vigorous kind of inflammatory response. And in animals that are exposed to diesel exhaust through inhalation or installation on a chronic basis, you see clear signs of a allergic inflammation and bronchial hyper-responsiveness, both of those things being hallmarks of allergic asthma.

So while none of these studies individually would, you know, provide causal evidence that diesel is responsible for causing allergy or asthma, they provide a very compelling kind of picture that diesel exhaust particles play a significant role in the enhancement of

the allergic response.

And again because allergy is so common in kids and allergic asthma is what predominates in children, I think these are a whole series of studies that would be important the include in the next version of the document.

CHAIRPERSON FROINES: Thank you.

SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: We're going the stop at 4:00.

SUPERVISING TOXICOLOGIST MARTY: Okay, we have --

CHAIRPERSON FROINES: Pick the shortest one you can.

PANEL MEMBER BLANC: By the way, you might also want to mention, at least in passing in the section, that allergic rhinitis not a trivial source of morbidity in the population. So that even if one didn't develop lower respiratory --

DR. LIPSETT: I'm sorry?

PANEL MEMBER BLANC: Even if one didn't develop lower respiratory systems.

PANEL MEMBER FRIEDMAN: Are you referring to prevalence or severity or for what?

PANEL MEMBER BLANC: Not on prevalence but actually quality of life. I means it depends on how you measure it. It doesn't result in hospitalization, but if

you look at other measures of health status, it's not trivial.

CHAIRPERSON FROINES: Thanks, Michael.

DR. LIPSETT: Thank you.

SUPERVISING TOXICOLOGIST MARTY: We're going the it's the fastest one left. Dr. Dave Morry is going to be presenting the information.

DR. MORRY: I'm going the talk about why we included vinyl chloride in the top 11, but in Tier 2 rather that in the top five.

(Thereupon and overhead presentation was presented as follows.)

DR. MORRY: For vinyl chloride there strong Data from animals that shows that exposures early in life result in a higher tumor yield and also more DNA adducts than exposures that occur later in life, that are given later in life.

Vinyl chloride is a human carcinogen we know from occupational studies. However, the exposures -- there are not lot of ambient exposure to vinyl chloride, rather it's a sort of a spot problem that occurs near hazardous waste landfills and some other things like that.

So the third bullet up there is the reason why it's not included in the top 5.

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DR. MORRY: There is quite a few studies that demonstrate differential effects of vinyl chloride. The three I'm going the talk about are first of all the Drew study of 1983, which is really the key study, and then there's two by the late Maltoni and others from '81 and '88 that I'll also discuss.

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DR. MORRY: The key study is this one buy Drew et al., the effect of age and exposure duration on cancer induction by a known carcinogen in rats mice and hamsters.

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DR. MORRY: This was a study of vinyl chloride by the inhalation route in rats, hamsters and two strains of mice, of female mice. And the exposure levels were -- there was one exposure level for each species, 100 parts per million by inhalation for the rats, 50 parts per million for the mice, and 200 parts per million for the hamsters.

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DR. MORRY: Okay. The overall design of the experiment was to test different scenarios of exposure. So for each of the three species, they tested zero to six months exposure, zero the 12 months, zero to 18 months.

For rats and hamsters only, they tested zero to 24 months exposure. And then for all three species they studied six to 12, six to 18, 12 to 18, 12 to 24 months. And then for the rats and hamsters there was an exposure from 18 to 24 months.

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DR. MORRY: Now, this was for the hamsters. And if you look at the hemangiosarcomas, six months of exposure produced 15 percent hemangiosarcomas, 14.8. And exposing for 12 months actually resulted in a lower percentage of hemangiosarcomas, probably because of mortality. And so six months of exposure is sufficient to produce all the yield of hemangiosarcomas.

It varies a little bit from one kind of tumor to another. You notice that for the stomach adenomas, six months of exposure resulted in 26 percent, and 12 months of exposure resulted in only six percent. So pretty much across the Board or a simple six-month exposure was sufficient to produce a yield of tumors in hamsters.

Next slide.

PANEL MEMBER BLANC: Woe, woe, woe, woe, woe.

DR. MORRY: Okay, back to that slide.

PANEL MEMBER BLANC: That's not the question you're asking whether six months the sufficient. What

you're making the argument is that exposure from zero to 6 months is more potent than exposure from six to 12 months.

DR. MORRY: Yeah, there's more data. That particular slide doesn't compare -- this is only is only zero to six, zero to 12 and zero to 18 but there are other parts to the experiment.

PANEL MEMBER BLANC: This is not the part to the experiment, therefore that you would argue is relevant to the issue at hand?

DR. MORRY: Well, it's relevant in that it shows that an exposure early in life is potent enough to produce a full yield of tumors that you don't get more by exposing longer, so it makes it look like that early period is the key period.

PANEL MEMBER BLANC: But you just said that you couldn't say what the mortality was in the animals or you said that maybe it's because of increased mortality.

DR. MORRY: Well, I think that's reason it fell off and the authors say that's the reason that the numbers fell off from 14.8 down the 7.7. But they say that as somewhat of a conjecture. They don't say that --

PANEL MEMBER BLANC: Do you they tell you how many died?

DR. MORRY: I don't recall that that data is give in the paper.

PANEL MEMBER BLANC: Well, if that's not given in the paper, it's almost impossible to interpret the paper isn't it, if you don't know the differential survival by exposure group?

DR. MORRY: For this part of the experiment that might be the case. I'd have to look at that in more detail.

CHAIRPERSON FROINES: Do they give the actual numbers of animals at each site?

DR. MORRY: Yeah. There's 50 some animals in each group.

CHAIRPERSON FROINES: Do they give the survival?

DR. MORRY: I think so. I'm not sure.

PANEL MEMBER BLANC: I guess we'll wait till you finish for this paper and then we can figure out whether we can say anything about this paper.

PANEL MEMBER FRIEDMAN: It just seems surprising that zero the 12 months on the last slide produced less tumors than zero to six months.

DR. MORRY: Yes.

PANEL MEMBER FRIEDMAN: Or that zero the 18 -- there was a another column that showed zero to 18 less than same of zero to 12. And it just didn't make sense. Those number just didn't seem to make sense.

DR. MORRY: Yeah, that's the percentage of

animals with those tumors.

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DR. MORRY: Okay. So this one is for the mice. And there's two strains. And, again, this is looking at zero to six, 12 and 18 months. And so the zero to six month produced almost the same tumor yield as zero to 12 months for the hemangiosarcomas. And likewise for the mammary gland carcinomas in the B6C3F1 mice.

And in the Swiss mice also zero the six months produced 43 percent hemangiosarcomas. And then longer exposure didn't really increase the number of hemangiosarcomas very much, so most of the induction of tumors occurs in the first six months of exposure.

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PANEL MEMBER BYUS: Were these all sacrificed at the same time? Do you see what mean, there was six months of exposure, but were they sacrificed at 24 months or were they sacrificed after six months?

DR. MORRY: Well, the first slide of the plan of the experiment showed that they were held until the end of the experiment.

PANEL MEMBER BYUS: Okay.

DR. MORRY: So they were all sacrificed at the end of 24 months.

Okay, so this for female rats administered vinyl chloride. And you see that here what we have is an exposure zero the 12 months and then another 12 months exposure starting at six months, six to 18. And so you get a high yield of mammary adenocarcinomas and liver hemangiosarcomas, if you expose for the first 12 months of the animal's life.

But if you exposure for 12 months starting at six months, the yield of those tumors goes down. And then if you expose for 18 to 24 months, it goes down even more.

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DR. MORRY: This is for hamsters. And, again, this is 12 months exposure yields a higher yield of each of these three kinds of tumors than the 12-month exposure if you start at six months. And it goes down even more if you go 12 to 24 months. So this is taking the same length of exposure, but moving it long in the lifetime of the animal. And if you give the exposure early in life, it's very effective. If you start it later, it's less effective. And then if you start it even later, the effect the very small. So I think this data is more relevant to our question than the first data that I showed.

PANEL MEMBER BLANC: It is more relevant if you,

assuming that you would adjust for length of follow up. And the question that you're asking is if I have the same amount of follow up does the dose given earlier induce a bigger burden of tumor adjusted for length of follow up since you would expect that the incidence of the tumors in question will go up with the factor of follow up. It actually won't be linear but rather probably the square of time or something.

So unless you've gone back and looked at the data or the data were presented in that way, since your entire argument on vinyl chloride rests on arguing that it's not shelf life, but it's rather very specifically that even taking follow up into account, the carcinogenic potency of vinyl chloride the greater with exposure in young age than at an older age, even taking length of follow up into account, which I can't say based on animals who are sacrificed at 24 months, I assume.

DR. MORRY: Yes. They are sacrificed at 24 months.

PANEL MEMBER BLANC: In other words, I need to see -- for example, I'd need to see a study where rats were exposed from zero to six months and sacrificed at 12 months compared to animals that were exposed from six months the 12 months and sacrificed at 18 months and so forth.

DR. MORRY: Well, I don't think we want to argue that shelf life isn't part of the reason for this. The animals that are exposed from zero the 12 months do have a longer time to develop their tumors than the animals that are exposed from six to 18 months, so that could be part of the reason why you see more tumors.

PANEL MEMBER BLANC: Well, have you tried to -- in fact that wasn't the argument. The argument that you made was it wasn't just shelf life. The argument that you made, at least in the initial overall presentation, was vinyl chloride. We chose vinyl chloride because it wasn't just shelf life. We know that's a generic issue you could make with any carcinogen, but for vinyl chloride there was specific data suggesting that taking shelf life into account, young animals were more susceptible over and above that.

DR. MORRY: Well --

PANEL MEMBER BLANC: Based on this one study.

DR. MORRY: -- we think the shelf life argument, if it's a valid argument, applies to any genotoxic Carcinogen, whether you have data that shows that's effective early in life or not. For this chemical, there's data in animals that shows that the chemical is more effective when exposures occur early in life.

PANEL MEMBER BLANC: Over and above shelf life?

DR. MORRY: I didn't say that.

SUPERVISING TOXICOLOGIST MARTY: It's intertwined. I'm not sure you can actually separate that.

PANEL MEMBER FUCALORO: Why can't you? I think if you don't, say from zero to 12 months and then at -- I don't know, six months later -- then maybe the best way zero to six months then 18 months. In other words, give the length of time the same after each exposure.

DR. MORRY: Well, the animals are getting -- if you give -- you can't do that for animals that are exposed say 12 to 24 months, because then you'd have to give them like another 12 months and they're getting much older.

PANEL MEMBER BLANC: Well, you could sacrifice these zero the 12 months at the end of 12 months.

DR. MORRY: Or you can record the data of the tumor incidents at that period of time.

PANEL MEMBER FUCALORO: Right.

DR. MORRY: I don't think the purpose of this experiment was to ferret out shelf life versus other effects. And we're not trying the use it for that purpose. We're just saying that there's more evidence here than simply the generic argument of shelf life.

PANEL MEMBER BLANC: You're saying that you have a study that established shelf life exists.

DR. MORRY: No, I don't think so, but --

SUPERVISING TOXICOLOGIST: The shelf life is a theoretical consideration. And it's Based on the model of cancer which increases the third power of age. So if you're living a lot longer, you've got more third powers of age to go through.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There's a couple of issues here. And, in fact, Jim Coliano of US EPA has done, I think at times, a tumor analysis of this experiment. And I think if you -- he presented this, you know, orally to us at one point. And my recollection is that he showed both the quote unquote "shelf life effect." In other words --

PANEL MEMBER BLANC: Latency survival.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: However you want to call it. But he also, I think, demonstrated an increase in underlying potency at the earlier ages. Now, that's something which may be, if we are going the take the opportunity to analyze this a lot further, we should perhaps dig that out.

But I think the point is that there is both the underlying latency consideration and the question of what's the potency at a particular age. And without vinyl chloride appears to be a case where both apply.

PANEL MEMBER BLANC: Well, to the extent that you're able to make the latter argument, I believe that it

would be a more convincing argument to consider this substance as having deferential effect on children. My scientific review would be that the fact that children survive longer to develop their tumors and ergo carcinogen in children the more important and we have, you know, a lab study which shows that the effect of survival long enough the get the tumors with chemical X has been shown and, you know, what in the rats species X, Y or Z.

That the not going to be convincing to me to move something up relative in terms of a prioritization. I suppose if you had information which supported an interpretation of these data which showed that you could tease out an exposure sensitivity effect in childhood that might be more convincing, and then I would have to weigh it against other issues like, you know, how much exposure is there in all those other things.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The observation of the latency effect tends to imply that we should regard, perhaps all carcinogens as potentially having a greater impact on children, but that it doesn't prioritize between carcinogens.

Whereas, the possible oxidation of increased potency at younger age of exposure tends to argue that we should prioritize this particular carcinogen versus other carcinogens in other words.

PANEL MEMBER BLANC: Yes, that is what I said. But I don't believe that this presentation suspends my disbelief in that regard. And although you may have heard an oral presentation of the EPA which reinterpreted this data in someway that would support that, this presentation itself or the paper on the face of it, from what you've said, doesn't.

And I'm sorry if I misinterpreted your earlier statements at the last meeting to suggest that there was, in fact, potency data here.

DR. MORRY: We also, in the case of this chemical, we have more evidence for a differential effect to children than we have for most genotoxic carcinogens because for most genotoxic carcinogens we don't have this kind of experiment where the exposures are done at different ages, and where the age of exposure is compared.

DR. MORRY: Why don't we skip through to the Maltoni studies.

Okay, this study was published in 1981, bioassay of vinyl chloride monomer --

CHAIRPERSON FROINES: I think it would be helpful to send the study to the panel. I think given what's presented --

The Drew study.

CHAIRPERSON FROINES: I don't think we can really

understand what happened with what we have so far.

DR. MORRY: Okay.

CHAIRPERSON FROINES: Unless I'm badly mistaken.

DR. MORRY: Okay. The 1981 study was a huge complex experiment with 7,000 animals. And they tested different species rat, mouse and hamster and different strains, different routes of exposure, inhalation, oral and concentrations ranging all the way from 1,000 to 30,000 parts per million, and they also tested different schedules of treatment.

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DR. MORRY: From this study they said that vinyl chloride was carcinogenic in the animals by inhalation and by ingestion. That the duration of treatment and the schedule greatly affected the neoplastic response that was seen in the animals. Species, strain and sex also greatly affected the response.

They concluded that newborn animals appeared to be extremely responsive and to easily develop liver tumors, both hepatocarcinomas and angiosarcomas. And also they showed that vinyl chloride produced carcinogenic effects on embryos via the placenta when they were expose in uterine -- when the mothers were exposed while the animals were in utero.

PANEL MEMBER FUCALORO: Now, the fourth bullet item would be what the standard we're looking for essentially to me, that younger, younger animals are more susceptible, right?

SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER FUCALORO: Isn't that right?

Now, are you saying newborn animals appear, of course that's a hedge word that makes me uneasy --

DR. MORRY: Well, it's a quotation from the conclusion.

PANEL MEMBER FUCALORO: Understood. Not that you're making it, appeared to be extremely responsive. Did the data show that? They must. I mean, I would guess, wouldn't they?

PANEL MEMBER BLANC: Well, in your read of the paper, did the show that?

DR. MORRY: Yes, uh-huh.

PANEL MEMBER BLANC: So your next slide is the data that support that.

DR. MORRY: We don't have slides on the data from this paper. It's a huge paper and we concentrated mainly the Drew paper.

PANEL MEMBER BLANC: Would you say the quality of the data from this study are better the quality of the drew data?

DR. MORRY: There's more, you know, animals, more different kinds of exposures, and also they looked at in utero exposures, which the Drew experiment did not look at, so they looked at a much greater variety of factors.

PANEL MEMBER BLANC: Did they seem to have a data analysis that could take into account both latency and period of exposure and adjust for latency?

DR. MORRY: I'll have to look at it in more detail to answer that question confidently.

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DR. MORRY: And the paper by Maltoni and Cotti 1988. This was carcinogenicity of vinyl chloride Sprague-Dawley rats after prenatal and postnatal exposure was done by inhalation seven hours a day five days a week at just two doses 2,500 and control, no exposure. The animals were exposed for 13-week old breeders and male -- they exposed 13-week old breeders and mail and female offspring. So the offspring were 12-day embryos. Yes, gestation date 12. And they were exposed for 15 or 104 weeks.

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DR. MORRY: In this experiment the hepatocarcinomas in male and female rats exposed as embryos was 51.2 percent compared to only 9.2 percent in

adults. And there were no hepatocarcinomas in the unexposed controls.

And the angiosarcomas were 64.6 percent in the exposed embryos and only 50 percent in the exposed adults. The latency period was shorter for the embryos than for the adults.

So the onset of neuroblastoma is affected by the length of treatment, the onset of hepatocarcinoma was affected by the age at the start and the onset of angiocarcinoma was affected by both the length of treatment and the age.

Next slide, please.

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PANEL MEMBER FUCALORO: I mean that's the data. I mean that's the data which supports the differentiation.

DR. MORRY: So our overall conclusions for vinyl chloride is that embryos in young animals are more sensitive to carcinogenic effects of vinyl chloride than are adults. And from other experiments, other papers, we have the information that young animals are more sensitive to DNA adduct formation by vinyl chloride than are adults, several fold more sensitive, six-fold in one experiment.

And animal experiments strongly indicate that infants and children would be more sensitive to the carcinogen effects of vinyl chloride, based on both the

carcinogenicity studies and the adduct studies.

SUPERVISING TOXICOLOGIST MARTY: We actually have Covlianos paper in here and cite his paper which was a quantitative cancer assessment, where he looked at the time to tumor model, and so he could account for the effects of latency versus time at sacrifice.

PANEL MEMBER BLANC: Is this is guy from the EPA that you referred to?

SUPERVISING TOXICOLOGIST MARTY: Yeah, right.

PANEL MEMBER BLANC: What are the other ones that you have left the present, obviously not today, but what haven't we heard?

SUPERVISING TOXICOLOGIST MARTY: We haven't heard glycol ethers and you haven't heard the dioxins in PCBs.

PANEL MEMBER BLANC: Which are together?

SUPERVISING TOXICOLOGIST MARTY: The Dioxins and the dioxin like PCBs are in one presentation and then the noncoplanar PCBs are in another because it's a different toxin.

PANEL MEMBER BLANC: So you have three presentation still.

SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER GLANTZ: Plus the ones that you and John added.

CHAIRPERSON FROINES: I think we'll determine

that based on what they come up with.

Gary.

PANEL MEMBER FRIEDMAN: Could you just say briefly how kids would get exposed to vinyl chloride. I know there was concern about workers and, in fact, there's -- but how do kids get exposed to it.

SUPERVISING TOXICOLOGIST MARTY: Through Exposures from hotspot sources. So stationary sources that emitted vinyl chloride, for example, a polyvinyl chloride manufacturer or if you lived near a big old landfill. Vinyl chloride comes off landfills because it's a microbial degradation product of a number of things.

But overall the reason it's in Tier 2 is because we don't think that there are huge exposures. It's certainly not a concern on a regional basis.

CHAIRPERSON FROINES: We're about to lose a quorum. Paul, what was the purpose of your --

PANEL MEMBER BLANC: Well, my practical suggestion would be that you circulate to us some suggestions on how you want to handle the next steps of the next meeting in terms of a procedure, because it alludes me how, exactly, we're going to --

CHAIRPERSON FROINES: All right. That was the question earlier that I think that we need to define well in advance how we're going to proceed to draw this to

closure at the next meeting.

PANEL MEMBER BLANC: I will say, overall, that I don't think that the oral presentations of each and every chemical have been particularly illuminating, overall. I mean, the sort of step by step ones. It's been sort of uneven, and a lot of times throws into confusion that which was, I thought, straightforward previously.

So maybe we need the think for the remaining three ones and for the ones that we've added how we want to handle the discussion. And it may not be by this sort of linear presentation of the section with slides. So that would be my question to you.

CHAIRPERSON FROINES: Yeah, we're going to have to -- you're going to have to -- we're asking for some additional new chemicals, but you're going to have to give us some heads up in advance as to whether or not there is sufficient evidence to bring them before the panel. I don't think we want to go -- we listed about ten chemicals, I think,

PANEL MEMBER BLANC: No, five.

CHAIRPERSON FROINES: No, by the time you and I finished it was closer to ten, I think.

PANEL MEMBER BLANC: No, there were some that you wanted them to recheck, but there were some --

CHAIRPERSON FROINES: I know.

PANEL MEMBER BLANC: But you're counting those?

CHAIRPERSON FROINES: Yeah, I'm counting those for the sake of the first cut. So that, as a result, we'll need to know very soon about the level of evidence for the compounds and, you know, in my cases you may be able to dismiss them very quickly. And the couple of the others like methylene chloride and manganese, it's going to be obviously more difficult.

So we're going the need get a heads up in the next week or two of what we can plan for the next meeting.

PANEL MEMBER BLANC: This is an important point of clarification John. You're actually saying something different than what we said before. What we said before was that the ones that -- I did give them a discrete group of ones that I wanted to see the sections on. There were several other additional ones, which we said we didn't need the see the summary sections on, but we did want them to recheck their references and double check a few things, but that unless something emerged, and it was at their discretion, we were not expecting to see summary toxicity review of.

But I am expecting to see the summary toxicity reviews of the ones that I mentioned, and those were only about four or five, I think.

SUPERVISING TOXICOLOGIST MARTY: I had six.

PANEL MEMBER BLANC: Six. So I just wanted to make sure that they're not --

CHAIRPERSON FROINES: What I'm worried about, Paul, is that I'm trying to get it so we make a judgment ahead of time about how many of those six of yours we need the actually have presentations at this meeting.

PANEL MEMBER BLANC: That's a different question. I need the see documents for all them.

CHAIRPERSON FROINES: We'll work on that level of communication, because if we can avoid, we should only have presentations on those that are --

PANEL MEMBER GLANTZ: Serious contenders.

CHAIRPERSON FROINES: -- quite serious. Otherwise, we'll end up getting documents that's literature reviews, but not necessarily have presentation.

We don't have a quorum, so we move the close.

Thank you very much.

(Thereupon the Scientific Review Panel meeting adjourned at 4:05 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing Scientific Review Panel hearing was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said hearing nor in any way interested in the outcome of said hearing.

IN WITNESS WHEREOF, I have hereunto set my hand this 21st day of May, 2001.

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