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CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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ORIGINAL

PUBLIC FORUM

MEETING OF THE SCIENCE ADVISORY BOARD'S
CARCINOGEN IDENTIFICATION COMMITTEE (CIC)

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THURSDAY, OCTOBER 7, 1999

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HELD AT:

1515 CLAY STREET- ELIHU HARRIS STATE BUILDING
OAKLAND, CA

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DR. JOSEPH LANDOLPH
DR. JOHN PETERS
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DR. JOHN FAUST
DR. GAIL KROWECH
DR. TOM MCDONALD
DR. PAGE PAINTER
DR. JEAN RABOVSKY
DR. ANDY SALMON

CYNTHIA OSHITA, Proposition 65 Implementation

AGENDA

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AGENDA, CONT'D

AGENDA, CONT'D

OAKLAND, CALIFORNIA.

THURSDAY, OCTOBER 7, 1999

DR. FROINES: I'd like to call the meeting to order. Since I know at least half if not more of the people in the room right now, many of you will recognize that I'm not Tom Mack. Tom is on his way. So I'm the stand-in chair for the moment. So why don't we just get started.

And the first item on the agenda is --

Oh, for the record, I'm John Froines. Why don't we get started. And our first item is, Dr. Joan Denton will provide us with some opening remarks.

DR. DENTON: Thank you, Dr. Froines. I want to take the opportunity to welcome all of you here today to the meeting of the Carcinogen Identification Committee. And it's my pleasure to introduce the individuals who are seated up here as well as the staff members.

Dr. Bill Spangler, Dr. Joe Landolph are here on my right, and on my left is Dr. Felton, Dr. Eastmond, and Dr. Peters. I'd

also like to welcome Dr. Eastmond to the Committee. He's a newly-appointed Committee member of the Carcinogen Committee. And Dr. Eastmond comes from UC Riverside, where he's an Associate Professor.

At the staff table, Val Siebal, Martha Sandy, George Alexeeff, Ed Weil, Colleen Heck, and Cindy Oshita. Then we also have some additional Staff members who will introduce themselves as they come up to the table to make presentations on the various items.

We have a very full agenda today. And in Dr. Mack's absence, we're going to not take up the criteria discussion and then move on to the listing -- the hazards identification documents discussion.

As you -- all of you who attend these meetings frequently know that the way we handle the public discussion portion of each item is for you to fill out cards, which Cindy has. And just -- basically has your name and the discussion item that you wish to address. And then you will be called up by the Chair at that time.

I think with that, then, Dr. Froines, I'll turn it back to you.

DR. FROINES: The one prerogative of the Chair is you get to make some of the early decisions. And so I decided to put myself last in the consideration of chemicals known to cause cancer. So we are going to start with 1-chloro-4-nitrobenzene. And Page Painter will be the presenter at the outset. And I believe the lead person on this is Dr. James Felton.

DR. PAINTER: 1-chloro-4-nitrobenzene is an industrial chemical, with a structure shown in the first slide. It is used as an intermediate in the synthesis of certain drugs, dyes, pesticides and other substances in commerce, and is not known to occur naturally.

Administration of 1-chloro-4-nitrobenzene in feed to rats did not produce tumors, but as shown in the next slide, administration in feed to mice produced vascular tumors (hemangiomas and hemangiosarcomas) in both male and female mice. It also produced hepatocellular tumors in male mice at the low

dose, but not at the high dose.

As shown in the next slide, it produced mutation in some but not the majority of tests using the Salmonella mutagenesis assay. In mammalian cells, it produced DNA strand breaks *in vitro* and *in vivo* and produced sister chromatid exchanges and chromosomal aberrations *in vitro*. One of the metabolites in 1-chloro-4-nitrobenzene in rabbits, rats, and humans is the known carcinogen, 4-chloroaniline.

Next slide.

In summary, there is evidence for the carcinogenicity of 1-chloro-4-nitrobenzene based on observation of vascular tumors in male and female mice, and on observation of liver tumors at the lower of two doses in male mice. Further evidence of carcinogenic potential is provided by observation of genotoxic effects in mammalian cells, both *in vitro* and *in vivo*, and by metabolism to a known carcinogen.

DR. FROINES: Before we ask Jim to comment, I just want to ask the entire panel if anybody has any questions for the

presenter?

DR. SPANGLER: Do you have a breakdown on the vascular tumors, how many were hemangiomas and how many were hemangiosarcomas?

DR. PAINTER: No. That's not in the study. We attempted to get further information by corresponding with Dr. John Weisberger, the author, and spoke to him on the telephone. And he said that information is not available. However, I want to add that NTP does not currently break down vascular tumors in mice in terms of distinguishing between hemangiomas and hemangiosarcomas. They consider them a spectrum.

DR. LANDOLPH: My understanding is these are very rare tumors, the hemangiomas and hemangiosarcomas. Is that your understanding? In humans, they're rare.

DR. PAINTER: They are quite rare.

DR. LANDOLPH: But they're not so rare in mice.

DR. PAINTER: In mice, the frequency depends on the strain. We don't consider them greater than -- it's rarer than 1 percent, is

the usual definition. In some strains, they're up to about 5 percent. The background incidence is historically around 5 percent.

DR. LANDOLPH: So they're rare in humans, a little more common in mice.

DR. PAINTER: I would consider them unusual, but not rare.

DR. LANDOLPH: And then the other question was, in the human study that was alluded to here with this compound is metabolized to 1-chloro-4-aniline, is that thought to be by bacteria containing nitro reductases in the gut?

DR. PAINTER: There's no information on whether this is biliary excretion and re-uptake of bacterial metabolites. Humans do have nitro reductase activity to some extent. I simply don't know.

DR. LANDOLPH: Thank you.

DR. FROINES: Is this an important metabolite?

DR. PAINTER: Oh. In humans? From the acetylated products context, in humans, it is roughly 30 percent of the metabolized fraction. Now, these are human studies where

an accidental industrial exposure was the source, and there's no way of knowing what the initial dose is. We can only look at the urinary metabolites, which is about 30 percent.

DR. EASTMOND: Could you please describe the type of tumors produced by chloroaniline in rodents?

DR. PAINTER: Oh. By chloroaniline, they're remarkably similar. It produces hemangiosarcomas in mice, both males and females. It also produced liver tumors in male mice in one study. And I noted in my preparation for this presentation that the levels were somewhat higher than what I would estimate the metabolized fraction in the Wiseberger study.

Also, I noted that other chloroanilines such as chloro-o-toluidine is a very potent producer of vascular tumors in mice. And another chloroaniline, which is 2, 4, 6 tri-chloroaniline, is a very potent and conducive to these vascular tumors in mice.

DR. LANDOLPH: I enjoyed reading your documents very thoroughly. One question is, I

noted you indicate that the IARC said this was unclassifiable; and from your mention of the human accident, is there any data of tumor induction in humans at all, or is there ambiguous data? What is the exact situation?

DR. PAINTER: We could not find any epidemiological study on 1-chloro-4-nitrobenzene, nor could we find any case reports associated with cancer with exposure.

DR. LANDOLPH: Thank you.

DR. FROINES: Further questions? No?

Why don't we ask Jim to give us his comments.

DR. FELTON: Sure, I'd be glad to.

Well, you heard pretty much all the data there is. There's rat data that the State's reported on. It was not significant, but it had a significant trend in that there were interstitial testicular tumors at significantly lower doses than gave the tumors we were just discussing in the mouse.

These were not statistically significant. One more tumor, I think, would have taken it over the edge. So we're one rat shy of being

significant, but the trend was significant.

The doses that were used in the rat were hundreds-fold lower than gave these tumors in the mice, if my calculations were right. The data was in p.p.m, and I converted it into milligrams per kilogram. And its looks like it's about -- it's over a thousand milligrams per kilogram with these high doses in the mouse that gave the tumors we were just discussing, where the rat studies could only get up into a maximum dose of about 5 milligrams per kilogram. So it looks like the rat just can't take the doses that the mouse can. And, well, that's the way it goes.

So the bottom line is, the mouse is one species, both sexes, two types of tumors in the mouse in this compound; no tumors that are significant in the rat. There's genotoxic evidence both base substitution data in Salmonella, but not frame shift, and then a number of different types of cytogenetic damage; SCE's, single-strand breaks, both *in vivo* and *in vitro*.

So the question is, what do you do with this compound? And then on top of that is the

metabolism data you heard, where you actually have a known carcinogen as a metabolite of this compound, both in humans and in rodents.

So the question is, what do you do with that data and is it -- are you convinced that it's a carcinogen or not. And it's one of these that's right on the edge, you know, one species. But we've talked about this before. And we've discussed the mechanistic data versus no mechanistic data.

In my opinion, when you put it all together, and it's right on the edge, I'd -- if I had to choose yes or no, I'd choose yes, just because of the mechanistic data coupled with the metabolite that's the potent carcinogen in the human. And I think that's what it comes down to.

DR. LANDOLPH: Can I ask Jim a question?

Mr. Chair?

DR. FROINES: Sure. You're breaking up my morning nap. Sorry. My fault. Sure.

DR. LANDOLPH: Jim, I found that data with the rat interesting because it looked like it was dose dependent -- 1, 4, 5 -- so the numbers went up. So it looks like an

unusual situation where there's a dose dependence.

DR. FELTON: Yeah. Well, according to -- maybe the State wants to comment on this -- I suppose they could do to a trend analysis on the significant slope for that data, but it isn't high enough for any individual animal to say it's a significant increase in background.

DR. PAINTER: It's significant by trend, clearly significant. And at the high dose, I think it's right at p=.04 or .05, around there.

DR. FELTON: I think you said by 5.7 or something.

DR. SANDY: That's correct.

DR. FELTON: That's pretty close.

DR. SANDY: 0.57.

DR. PAINTER: It's very close, but not at the threshold.

DR. LANDOLPH: Like you, I respect the dose response. I was curious about this.

DR. SANDY: I think the significance by trend is .001 --I'm sorry, .01.

DR. FELTON: I think this is one of these cases, one more tumor, and we wouldn't be

discussing this compound. That's how close it is, being two species, etc. So I think you just have to weigh in the other data. And when I do that, with the trend and everything else, I think you have to consider this a carcinogen.

DR. SPANGLER: I'll have to disagree on the basis that we're talking about compounds that are clearly shown to cause cancer. And I think this is a good example of a compound that's not clearly shown. If certain criteria were met, we might have to say that this did meet the criteria for a compound that caused cancer. Testicular tumors in rats are not a compelling, biological event, in my perspective, at least, as are liver tumors in mice.

And so we've got a compound here that may produce testicular tumors in rats. If we had one more tumor, it would be significant. But, you know, if we had one more tumor, it would just take missing one so that it wouldn't be significant. And so I just don't find this compound a compelling compound to list.

I agree with everybody that this is one

that's right on the edge, but I think that's what we do, is take those on the edge and say, well, is this clearly shown to cause cancer or is it not clearly shown to cause cancer. And I'll have to come down on the "this is not clearly shown".

DR. LANDOLPH: Now, I was looking at the vascular tumor data. In Table 1, for both males and females, it's dose-dependent. So both those inductions are dose-dependent in males and females.

The backgrounds are a little high, I agree. And the hepatocellular carcinomas was positive at one point, but not dose-dependent. But it was a four-fold increase over background. So there is positive data here.

DR. SPANGLER: I think my point is, there's positive data. I think there's positive data in all these studies, but this is not compelling.

DR. FELTON: I think -- Can I comment?

DR. FROINES: Go ahead.

DR. FELTON: I mean, the one thing we've struggled over in the last few years; if it's two species, dose-dependent, etc., then

everybody's happy and convinced. When it's on the line, like this one -- we had a number of these -- we looked at some of them where we looked at the genotoxic activity. And I remember a few years ago, we discussed one of the compounds I think Joe was dealing with. It was really a strong genotox. And was it positive in one species? And we said yes, carcinogen.

Again, I think this one may not be as strong a genotox as that one, but it's not just positive in one test. It's positive in a number of genotox tests. And with 4-chloroaniline being a metabolite, it puts a big flag up for me, because that's a really potent carcinogen. And if you're making that compound from this one, then it's something to worry about.

So that's sort of the rationale you've got to use if you call it positive.

DR. FROINES: Dave? I thought you wanted to ask --

DR. EASTMOND: No. I don't have a question; rather, a comment. My opinion.

I largely agree with Jim in that this

is -- I think that there's clearly a dose response seen in both males and females in vascular tumors. And it is substantially over historical controlling instances, it seems. So you have a real definite positive in this animal bioassay.

If you look to supplemental supportive evidence, you have lots of positives in genotox assays. But you also have chloroaniline as a metabolite, and it gives the same type of tumors that are seen with this compound. And I think that combination of evidence, although this is clearly one that we consider a difficult decision, but it seems to lean in the -- I would lean towards the listing of it as being an animal carcinogen.

DR. FROINES: I want to make a comment that -- well, since I will chair for a few more minutes, and then I'll retire, I want to make it now.

I would appreciate it if the panel would try and talk to other members of the panel. I think that this panel should be set up so that we're facing each other, because I think it's not entirely appropriate for the panel to be

addressing the audience when we're trying to decide what we think about the chemical.

And in the future -- I've made this point in the past -- I would prefer a U-shape, so we're not talking to an audience. I think this panel has to deliberate amongst itself. And it should. And so I want to emphasize that. I feel very strongly about it. On the Scientific Review Panel, I always insist on that kind of framework. So Dave is talking to Jim, and Bill's comments not of somebody -- all due respect to the people who are out there.

DR. DENTON: We could change it now.

DR. FROINES: No. No. No. It's okay. This will do for the moment.

I want to make a comment that's generic. I think this is actually a very important chemical, because I think it's indicative of the work that this panel is going to be asked to do now and in the future.

We have all gotten used to relying to some extent on the National Toxicology Program bioassays that were conducted in the 70s and 80s. And they -- I don't remember the exact

numbers, but they're 400, 500, 600, but there was a large number. And then with studies that were done by industry and other academic institutions, we had a fairly sizeable database on animal carcinogenicity.

What's happened is, the compounds that were the low- hanging fruit, where we had rats and mice data, have been designated by IARC or other bodies. And so they come in as authoritative body findings. So in a sense they become issues that this panel doesn't necessarily address.

This panel is actually addressing the very high fruit in that respect, insofar as we're now looking at compounds which by and large may have one NTP bioassay, may have one study done by others, but the actual number of bioassays in the animal carcinogen sense is extremely limited. And we have to recognize that that's going to be the nature of the data that comes before this Committee for the future.

Therefore, it seams to me -- and this partially relates to the criteria issue -- it seems to me that one of the things that the

panel really has to ask itself is, to what degree do we take seriously the role of mechanistic considerations in making our decision.

Because I think what we're going to see is, we're going to see some animal data. We're going to see no human data, for the most part, limited animal data, and then we're going to have genotoxicity and other mechanistic, for example, toxicogenetic, considerations.

So this is the kind of thing that we're going to have as the rule, not the exception. And I think, in my point of view, then, I would way mechanistic data very heavily, because I think that's what we have to use to make these decisions. I think we have to realize that the amount of animal data is not as great as one would like and in fact, given the fact that NTP is doing only 5 or 6, if that, bioassays per year, the actual database is going to shrink. At least the database of the compounds coming before us is going to shrink.

So I say all that as a kind of general

background to this issue, because I think it means that we have to ask ourselves, do we take toxicokinetic information, do we take genotoxicity -- and other structure activity, I think, becomes, very important -- and so forth. So those considerations, I think, become central themes within the context of this decision-making process. And I think this is one example of that.

Joe?

DR. LANDOLPH: I am, at this point, am a little bit split, so I side with Dr. Felton and Dr. Eastmond's comments. I view this as a procarcinogen for tri-chloroaniline. And there is evidence for metabolism of that in humans. I respect the genotoxicity data in bacteria and the chromosomal breakage data in mammalian cells. And I do see tumors here.

I would be delighted if I could ask my good friend, Bill, to the right, here, to instruct me a little bit more on these vascular tumors and the worries that one would have about them, because I'm not that familiar with them. So if you could help educate myself a little bit more about that.

DR. SPANGLER: Of all of the considerations for this particular compound, I think the vascular tumors in mice are the most worrisome, as far as a legitimate reason to think that this might be a carcinogen based on the information that we have here.

Vascular tumors occur in mice -- I would consider vascular tumors to occur commonly. If you had a list of tumors that you expected to see in old mice, and you will see a lot of tumors in aging, old mice, vascular tumors are going to be very high on that list of tumors. So for the most part, they're going to be hemangiomas, benign tumors that really don't progress or don't do anything. There will be some of the malignant variety, however. So I find that the most, troublesome.

I have no problem with liver tumors in mice. Liver tumors occur in mice. They seem to occur very commonly with almost any compound. I'm not convinced that there aren't a variety of physical occurrences that precipitate liver tumors in mice as well.

So I think my point is that this information is not compelling. If there were

an unusual tumor in one species one mouse study, if it was a highly unusual tumor and they were occurring in large numbers, then I would say that was compelling evidence that this compound caused cancer.

In this case, we've got very low numbers, fairly low numbers. We've got a compound that is not producing tumors in rats. I personally consider mechanistic data, and I consider mutagenesis data, that sort of thing. But I have to consider it with a very light hand, because we are here to tell the Governor that these things clearly cause cancer.

And to me, based on the information that we have here, I have a real difficult time telling anybody that this clearly results in cancer. It does. I accept the information we've got here. But for me to say that this clearly causes cancer, with a name like 1-chloro-4-nitrobenzene, I think most everybody is going to stay as far away from this as they possibly can get, anyway -- and cancer maybe one of the lesser evils in this compound.

DR. PETERS: I would just say that I'm

not an expert except on animal carcinogenesis, but I can't think of anything more compelling than having a compound metabolize 30 percent to a known carcinogen. I find that compelling.

DR. FELTON: I think the one thing you have to look at in the mouse tumor data is the species of the strain that was used. This HAM/ICR strain has quite a bit lower levels of these vascular tumors than some of the other strains. And actually, they list it in the report. I mean, there is two different controls that were used. There was a pool control group and a specific environmental control.

I mean, one was 0 percent in both species, and the other showed up to 9 percent in the female. But the highest dose in the female gave 39 percent. So that's quite a bit of difference. This isn't even close in my opinion.

For this particular strain, there's really a large significant increase in tumors that these different doses -- and in both sexes. So I don't think there's any question

about the mouse data.

I have to disagree with the use of this compound. I mean, this is a precursor for a number of chemicals, including Tylenol and drugs that all of us use. So that if the manufacturing is going on in your community, this is a significant risk to somebody that handles this compound if you consider it a carcinogen.

So yes, this isn't something you buy in the grocery store. But it's definitely something you find in the manufacture of a whole series of products.

DR. EASTMOND: I requested from the Staff some information on the background instances of tumors in this particular strain of mouse, actually during this period of time in the 70s. And there are two articles that were faxed to me from the *Journal of National Cancer Institute*. And generally, the frequency of these vascular tumors tends to be lower somewhat, maybe 3 at the high, but some are down to 0.5 percent for the thousand animals that they looked at. So this is not a real high-frequency tumor, as I read this

information.

And so the increases that are seen by this chemical are really fairly substantial in light of the background of historical tumor incidences.

DR. FROINES: Do we have comments? We have no blue cards. Cynthia?

DR. DENTON: Cindy, do we have any public comments on this compound?

MS. OSHITA: No public comments.

DR. FROINES: Is there further discussion? Any comments from the Staff? Then, John.

DR. PETERS: I'd like to move that this compound be listed.

DR. FROINES: Please indicate by a show of hands if in your opinion chloro-nitrobenzene has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

5 votes.

Please indicate by a show of hands if in your opinion chloro-nitrobenzene has not been clearly shown through scientifically valid

testing according to generally accepted principles to cause cancer.

So the vote carries 5 to 1.

The second compound is -- how do you pronounce this compound? Estragole.

DR. MCDONALD: Well, Good morning. I'm Tom McDonald. I will present a brief summary of the evidence of the carcinogenicity of estragole. This summary will be prefaced with a slide describing the use, production, and occurrence of estragole.

Next slide.

Estragole is used for its flavor and fragrant properties in many products, including foods, beverages, soaps, perfumes, and cosmetics.

Next slide, please.

Production estimates in the United States exceeded one million pounds per year in 1990. Recently, I obtained additional information from U.S. EPA, as part of the TSCA Inventory Update Rule, which indicated that in the last two reporting years, 1994 and 1998, estragole was also produced in exceedence of one million pounds per year in the United States.

Outside the U.S., the Organization of Economic Cooperation and Development listed estragole as a high production volume chemical; that is, chemicals that are produced or imported at levels greater than two million pounds per year in at least one Member country.

The Flavor and Extract Manufacturer's Association (FEMA) reported that an estimated 1,234 pounds of estragole was added to foods as a flavorant in 1995 in the U.S. Thus, the production estimates exceeding one million pounds of this agent may point to significant occupational or non-food exposures to estragole.

Estragole is the major component of the volatile oils of anise, bay, tarragon, basil, and other herbs. Indeed the synonym for tarragon is estragon. Estragole is a minor component of the oil of fennel, marjoram, chervil, and oil of turpentine. It is also a minor component of tobacco smoke.

Next slide.

With respect to the carcinogenicity of estragole, no cancer studies in humans exposed

to estragole were located. In animal studies, there are 8 cancer bioassays in mice reported among 3 publications: *Drinkwater et al., 1976, Miller et al., 1983, and Wiseman et al., 1987.* These studies involved three different strains of mice and covered three different routes of administration.

Next slide, please.

This slide provides a summary of the 8 cancer bioassays of estragole in mice. For the sake of brevity, I'm not going to present slides that show the incidence data. However, I have slides prepared, should the Committee want to discuss the details of each of these studies.

Three of the cancer bioassays involved oral exposures. Male newborn CD-1 mice were administered gavage doses of estragole, twice per week for 5 weeks, for a total of 10 doses. The mice were sacrificed at 14 months.

Increased incidence of hepatocellular carcinoma relative to vehicle controls were reported. Female newborn CD-1 mice similarly administered 10 gavage doses and sacrificed at 14 months also showed a slight increase in

tumors, but was not statistically significant relative to controls. That p-value is .16.

Adult female CD-1 mice were administered 2 doses of estragole via the diet for 12 months and observed until 20 months. Survival to 10 months was high; 96 to 98% for the high and low-dose groups, respectively. Statistically, significant increases in hepatocellular carcinoma relative to vehicle controls was observed in both dose groups. And a dose-related increase in the incidences was observed over the two dose groups.

Male CD-1 mice and B6C3F1 mice were given 4 intraperitoneal injections of estragole, 1 dose on days 1,8,15, and 22 of life. CD-1 mice were sacrificed at 12 months, and the B6C3F1 at 18 months. In both cases, increases of tumors, $p<0.001$ were observed compared to vehicle controls.

In a separate bioassay, male newborn B6C3F1 mice were given a single injection of estragole at 111 milligrams per kilogram body weight on day 12 of life, resulting in nearly 100% incidence of liver tumor incidence by 12 months. Female A/J mice, a strain sensitive

to lung tumor formation, were give estragole 2 days per week for 12 weeks. No increases in lung tumors we observed by 8 months.

Additionally, two groups of male newborn CD-1 mice were given 4 subcutaneous injections of estragole. Mice were sacrificed at 15 months. There was no indication that the MTD was exceeded since survival to 12 months was high, and survival in the high dose group was actually better than that of the controls.

A dose-response increase in the incidences of hepatocellular carcinoma was observed over the control low and high-dose groups. In pairwise comparisons, however, only the high-dose group reached statistical significance.

Next slide, please.

Also reported among those three publications were cancer bioassays of 1-prime hydroxyestragole, the putative toxic metabolite of estragole. 1-prime hydroxyestragole induced high incidences of hepatocellular carcinomas in several studies. These studies included administration of estragole via the diet to female CD-1 mice by

i.p. injection to newborn male mice (strains CD-1, B6C3F1, CeH/HeJ, and C57BL/6J), and via subcutaneous injection to newborn male CD-1 mice.

It should be noted that no increases in liver tumors were observed in male rats given 20 subcutaneous injections of estragole, or in female newborn mice given 4 intraperitoneal injections.

Next slide.

The carcinogenic mode of action for estragole in mice has been well characterized and proceeds through a genotoxic mechanism. Estragole is metabolized to 1-prime hydroxyestragole, which is further conjugated to a sulfate group leading to a sulfuric acid ester. The sulfate group readily leaves, leaving a reactive carbonium ion, which readily binds with DNA, leading to liver tumors.

The mechanism of action is the same as for safrole, a Proposition 65 listed chemical. Six DNA adducts have been characterized for estragole. Six equivalent DNA adducts are seen for safrole. Studies of estragole,

safrole, and related derivatives in which the sulfation step was inhibited, resulted in reduced DNA adduct formation and prevention of liver tumor formation in mice.

As depicted in Figure 2, page 31 of the draft HID, the metabolism of estragole to 1-prime hydroxyestragole appears to be quantitatively consistent between humans and rodents.

Next slide.

Other relevant data include genotoxicity data. Estragole and 1-prime hydroxyestragole had mixed results in standard bacterial mutation assays. When the sulfation cofactor PAPs was added to the test system, we saw increases in mutations in Salmonella strain 1535 in the presence of activation enzymes.

In rat hepatocytes and in human cell lines, estragole and 1-prime hydroxyestragole induced unscheduled DNA synthesis. As I mentioned, liver DNA adducts have been observed. The levels of DNA adduct formation after exposure in mice to estragole, safrole, and other alkenylbenzene compounds were found to correlate well with the observed liver

tumor incidences in mice dosed in the same manner and observed for over a year.

Similarly, the ability of different alkenylbenzene compounds to induce unscheduled DNA synthesis in rat hepatocytes also correlates well with their ability to induce liver tumors in mice.

Next slide, please.

Other relevant data includes structure-activity relationships. Strong supporting evidence of estragole's carcinogenic potential comes from structurally similar compounds, especially safrole and methyleugenol. Safrole has been shown to produce hepatocellular carcinomas in rats and mice.

1-prime hydroxysafrole, like 1-prime hydroxyestragole, produced high incidences of liver tumors in mice. Estragole and safrole, as I mentioned before appear to function through equivalent mechanisms. Methyleugenol or 1-prime hydroxymethylgenol also induced high incidences of liver tumors in mice exposed as newborns.

Methyleugenol was recently tested in

gavage studies conducted by the National Toxicology Program. Methyleugenol induced clear evidence of carcinogenicity in male rats, female rats, male mice, and female mice. One should note that the doses used in the methyleugenol NTP bioassay were comparable to the doses used in the studies I described for estragole earlier.

Also, several other alkenylbenzene compounds were shown to cause liver tumors in mice.

Next slide, please.

In summary, there is evidence from carcinogenicity studies that estragole induces cancers in mice. Estragole induced liver cancers in multiple strains and both sexes of mice exposed by several different routes of administration. Estragole has not been adequately tested in the rat, although two closely-related compounds, safrole and methyleugenol, both caused cancer in rats.

Further evidence of estragole's carcinogenic potential includes observations in genotoxicity in several short-term tests, DNA adduct formation *in vivo* and *in vitro*,

chemical-structural analogies with recognized carcinogens, and a relatively clear understanding of the carcinogenic mode of action.

Thank you.

DR. FROINES: Could we have the lights?

Jim?

DR. FELTON: Can you summarize the authoritative body findings on this compound for us? What does the IARC say and --

DR. MCDONALD: To my knowledge, this has not been looked at by an authoritative body.

DR. FELTON: So we'll be the first to make that decision?

DR. MCDONALD: Right.

DR. EASTMOND: Tom, in the mouse dietary exposure you reported, *Miller, 1983*, it's my impression in looking at this, and actually, I did some analysis on it, that in addition to significant increase in hepatocellular carcinomas, there was also an increase in the vascular tumors in rats. You think they were studied as well?

DR. MCDONALD: Only for the 1-prime hydroxyestragole, is my understanding, not of

estragole itself.

DR. EASTMOND: Well.

DR. MCDONALD: I'd have to go back and look at the data.

DR. EASTMOND: Well.

DR. MCDONALD: I'd have to go back and look at the data, but that's my understanding.

DR. EASTMOND: Well, what it comes down to is, the control is zero, the low dose is zero, and the high dose is 4. And actually, that does come up with a sample size they used in a trend test. It does give you a trend. And I believe the high dose is even marginally increased above background because of the control frequency being zero.

DR. FROINES: Are there further questions? The lead on this is David Eastmond, so why don't we turn it over to him.

DR. EASTMOND: Can I ask one more question.

DR. FROINES: Sure. Why don't you just go ahead, then.

DR. EASTMOND: Well, I've started talking.

Can you hear me okay? Speaking like this, I prefer not to lean over, if I can help it.

This is, as indicated by Tom -- I appreciate your presentation and document that you provided as well.

In some respects, this is a compound in which we have a lot of data. A lot of studies have been done. Not only do we have *in vivo* carcinogenesis bioassay data, we have genotox data, we have metabolism work, we have DNA adducts, and we have structure-activity relationship data. So on one hand, it's a very nice package. There are a few challenges in these studies, and I thought I'd highlight a couple of these.

These studies were done, reported in three separate articles, primarily on estragole itself. And these were studies conducted by one research group, a very well respected group, Miller and Miller out of University of Wisconsin. And their focus was to investigate the mechanism of carcinogenesis. And it was not set up as a standard testing sort of experiment.

And so they were trying to use procedures which would give them a very rapid turnaround. And so they were using injections, either intraperitoneal or subcutaneously into newborn mice. And while that is used by a number of different investigators, it's not the common sort of approach. And In some cases, they were injecting these mice as early as one day of age, which in some ways is a challenge --

DR. FROINES: I would imagine.

DR. EASTMOND: -- technically. But what is striking about this -- the other aspect about this study is the doses were fairly high.

Tom, do you have any feel, like in terms of -- on how the doses relate to toxic effects seen in short-term sorts of bioassays?

DR. MCDONALD: Well, the doses, if you want to think of them in terms of milligram per kilogram body weight; in the adult female CD-1 bioassay by the diet, those are equivalent to approximately 300 and 600 milligrams per kilogram per day, although there's some loss due to volatilization, so

that those numbers are a little bit high.

The gavage studies for the 10 gavage doses are 371 milligrams per kilogram per day, although the i.p. injection is hard to -- it's hard to estimate exactly what was given in those, because the animal weights were not recorded. But they did report in a metabolism study the weight of a 21-day-old mouse as 16 grams.

So if we use that as the basis, we can calculate. For example, on the day twenty-second, the last dose, they're on the order of say, in one case, about 47 milligrams per kilogram or 30 milligrams per kilogram. And in that one single dose, in other words, the single-dose study, that was 111 milligrams per kilogram body weight.

So, and the subcutaneous injection on the fourth dose, that's approximately 26 milligrams. So those are much lower doses given by i.p. and subcutaneous versus the oral.

DR. EASTMOND: Do you have any information on what sort of acute toxic effects -- where you start seeing acute

toxicity with this?

DR. MCDONALD: No. I can only point you to what they observed for -- well, they did report in the *Miller et al, 1983*, that in the newborn mouse studies, they did make a statement. That is, "In the case of the mice that were treated prior to weaning, the tumors developed in livers that were otherwise normal". And that's about all we have to go on.

If we look at the methyleugenol NTP bioassay, they used doses of zero, thirty-seven, seventy-five, and a hundred and fifty milligrams per kilogram per day, and they didn't see really morbid animals until about a thousand milligrams per kilogram.

DR. EASTMOND: Well, I look at this from simply, what do we see in an acute LD-50. And those values tend to be about 1,100 to 1,200 in both mice and rats. And IPC's were very similar in oral exposure. So, in this case, the bioassays are being conducted at levels which range from probably one-third of the LD-50 down to maybe one-tenth of LD-50. So fairly high doses. We don't know what the

slope is on that line, but relatively high doses.

And another thing to keep in mind, the B6C3F1 mice has a much higher background incidence of liver tumors. But never -- certainly reviewing the NTP data, you never see these sorts of frequencies approaching 95 percent in one case. And certainly, within this short period of time, most of these studies were conducted within 10 to 12 months. So in many respects, it's compelling that there's tumors seen.

The study that I think is the most consistent of the traditional sort of bioassay is the one study which is a dietary study conducted in female CD-1 mice. And in that case, there was a strong increase that was seen.

This was administered for, I believe, 10 to 12 months -- a 12-month study. And they started when the animals were 8 weeks of age. So it's unusual. And in this one, there was a clear and significant dose-related increase in hepatocellullar tumors and this apparent, marginal, you might call, increase in

angiosarcomas.

The reason I point this out is, the primary metabolite, which is considered to be on a pathway to exert genotoxic effects gives a much higher frequency of these angiosarcomas, as did the structural analogs for safrole. So it's consistent with it having a different sort of, a second tumor site in this particular study.

Just to go on briefly, there were a lot of studies on metabolites conducted. Generally, the 1-prime hydroxylated estragole is quite consistent and reactive and more active than the parent compound, and seems to feed into the mechanism that Tom alluded to.

There's also been -- the genotoxicity data, in my opinion is more mixed largely -- the *in vitro* studies for certain bacteria are largely negative, with the exception of one where they added in the PAPS cofactor. That's in some ways to be expected, because you have a multiple step stage of metabolic activation, and it's not likely that all these steps would be existing in the particular cell line.

When you use cell lengths which would be

more competent such as liver cells, it was seen in numerous kinds of unscheduled DNA synthesis that would indicate DNA damage. There are DNA adducts which have been observed in these mice that have been characterized in a series of these adducts. In addition, there are really some striking similarities between the effects seen with this compound and safrole, which is structurally very similar to methyleugenol.

So my evaluation of looking over the data, kind of summary overview is, I think I would lean -- again, this is one that has some judgement required -- the consistent increase of hepatocellular carcinomas up to very high frequencies seen, which are much higher than seen in historical controls, with the addition of the genotoxicity information and the mechanistic structure-activity relationship really has me lean towards giving a clear --

DR. FROINES: Jim?

DR. FELTON: Dave, in the newborn mouse studies, it looks like the female was resistant to the tumors. Is there an explanation for this? And why, when they did

the feeding studies starting at, you said, 8 weeks, it looked like the female was positive. But as a newborn, it looks like it's pretty consistent.

DR. EASTMOND: I'm not aware of any explanation. That was something unusual in the first study. It was reported in *Miller et al, 1983*. There was no effect seen in the female mice. However, I think they followed-up in the Geizer study because of that. But I don't know why.

DR. FROINES: The sacrifices in the female newborns are at (inaudible) 14 months.

DR. EASTMOND: One of the arguments is that they didn't save them all.

DR. FROINES: Right. We have two studies at 14 months in the CD-1 mice.

DR. EASTMOND: Joe?

DR. LANDOLPH: I was very impressed looking at the structures which were lined up so nicely in this document between estragole and safrole in a hydroxylation at that one prime position. And then a sulfation of that and the release of that would generate carbonium ion, which could be resonant

stabilized, both by the benzene ring and the allylic double bonds. So those compounds look like they would be metabolized very similarly.

And the fact that the estragole is metabolized in the rat and the mouse and the human to 1-prime hydroxyestragole, that condition further convinces me that there's a chemical similarity between these two compounds in terms of carbonium ion generation and adduct formation.

So that, with all the other data that was listed, pushes me further in a direction of listing, particularly because safrole is listed already. And these compounds are so similar.

DR. FROINES: I think you'd like for me to make a comment about that.

You have an epoxy group in a para-position as well, which is going to donate electrons to further stabilize that carbonium ion. So that I think you're point is well taken.

DR. SPANGLER: I think that this is all real interesting science, but I'll have to dissent again, and say that, you know, there's

a massive amount of data here, and I think it's all really interesting. But for me to say that this compound has been clearly shown to cause cancer when it is only causing tumors or an increase of common tumors in one species, and in some cases, one sex, I think this just does not rise to the occasion to be classified as to be clearly shown. I can't in good conscience go and say this compound has been clearly shown to cause cancer.

I'm thinking not in mice, I mean this compound has been clearly shown to cause cancer in mice, but we're here to try to, to try to make some judgement about whether this is going to be reasonably expected to cause cancer in people. Because this is what it's all about.

This compound has caused tumors in mice only. It was given to rats. And there weren't as many studies. You wouldn't imagine there would be as many studies. It doesn't take but one or two negative studies and people are saying, "We're not going to spend our money shooting this stuff into rats, because it doesn't cause cancer".

The sensitivity of these assays have just been increased out of proportion to anything that we're used to dealing with. And if we accept these kinds of assays as evidence that this material causes cancer, is apt to cause cancer in people, then I think we've re-defined the interpretation of bioassays, here. So I just can't in good conscience say that I think that there's sufficient evidence to say that this has been clearly shown to cause cancer in the context of what we're here to do.

DR. EASTMOND: It's my knowledge that estragole itself has not been tested in rats. Some of the metabolites were tested, but estragole itself has been tested.

DR. FROINES: And the findings --

DR. EASTMOND: But the metabolites were negative. And no increase was seen, using the same *Miller et al*, 1983 data. There were no significant increases in tumors seen during the period that followed that.

DR. FROINES: Does the panel have further comments?

DR. FELTON: I'd just like to reiterate

what Joe said. The structure activity stuff here is about as strong as it gets. I mean, it's going through the same metabolic steps forming the adducts. And the safrole we've already been convinced is a carcinogen. There seems to be just such close similarities to this compound and everything about it, that it seems pretty hard to believe that this isn't going to give you the same results as the safrole, although as we know, safrole, if I remember, is positive in rat tumor study. The question is why isn't this one. I don't know the answer.

But from all the mechanistic data and the structure activity data, it looks like it's the same basic pathways and the same result in that you get DNA adducts.

DR. FROINES: Joe?

DR. LANDOLPH: It is a problem. I agree with Bill to a certain extent. This data wasn't set up, as Dave pointed out, through bioassays. It was a mechanistic study by Jim Miller's group on an NIH grant, which I'm sure were funds limited, and they were under pressure to get results.

I was a little bit bothered that a lot of the studies were i.p. injection. I agree that that is not the best way to test the stuff. I did notice in that Table 2 that that was a feeding study. And it was pretty positive, up to 56 percent of the mice, and 71 percent of mice get hepatocellular carcinomas. That's the age-old controversy about that endpoint being all too frequent in mice. But I guess that's what you're going to -- you just have to try and integrate that data and make a decision as best you can.

I certainly see a lot of positives here. So I don't see zeros in tables. So that's adding to the weight of evidence, in my opinion, with the qualifications Bill mentioned.

DR. FROINES: I think there's some comments.

Jay Murray.

DR. MURRAY: Thank you. I'm Jay Murray. I'm here on behalf of the Flavor and Extract Manufacturer's Association, or FEMA, which is the U.S. Trade Association of the flavor industry.

Most of you have weighed in on this substance already. So I hope you keep an open mind as you listen to what I have to say on this. You should have also received written comments from me earlier on this subject. And I'm going to try not to repeat things that you've already heard. I think Dr. McDonald did a fine job of describing the data to you.

He did describe estragole's uses. It is a flavoring substance that occurs naturally in foods and spices. There are a few that he left out, so I'll read my list: Anise, basil, fennel, licorice, nutmeg, oregano, rosemary, sage, and tarragon. Sounds like an old Simon and Garfunkel song.

Estragole is not an unwanted contaminant in these foods. Estragole is what gives a number of these spices their characteristic taste. So, you know, probably chemically, there's a way to remove estragole from basil, but it isn't going to taste like basil anymore.

People all over the world consume large quantities of estragole in foods and spices with no known or suspected carcinogenic

effect. Many Italian foods contain relatively high amounts of estragole; for example, pesto, which is ground-up basil, pizza, which is seasoned with a number of spices like oregano, which contain estragole.

Interestingly, 99 percent of human exposure to estragole is exempt under Proposition 65 because it is naturally occurring in a food. It's only 1 percent of human exposure to estragole which is attributed to its use as a direct flavor ingredient which is not exempt under Proposition 65.

You already have discussed the animal evidence. You know it's limited to an increase in tumors in one species, the mouse, in studies from one laboratory. You've already commented on the fact that all of the studies come from a single laboratory. It's McArdle. The work was done by the Millers, well respected. But your proposed criteria also underscores the importance of having data in studies from more than one laboratory.

More importantly, and certainly, you've already mentioned this, these studies were of

an unconventional design, and I would contend don't represent scientifically valid testing, which is part of your criteria in determining whether you recommend this for listing.

I have detailed a lot of the problems with these studies in my written submission. I'm not going to go back through all that. Some of them, a number of you have already mentioned here -- let me just highlight a few just by touching on them:

Massive doses by intraperitoneal or subcutaneous injection, no attempt to define a MTD, in many of these studies, only a single dose level used.

There was an apparent tolerability problem, which caused them to have to re-up the dose as they were doing it. Someone mentioned the dosing at post-natal day one, intraperitoneally. If you've ever tried to dose a one-day-old mouse intraperitoneally, it's not easy. And regulatory agencies do not recommend that kind of design. For early studies, they'll recommend starting dosing in weanlings, which is usually around day 21.

No reporting of standardized survival

rates, no historical controls, no consistent classification of tumor types: For example, in one of the studies, it's unclear whether these were benign or malignant tumors. They were described as hepatomas types A and B. The only clear statement about the basis for classification of hepatomas in that study is that they must be at least two millimeters in diameter.

There are many more weaknesses in these studies that lead me to consider that it's not scientifically valid testing.

One piece of information which Dr. McDonald did not include, which I think is important for you to know -- and I apologize, Tom, if you covered it and I missed it -- NTP is planning to do a bioassay on estragole. Because of the limitations in the existing studies, NTP recently decided to conduct a state-of-the-art carcinogenicity study on this compound. And according to NTP's Management Status Report, which you can read on their web site, it is currently in a group of chemicals designated as chemicals with project leader assigned study in design.

So the study hasn't started. I was told by a top-level scientist at NTP that the existing studies are considered inadequate for any regulatory agency to take action. It's my understanding that NTP believes the dose levels were too high in the old Miller studies. And that's one of the reasons why they want to do a bioassay.

Also, prior to conducting a bioassay, NTP plans to conduct a 90-day study to select proper dose levels for the bioassay. So the thing you need to ask yourselves is, if estragole has been clearly shown to cause cancer or if it has been adequately tested by current standards, does it make sense that NTP would be putting this on the list of substances to perform a bioassay?

And I agree with something that Dr. Froines said earlier. He talked about the low-hanging fruit. And you're going to see fewer and fewer studies coming on these agendas where you have an NTP study. This is one of the exceptions. This is one where you are going to have an NTP study.

I would encourage you to think about

waiting for that NTP study. Another question that Dr. Felton asked was had other scientific or regulatory agencies weighed in on this. No scientific or regulatory agencies ever classified this compound as a carcinogen. It has not been classified by IARC, EPA, NTP, NIOSH. FDA has it on its GRAS list of food additives.

So if you were to determine that estragole is clearly shown to cause cancer, this would be the first time that estragole was classified and regulated as a carcinogen, to the best of my knowledge, anywhere in the world.

So my conclusion is that I recommend you postpone consideration of estragole until the results of the NTP bioassay are available so that you can consider them. You know you will have scientifically valid testing when NTP gets done with this thing.

The current evidence is limited to studies in one species, one lab. It's not scientifically valid testing by today's standards. You know that the public health consequences of not listing it would be

insignificant because 99 percent of human exposure is exempt anyway, because it's naturally occurring in foods. So the public health consequences of waiting until a scientifically valid test is available from NTP are virtually nil.

So unless you're certain that estragole has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer, you should wait. And you should wait for the NTP study.

Thank you.

DR. LANDOLPH: You know, Jay, I read your report. It's a very nice summation. It struck me very interesting, because I think, you know, this opens the flood gates. This obviously -- I think this compound is probably an example of plant/animal warfare. It's a biocide that plants manufacture, most likely that's not even really substantiated. I bet there's a lot more out there. So we should give some thought to this one as well.

But I'm struck by how similar this is to safrole, which is a strong carcinogen and has been listed.

DR. FELTON: You know, this is an interesting -- I mean, Dr. Miller is the grandfather of all chemical carcinogenisists in the world. If you look at the people doing the work, they all turn to this man.

On the other hand, though, I have to agree that these studies were not done as standard carcinogen testing protocol. These were done to look at mechanisms of the action of these chemicals, as was said. And the evidence -- since this is a dietary carcinogen, you want to see good dietary studies.

And newborn mouse experiments are really great when you're compound limited and you've just synthesized it in your lab, and you don't want to waste it, etc.

So the amount of evidence here in the mouse is not that much. If you really look, it's just the feeding study. Unless it's done under standard protocol, and it -- this is a tough call. But, you know, Dr. Miller's lab is as good as they get, back when he did these experiments. But, as we said, it's not done as a standard cancer assay.

DR. FROINES: The irony, however, of course, is that the studies we do now are 52 weeks, at least. And we would be very critical if somebody walked in here and said, "We've just done a study and sacrificed the animals at 14 months and found negative results". We would end up saying the negative results may have occurred because of the short-term sacrifice.

So we may look at this data and say it's limited. It's hard to say that the Millers did anything that was limited. But I think it's a good point. And I think that the -- we should also ask ourselves, how do we consider the findings we have here in terms of the other data that we're comparing it to; for example, the DNA adducts and the genotoxicity and the structure activity.

I think that the important thing that we have to get ourselves into is looking at the whole picture, not pieces of the picture. I think we have to be careful not to get put in little boxes and little cubby holes. And we have to look at this compound and all the compounds in terms of the totality of the data

that we can draw a decision from.

Dave?

DR. EASTMOND: I thought that Jay had some very good points. I mean, as I reviewed through this, you know, you have to deal with this and say what is a valid sort of study? Do you consider this adequate?

My focus came down to saying that eight weeks -- this dietary study in the female mice was the one that seemed to be the most standard. And the others were kind of add-on evidence on that. And that's really what I have focused on.

But he's correct when you look and say these are quite high doses. We don't know exactly how high, because there wasn't information prepared. But it does appear that they're well within, you know, certainly within an order of magnitude, or probably much closer to that of the LD-50 values.

So you're pushing acute toxicity and saying this is a chronic study. The wording is somewhat difficult to figure out exactly how many animals were actually started and, you know, how many survived to 10 months or 12

months.

But when I looked at it and thought -- if you put this context -- what I'm saying -- here is a situation where you have, certainly, dose-related increases in one tumor type, possibly a second. You have all these other studies which are supportive. You have structure-activity relationship information from very similar compounds. You have DNA adduct information. You certainly get the whole picture, for me, that this, you know, shifted the weight in one direction for me.

That's not to say there is some -- I mean, I do look forward to hearing more about the NTP bioassay that goes forward. Apparently it is moving forward. One difficulty we'll face is the NTP is under increasing pressure to cut costs and reducing chemicals and trying to move to transgenic animal bioassays. And they will be a real challenge for this committee, as much as any of these older studies as well.

DR. FROINES: Going back to the Staff, Dave, the argument about high doses -- the disadvantage of growing older is that you

begin to hear the same arguments every time you hear about a chemical. And the high dose argument is one we have all heard with every chemical from the time we started in this field.

So, sometimes it's valid, and sometimes it's not. And we all have to try and make judgements about the high-dose argument. And so my question is, what do we know about survivability at those high doses? What do we know about toxicity at those doses? What is the actual evidence beyond the ideological point about the high-dose issues?

I'm asking the State, Jim.

DR. MCDONALD: Yeah. The evidence that we do have -- let's focus on the dietary study at 10 months. Excuse me. It goes for 12 months. But they reported evidence of survival to 10 months.

In the low dose and high-dose groups it was 98 and 96 percent of the animals were still alive at 10 months, almost completing the entire dosing cycle. That's one line of evidence that the MTD may not have been exceeded.

On the other hand, we have body weight information that the body weights were reduced in these doses.

DR. FROINES: Do you happen to know what percentage?

DR. MCDONALD: From memory, I think it's about 50 percent reduction at the 10-month timeframe.

DR. FROINES: 50 percent reduction? I don't think so. They would sacrifice animals if that was the case.

DR. FELTON: I don't remember for sure, but I think 20 to 30.

DR. MCDONALD: 20 to 30 percent?

DR. FROINES: At UCLA, if we have a 20 percent drop in rate, we euthanize the animals. We don't get to go below 20 percent. In a mouse that's 50 grams, that's -- 20 percent of 50 grams is a pretty significant reduction. So that I think this is a point that needs -- it would be better if we had better data on it.

Jim, you think it was 20 to 30?

DR. FELTON: Yeah. But I'm not positive.

DR. FROINES: We'll hold you to it.

Joe?

DR. LANDOLPH: Yeah. I was looking at Table 2, and one thing listed was those feeding studies. And the question I was interested in was, how potent is estragole compared to safrole? And there's no dose response group here. I wish there was.

DR. FROINES: What table are you on?

DR. LANDOLPH: It's called Table 2 on page 7. And the two doses of estragole that are tested are very close to the doses of safrole that are tested. And you're getting between 56 and 71 percent tumors for estragole and 72 and 80 percent tumors for safrole. So they're comparable. And we know safrole is a pretty strong carcinogen.

And then the other thing is that 1-hydroxyestragole, which is the hydroxylated form, is also giving about 56 percent tumors. So A, those are strong responses, and B, the safrole and the estragole are comparable. But it's only one point. We don't have a dose response. That's the way it is.

And the other one called Table 1 on page 6, if you look in the males for estragole and

safrole, you're getting similar numbers in tumors; 36 for estragole and 30 for safrole in males, and 4 for estragole and 6 for safrole in the females. So that's both sexes. And you're getting comparable numbers. So it's certainly not weak compared to safrole. It says it comparable, approximately.

DR. MCDONALD: Just to clarify; it's not total weight. It's 50 percent reduction in 8 months in weight gain. So I don't have the absolute weights of the animals. And at 4 months, it was a slight difference. At 8 months, it's about a 50 percent difference in weight gain.

DR. SANDY: The controls gained 8.1 grams per mouse at 8 months. And the highest dose?

DR. MCDONALD: The controls at 8 months gained 8.1 grams versus the high-dose estragole gained 8.3 grams at 8 months. So that's the data that we have.

DR. FROINES: So there was some sign of toxicity.

DR. EASTMOND: Also, there's evidence of toxicity. It talks about it in the pathology. It talks about the chronic damage in the

livers. You are seeing liver toxicity in addition to the cancers. That's not particularly surprising. It's mentioned in the pathology description. If you want to make it -- histologically, these livers combine for safrole, 1-prime hydroxyestragole and estragole show various degrees of chronic inflammation, total fibrosis, bile duct proliferation, various (inaudible).

DR. MCDONALD: Just to add to that, in the methyleugenol NTP bioassay, in all those, they had similar observations in the livers of those mice.

DR. FROINES: Do we know what happened to with safrole?

DR. EASTMOND: (Inaudible.)

DR. FROINES: So that they're seeing liver toxicity in safrole as well.

Does anybody want to make a motion? Well, shall we vote, then? I don't think we need a motion every time we take a vote.

DR. LANDOLPH: The primary reviewer is not going to make a motion?

DR. EASTMOND: Give me just a second.

I move that we list estragole as a

Proposition 65 chemical showing clear evidence of cancer.

DR. FROINES: I'm going to follow the language that's been developed that comes out of the statute.

Please indicate by a show of hands if in your opinion estragole has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

The record will reflect there were -- Oh. I'm going too fast. How many of you raise your hands? 5.

Please indicate by a show of hands if in your opinion estragole has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

One.

How many abstentions? One?

So the vote is 5, 1, 1. 5 In favor, 1 against, 1 abstention.

And let's take a 10-minute break so we can integrate Tom into this process now that I've done all the hard work.

(Whereupon a ten-minute break was taken.)

DR. MACK: All right. Let's go on to the next compound on the list, trichloroacetic acid.

Dr. Landolph? Where did he go?

DR. LANDOLPH: Over here, on your left.

DR. MACK: There he is.

Andy, are you ready?

DR. SALMON: Okay. Well this is the presentation on Trichloroacetic Acid. It's structure is shown on the first slide, here. If I could have the next slide, please.

The -- is that better? Thank you.

Trichloroacetic Acid has uses as a synthetic intermediate in the chemical industry, and also minor uses, in quantitative terms, as a medication and a reagent. There was a former use as a selective herbicide; however, this is apparently no longer the case. The most recent registration was cancelled in 1992. However, there is another important source of public exposure to trichloroacetic acid. It's one of the major by-products of water chlorination for

disinfection purposes.

If I could have the next slide, please.

Concentrations of trichloroacetic acid in drinking water have ranged -- quite a considerable range -- in one study, 4 to 103 micrograms per liter. It's formed with various other products, including other chloroacetic acids and halomethanes by reaction of chlorine or hypochloride with organic substances in water.

In addition to disinfected drinking water, it's also found in other situations -- and one, which obviously results in quite an important public exposure -- is the use of chlorine for disinfection of swimming pools.

All right. Can I have the next slide, please.

The carcinogenicity data that we have to consider -- there are no data for exposure of humans. We could find no epidemiological studies or case reports. However, there are a number of bioassays which are being described. Trichloroacetic acid appears to be a hepatocarcinogen in the mouse and --

If I could have -- Could you put this

slide aside and go to the next one please.

This is a summary of the studies that we have to consider. I will point out that some of these studies were in fact designed not as simple classic bioassays, but rather as studies designed to look at tumor promotion effects as well as the tumor induction effects.

This has resulted in some of their study designs being somewhat different and reporting also being somewhat different that what you expect for a standard bioassay. So I'm going to concentrate on describing the tumor induction effects. Also, I do have all the details of the actual individual study results here. But in order to save your time, and obviously, those results appear in the report, I'm just going to talk to this summary for this presentation.

We have a group of studies in the B6C3F1 mouse. And in general, these have found a dose-dependent induction of hepatocellular adenoma and carcinoma. This has been observed in both male and female mice, and by several different groups of investigators.

There's also one study in the Fisher rat in which no increases in tumor incidence were observed. I don't know whether the panel members want to discuss individual studies at this point, or shall I proceed with this and you can call for the details later?

Okay.

(Panel motioning Dr. Salmon continue.)

Could you go to slide No. 12, please, Martha.

This is a brief summary of the findings in tumor initiation promotion. The studies include several which were described previously for the tumor induction side of things. But basically, the observation is again, in both male and female mice, there is induction of either hepatocellular tumors or in the case of some of these studies, they were actually looking at foci of altered hepatocytes, particularly ones which are distinguished either by eosinophilic or basophilic staining, or by induction of histochemical markers such as the gamma glutamyl trans peptidase.

The other observation which we have here

is the study in rats. These were the male Sprague-Dawley rats. There was, actually, a positive finding promotion of the gamma GT positive liver foci.

All right. Could I have the next slide, please.

To summarize, we have multiple, independent studies in a single strain, which is the B6C3F1 mouse, and the finding is of liver adenoma and carcinoma. Basically, all the studies were positive. There's one marginal result in the female mouse. But the study authors actually think that the reason that they didn't see a significant increase was because they terminated the study early.

And so the observation is in both sexes. On the other hand, in rats, there is a single study in which no carcinogenic effect was observed.

If I can have the next slide.

The genotoxicity, in fact, most of the results which are being reported, are essentially negative. We have negative on bacterial mutagenicity in particular. A couple of positive reports on mammalian cells

in vitro. One of these was a very weak response, according to the authors.

And there is some question as to whether some of the effects which are being observed in this test system were actually an effect of the pH, because they added buffered trichloroacetic acid to the cells in one experiment. And obviously, this is a highly acidic compound. The effect went away when the TCA was buffered back to neutrality.

There are some positive reports in mammals *in vivo*, primarily chromosomal effects. However, some of these are rather inconsistent and/or appearing at high dose only.

May I have the next slide, please.

Considering the genotoxicity, in particular, effects on oncogenes and DNA, there are some indications of DNA strand break induction. And several experiments describe this effect. And it does appear that mice are more sensitive than rats to this effect.

There was one report of some oxidative DNA damage occurring, although a subsequent follow-up investigation of this failed to find

the effect. So this is an inconsistent finding. Several investigators have looked at the effect on proto-oncogenes, and oncoproteins. There appear to be consistent changes which are characteristic of tumors induced by trichloroacetic acid. And one in particular finding of interest is that dichloroacetic acid, which is also a mouse hepatocarcinogen, appears to produce a different spectrum of proto-oncogene modifications from that seen with TCA.

Studies of DNA synthesis have also shown an increase in DNA synthesis.

DR. FROINES: Could you say more about that? (Inaudible.)

DR. SALMON: Okay. I'll refer to the written report, the full report here. The one study, *Ferreira-Gonzalez and colleagues*, evaluated RAS mutations. And they compared spontaneous hepatocellular tumors and TCA and DCA-treated mice. And they were looking at codon 61 RAS gene mutations. And they occurred similarly in the spontaneous tumors and in the TCA-induced tumors -- or, the DCA-induced tumors. The mutational spectrum

was similar. The actual mutations at this codon were similar for spontaneous tumors and TCA-induced tumors, but it was different for DCA-induced tumors.

There was also a study of mutations in the c-jun and c-fos oncoproteins. This was actually using an immunochemical assay. And in this case, the DCA-induced liver tumors were immuno-reactive to anti-c-jun and anti-c-fos antibodies. However, the TCA-induced tumors did not show immuno-reactivity to either of those antibodies. And then, there was also a study of TCA-promoted tumors. The initiator here was N-methyl-N-nitrosourea.

DR. FROINES: Why don't you go ahead.

DR. SALMON: Okay. Yeah. If you want more details, it's in the big script.

So, perhaps I could have the next slide.

For structure activity comparisons, I've mentioned now, at perhaps more length than I initially expected, the fact that dichloroacetic acid is also a liver tumor-inducing agent in mice. An experiment with monochloroacetic acid was not positive.

However, the authors did comment that because of the severe toxicity of this compound, it's possible that this experiment, at least the mouse experiment, wasn't necessarily an adequate test of the possible carcinogenic effect of that acid.

Another point which is of interest, perhaps worth noting, is that trichlorethylene and perchlorethylene are both metabolized to various compounds, including trichloroacetic acid. They are both identified as carcinogens for the purposes of Proposition 65. And the tumors which those compounds induce include, although not necessarily are restricted to, the hepatocellular adenomas and carcinomas, which are discussed in the case of TCA.

If I can have the next slide.

One of the very considerable issues for discussion with this compound has been the mechanism by which the observed tumorogenic response in mice is produced. Obviously, one question is, is this a genotoxic or DNA reactive type of mechanism?

And the experimental data for this proposal include the observation of some

clastogenic effects in the mammals *in vivo*, and also the observations of DNA strand breakage. And if you believe the oxidative damage finding, then that would be in this category too.

Against this proposal, most of the genotoxicity results, including the sorts of classical studies, which are easier to interpret, are negative. And the few positive findings, by and large, are somewhat equivocal or inconsistent. There's no reason, looking at the chemistry of trichloroacetic acid, to think that it would be intrinsically reactive to DNA, nor is there any evidence of metabolism to a reactive intermediate. So I think the consensus in the scientific literature appears to be that whatever the mechanism is, it probably does not involve direct reactivity to DNA.

If I could I have the next slide, please.

So considering the options for a so-called non-genotoxic mechanism, I have to put that in inverted commas, because of course, we've already discussed the fact that there are genetic changes in tumors induced by

TCA. But nonetheless, this is the popular terminology for a mechanism which doesn't involve a direct modification of DNA by the compound or its metabolites.

Peroxisome proliferation has been observed in rodents exposed to TCA and DCA. It's considerably more marked in mice than in rats. On the other hand, even in mice, the effect observed has not been a large one, even in comparison -- well, particularly in comparison, with the things clofibrate and wyeth, whatever the number is, the classic hyperlipidemic drugs, which are well known as rodent carcinogens and peroxisome proliferation inducers.

Although, clearly, you know, this is a phenomenon which is observed, I think there are some significant questions as to how significant it is as explanation of the observation of tumor induction. In particular, we are seeing peroxisome proliferation, but the tumorogenic effects are different between DCA and TCA. So obviously, there is some other factor involved besides this process, which is resulting in

substantially different effects at the oncogene level.

Also, the reports of DNA oxidative damage, which would be one mechanism which implicates the peroxisome proliferation process, are in fact not substantiated. I think the conclusion here is that clearly, peroxisome proliferation does occur, but that its actual role in TCA carcinogenesis is not established. And whether that's a contributory role or a primary role is simply unknown. But it doesn't look as if it's by any means the only process that needs to occur in order to produce the observed result.

If I can see the next slide, please.

Further proposed mechanisms typically have involved the observation of enhanced cell proliferation. It's been suggested that this may be simply a result of cytotoxicity, whereas there is cytotoxicity in the liver observed particularly in the highest doses used in the bioassays.

And there is observation of enhanced cell proliferation. The extent of that enhancement of proliferation is probably not sufficient

alone to explain the tumor formation as a result of amplification of background mutation rates. And I think there's also a material question as to whether this is a cause or an effect, if we're discussing the causation of the tumorogenic response.

So if that proliferation enhancement isn't a primary explanation, then we're basically left with consideration of some other growth regulatory effect on the hepatocytes. This may be a good explanation, except there really isn't enough detail to evaluate any specific proposals in this area. We simply don't know what's going on. So I think our overall conclusion has to be that there's insufficient information to determine and characterize the mechanism of action.

If I can have the summary slide, here.

So to summarize, there is animal evidence for carcinogenicity, positive in both sexes, one strain of the mouse, multiple experiments; also tumor promotion in both rat and mouse livers, although negative in one study in the rat. So in isolation, the usual criteria that we recommend, this would be considered

sufficient evidence of carcinogenicity in animals.

However, the other issues for you to consider are the weak evidence for genetic toxicity, much of it being negative or equivocal, and the mechanistic arguments which have being raised against the human relevance of the finding, although there is no clear proof of mechanism. And also, I think, you know, the question which we would be looking to the Committee for direction on is whether this is something that we would be considering at the dose response assessment stage rather than during the identification phase.

And this is the end of what I have to say.

DR. MACK: Thanks, Andy.

You want to go ahead, Joe?

DR. LANDOLPH: Yes, please. Could I start by asking Andy a couple of questions?

DR. MACK: Yeah, please.

DR. LANDOLPH: In each of the experiments, did you look for a dose response, and what were your conclusions on those?

DR. SALMON: Well, the experiments --

most of the larger experiments -- did include several dose levels. And yes, there is an apparent dose response. It's not one of those things where you have 3 or 4 dose levels, and nothing happens, and then it's just the high dose. That is not the observation.

I don't know whether you want the slide up, but we could, for the sake of argument, look at the slide No. 8.

DR. LANDOLPH: It would be good to see it.

DR. SALMON: If you could just put that up -- this is the DeAngelo and Daniel -- I'm afraid the report here, which is extracted from an internal U.S. EPA report, isn't actually quite as detailed as you might have hoped to see. But they reported percentage increases in tumors. And what I'd like to draw your attention to is in the Experiment 1.

We have, in fact, controls in three dose levels of TCA in drinking water. And the control incidence for these male mice was 13 percent, which is not particularly unusual for this strain of mouse. There wasn't a significant increase at the lowest dose of

TCA. But at .5, we were seeing a 40 percent incidence of the tumors. And at the top dose, 5 grams per liter in drinking water, we were seeing 55 percent incidence. So these are substantial in dose-related increases.

And the various other experiments are somewhat, you know, where they presented an experimental design that would address that question, they found somewhat similar findings.

This is probably -- the work by DeAngelo and Daniel is probably the most comprehensive study from the point of view of a bioassay-type design as opposed to being an initiation promotion study, which happened also to report tumor induction.

DR. LANDOLPH: And a question about this data. Certainly the 5 grams of TCA is a high dose for TCA.

DR. SALMON: It's a substantial dose, yes.

DR. LANDOLPH: And the question was, was there any overt toxicity, liver toxicity?

DR. SALMON: At the highest dose, yes. There is histopathological evidence of damage

in the liver at that highest dose. But it's obviously reduced or minimal at the lower doses.

DR. LANDOLPH: And at the next highest dose, where you also have a significant increase, was there frank toxicity there as well?

DR. SALMON: I believe there was some. I'm just -- I think it was -- I think it was less noticeable, certainly. Allow me to -- I was looking to see whether I'd included that in the summary. But my recollection from reading the report is that basically, by the time you get down to the .5 dose, I won't say that there's no toxic effects, but the frank toxicity and the necrosis, which you were observing at the highest dose is not observable to the same extent.

DR. LANDOLPH: And in the other -- Geez, there's approximately 8 studies here. In the other 7 studies, were there dose responses in those?

DR. SALMON: In the cases where they included multiple treatment dose levels, yes.

DR. LANDOLPH: There was a dose response?

DR. SALMON: Yes. Yes.

DR. LANDOLPH: And then the other question was, Bernie Daniel is an EPA investigator. Has the EPA taken an official position on TCA, the U.S. EPA?

DR. SALMON: I don't think that they have actually come out with any pronouncements very recently. The group of studies by Dr. Daniel and his colleagues, this was work which they initiated when they were up at the Cincinnati office. In fact, I think Dr. DeAngelo moved to North Carolina. And he's been the one who's continued the work.

I think that was initiated specifically by the EPA, because they wanted a further investigation of what was going on with a variety of chlorinated contaminants in drinking water about which they were concerned. But I don't think they've taken any particular classificatory or regulatory measures as a response to the appearance of these studies at this point.

DR. LANDOLPH: So this is an interesting one. I mean, I've read this report six times. I think it's extremely well written. I want

to congratulate Dr. Salmon and his colleagues on this. It's a comprehensive and concise summary of the data. It's very fairly analyzed.

There are about seven mouse studies done. They all show hepatocellular carcinoma. There's data in male mice. There's data in female mice. I agree the genotoxicity data is either equivocal or negative. So I agree with all your conclusions. I'm worried, because there's not real good mechanistic studies on this. So it doesn't allow us to enhance our confidence.

You know what I'd like to do on this one? I'd like to be a real chicken on it and request the Chairman or the State to have a discussion with the EPA officials, because I actually did an internal grant review there one time, and I know they're doing some of the most sophisticated work on mechanistic studies possible.

I think if they're not willing to stick their tail on the line, I think we should step back a bit and find out why that's the case before we plunge ahead. So I'm sorry that's a

chicken type of decision, but I think it's fair.

DR. MACK: It is a chicken kind of decision, and you're not going to get it done today. So I think you've got to decide what we're going to get done today.

DR. LANDOLPH: Can I make a motion to defer?

DR. MACK: Well, why don't we hear from the other people on the Committee before you do that. But you can certainly be thinking about what you might do.

John, do you have any ideas about this one?

Well, first let me ask Joe. What's your -- you didn't discuss mechanism. Did you agree completely with Andy's summary that basically, it's up for grabs, we really don't know what's going on?

DR. LANDOLPH: Yeah. I think we don't understand the mechanism. I think the 8 peroxisome studies are intriguing. They could also be non-specific, because of toxicity and oxidative stress generated by non-specific mechanisms. I don't feel comfortable about

this mechanism. It's an order of magnitude less than the mechanisms for estragole and safrole. I don't know what this stuff is doing.

DR. MACK: But we probably cannot say that it's a mechanism that's irrelevant to humans with any degree of certainty.

DR. LANDOLPH: Well, I think there was a very long and appropriate discussion that Dr. Salmon made. And there is some question as to whether peroxisomal proliferation is indeed mechanistically related to carcinogenesis or whether these are parallel processes and not necessarily linked in sequence.

So I think we have to back off from that and say we still don't really understand with strong certainty what that mechanism is. I don't think I know what it is. Anyone else that's more well versed should feel free to stand up and say so. But I don't think I know what it is. And I agree with Dr. Salmon's assessment. It's a nebulous area still.

DR. MACK: John, do you have any comments?

DR. FROINES: I just have one. This is a difficult one, I think. I think that we have to avoid sort of common things that become more than they are. I mean, we talk about proliferation, but there's a lot of debate about proliferation, and we need to think carefully when we use it as not just an excuse, but it really has scientific validity.

One of the interesting things that I asked Andy about was this issue of the fact that in the mutational spectra in the ras genes that the TCA and spontaneous tumor spectra were the same, which would indicate to me that the TCA isn't causing that mutational factor. And that would suggest that the tumors that were seen are not necessarily created. And so that ras gene work, I think is important.

I think the notion of looking -- we all treat short-term tests like we did in the 70s. You know, people talk about whether it's positive or negative in the Ames tests. We really need to move on to looking at mutational spectra in a molecularbiological context, because it's so much more

sophisticated and informative. And the traditional short-term tests, you know, represents another era.

I also think, though, just as a policy matter, in a sense, that I think Joe said it right. The weakness in the mechanistic information, you would like to use the mechanistic information to enhance your confidence in your finding. That's the role it plays, it seems to me.

I don't agree with the notion that we have to demonstrate human mechanistic relevance as a basis for decision. I strongly disagree with that. But mechanistic information, I think, is extremely important to help us understand more clearly what's going on. And so in that sense, the mechanistic data that we have is very limited, and therefore it's troubling in that respect.

DR. LANDOLPH: Yeah. I was really very conflicted, you know, about this one. In Table 1, there are 7 positive mouse studies. So I can't ignore those. They're positive. And Dr. Salmon discussed those in detail.

The rat study is negative. And the mode

of administration here is relevant to humans; it's drinking water. So there's a relevant mode of administration, and there's a replicability of studies for the mouse. But I have significant concerns as to why EPA hasn't listed this. They've studied it to death. Very qualified investigators have studied it. So there's something funny going on. And I need an answer to that question.

DR. MACK: There are a lot of funny things going on at EPA.

DR. LANDOLPH: I did not imply that pejoratively with regard to EPA, just that there's something missing in this logic tree for me to make a final decision.

DR. EASTMOND: I wanted to comment. It seems to me that the key studies that have been done at EPA have really never been published. I mean, two of them are published abstracts and toxicologists, and the other one's an internal document that has not been -- I assume it has not been released publicly. Do you have any explanation or understanding of why that is the case?

DR. SALMON: No, essentially. The rat

study, interestingly enough, was published as a full paper. It may have just been a sort of a historical accident, because, you know, the HERL people were moving from Cincinnati to North Carolina at the time. And they may have just had too many damn things on their plate to deal with it properly. I have absolutely no knowledge of why that would be.

DR. EASTMOND: My concerns on this is that this is in a strain of -- we're really looking at all the studies in one strain of mouse, which is prone to quite high background spontaneous frequencies of this particular type of tumor. And in fact, if you look at the summary results from, like, the National Toxicology Program, the frequencies seen in these controls are really low compared to what's normal in the animals.

In some cases, the positives are about where you -- the TCA-induced frequencies are about where you would expect -- are frequently control frequencies in many of these studies. So that is one concern I have.

This idea that we don't have a clear mechanism, and we don't have real obvious

genotoxicity information concerns me. Indeed, the mutational spectra data appears that what we may simply have is a compound which is promoting spontaneous tumors. And indeed, so rather than these tumors developing late in life, they're developing a little bit earlier, stimulated by this particular chemical. And it makes me uncomfortable.

I'm also uncomfortable that these things haven't been published in a more full respect. I mean, I think that the Staff has done a very good job of pulling information together. They had to take some heroic efforts because of --

DR. SALMON: I think the report from Daniel is available through NTIS, you know, if you know it's there. It's not that it's some dark secret. Well, need I say more?

DR. MACK: Jim?

DR. FELTON: Well, just to summarize what I think I'm hearing, you know, on the previous two, we had mechanistic data. We had gene tox data. We had some plausible mechanism, even though it was positive in one species and not in the rat. Here, we have all the data in one

species, one strain, one tissue type. And as Dave said, it's fairly common to see tumors in the -- hepatocellular carcinomas in the mouse.

So, you know, here's a case where we have the one species result, but we don't have much else to go on. And since all these seem to be on the edge, on the knife edge, at least I'm leaning to saying I think this one doesn't have the criteria to push it over. So, that's my feeling.

DR. MACK: Do you have anything, John?

DR. FROINES: No.

DR. MACK: Bill?

DR. SPANGLER: No, I don't have anything to add.

DR. MACK: Are there any -- is there any public comment on this compound?

DR. NORTH: (Distributing letter to the panel.) I have a few more copies, but probably not for everybody in the room.

My name is Warner North. I am here under the sponsorship of the Chlorine Chemical Council. And I might add, they asked me to do this a relatively short time ago. When I looked through the data, I had the same

reaction that many of you did.

There is no debate over the fact that TCA causes hepatocellular neoplasms in B6C3F1 mice. Clearly, it does. The issue is one of interpretation, particularly questions of mechanisms. I like the way you've put it in your discussion already. We need to understand these mechanisms, and in particular, we need to understand the relevance of the mouse response to human cancer.

The usual default assumption we use in assessing carcinogens is that if we have a reaction in a rodent that that applies to humans. The question is, do we know enough to depart from that default assumption.

The State has looked at the issues of peroxisome proliferation, and you've just heard their conclusion. I'd like to give you another conclusion from what I regard as a very authoritative source.

When I received this assignment, I thought, who is the person I know who knows the most about peroxisome proliferation from the point of view of hands-on lab work,

involvement in the EPA Science Advisory Board, I believe involvement as an EPA contractor in that they sponsor his studies or at least give him grants -- in fact I think I can say that for certain -- and furthermore, somebody who has been highly involved in the work groups of IARC, and in particular, the IARC working group on use of mechanistic data and cancer risk assessment in 1991, and from 1997 on, as a member of the IARC working group on the mechanisms of carcinogenesis that may be species specific.

So Dr. Swenberg was kind enough, also under the sponsorship of the Chlorine Chemistry Council, to prepare a short letter which I have just handed out to you. And I'd like to go through that rather briefly. I think in the interest of your busy schedule, I shouldn't try to read it all. But I will certainly try to address what I regard as highpoints, and I will do my best to answer any questions you might have on this material.

First, "TCA is a potent inducer of peroxisome proliferation in the mouse liver but a very weak inducer of this response in

the rat".

I'm reading from the bottom of page one on to page two.

"Evaluations of the weight of evidence of TCA's genotoxicity have repeatedly concluded that it is not genotoxic. The occasional positive result is totally compatible with the induction of oxidative stress by mechanisms that would not occur under conditions of human exposure. These data strongly support peroxisome proliferation as a key event in the induction of liver tumors to mice exposed to TCA."

And then there are several paragraphs about what is known about the mechanism. Much of this information is relatively new. And I'm not sure how much of it has worked its way into the resources or the literature that the State has reviewed in its evaluation.

Dr. Swenberg describes, "The peroxisome proliferators act by a common mechanism, activation of a Peroxisome Proliferator Activated Receptor (PPAR). These responses induced by exposure of rats and mice to peroxisome proliferators include both

biochemical and morphological changes in the liver." And I'll skip the details on what they are.

"The human studies include direct comparisons between human and rodent hepatocytes exposed to chemicals, drugs and their metabolites, as well as epidemiologic studies on human beings treated with hypolipidemic drugs.

Human hepatocytes do not exhibit the responses seen in the rodent hepatocytes when exposed to TCA *in vitro*. There was no increase in hepatic cancer or induction of this set of biochemical responses in humans taking pharmacologic doses of hypolipidemic drugs, even though plasma concentrations in humans were equal to those measured in rodents from the carcinogenicity bioassays. There is also no evidence that TCA causes peroxisome proliferation in humans.

Recent advances in molecular biology have provided the scientific community with a much greater understanding of the responses to peroxisome proliferators." Again, I'll skip the details and go on to his conclusion.

"Differences in expression of PPAR alpha," that's the specific receptor, "appear to be partially responsible for differences in responsiveness between rodents and humans. Although primates and humans have some of the same isoforms of this receptor, current evidence suggests that PPAR alpha is only present at 1-10 percent of that found in rodents.

In addition to having low numbers of PPAR alpha receptors, the peroxisome proliferator response element, " and then the technical description is given here, this substance, the Oxidase enzyme, "was unable to activate transcription in 23 out of 23 human samples. In contrast, it was active in all the rodent samples."

So here we have very specific comparisons of how the human response occurs compared to the rodent response. Now there's one last step that could be taken further that has on some peroxisome proliferators, and this is a study in a knockout mouse, where this alpha receptor is not present. Now, that hasn't been done with TCA. That's probably the gold

standard of proof. But this study could easily be done in a reasonable timeframe.

Dr. Swenberg concludes, "It is my professional judgement that TCA should not be listed under Proposition 65 at this time. If new information arises to suggest that the proposed mechanism of action is not correct, these data can be brought forward for future consideration."

So it seems to me you have a very strong statement from a very authoritative, in my judgement, expert weighing in on this issue more or less in the opposite conclusion that you just heard from the State with regard to what we know about peroxisome proliferators and their relevance to human cancer.

I should give some of my history on this. I was on the EPA Science Advisory Board when it considered peroxisome proliferators. We considered that the research was promising, but there wasn't enough evidence to depart from the default assumption. That was back in 1987. This is noted on page 100 of *Science and Judgement in Risk Assessment*, a National Academy report that I had the privilege of

participating in.

And that same conclusion is used as an example of the problem of getting enough information to meet the burden to depart from a default. And we recommended to EPA that it needed to do a better job of establishing criteria for departure from default.

I think you have that problem with respect to your criteria development. You have a very specific example on this substance. I've already heard you describe how some of you are troubled by this situation. It troubled me when I was first given this assignment.

Why did IARC, EPA, and NTP not reach a conclusion of sufficient evidence, but rather, one of limited evidence. And I think the information on mechanism is probably an excellent explanation. That's certainly Dr. Swenberg's opinion. And I'm glad I asked him to prepare this letter, because it seems to me it's extremely informative.

I'd like to conclude with one last thought, and this is my background on decision analysis. I instinctively look at the

decision context for scientific issues. Here we are dealing with a substance that results from the chlorination of water, which is done for a variety of purposes; drinking water, swimming pools, beverages, etc.

There is a discharge provision under Prop 65, which as I understand it, permits no consideration of dose or assessment of risk. Rather, is says, "No. You can't do it." So it seems to me in this context, your decision on the listing of TCA is extremely important for the People of California. I would recommend that you wait for further information, such as a knock-out mouse study, and take the decision not to list it at this time.

Thank you.

DR. MACK: Thank you, Dr. North. That was very helpful, and the letter is also very helpful.

Just to correct one thing: It is not our task to make any risk analysis or any intervention judgements. We only are here to decide whether something causes cancer. So your last remarks were not pertinent to this

operation.

DR. NORTH: Well, I --

DR. MACK: They may be pertinent to subsequent operations, but not this one. But that's a very minor issue in what you've presented us.

DR. NORTH: Let me clarify that my intention in making those remarks was to ask you to take this one particularly seriously, because I think your job is particularly important here.

DR. MACK: We really try to take them all seriously. Believe me.

Now, do other people have questions for Dr. North?

DR. PETERS: I recognize Dr. Swenberg as an expert, but there are a couple of things in the letter that I would like to point out that I might not agree with. And that is, in the last paragraph, he talks about, "There is a very strong database that demonstrates that humans are not at any significant risk for cancer from TCA exposure. This includes the very low exposure to humans from disinfection by-products. This does not necessarily" --

it goes back to his very strong database. "And likewise, the epidemiologic evidence of human carcinogenicity being lacking".

The studies haven't been done, so obviously, it's lacking. So I think two out of four of his reasons for having a very strong database, demonstrating that humans are not at significant risk are not valid.

Would you like to comment on that is the question I have.

DR. NORTH: I asked him to write this letter to elucidate what was known about the mechanism of peroxisome proliferation. And that's the part of it that I'd like you to consider seriously. I didn't read those two sentences. And frankly, that was deliberate.

DR. MACK: Anybody else have questions for Dr. North?

Joe?

DR. LANDOLPH: Yes. Thank you for that letter. So, as I understand it, the wyeth compound in the transgenic mice causes no hepatocellular carcinoma and no peroxisomal proliferation?

DR. NORTH: Yeah. As I understand those

experiments, the receptor for the PPAR alpha is knocked out of the mouse. It's not there. So you have a direct test, whether you see a carcinogenic response in that altered mouse. And my understanding is, on the experiments that have been done, they show no elevated tumor response.

DR. LANDOLPH: And that's been published in the peer review literature?

DR. NORTH: I would have to refer you to Dr. Swenberg's articles on this. I have several articles with me. I'd be happy to do that over lunch.

DR. LANDOLPH: So a key piece of data that is missing is those same experiments with TCA. We don't have that data.

DR. NORTH: Yeah. Those experiments have not been done on TCA.

DR. MACK: I think what we might do is ask that either you directly or Staff directly, with Dr. Swenberg, try and get the documentation for these studies and some of the others that he mentions that were unavailable to Staff.

DR. NORTH: I'm sure Dr. Swenberg would

cooperate fully.

DR. MACK: I'm sure he would too. Whether or not we make a decision pro or con, it would useful to have them in the file and ready for the next consideration.

Andy?

Thank you, Dr. North.

DR. SALMON: Yeah. I was just going to say that we are, of course, familiar with quite a number of the studies which Dr. Swenberg referred to. In fact, we have some of the studies referred to available, because we have been following this issue with great attention for some time.

So I think I'm right in saying that some of the work which Dr. Swenberg referred to in his letter may or may not at this instant have appeared in the published literature. So there may be some additional things that we don't have. But I don't exactly recall the details of some of the things he referred to as being in papers that I know we have. So that's something we would have to follow.

I think another point that the panel might want to consider in relation to this

issue is certainly as regards the studies of PPAR alpha activation by known peroxisome proliferation-inducing agents. These are the cases where, for instance, the knock-out mouse doesn't produce any of the results.

I think that there's fairly good evidence for those compounds that there's a link between activation of the PPAR alpha receptor and the carcinogenic response. It's not clear from those experiments, as far as I can see, and I think as far as a number of other people who have examined this literature is concerned, that the link is via the induction of the oxidative enzymes. It would appear, at least it's likely, that in fact what is happening is that the PPAR alpha activation is resulting, well, probably a considerable range of different responses.

On the one hand, it may be resulting in a response which causes the appearance of additional oxidative enzymes and proliferation of the peroxisomes and the increased oxidant production. Now, that's an observation which is characteristic of rodents. It may also, in fact, be producing some kind of cell-

stimulatory response which is separate and independent of that, and in fact may be the one which is important for the observation of carcinogenesis in those same rodents.

So the question of whether or not you observe the oxidant response in human tissues is -- is that relevant or is that not? Well, I mean, I'm not presuming to answer that question. But I'm pointing it out to you as a dilemma in the interpretation of the data.

There's also, I think, some debate about this question of, you know, how much of the receptor do humans have. And I think that the theory about how these receptors interact with their response elements in the genome doesn't necessarily assume that a higher copy number implies greater responsiveness. The two aren't necessarily linked. So again, this is a -- I know. You know, is this a key observation or is it a fact on which we are unable to interpret?

So I think what I'm saying is, yes, this is fascinating stuff. We all follow it with great attention. I think specifically with regard to TCA, one of the problems is that

clearly, we have this observation that it does cause peroxisome proliferation.

My concern, which I was presenting to you in the analysis is, even given that, you know, obviously, you know, we agree with that, it's an observation, we are unclear whether that has any bearing or not on the observation of tumor induction by TCA. We're not necessarily disagreeing with what happens with clofibrate or --

DR. MACK: I think you've made that -- you're making that very clear. Thanks, Andy.

Does anybody else --

DR. FROINES: I strongly agree with what he just said. I think it's very important that the traditional linkages for peroxisome proliferators can be seen as an oversimplification of a complex process.

DR. MACK: Are we ready to call the question? Does anybody have anything else to add?

All right. Let's have a show of hands from those people in whose opinion trichloroacetic acid has been clearly shown through scientifically valid testing according

to generally accepted principles to cause cancer.

Well, my goodness. Let the record show that there were no votes to list the chemical.

Please indicate by a show of hands if in your opinion trichloroacetic acid has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

1, 2, 3, 4, 5, 6.

DR. FROINES: I think we have an abstainer.

DR. MACK: I think we have an abstainer.

DR. LANDOLPH: Yeah, that's me. I want some more information from the EPA.

DR. MACK: All right. So the record shows that there were 6 votes not to list the chemical; none to list it. And we will therefore not list it. And at Joe's request, we will try to find out from EPA by one means or another, Warner, what went on. Okay?

Now, it is quarter to one. Should we break for lunch, or should we go to the last one?

What's the pleasure of the Committee?

What's the grumbling of the Committee?

Okay. Let's go through the last one. Does everybody agree with that?

DR. PETERS: No.

DR. MACK: John has a veto.

DR. FROINES: What did John say?

DR. MACK: He says, "Let's eat".

You look poised. Are you poised?

DR. FROINES: As the lead person on this chemical, I will defer to the body at large.

DR. MACK: Okay. Let's eat. And let's get back again at -- how much time should we give?

DR. DENTON: A half an hour?

DR. MACK: That's pretty fast. You don't know how John eats.

Let's make it 1:30. Let's reconvene at 1:30.

(Lunch recess was taken from 12:45 to 1:38 p.m.)

DR. MACK: In the absence of Froines, let's jump to the delisting and go to No. 2, where Dr. William Spangler is going as to tell us about the glories of chlorodibromomethane. I'm sorry. A Staff person first.

DR. DENTON: Dr. Martha Sandy is going to address the Committee.

DR. MACK: All right. When Martha Sandy gets her act together.

DR. SANDY: We wanted to say a few words about this, since you haven't ever considered a chemical for delisting before. And both I and Ms. Heck will be addressing you.

Just for some history, at the CIC, September 25th, 1997 meeting, OEHHA reported to you on the results of the systematic review of chemicals listed as causing cancer via the authoritative body's mechanism. At that time, OEHHA had identified five chemicals, namely, allyl chloride, chlorodibromomethane, 1,1-dichloroethane, para-toluidine, and zineb, which appeared to be no longer formally identified as causing cancer by the authoritative body which served as the basis for the listing. In each of these cases, the authoritative body was the U.S. EPA.

As Ms. Heck will explain in more detail, if the lead agency finds that a chemical is no longer identified by the authoritative body as causing cancer, the listing under the

proposition can be re-considered. These five chemicals have been referred to the CIC as the State's qualified experts for carcinogenicity determinations under Proposition 65, so that the Committee may make a recommendation as to whether the chemical should remain on the list.

Consideration of three of these chemicals was originally scheduled for the December 10th, 1998 meeting. At that meeting, consideration was deferred in order that assignments for lead reviewers for each chemical could be made. At last year's meeting, the CIC also asked that OEHHA provide information on specific use and exposure to each of these chemicals in California.

Such information has been provided, when available, in a summary document you have before you today for each of the five chemicals. This document was released on August 27th, for a 30-day public comment period. We received one comment on chlorodibromomethane, which has been forwarded to the Committee members.

And now Miss Heck will add a little more.

MS. HECK: Thank you, Martha.

I just wanted to briefly touch upon the regulatory status of the delisting process, and that is that the relevant regulation requires that when the lead agency, OEHHA, determines that the underlying authoritative body whose work originated the listing no longer considers or no longer identifies the agent, it should be considered as to whether or not it should remain on the list.

The regulations calls for the Committee to determine whether or not it should remain on the list or be removed from the list. And reading together the statutes and the regulations as to the standard that guides your judgement, it is the same standard as you would use in determining whether or not to list the chemical, that is, whether or not it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

If you make that finding, your vote would then be to have the chemical remain on the list, despite the change of status, vis a vis the authoritative body. If you make the

opposite finding, your vote would be to remove the chemical from the list.

Thank you.

DR. MACK: Now, is somebody going to address the specifics of chlorodibromomethane?

DR. SANDY: Yes. It will be Dr. Gail Krowech.

DR. KROWECH: This first slide shows the structure of chlorodibromomethane, or CDBM

CDBM is a volatile organic compound and is one of several trihalomethanes which are formed as by-products of the water chlorination process. In California, CDBM has been detected in runoff from agricultural peat soils and in drinking water sources.

CDBM was listed as causing cancer under Proposition 65 in January 1990 based on a U.S. EPA evaluation which classified the compound in Group B2. In a subsequent evaluation, CDBM was reclassified as a Group C carcinogen. The reasoning for the reclassification is unclear, but it does not appear to be based on significant new information.

Next slide.

CDBM has been reviewed by two other

authoritative bodies. In 1991, IARC classified CDBM as a Group 3 carcinogen, based on the absence of evidence in humans and limited evidence in experimental animals.

NTP, based on its 2-year bioassays, concluded that there was some evidence for the carcinogenicity of CDBM in female mice and equivocal evidence in male mice. NTP found no evidence in male or female rats.

There are no epidemiological studies on the carcinogenicity of CDBM alone. Several studies have suggested a positive correlation between drinking chlorinated water and the incidences of several human cancers; particularly bladder, rectal, and colon cancer.

The data on the carcinogenicity in experimental animals is mainly that reported by the NTP. In the NTP studies, there was a statistically significant increase in the incidence of hepatocellular adenoma or carcinoma combined in high-dose female mice. In male mice, the incidence of hepatocellular carcinoma was significantly increased in the high-dose group, but the combined incidence of

adenoma and carcinoma was not.

A long-term drinking water study in mice by *Veronin et al* reported no increases in tumor incidence. However, it is not clear whether necessary precautions were taken to minimize volatization of CDBM from drinking water. IARC also commented on the incomplete reporting of this study.

In the NTP rat studies, no treatment-related increases in tumor incidence were observed.

US EPA also reported on the preliminary results of an unpublished 2-year study by *Tobe*, in which no increased tumor incidence was reported. However, only a small number of rats at each dose group were examined after 18 or 24 months of exposure.

Next slide, please.

In the NTP mouse studies, groups of 50 male and female B6C3F1 mice were given 0, 50, or 100 milligrams per kilogram of CDBM in corn oil by gavage for five days a week for 105 weeks. In female mice, the incidence of combined adenomas and carcinomas in high-dose animals was significantly greater than in the

control group. In male mice, the incidence of carcinomas was significantly greater in the high-dose group compared to the control. As noted earlier, the incidence of combined adenomas and carcinomas was not significantly increased.

In male mice, the incidence at the low dose was not appropriate for statistical analysis, as 35 low dose males died from an accidental overdose in week 58. Also, nine high-dose male mice died in week 82 of the study. There was no explanation for these deaths provided.

Next slide.

Other relevant data concerning the carcinogenicity of CDBM include mostly positive genotoxicity studies. Results in Salmonella were mixed, but CDBM was generally positive when tests were conducted in closed containers. CDBM was positive for gene conversion in Saccharomyces but negative in a reverse mutation assay.

CDBM increased the frequency of sister chromatid exchanges in human lymphocytes, rat leukemia cells, and mouse bone-marrow cells *in*

vivo. Increases in sister chromatid exchanges have also been demonstrated with other trihalomethanes.

CDBM increased chromosomal aberrations in mouse lymphoma cells, Chinese hamster cells, and rat bone-marrow cells *in vivo*. An *in-vivo* study in mouse bone-marrow cells was negative. CDBM was negative in a mouse bone-marrow micronucleus test.

CDBM did not cause unscheduled DNA synthesis in rat liver and did not produce DNA strand breaks in rat kidney cells *in vivo*. Other trihalomethanes were also tested in these two latter studies, and also gave negative results.

Next slide.

The other trihalomethanes are chloroform, dichlorobromomethane, and bromoform. They are all classified by U.S. EPA as B2 carcinogens. Chloroform, dichlorobromomethane, and CDBM all cause liver tumors in mice, but not in rats. The dose-response relationship for the induction of liver tumors is similar for these three trihalomethanes as will be shown in the next slide.

As mentioned earlier, trihalomethanes have given similar results in several gentoxicity studies. The mutagenicities of the brominated trihalomethanes (CDBM, dichlorobromomethane, and bromoform) have been shown to be mediated by theta-class glutathione S-transferase in the Salmonella strain RSJ100. These trihalomethanes also produced nearly identical mutation spectra at predominantly a single site, suggesting the involvement of a common reactive intermediate or class of intermediates.

In the delisting document for CDBM, chloroform was mistakenly included with these trihalomethanes. The summary document should have cited methylene chloride instead as the fourth halomethane.

The dose-response relationship for the induction of liver tumors in female B6C3F1 mice exposed to the trihalomethanes (CDBM, chloroform, and dichlorobromomethane) is shown here and was adapted from *Dunnick and Melnick*. The tumor incidence shown is the combined incidence of adenoma or carcinoma except for chloroform, where the tumor incidence is the

incidence of carcinoma.

These three trihalomethanes show similar potencies in inducing liver tumors in female B6C3F1 mice. The doses in the CDBM study were the lowest of the three trihalomethanes. There is one overlapping data point here at the tumor incidence of .4, and that is at the high dose of CDBM and the low dose of bromodichloromethane. The tumor incidence at this dose is the same for both chemicals.

In summary, the evidence of carcinogenicity is a significant increase in combined adenomas and carcinomas in high-dose female mice. The incidence of carcinomas was also significantly increased in high-dose male mice. However, the combined incidence of adenoma and carcinoma was not.

There were problems with this study, as mentioned earlier. An accidental overdose caused the death of 35 low-dose males. And 9 high-dose males died during one week of the study with no explanation of these deaths provided.

Other relevant data include mostly positive genotoxicity data and structural

similarities with other carcinogenic trihalomethanes.

DR. MACK: Okay.

Bill?

DR. SPANGLER: Well, you can probably -- based on my performance this morning, you can probably anticipate how I feel about this compound.

I just wanted to ask a question: It is part of the law that these things have to be brought to the CIC or Scientific Advisory Board?

MS. HECK: Yes. If the lead agency, OEHHA, finds that the authoritative body no longer identifies the agent as causing cancer, there is a provision in the regulations that requires its referral to the appropriate committee.

DR. SPANGLER: That's thinking ahead.

DR. MACK: Does that make you feel a lot better?

DR. SPANGLER: No. I would say, if you live by the sword, you die by the sword. And if you were listed by that mechanism, then you could be delisted by that mechanism.

But, again, I found no compelling evidence in the data that was presented that this material is -- that this is something that I could say clearly caused cancer. Again, we have a situation where we have -- the compound produces neoplasia in mice. And it takes a lot of hepatocellular carcinomas to convince me that there's a real risk to the population, in addition to the fact that it's negative in other rodent species. So I would support the delisting of this compound.

DR. MACK: Okay. Who else would like to speak to this issue?

David, you're furrowing your brow.

DR. EASTMOND: Give me a minute. I'm formulating my question.

DR. MACK: Let me just ask Bill: What do you think about the analogy with the other trichloromethanes? That graph she showed looks like it's going to do something bad if you get enough of it.

DR. SPANGLER: That may be the case. You know, I just have to stick with what I know, pretty much, and that is animal pathology and how that relates to this whole field.

We're considering this particular compound. Even though it may be valid to compare it against other similar compounds, still, it's what this compound does and what we know it does, and.

not what something else does and we think this might mimic. That's my feeling.

DR. MACK: Are you ready, David?

DR. EASTMOND: I am not ready.

DR. MACK: Jim?

DR. FELTON: Well, I just wanted to -- the mistake that was made on that NTP study, was that the only significant dose response, then, that we had, or did the other studies show some dose response? We're discounting -- I'm a little confused.

DR. KROWECH: Well, it was the low-dose animals. And actually, it was the females and the males. They received, I think it was seven times the dose that they should have had at week 50, or at some week. And they died shortly thereafter. So it wasn't the high-dose animals that received that.

DR. FELTON: Okay. So without that, we have no dose response in the NTP studies,

because it was just the two doses and the control?

DR. KROWECH: Right.

DR. FELTON: So we had the high dose with the response, but we had no dose response.

DR. KROWECH: There was an increase in the females. Although they were overdosed, these deaths did not occur. And there was an increase in tumors but not significant compared to the controls.

DR. FELTON: The other thing I was going to ask you is, this one that's significant, the .03, of course, depended on that particular control group. But the other control group had a higher level. So, can you explain that?

DR. KROWECH: Oh. Oh. Okay. Below -- Under males, there's the hepatocellular carcinoma and then the hepatocellular adenoma and carcinomas. So there were many more adenomas in the controls.

DR. FELTON: So it's the same carcinomas, and then they added on the adenomas.

DR. KROWECH: Right.

DR. FELTON: Okay. All right.

DR. MACK: How does that help you, James?

DR. FELTON: Not much. I was trying to figure it out.

DR. MACK: John? You have joined us. Do you have anything to say?

DR. FROINES: (Shaking his head.)

DR. LANDOLPH: Yeah. I'm a little bit puzzled. I wonder if you could help me. Why is dichlorobromomethane remaining as a B2 carcinogen for the EPA, and CDBM --

DR. MACK: Joe, you've got to have a microphone. Otherwise, I'll ignore you.

DR. LANDOLPH: That's okay. You do that anyway.

Why is dichlorobromomethane still remaining on the EPA list as a B2 human carcinogen, CDBM is proposed to be taken off, and all these seem to fit a similar dose response curve for animal carcinogenicity. Do you have any insight into that you can help us with? I don't mean to put you on the spot. It's just, it's puzzling me.

DR. KROWECH: I don't know. I suspect that the animal data is stronger for the dichlorobromomethane. But I don't know.

DR. MACK: David?

DR. EASTMOND: I am very confused. I came in here late. Things are bouncing around, and I'm not sure I'm even working on the right tables.

DR. MACK: So why should you be any different than the rest of us?

DR. EASTMOND: Well, it's somewhat embarrassing. Can you review exactly where we're at in this process?

DR. MACK: Yes. We are -- we went to the delisting, because John Froines was not present to go ahead with the last one.

DR. EASTMOND: Okay.

DR. MACK: And we are dealing with the second delisting, chlorodibromomethane. And we have just heard a summary of that, and a general denial by Dr. Spangler that any of this is worthwhile.

DR. EASTMOND: That's kind of where I thought we were at. But I wanted to make sure before I really opened my mouth and embarrassed myself.

I thought about these -- just as far as comments -- it's more of a philosophical

thing. If the listing by the EPA was the basis for -- if the classification by EPA was basis for the listing, and the EPA decides based on their evaluation that the evidence is no longer sufficient in their minds, from my point of view, it really makes perfect sense that we would delist it.

And it may be that we would want to re-examine that later. But in essence, we don't have a full evaluation. These are not nearly as complete evaluations as for the other chemicals.

DR. MACK: Let's just ask if that's true. I don't think that's true. I think this is all the data we have available. In other words, it is just as complete as the other chemicals; is that not true?

DR. KROWECH: We have not been as verbose, perhaps, but we've looked for all the available data on these chemicals and presented it to you.

DR. MACK: Okay. So it may not be true. Okay. But it's a much more synthesized presentation, from my reading of it.

DR. FROINES: I would like to comment on

that. I understand the logic, and there's a part of me that would like to agree with it. But we've all had experience with EPA over our lifetimes. And some of us have had multiple lifetimes. And therefore, we've had multiple experiences.

Quite frankly, in my committee, the S-Scientific Review Panel, AB-1807, we actually look hard at what the EPA's done, because we often disagree with it. And in fact, on some compounds, most notably perchloroethylene, for example, we think EPA was definitely wrong in their evaluation.

So, yes, it seems to me that our knee-jerk reaction might be to just follow what they do, but I think it's still worthwhile for us to do as thorough a review as we can to make sure we're comfortable within any decision that we make.

DR. MACK: But beyond that, we have the legal mandate to do that. I mean, it isn't a matter of us just -- it's like, Bill would have said the same thing, "If they delisted it, let's forget it". But as Colleen told us, we have a legal mandate to evaluate it just

like the others.

Joe?

DR. LANDOLPH: Tom, I was looking at this very nice paragraph that was written in the State's document. And it indicates that the other trihalomethanes are also genotoxic, and the mutagenicities of all of them are mediated by thetaclass glutathione transferase, and mutational spectra produced by each of the trihalomethanes is nearly identical, suggesting a common intermediate or class of intermediates.

So this actually enhances a prior impression I had that there's a commonality. And it would almost be an inconsistency if we delisted the one but not the others. And we're stuck, because the EPA hasn't delisted the others. It's that logical flaw that I'm being reinforced on.

DR. MACK: That helps a lot. Have we said everything we have to say? Shall we take a vote?

DR. FROINES: Public comment?

DR. MACK: Oh. My God. All right.

Jim?

DR. COUGHLIN: Thanks, Dr. Mack.

DR. MACK: I'm sorry. This is James Coughlin.

DR. COUGHLIN: Jim Coughlin, toxicology consultant. And I've got a general comment, because I'm going to be addressing four of the separate delisting chemicals, a very brief general comment.

About 450 carcinogens have been listed by Prop 65. And a third of them, about 150, have been listed by the authoritative body mechanism. So there's a very important mechanism that's been used to list a third of the chemicals. So I think it's important to look at what the other authoritative bodies and the same authoritative body looked at in determining why the chemical came on the list. I think you should look at all the bodies, to take a look at them when looking at taking a chemical off the list.

I just have one overhead.

Dr. Krowech had most of this information up there correct, but I want to correct one thing. EPA's IRIS, the Integrated Risk Information System database, revised this

chemical to Group C, down to possible human carcinogen from a B2 probable on November 1st, 1990. And what you've cited in the backup document is, you looked at the 1997 IRIS, the date on the IRIS document itself, but when you actually dig into the document, they verified and changed their decision back in November 1st, '90.

They originally had listed it as a B2 in their HEAST document, which is their Health Effects Assessment Summary Table, in '89. IRIS notes that this document, the HEAST, really showed, "inadequate human data and limited evidence of carcinogenicity in animals". Not sufficient evidence; that's why it fell back to a Group C.

IARC looked at it in 1991, called it a Group 3, not classifiable. There was no human data, and the animal evidence was determined there to be limited. The NTP bioassay referred to was perfectly described; no evidence, equivocal evidence, and some evidence. It's the female mouse liver.

I think -- it was the precursor to OEHHA -- DHS, the Department of Health

Services, acted -- and you've heard me complain about these kinds of things before, acting on draft documents that aren't final -- they acted on the EPA's HEAST summary table, which was just a list of chemicals with alphabetical entries, A's, B's, C's, and D's.

If they had waited just eleven months for EPA to come up with the final IRIS document; it was already verified, and it just hadn't been loaded up on the computer -- was verified in 1989 -- this could not have been used as the basis for authoritative body listing, as there wasn't sufficient evidence. So EPA changed their mind, and the other bodies don't have sufficient evidence.

DR. MACK: That's true, but it was, and we're here.

DR. COUGHLIN: Yes, sir. And that's why I'm here.

DR. MACK: Thank you, Jim.

Do you have a question for Jim?

Go ahead, Dr. North.

DR. NORTH: Thank you. Warner North. I'll be brief in my comments, here. I would like to pick up on Dr. Froines' point about

experience with EPA.

When I was on the Scientific Advisory Panel, along with Dr. Spangler and Jay Murray back around 1989, we had quite a lot of controversy about authoritative bodies. Some of us were very concerned about who speaks for EPA. And this, I think, is an example, where the State picked up one table from EPA, and there were some problems with it. This was not unusual.

In *Science and Judgement in Risk Assessment*, page 265, we recommended specifically efforts to clean up the data in the IRIS database. There were a lot of problems like this. This isn't a unique situation.

And I think to EPA's credit, the Carcinogen Assessment Group, CAG, was asked to review the evidence on CDBM. And on September 7th, 1989, this was reclassified as Category C, possible human carcinogen, limited evidence in animals. So I'm correcting the previous speaker, that it was actually earlier than that. And as far as I can see, this was simply an administrative problem of not

picking up the right who speaks for EPA.

I think it should be a concern to the State that it's taken nearly ten years to bring this before the Committee so that a delisting decision can be made. I would hope that you could go through the file in such situations -- and I suspect there are a number of others -- and bring these issues quickly to the CIC so that the listing decisions can be made with all due speed.

Now, I think others of you have summarized the information on the animal studies; gavage studies, one strain of mouse. I think an important point is, there appears to be no new information on this chemical beside that which has been considered by EPA and the other authoritative bodies. So I would hope your decision to go with the delisting is reasonably clear.

Thank you.

DR. MACK: Thank you, Dr. North. You must remember that it may -- these issues may be brought before the CIC, but if we don't get through the day, we don't have time to consider them.

David, did you want to make a comment now?

DR. EASTMOND: I wanted to ask a question. Slide No. 9, the composite of the three trihalomethanes, when was this devised, who devised it, and when?

DR. KROWECH: This was from a paper by *Dunnick and Melnick, May, 1993*, published May of 1993.

DR. MACK: Is that Ron Melnick?

DR. KROWECH: Yes.

DR. EASTMOND: Thank you.

DR. MACK: Okay. If there are no more comments --

DR. FROINES: I do.

DR. MACK: Okay. I can always count on you.

DR. FROINES: I haven't said a thing on this topic yet.

DR. MACK: I know. And you said you weren't going to say anything.

DR. FROINES: I lied.

I just want to point out an interesting thing. Unless I'm mistaken, and somebody can correct me, but the issue that got us to this

place is that there's quite a bit of evidence on bladder cancer associated with chlorinated hydrocarbon trihalomethanes associated with drinking water. So that the target tissue seems to be the bladder cancer in humans. Am I right on that? That's been the matter of concern with chlorinated water.

Now, the interesting thing is, when you look at all these compounds, whether it be chloroform or dichlorobromomethane, we don't find any bladder cancers. So we have the animals operating differently, at least according to the data that we have in front of us, than what apparently happens in humans.

And so we have a number of problems, it seems to me, because it does seem to me that we have to find out why people are developing cancer from drinking chlorinated water. That seems to me to be the issue. And when we bite off each little compound so we can pick at it in its narrow context, it seems to me that we start to lose the forest for the trees.

I think we have a problem at this point in delisting, when we really are dealing with a deck that is very partial in nature. And I

think the evidence tends to make us move in that direction, but I find the whole thing to be dissatisfying given the available information we have to make a decision.

DR. MACK: That seems to be a general feeling.

Is there anybody else who wants to express their impression?

DR. FROINES: That makes me worry about delisting --

DR. MACK: Yes. I know. I understand.

Of course, just to comment on the animal versus man problem, there's lots and lots of reasons why one might not find bladder cancer. I mean, presumably, it has to do with the long-term exposure to contaminated urine in the bladder. And the actual mechanics and duration of exposure may make a big difference. I have no idea how frequently and how completely mice pee, which may be a pertinent issue.

DR. FROINES: I have 400 animals on tests right as we speak. And they're peeing every day.

DR. MACK: The question is not whether

they're peeing. The question is, how long does a given drop of water stay in the bladder. And I'll bet you don't know that.

DR. FROINES: But I'll bet you we're having a lot of hyperplasia in these animals that are peeing and drinking every day.

DR. MACK: Okay. Are we to the -- Oops. Yes, ma'am.

DR. SANDY: I'd just like to clarify, there is at least one piece of new information since EPA made its decision to classify this as a "C", and that's the glutathione transferase beta gene mutational spectrum story, which came out in '97. That's where you see similar mutational spectra between --

DR. FROINES: Oh. Yeah. That's a very important finding, I think.

DR. MACK: Is that --

DR. SANDY: The author is --

DR. EASTMOND: Oh. It's David DeMarini, I believe.

DR. SANDY: Yeah.

DR. MACK: All right. Are we ready to vote? Let me get my little statement, here.

Everybody indicate by a show of hands, if

in your opinion chlorodibromomethane has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer, which would indicate that it will not be delisted.

I'm ready for a show of hands. The show of hands is for those people who think that this is a carcinogen, who want to keep it listed.

We have 1, 2.

How many people believe that it is -- I'm sorry. I have to read the whole thing.

Please indicate by a show of hands if in your opinion cholorodibromomethane has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be delisted.

4 to 2, and 1 abstention.

All right. I think we should go on to the other in this category just because it might be more efficient to do that rather than go back to the big one.

DR. FROINES: Why don't we get mine over with, go back to the first one.

DR. MACK: You want to go back to the first one?

DR. FROINES: I don't think it will take long.

DR. MACK: All right.

DR. FROINES: It doesn't matter to me.

DR. MACK: Well, it obviously does, or you wouldn't have said it.

Okay. We'll go to bis (2-chloro-1-methylethyl) ether. We just want to keep the Staff on their toes.

DR. FAUST: Good afternoon. I'm John Faust. The next agent under consideration is technical grade bis (2-chloro-1-methylethyl) ether, hereafter referred to as BCMEE. The structure of the primary component of BCMEE is presented here along with its molecular weight.

Could I have the next slide, please.

The components of technical grade BCMEE are shown on this slide. They are the structural isomers bis (2-chloro-1-methylethyl) ether at approximately 69-71 percent, 2-chloro-1-methylethyl (2-chloropropyl) ether,

also known as the "mixed" isomer, at approximately 26-29 percent, and bis (2-chloro-n-propyl) ether at approximately 2-3 percent.

Next slide, please.

BCMEE is a beta-haloether. The primary occurrence of this compound is as a by-product of the manufacture of propylene glycol and propylene oxide. This occurrence has been shown to produce measurable amounts of BCMEE in effluents from facilities where such manufacturing occurs. U.S. EPA's 1996 Toxic Release Inventory estimated that approximately 4,100 pounds of BCMEE were released primarily as stack air emissions.

BCMEE itself has also been used as a component of paint and varnish removers, as an intermediate in dye synthesis, and as the active ingredient of a pesticide used in Japan.

With respect to authoritative body evaluations, in 1999, IARC published an evaluation of this compound and placed it in Group 3, unclassifiable as to its carcinogenicity, based on inadequate evidence

in humans and limited evidence in animals.

Next overhead, please.

This overhead summarizes the major carcinogenicity data available from humans and experimental animals. No data are available regarding the carcinogenicity of BCMEE in humans. The major studies available from experimental animals are mouse bioassays published by the National Toxicology Program in 1982, rat bioassays by the National Cancer Institute in 1979, and mouse bioassays by *Mitsumori and others* in 1979.

In the NTP bioassay in mice, the primary findings were an increase in liver tumors in male mice and increases in lung tumors in both male and female mice. A small number of forestomach tumors were also observed in both male and female mice.

To briefly summarize the study, male and female B6C3F1 mice, 50 per group, were treated for 103 weeks by oral gavage with 0, 100, or 200 milligrams per kilogram body weight, technical grade BCMEE dissolved in corn oil.

This table summarizes the primary incidence data for tumors in the male mice.

Significant increases in lung adenomas and combined adenomas and carcinomas were observed in the low-dose group. Significant increases in liver carcinomas and combined liver adenomas and carcinomas were observed in both the low and high-dose groups. A single forestomach squamous cell papilloma was observed in each of the BCMEE treated groups as well.

Next overhead, please.

The second table summarizes the primary incidence data for tumors in the female mice. Among animals in the high-dose group, a significant increase in both lung adenomas and combined adenomas and carcinomas was observed. One squamous cell carcinoma and two squamous cell papillomas of the forestomach were observed in female mice in the high-dose group. NTP's conclusions were that BCMEE was carcinogenic for B6C3F1 mice.

Okay. Next overhead, please.

Among non-positive findings, the National Cancer Institute also published the results of bioassays in male and female Fisher F344 rats. The treatment protocol is similar to that

described previously in the NTP bioassays. However, in this bioassay, body weight and survival were significantly affected by BCMEE treatment such that almost no animals survived to the end of the study.

Inadequate numbers of animals were considered to survive for the observation of late-appearing tumors. Among the animals examined, no increases in tumor incidence were observed. NCI concluded that "under the conditions of this bioassay, the technical grade test material was not carcinogenic for F344 rats of either sex."

Mitsumori and others --

DR. FROINES: Did they discuss that? I mean, do you have any idea how you can have a study in which they acknowledge that there's insufficient numbers of animals to make a finding and they make a finding? There's a contradiction there.

DR. FAUST: Yeah. These are the statements that were made in the report. They didn't go into further detail about what they considered adequate for making that conclusion.

DR. FROINES: It's just so -- this particular study, the contradictions are so glaring, that to have drawn a conclusion one way or the other seems to me to be problematic.

DR. FAUST: All right.

Mitsumori and others also published the results of a bioassay in ICR mice fed diet containing BCMEE. In this case, the test compound was stated to be 98.5 percent pure. In this bioassay, the study design limited the number of animals surviving to the end of the experiment at 104 weeks. No significant increases in tumor incidence were reported in the BCMEE exposed groups.

Next overhead.

BCMEE has also been tested in numerous bacterial and mammalian assays for genotoxicity. BCMEE has produced mixed findings in Salmonella reverse mutation assays, with some positive findings with and without metabolic activation. A reverse mutation assay in E. coli was not positive.

Positive findings in mammalian cell assays, primarily using test material in the

NTP chemical repository, include the mouse lymphoma forward mutation assay, a test for chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells, and an induction of S-phase DNA synthesis in mouse hepatocytes.

Next overhead.

BCMEE also has structural similarity to several other carcinogenic haloethers, including compounds which cause tumors at the same sites as BCMEE.

Bis chloroethyl ether is a beta haloether which has been shown to induce liver tumors in two strains of mice and is a direct-acting mutagen. Bis chloromethyl ether is an alpha haloether and a potent lung carcinogen in mice, rats, and humans. Technical grade chloromethyl methylether, which contains bis chloromethyl ether, has also been associated with lung cancer in humans. These three compounds are on the Proposition 65 list of chemicals known to cause cancer.

Next overhead, please.

To summarize, the evidence on the carcinogenicity of BCMEE, it includes the

induction of lung tumors in male and female mice and the induction of liver tumors in male mice. A small number of rare forestomach tumors in both male and female mice is suggestive of a compound-related effect. Other relevant data include evidence of genotoxicity and the structural similarity of the compound to other chemicals, particularly haloethers, known to cause cancer.

DR. MACK: Thanks.

Okay, John.

DR. FROINES: Well, I should start out by saying that I have a bias on this one, because the most of us who got into this field in the early 70's were aware of what happened with BCMEE at the Rhom and Hass Plant in Pennsylvania. And many of us have read the book, *"54 Who Died"*.

BCMEE is clearly a very potent carcinogen. It's produced in non-smokers. It was quite a scandal for a period of time. And so, one of the things that's clear, both from the epidemiology and from the animal studies, is that BCMEE was a compound of great significance, unfortunately. So, we start out

with that knowledge, and then we start looking at this particular information.

I wanted to show you an overhead.

Martha, can you --

I want to show you how I can turn this compound into BCMEE. And I think it's relatively easy to do that.

If you'll notice, that's the compound of question at the top. But if you lose the chlorine and form a carbonium ion -- everybody in here who's a chemist knows that primary carbonium ions are not very stable, and so don't like to sit around. And so that methyl group is truly going to rearrange the bind with that methylene group there, giving you the compound you see below, where you have formed a secondary carbonium group. And that compound can undergo alkylation and other kinds of reactions.

As you look, that compound there, then, has the same resonance stabilization that you would get with BCMEE. It's in fact identical. So that in a sense, by a molecular rearrangement, which is likely to happen under certain circumstances, you will end up with

something that looks like BCMEE.

I'm not arguing that that actually happens. What I'm arguing is that this compound does have similarities to BCMEE, and that it is at the outset a very worrisome compound in that regard.

Now, the second thing that I'm not sure was mentioned is that -- go up to the top, raise the bottom. Show the propylene oxide. Of course, the people who did the metabolism work wrote somewhat extensively about the importance of the oxygen group there, knocking out that chlorine and forming the propylene oxide.

I'm not sure whether the oxygen group forms the epoxide first or whether you get cleavage of the ether. But either way, you end up as a metabolic product of propylene oxide, which is a carcinogen, and it's designated as such.

So that pathway that formed that intermediate, which is one of the metabolites of the compound under question, is another example of a compound that would raise your sense of awareness.

I think what we have here is, then -- what we're dealing with is three things, as far as I'm concerned. What we're dealing with is a good NTP bioasssay, a solid NTP bioassay, which is positive for lung, liver, and some indication of forestomach cancers. So we have relevant cancer endpoints, I think, and a well-conducted study. The other two studies obviously had limitations.

We have multiple target sites, multiple sexes, but only one species. And that obviously is the limiting factor that has caused the concern. We certainly have significant evidence for genotoxicity.

And so as far as I'm concerned, when you consider the structure-activity relationships that we've just gone through here -- and one can do much more than I've done -- when you take structure activity, when you take genotoxicity, when you take the metabolism-producing propylene oxide, and when you take the NTP bioassay, I think that taking all that together, I would argue that the compound should be designated for listing.

DR. MACK: Thank you.

Other members of the Committee want to weigh in? Bill, does this one convince you?

DR. SPANGLER: No. I'm just not going to be convinced based on the presence of tumors in mice. You know that, by itself, admittedly along with the rest of the stuff, forms a story. I can't bring myself to say that this is clearly shown to cause cancer. I mean, it's clearly shown to cause cancer in mice, but that doesn't quite go as far as we need to go, I think. So that's, you know, that's my opinion.

DR. MACK: Joe?

DR. FROINES: I think -- Can I just comment on that?

DR. MACK: Yeah.

DR. FROINES: I think that it's one thing to say that you don't like liver cancers in B6C3F1 mice. I think it's another thing to say you don't want to count forestomach cancers or lung cancers in particular as relevant. I think lung cancers are highly relevant in this particular circumstance. And I think that one would have to demonstrate why the lung cancers aren't relevant under these

circumstances.

DR. SPANGLER: My -- I'm not sure how many, what the background of cancer was in this study.

DR. FAUST: In the control animals or among the historical controls?

DR. SPANGLER: Um-hm. Yes.

DR. FAUST: I think there were one each.

DR. SPANGLER: Okay. So these are carcinomas, 1, 2, and 2 -- no this is the female.

Okay. In males, carcinomas -- just in my experience in looking at mice bioassays, you know, adenomas of the lung in mice are something that you run into. This data suggests that there are more of them in the treated groups, but it doesn't look like you have a good dose response.

DR. MACK: Are you saying that about the four carcinomas?

DR. SPANGLER: Adenomas.

DR. MACK: No. There are four carcinomas.

DR. SPANGLER: Oh. Four carcinomas.

DR. MACK: Four carcinomas in the treated

group, and one in --

DR. SPANGLER: That's -- the carcinomas, I just don't find that compelling, the carcinoma data compelling.

DR. MACK: Okay.

Joe?

DR. LANDOLPH: I agree with John on the structural similarities of these compounds. BCMEE is a defined, strong, human lung carcinogen. There's no question about that. This compound is so structurally similar, it's almost impossible to ignore. The extra presence of the methyl will stabilize the carbonium ion further. So I would predict from an organic principles basis this would be at least as bad, if not worse.

Bill has good comments here. I mean, you know, it's one strain of mice. We're going to go through that forever. But there's lung, there's liver, and an odd forestomach tumor. And there's males and females. So this is a lot of data. In addition to that, there's a lot of genotoxicity data.

So it's just my own personal opinion. I appreciate everybody's comments and respect

all the comments, but I'm weighing in positive.

DR. PETERS: I think I have nothing to add. But I agree with John and Joe.

DR. MACK: Jim?

DR. FELTON: I have to agree with Joe. I mean, we're trying to be consistent here in how we're doing this. We've been analyzing all these different chemicals that are positive in one species. But again, here we have all the additional mechanistic, structural analogies, and gene tox data which supports it. So again, this one looks like the others.

DR. MACK: David?

DR. EASTMOND: The additional question which I might ask John is, it's my understanding that BCMEE, when tested in mice, also causes tumors in the respiratory tract. Are they the same type? Are they both adenomas and carcinomas? Do you know?

DR. FAUST: The bioassays results for BCMEE? I could not tell you.

DR. EASTMOND: Okay. Because it does say in the document that you do see respiratory

tract tumors with BCMEE, which is for me, another evidence, because you see the same tumor types in the bioassays. But I wasn't sure about --

DR. FROINES: Well, I mean, the obvious is, you see the lung cancers in humans. So there is that comparison as well.

DR. MACK: All right. I gather there are no public comments?

Are we ready to take a vote?

Please indicate by a show of hands if in your opinion BCMEE has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

A show of hands for those who believe it does. 1, 2, 3, 4, 5, 6.

And a show of hands if in your opinion BCMEE has not been clearly shown through scientifically valid testing (to cause cancer).

Bill, your hand is up, I presume?

Okay. 6 to 1.

All right. Let's go on to the next delisting chemical, which would be allyl

chloride. John is up.

What do you want to do?

DR. FROINES: Could you go to the next one and come back to me?

DR. MACK: All right. John wants a break. Okay. We'll go to the third one, then. I understand. Just like your mice.

1,1-Dichlorethane. We're doing Joe Landolph's 1,1-Dichloroethane.

DR. MCDONALD: Greetings, everyone. I'm Tom McDonald again. I'll be briefly describing the listing history and carcinogenicity evidence of 1,1-Dichloroethane, which will be abbreviated as 1,1-DCA.

1,1-DCA is used as a solvent for plastics, oils, and fats, as a cleaning agent/degreaser, as an extraction solvent, and as a chemical intermediate. Reporting of 1,1-DCA to the Toxic Release Inventory has been required since 1994. No company has filed a use report for 1,1-DCA in California from 1994 to 1998.

According to the California Air Resources Board, total emissions of 1,1-DCA, as reported

under the Hot Spots Program, were less than 30 pounds per year. There have been reports of 1,1-DCA-contaminated groundwater near aerospace manufacturing facilities in California. Additionally, some consumer products, such as lubricating oils and specialty cleaning products, may contain 1,1-DCA.

Next slide, please.

1,1-DCA was listed on the Proposition 65 list in 1990. This listing was based on a classification of B2 by U.S. EPA in 1989, in its Health Effects Summary Tables. The listing was based on findings in the NCI 1978 bioassay.

In 1990, U.S. EPA revised its classification of 1,1-DCA, as posted on IRIS, to Group C. The Group C classification was based on lack of evidence in humans and limited evidence in rats and mice. Although the reasons for the change in the classification were not described in the IRIS file, subsequent discussion with U.S. EPA scientists have indicated that the change was made on professional judgement in the weight

of the evidence, since no new information had been published on this chemical.

Next slide, please.

The carcinogenicity studies of 1,1-DCA are shown in this slide. No human studies are available. In animals, there is only one series of studies conducted by the National Cancer Institute in 1978. These included gavage studies in male and female B6C3F1 mice for 78 weeks followed by a 13-week observation period, and gavage studies in male and female Osborne-Mendel rats for 78 weeks followed by a 33-week observation period.

Next slide, please.

Before describing the tumor findings, I would like to note that there were significant concerns about study quality with respect to dosing and survival. As often occurred in early NCI studies, an irregular dosing pattern was employed in which doses were either increased or decreased based on observed tolerances of the compound.

Doses of 1,1-DCA used in this study were high and were, on average, roughly 1500 to 3000 milligrams per kilogram body weight in

low and high-dose groups in the rats and roughly 400 to 1000 milligrams per kilogram per day in the mice respectively.

As you can see from this slide, the percentage of the animals surviving to the end of the study was low. Tumors appeared relatively late in the experiment, thus early mortality was not due to cancer. In the male and female rats, survival was particularly low, which NCI attributed to widespread infection, that is, pneumonia in the animals.

Next slide, please.

This slide shows the tumor incidence observed in mice. NCI observed an increased incidence of hepatocellular carcinoma in the high-dose male mice for those surviving past 52 weeks. The liver tumors were also significant by trend test. In the high-dose female mice, an increased incidence was observed for endometrial stromal polyps of the uterus, which is a benign tumor. Results were also significant by trend test.

It should be noted that Dr. Louis Gold and colleagues conducted a Cox-type survival analysis on the individual animal data and

found an even stronger association.

Next slide, please.

DR. MACK: Lois Gold.

DR. MCDONALD: I'm sorry. Lois Gold.

Here, we have the observed tumor incidences in rats. In male rats, no treatment-related tumors were observed. In female rats, however, an increased incidence was observed for hemangiosarcomas of the circulatory system, an uncommon tumor, which was statistically significant only by trend test. An increased incidence of mammary gland adenocarcinoma was reported but was not significant by pairwise. Survival analysis conducted by *Gold et al* found a significant association for both of these endpoints in the female rat.

Next slide, please.

With respect to other relevant data, in tumor-promotion studies, 1,1-DCA did not exhibit initiating potential. However, 1,1-DCA was positive for tumor promotion in two reports and was inconclusive in another.

In DNA binding studies, 1,1-DCA administered *in vivo* to rats or mice bound

covalently to DNA and other cellular macromolecules.

Next slide.

1,1-DCA generally exhibited positive genotoxicity. 1,1-DCA was negative in Salmonella reverse mutation employing standard, open test systems, but was positive in closed systems. Positive findings were reported for various short-term assays shown here in Aspergillus, rat and mouse hepatocytes, and hamster embryo cells. In an *in vivo* mouse study, 1,1-DCA was negative for alkaline DNA unwinding.

Next slide, please.

Structure-activity comparisons: It is interesting to compare the results of the NCI gavage study of 1,2-DCA to those obtained from the NCI gavage study of 1,1-DCA. As you can see from this slide, 1,2-DCA exhibited many of the same tumors at the same species as 1,1-DCA. 1,2-DCA is on the Prop 65 list and is considered a Group B2 carcinogen by U.S. EPA.

It should be stated, however, that 1,2-DCA was found to be non-positive for

carcinogenicity in two long-term inhalation studies and in a one-year drinking water study.

Next slide, please.

To summarize, (there were) observations of increased tumor incidences in the liver of male mice, the uterus of female mice, and the circulatory system and mammary gland of female rats. However, there were problems with study quality, particularly with the use of high dose and with low survival.

Other relevant data include generally positive findings of genotoxicity, and some indications of chemical structural analogies, and tumor-promoting activity.

DR. MACK: Thank you, Tom.

Joe?

DR. LANDOLPH: I'm a little bit bothered that the EPA listed it, and then based on "professional judgement" with no extra data, they delisted it. So that bothers me. And I don't know what that means.

There is some evidence for tumorogenicity in that very nice summary that was presented. It seems like you have to confine this

material to get genotoxicity from it. And it looks like there may be N-stage P450 activation to an aldehydic metabolite, which may be responsible for it's genotoxicity. But that's not even clear.

So we have a paucity of mechanistic information. We do know it's metabolized to acetic acid and chloroacetic aldehyde. But there's no real good genetox data. And this is the case with volatiles, you often have to go through hoops to get them to show gene toxicity. Unless you confine them in a closed vessel, you don't get many results. So if you do that, you do get some genotoxicity.

But I'm worried about the EPA's reassessment. I think this is what I was worried about in the beginning, that these things are not well thought out. And I hate to see this continual flip-flop. So, I'm a little bit ambivalent about this. The structural analogy certainly is clear, but there are holes in this database. Certainly, one would like to see more data.

DR. MACK: John, do you have any comments on this one?

DR. FROINES: No.

DR. MACK: Jim?

DR. FELTON: (Shaking head.)

DR. MACK: David?

DR. EASTMOND: The key point to me in the document is that much of the driving force behind classification is based on this study by NCI, which is the mouse and the rat. And the conclusions of the study say that they didn't find any evidence.

As it describes here in the conditions, there was no conclusive evidence for carcinogenicity in either the rat strain or the mouse strain. And for me, that's really a very key point. In a re-analysis done by Gold and Zeiger, you know, they did pick up some trends. And there may be some positive things. But for me, it's certainly not a clear-cut increase in tumor incidence.

DR. MACK: Let me ask our dyspeptic pathologist about hemangiosarcomas. How often do you see those in rodents?

DR. SPANGLER: Well, in rats, I don't think as often as you do in mice.

DR. MACK: But you see them fairly often

in mice?

DR. SPANGLER: In these studies, they say they occurred in rats. These are studies in which they concluded that there wasn't any evidence.

DR. MACK: Yeah. I know. But that's -- we're sort of looking at it from the outside, though. And we can't necessarily rely upon their judgement, I think. I mean, that's the one thing that bothers me about this particular compound. Because these are unusual tumors. That bothers me.

DR. SPANGLER: Biologically, these kinds of tumors bother me. But statistically --

DR. MACK: Okay. Anybody else have anything to say? Do we have any comments from the -- Jim?

DR. COUGHLIN: Dr. Jim Coughlin, Coughlin and Associates. We recognize the format. It was the same five authoritative bodies. Tom had everything right. All the authoritative bodies did what you said they did. It did happen about 10 months after the listing. The IRIS thing was finalized on October 1st, 1990.

Based on that same HEAST table, which, I

don't know how that gets made -- but to address Dr. Landolph, this IRIS process, the RFD/RFC working group, was an EPA process. It's now been disbanded. But it acted for 10 or 12 years. 20 people, 25 people got together in a room and studied the heck out of this. And then they verified the carcinogenicity and put it up on the IRIS.

So it's not a whimsical change, I don't think, in the EPA's mind. I think it was a temporary thing that was sitting on the HEAST table, and then they really looked at it. And then October 1st, 1990, they said it's Group C.

Let me jump you down to the last point. OEHHA, on its web page, where it addresses public health goals for drinking water -- there's a law that requires them to look at California public health goals -- has a Table 2. And the key thing on this table -- Table 1 has chemicals that already have public health goals. Table 2 is chemicals -- can everybody see that -- Table 2 in this June '98 document lists a whole bunch of chemicals that go on for ten pages -- that don't have a public

health goal. And there's columns that describe what kind of public endpoint it is.

A lot of the chemicals in those columns have cancer endpoints. And there's MCLG's, Maximum Contaminant Level Goals, set by EPA, of zero. There's also calculated cancer risks for a lot of the chemicals. But, in this very OEHHA document, the listing for this chemical is that the chronic toxicity was due to increased death rate of the rats, not carcinogenicity.

At the California MCL of .005 milligrams per liter, the entry was "N/A"-- and that's a footnote I've got in quotes. N/A is "no cancer risk is calculated for chemicals considered non-carcinogens". So another branch of OEHHA or different people within OEHHA are calling this chemical a non-carcinogen, just like EPA did when they changed their mind back in 1990.

Do I have that wrong? It sounds like I'm generating some discussion over here.

DR. SALMON: (Inaudible.)

DR. COUGHLIN: It's not the cancer risk calculated at the California MCL?

DR. SALMON: (Inaudible) Without California public health goals. I think that's the table which is quoted in the U.S. EPA figures, and they're quoting that determination.

DR. COUGHLIN: Okay. So that's not a separate OEHHA determination? Okay. Thank you for the clarification.

DR. MACK: Does anybody else have any insight on this hemangiosarcoma business? All right. I guess we have to make a vote.

DR. FROINES: This is an interesting -- I said I wasn't going to talk, but --

DR. MACK: I bet you are.

DR. FROINES: I'll just say one thing.

I think the fact that you -- in contrast, I think every other chemical we've dealt with today, this is the first one where you actually do find some data in rats.

DR. MACK: Yeah. And it's an unusual tumor.

Please indicate by a show of hands if in your opinion --

DR. LANDOLPH: Tom?

DR. MACK: Hi, Joe.

DR. LANDOLPH: Hi Tom. Do we know whether the induction of those hemangiosarcomas were dose dependent?

DR. MACK: They were all in the final dose column.

DR. LANDOLPH: All at the highest dose column.

DR. SPANGLER: But it was not statistically significant for pairwise comparisons.

DR. MACK: Yeah.

DR. SPANGLER: It was significant as a trend.

DR. MACK: Right.

DR. SPANGLER: And also, we're looking at data, here, where we're really trying hard.

DR. MACK: Yeah. But I mean, I come back to the fact -- and that's why I asked you, how often do you see them? To see four, second heads on somebody's body might not provide a significant trend. But I would be most concerned.

DR. LANDOLPH: Did those tumors appear in the control column at all?

DR. MACK: No.

Is that correct? I think that's correct.

Okay. Please indicate by a show of hands if in your opinion, 1,1-dichloroethane has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should remain on the list.

I'm actually going to go for this one, just for the hell of it.

My goodness.

DR. SPANGLER: I'm not voting for the hell of it.

DR. MACK: Well, we've got 1, 2, 3, 4, 5.

Please indicate by a show of hands if in your opinion, 1,1-dichloroethane has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be delisted.

2. All right.

Now, John, is your bladder willing to take on the task of doing allyl chloride?

DR. RABOVSKY: My name is Jean Rabovsky. I will be speaking to you about the allyl chloride, which is being considered for

delisting.

Allyl chloride is used as an intermediate in the manufacture of industrial and consumer products. Primary stationary emission sources in California are automotive repair shops, metal industries, and educational services. And in 1997, about 270 pounds per year were emitted into the air. Allyl chloride could contribute to indoor air pollution. However, a 1990 indoor sampling monitoring study did not reveal measurable concentrations in the samples.

Next slide, please.

Allyl chloride was listed by California in 1990 as a carcinogen under Proposition 65. The listing was based on a 1987 U.S. EPA report in which evidence for allyl chloride carcinogenicity included limited experimental animal data and supporting data on mutagenicity, alkylating properties, and metabolism to epichlorohydrin.

In 1990, U.S. EPA revised the classification to a possible human carcinogen, that is, Group C, on the basis of lack of evidence in humans, a low incidence of

forestomach tumors in mice, and positive genotoxicity test results.

Next slide, please.

Two authoritative bodies evaluated the evidence of allyl chloride carcinogenity. IARC concluded the carcinogenicity was not classifiable based on inadequate evidence in experimental animals and absence of data in humans. NCI concluded there was suggestive evidence for carcinogenicity in male and female mice based on the low incidence of a rare neoplastic forestomach lesion.

Two other authoritative bodies, NIOSH and FDA, do not appear to have evaluated the carcinogenicity of allyl chloride.

Next slide, please.

Three epidemiologic studies on workers were carried out between 1990 and 1996. The studies, however, are not informative about allyl chloride carcinogenicity because the primary exposure was to epichlorohydrin. Allyl chloride exposure could only be inferred for some of the workers, depending on their work assignments.

Next -- yeah, next slide.

Four bioassays have been reported by three authors, NCI, *Theiss*, and *Van Duuren*. In the NCI study that is on the board before you now, in this study, B6C3F1 mice and *Osborne-Mendel* rats were exposed by gavage to allyl chloride.

The major finding in the NCI mouse study was an increased incidence of squamous cell carcinoma among the low-dose female and male mice. Survival among high-dose males was poor and was adequate among low-dose males and low and high-dose females. Statistical significance, however, was only revealed by a binomial distribution analysis.

Metastases were observed in the low-dose males, and squamous cell papillomas were observed at the same site among low dose and high-dose females. No forestomach tumors were observed in vehicle or untreated control mice.

The historical female B6C3F1 mouse control rate for squamous cell carcinoma or papilloma, which the authors describe as "infrequently observed in B6C3F1 mice", was less than the rate observed among the treated female mice.

Next slide, please.

Among the mice exposed to allyl chloride by i.p. injection, the high-dose males exhibited an increased number of lung adenomas per mouse compared to vehicle control. The authors rated the carcinogenic effect as intermediate because significance was positive for only one of two statistical tests.

Next slide, please.

Among the rats in the NCI study, no increased incidences of tumors compared to controls were observed in the low-dose female or male rats. The high mortality among the high-dose rats of both sexes precluded tumor analysis on these animals. The authors concluded there was no evidence for carcinogenicity of allyl chloride in rats and also noted the low power of the study due to high mortality, especially in the high-dose groups of both sexes.

Next slide, please.

Female mice receiving topical applications of allyl chloride for over a year did not exhibit skin papillomas or carcinomas in a complete carcinogenesis bioassay. When

tested in an initiation/promotion bioassay, an increased incidence of skin papillomas appeared in the mice that were first initiated with allyl chloride and then treated with a promoter.

Next slide, please.

Allyl chloride was mutagenic in two bacterial species, and in yeast and in fungus. It caused *in vitro* unscheduled DNA synthesis in HeLa cells and bound to DNA *in vitro*. Mutagenicity can be demonstrated in the absence of metabolic activation. However, such activation enhances the mutagenic effect, probably through alternative pathways, and several active genotoxins formed during the operation of these pathways have been suggested on the basis of urinary metabolite analyses.

Next slide, please.

Allyl chloride binds to DNA *in vitro* with the formation of guanine and adenine adducts, plus adducts of unidentified structure. Although metabolic activation is not required, it does lead to enhanced mutagenicity.

Two proposed genotoxins based on urinary

metabolite analysis and enzyme inhibitor data are epichlorohydrin and glycidaldehyde. Each is an epoxide and each leads to DNA binding and DNA adduct formation *in vivo* and *in vitro*.

Next slide, please.

Several allyl compounds are known mutagens and/or carcinogens. Among the mutagens are 3-chloro-2-methylpropene, 1-chloro-2-butene, 2,3-dichloro-1-propene. It's interesting to note that in safrole, there is also an allylic structure, just as we were discussing with allyl chloride, which has been listed as a carcinogen under Proposition 65.

Two proposed metabolites, epichlorohydrin and glycidaldehyde, each of which is proposed on the basis of urinary metabolite analysis, are listed under Proposition 65 as carcinogens. Epichlorohydrin was classified by U.S. EPA as a probable human carcinogen on the basis of sufficient evidence in experimental animals, and by IARC in 1987, as a probable human carcinogen on the basis of sufficient evidence in animals and positive results in short-term genotoxicity tests.

Last slide, please.

In summary, allyl chloride causes a rare squamous cell forestomach tumor in female and male mice. The confidence in these findings is reduced by toxicity and mortality, and marginal statistical significance. Increased confidence in the findings results from precancerous and cancerous lesions in the forestomach of female and male mice.

Positive genotoxicity results in a number of test systems, structural relationship to known mutagens and carcinogens, and the suggested formation of allyl chloride metabolites of known carcinogenicity.

DR. MACK: Thank you.

DR. FROINES: Martha, could you show this?

I think that -- without overdoing the chemistry lesson too much -- allyl chloride is at the top. You see when it forms a carbonium ion by loss of chlorine, it has resonance stabilization. So that one would tend to be concerned about allyl halogens as potentially strong alkylating agents.

So I'm starting off with a little

resistance or hesitation to delist a compound that I think structurally appears to be a reasonably strong alkylating agent. And as we know, alkylating agents have potential carcinogenesis.

Some could argue that strong alkylating agents will tend to bind protein and all sorts of other macromolecules and may not even make it into the nucleus. But I think that based on the structure-activity relations, one wants to approach the question with some conservatism.

This particular issue is extremely important in California, because the compound that's just below there, Telone, which is 1,3-dichloropropene, is a compound that in about 1990 to 1992 -- actually, it's license was suspended because of the risk assessment. It has been found to be a rather powerful animal carcinogen.

There is some human evidence. 1,3-dichloropropene was suspended from use in California. It's a nematocide. And one of the interesting things about it is, it's in one of the compounds that will be used when

methyl bromide is eliminated. So this issue of allyl compounds is important.

We're way up to about 2 million pounds in California at this point for Telone. So I say all that only by way of saying that we need to be cautious about allyl chloride compounds, I think, in terms of how we go about them.

All right. Secondly, you've seen the data on the forestomach cancers.

In your last slide, you didn't include the lung tumors as well. I would have included that, because the conclusion was that allyl chloride tumorogenicity in this experiment is raised as intermediate, so that there is some evidence, albeit limited.

Third, it clearly is -- the allyl compounds are clearly genotoxic, and I think that's important. And fourth, we have the metabolite of epichlorohydrin and the glycidaldehyde.

So, when you take those, the structure activity, the mutagenicity, the animal data together, I would be hesitant to delist this particular compound, recognizing that there's more information that we would like to have to

further confirm its carcinogenicity.

DR. MACK: Joe?

DR. LANDOLPH: John, is there any evidence that you get epichlorohydrin or glycidaldehyde formed in humans? Is there any data like that out there? I side with you. I feel the same way. But my question is, do we know that we have epichlorohydrin and glycidaldehyde formed in humans? Is that data available?

DR. FROINES: You know, this is one of the -- I don't want to get on my soap box, but this is one of these compounds that -- my guess is that the amount of actual exposure to human beings is relatively limited, even the massive 270 pounds that's reported here.

So I think the data on humans is relatively limited. I don't think we have an answer to that. And I don't think we want to put anybody in a chamber to find out.

DR. MACK: Jim?

DR. FELTON: This gives me a real problem. I mean, I'm not a biostatistian, but of all the data we looked all day today, this is the weakest carcinogenistically. I mean,

you just don't fall out of your chairs. I think this is one tumor past being significant for one dose. I mean there's just almost nothing there.

I have a hard time with this one. I agree with you on the mechanistic, but I like to use the mechanistic data and analogy data to back up the strong carcinogenicity data, at least in one test, but here, being one species, I can't do that. It looks like a delist to me.

DR. FROINES: I don't disagree with that, Jim. I'm concerned about a compound that I think is a carcinogen to delist it. That's what bothers me. I think if you ask me, would I list it, I might have a different view than if you asked me whether I wanted to delist it.

DR. MACK: David?

DR. EASTMOND: Well, I have many of the same concerns. If you look at the chemistry, if you look at the background, the mutagenicity, etc, this is one that you don't feel -- you know, you're not real comfortable with. But when you look at actually what is seen in these animal bioassays, the evidence

is certainly murky for me.

Now, there is some consistency in that if it is a direct-acting agent, you would expect that it probably react directly where it's administered. And that's what you do see. But the increases are certainly not by concurrent controls. This has got to be looking at historical controls and pooling things and doing all -- you know, I mean, that's the rationale that I see on the evidence.

DR. FROINES: You do see the lung tumors with i.p. injection -- in the female, the Strain A mice were i.p. injected so that the adenomas were identified via i.p. And that is not -- presumably, we can argue with whether i.p. injections always go through the liver or not.

The allyl chloride appears to last long enough to get into the lung.

DR. MACK: Joe?

DR. LANDOLPH: It's just that I'm a little bit concerned that epichlorohydrin is listed as a metabolite. And that's already on the Prop 65 list. And so therefore, this

could be a procarcinogen for epichlorohydrin in addition to its other carbonium ion formation.

DR. MACK: Yeah. I think there's a big split here between the empiric data and what ought to be seen, both on the basis of the metabolism and on the basis of the structure function. I agree that it's stronger evidence for stopping delisting than it is for listing.

Anybody else? Anything from the -- yes, indeed. Well guess who.

DR. COUGHLIN: I should have Dr. Mack give my presentation. Dr. Jim Coughlin, Coughlin and Associates. And this is more of a procedural thing. This is the first time it's been a draft document.

In 1986, the listing was moved on because it was a draft, a final draft document from EPA in '86. IRIS came along in September 1, '90, and said it was limited evidence, and said it was hard to interpret, very big inadequacies in the data.

However, IARC has looked at it three times. Three groups met -- in '85 was the original monograph. They looked again when

they re-evaluated all of them in '87. And then in 1998, they did a third evaluation. And a lot of times, IARC gives something a Group 3 when it's limited animal evidence and no human data. But this is inadequate. That's the lowest standard that IARC finds for adequacy of data. The bioassay, there was no strong evidence in the bioassay that was discussed.

But this is a procedural thing that I just want to point out. You know, they acted on a draft document. If they had just waited a few more months, the final IRIS process where 20, 25 EPA scientists come together and fight it out for several months and determine a final listing, this would not have been listed in 1990, because there was no sufficient evidence.

DR. MACK: Well I wish we had a time machine for you, Jim.

DR. COUGHLIN: Why is that?

DR. MACK: So you could get back there and prevent these things from happening.

I think the inadequate evidence by IARC means that there isn't evidence as opposed to

that the evidence was negative. It basically is saying there is no good evidence. So, it's not a negative connotation, it's an unknown connotation.

Anybody else?

DR. COUGHLIN: Thank you.

MS. HECK: Dr. Mack, can I just briefly address the Committee?

There's been some discussion here, in the last few minutes about --

DR. MACK: Where has there been that discussion?

MS. HECK: Among the Committee members about their uncomfortableness with this as a delisting as opposed to if it were an initial listing.

For your purposes of your vote, it is as though it were an initial listing. It got here mechanically because the authoritative body no longer considers it. But the issue before you and the standard you must reach is the same as though it were an initial listing.

DR. MACK: We know that in our heads, but in our hearts, it's not as easy.

Are we ready to take a vote? Where's my

vote book.

Indicate by a show of hands if in your opinion allyl chloride has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be maintained on the list.

I'm going to list it. I don't like -- I'm a conservative person. I don't like to see the evidence, both the metabolite and the --

DR. FROINES: (Raising hand.) No. No. No. I was going to abstain. And I decided, I presented it, and I argued for it, so I'll --

DR. MACK: So you'll abstain.

DR. FROINES: No. I'll vote for it.

DR. MACK: Okay. So we have 2.

Please indicate by a show of hands if in your opinion allyl chloride has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be delisted.

1, 2, 3.

DR. SPANGLER: And I think this is the

conservative position.

DR. MACK: Okay.

And abstentions? 2 Abstentions. They're getting sleepy.

DR. LANDOLPH: No. Actually, I was doing some more thinking about this. Maybe it just doesn't make enough epichlorohydrin.

DR. MACK: Then you should say no.

DR. LANDOLPH: No. That's an abstention. We don't have enough evidence. I need more data.

DR. MACK: All right. That takes care of that one.

DR. FROINES: This is -- we need to communicate when OEHHA --

AUDIENCE MEMBER: Can you repeat the vote, please?

DR. MACK: The vote was 2 to 3 to 1.

DR. FROINES: 2 to 3 to 2.

DR. MACK: 2 to 3 to 2. So it is delisted.

MS. HECK: That's correct. It took 4 affirmative votes to keep it on the list.

DR. MACK: What?

MS. HECK: It would have taken four affirmative votes to keep it on the list. So the consequence is, it is a vote to delist.

DR. MACK: Is everybody clear on that.

DR. FELTON: Can you explain that? I mean, if we have abstentions and still a majority to do something, it won't -- you need a majority of the Committee to list something.

MS. HECK: That's right. But you were taking what in effect is an initial vote, because it takes a majority of the quorum to list the chemical. You reconsidered it. There were not enough affirmative votes to keep it on the list.

DR. MACK: In other words, the action here is not what it would seem. In other words, in all cases, the action is to say it's bad. And so you need a majority of the quorum to say it's bad. Otherwise, it's not bad.

MR. WEIL: If it would help the Committee -- my name's Ed Weil, from the Attorney General's office -- I think the way to look at this is that you have a chemical that was only on the list because of an authoritative body finding. The authoritative

body changes its mind. All right?

It might seem prudent to just say, "Well, the rug has just been pulled out from this chemical. It now goes off the list". But as a matter of priority setting, the way the regulation works is, they say, "Before you would take it off the list, let's go back to the Committee and see if they think it ought to be on the list on its own merits anyway. And if they say it should be, then it will remain on the list".

But if there aren't four votes to say that it should be on the list, then since the authoritative body no longer views it the same way, it will go off the list.

DR. MACK: Like I said --

MR. WEIL: Exactly like Dr. Mack said.

DR. FROINES: I want to go back to something I said this morning. And that is, we voted a number of chemicals to be listed. We've voted a number of chemicals to be delisted. So we've done both. I think, however, that it's fair to say that there was no chemical whatsoever which had really as strong an evidence as we would like.

I think by and large, we are again dealing with compounds where the available data is limited. And I think that when we have this, that OEHHA should communicate to EPA and to NIHS and NTP, and tell them where they have identified gaps in information so that we can put some pressure on those federal agencies to try and fill in gaps where we think the compounds are sufficiently important to require further studying of priorities.

Allyl chloride may not be the hottest compound in America. But there will be those that have significance. We really need to fill the gaps in.

DR. MACK: Good point.

No let's go on to p-toluidine.

DR. FAUST: Thank you. I'm John Faust, again. The next chemical under consideration for delisting is p-toluidine.

So on this first overhead is the chemical structure, molecular weight, and CAS registry number.

Next overhead, please.

Para-toluidine is an aromatic amine used primarily in the manufacture of certain dyes

and other compounds. Para-toluidine was placed on the Proposition 65 list of carcinogens on January 1, 1990, based upon a U.S. EPA evaluation which placed the compound in Group B2. A subsequent evaluation reclassified the compound in Group C.

Next overhead, please.

Para-toluidine has been reviewed by two other authoritative bodies, NIOSH and FDA. In 1992, in its *Recommendations for Occupational Safety and Health Compendium of Policy Documents and Statements*, NIOSH noted para-toluidine's potential for cancer and that its health effects included tumors of the liver in animals.

NIOSH's recommendation to the *Occupational Safety and Health Administration* was that para-toluidine should be designated as an occupational carcinogen. In their testimony regarding OSHA's permissible exposure levels, they described the scientific evidence supporting their determination. No more recent determinations were identified by NIOSH.

Also, the *Food and Drug Administration*

identified para-toluidine as a carcinogenic chemical present as an impurity in D&C Violet No. 2, an additive dye used in some surgical sutures and meniscal tacks used in surgery. These determinations were made in 1998 and 1999 for these two uses, respectively.

Next overhead, please.

No data are available concerning the carcinogenicity of para-toluidine to humans. The scientific data concerning the carcinogenicity in experimental animals is that reported by *Weisburger and others* in 1978. In this study they reported an increase in hepatomas in both male and female mice following long-term dietary administration of para-toluidine. A similar study in male rats showed no significant increase in tumors.

Next overhead.

To describe the mouse studies more specifically, groups of 25 male and female CD-1 mice were fed diet containing 1000 or 2000 milligrams para-toluidine per kilogram diet for 6 months, followed by a reduction to half those levels for 12 months more. The study was terminated following 3 months on the

control diet.

The incidences of hepatomas among male mice were increased in the high-dose group relative to the simultaneous control group and in the low-dose group relative to the pooled control group. Among female mice, the incidence of hepatomas was significantly increased relative to the pooled control group.

Next overhead, please.

Other relevant data concerning the carcinogenicity of para-toluidine include assays for genotoxicity and cell proliferation. Studies in Salmonella and E. coli have not demonstrated mutagenicity. Rat hepatocytes treated *in vitro* with para-toluidine showed an increase in unscheduled DNA synthesis. Oral treatment of mice with para-toluidine has been shown to decrease testicular DNA synthesis.

Finally, *Brock and others* reported binding of para-toluidine to hepatic macromolecules including DNA following oral exposure.

Last slide, please.

As a general summary, therefore, NIOSH, in 1992, and FDA, in 1998 and 1999, appear to have identified para-toluidine as a carcinogen. The scientific evidence supporting their determination was positive bioassays in male and female mice showing the development of liver tumors. Other relevant data include effects on cellular DNA synthesis and studies showing hepatic DNA binding.

That's it.

DR. MACK: Thanks, John.

Jim?

DR. FELTON: It seems pretty limited to me. I mean, I think the mouse data is clear. It's got a dose response. It's enough to convince me that the mouse hepatomas are real. I know how Bill feels about mouse hepatomas, but they're there. No rat data, no standard mutagenicity data, although there's some effect on DNA binding and possibly repair. So it's pretty limited. I'd have a hard time taking this one from scratch and putting it on our list. So I would be against taking it off.

DR. MACK: Say that again?

DR. FELTON: No. I'm saying that I'd have a hard time putting it on the list if it came up for the first time. So I'm for taking it off.

DR. MACK: Right. All right.

David? Comments? You don't have to.

DR. EASTMOND: Give me a minute. I did have a question on the -- you indicated that NIOSH and FDA had called this a potential carcinogen. Now, is that in a formal sort of listing, or is this just in a document they were writing where they had mentioned it in such terms?

DR. FAUST: In the case of NIOSH, it did appear to be on a list of chemicals which they were recommending as occupational carcinogens. In the case of FDA, it appeared in Federal Register notices.

DR. EASTMOND: So it was a notice.

Now, one of the questions is, and maybe it's -- what is required through the -- essentially, the generally recognized -- there's a procedure for getting things on the list by authoritative bodies. What is required -- since NIOSH is one of those, what

listing does NIOSH have to use in order for it to be considered?

MS. HECK: There's a regulation that implements the statute on the authoritative bodies listing. There's quite a few specific regulatory and scientific criteria that the lead agency, OEHHA, has to find as present in order to take the NIOSH work or U.S. EPA, or U.S. FDA, any one of the five authoritative bodies, and actually place it on the list.

The key trigger is that there have been formal identification by the agent as causing cancer. Then there's the sufficiency of the evidence review that OEHHA does. And if those are met, then it goes on the list.

DR. MACK: Jim?

DR. FELTON: I'd just like to add another point.

When you look at a compound like this that's -- it's a methylanyline, essentially, I mean, you'd expect the activation of the amino group. And this should form genotoxic intermediates. And the fact that it doesn't makes me not care as much about this compound.

DR. MACK: And to my right.

DR. FROINES: I didn't understand what she said. Is it listed by NIOSH or is it an authoritative body?

DR. MACK: It's a matter of whether NIOSH made a formal identification.

MS. HECK: The original authoritative body basis for this listing and all the others before you today was a U.S. EPA document. The question of had NIOSH built into it, the standard, scientifically and regulatorily, would be the same for any of the five. But the actual fact in this case was that it was a U.S. EPA listing.

DR. MACK: Anybody have any comments on the biology over here? Bill's happy.

Joe?

DR. LANDOLPH: No. It's, you know, it's a puzzle. I mean it's an aromatic amine. The question Jim asked is the same one I had. It's not mutagenic. It's a real puzzle. And the animal data is kind of weak.

DR. MACK: John?

DR. FROINES: I think this should be delisted.

DR. MACK: Do we have any blue cards?

Blue cards. Yes, indeed. Why don't you just sit up here, Jim?

DR. COUGHLIN: There's a couple of small differences here, and it's mainly a procedural point. Historical, not -- you'll see my title has changed. The other three, I was asking for delisting. And my main conclusion here is this should not have been listed in 1990.

This is the first example where the draft report was December '86. But EPA finalized that very report in June of '88. And 18 months later, DHS only acted on the draft document; could have found, I guess, the final document. It was limited animal evidence.

There was no sufficiency of evidence. So if they had just -- the other three examples -- if they had just waited 9, 10, or 11 months, they would have seen a final, final EPA thing. In this case, it happened 18 months before the decision to list. And I actually weighed in on this ten years ago and wasn't listened to.

But there is no IARC and no NTP, so I am not bringing you a total body of evidence that it really weighs heavily with lots of

authoritative bodies weighing in against the listing. And NIOSH and FDA have heard their discussion.

Thank you.

DR. MACK: Thank you.

Shall we take a vote on this one?

Indicate by a show of hands if in your opinion para-toluidine has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be maintained on the list.

Zero.

Please indicate by a show of hands if in your opinion para-toluidine has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be delisted.

1, 2, 3, 4, 5, 6, 7.

Thank you. We proceed to zineb.

DR. FAUST: All right. The final chemical under consideration for delisting today is zineb. Presented on the first slide are the chemical structure, molecular weight,

and CAS registry number.

If I could have the next overhead.

Zineb is an ethylene bis dithiocarbamate fungicide. Registration for all pesticide products containing zineb is currently inactive in California. Zineb was placed on the Proposition 65 list on January 1st, 1990, based upon a U.S. EPA evaluation which placed the compound in Group B2. This classification appears to be based on toxicity information of its metabolite contaminant and degradation product, ethylene thiourea.

U.S. EPA initiated a special review process, at the time termed a rebuttal presumption against registration in 1977, of several of the ethylene bisdithiocarbamate fungicides, including zineb, mancozeb, maneb, metiram, and nabam.

During the course of this special review, all registered uses of zineb were cancelled. Subsequently, zineb appears to have been dropped from the special review process and has not been reclassified. No documents have been located suggesting a current classification by the U.S. EPA.

Next overhead, please. Zineb has been reviewed by IARC, which in 1976 and 1987, classified it as a Group 3 carcinogen, based upon insufficient evidence from animal data, and no human data regarding zineb's carcinogenic potential.

DR. FROINES: In 1987, was that a full review?

DR. FAUST: No. That was the supplement --

DR. FROINES: The what?

DR. FAUST: That was the supplement where it was merely reiterated.

DR. FROINES: Yeah. Well, can you make sure you tell people that, because it creates a false impression. It creates an impression that there's been a recent evaluation of it. And what you're talking about is a 1976 evaluation. And that's a different period of history.

DR. FAUST: Yeah. Thank you for the clarification.

No data have been located concerning the carcinogenicity of zineb to humans. Several studies have been conducted in experimental

animals. All of them are limited with respect to study, design, and/or size.

Chernov and Khitsenko conducted short-term studies in mice, showing increased incidence of lung adenomas in C57BL mice. *Mitsumori and others* conducted long-term studies showing the induction of thyroid tumors, primarily cystic adenomas in rats.

To provide a little more detail of the studies, *Chernov and Khitsenko* administered zineb 6 weekly oral doses to C57BL and Strain A mice weekly at two doses. A statistically significant increase in lung adenomas was observed in the C57BL mice in the high-dose group. Low-dose C57BL mice and Strain A mice did not show a significant increase in lung tumors.

Mitumori and others fed JCL-Wistar rats diet containing 4 doses of zineb for 130 weeks. Among male rats receiving 5000 parts per million of zineb, there was a significant increase in the incidence of thyroid tumors, with tumors appearing in 37.5 percent of treated animals and 11.3 percent of controls. These tumors were primarily late-appearing

cystic adenomas of the thyroid. An increase in subcutaneous fibromas was also reported in this dose group.

Next.

Among non-positive studies are small, less-than-lifetimes studies by *Innes and others* in two strains of mice. Single-dose subcutaneous injection studies in mice reported by NTIS was also a small study and less than lifetime; long-term gavage and subcutaneous implant studies in rats by *Andrianova and Alekseev*, the oral portion of which showed poor survival; and long-term studies in rats with small dose groups by *Blackwell-Smith and others*.

Other relevant data concerning the carcinogenicity of zineb include several assays showing the compound's genotoxic potential. Tests in Salmonella have been negative; however, positive tests for mutagenicity have been reported in *Bacillus and Saccharomyces*. Genetic damage to somatic and germ cells has been reported in *Drosophila*, and human lymphocytes exposed to zineb have shown chromosomal aberrations.

Zineb also has structural similarity to other ethylene bisdithiocarbamate fungicides. These include mancozeb, maneb, and metiram, which are all on the Proposition 65 list of chemicals known to cause cancer.

Zineb is also metabolized and degraded to ethylene thiourea, a compound which has been shown to produce liver tumors in mice and thyroid tumors in rats. This compound is also on the Proposition 65 list of chemicals known to cause cancer.

So finally, animal evidence for the carcinogenicity of zineb includes studies showing the induction of lung adenomas in mice and primarily benign cystic adenomas in male rats. Supporting evidence includes some evidence of genotoxicity, structural similarity to known carcinogens, and metabolism and degradation to ethylene thiourea, a known carcinogen.

DR. MACK: Thank you.

This one is mine. I find no evidence whatever, empiric evidence that this stuff causes a non-adenoma, an actual invasive neoplasm. So the things that concern me are

its structural similarity to the other known carcinogens, and most especially the fact that allegedly, a metabolite is ethylene thiourea.

Now, I don't know what kind of tumors ethylene thiourea causes. You mentioned there was liver and thyroid. But the degree of neoplasia is what I don't know. I presume they're carcinogens. I mean they're carcinomas.

DR. FAUST: The evidence for ethylene thiourea, yes, I believe --

DR. MACK: I mean, that's to me the crucial piece of information. And even then, it suggests the same dichotomy that we saw before, namely a reason why it ought to be producing tumors. And yet, empirically, there doesn't seem to be any evidence that it does.

Does anybody have any familiarity with ethylene thiourea and its effects?

DR. EASTMOND: In a very crude sense. I believe this class of compounds, ethylene thiourea interferes with, I believe, thyroid peroxidase. And so that you actually get alterations in thyroid hormone levels. And it's by chronic imbalance of thyroid hormones

that it's believed that you get this alteration. You get compensation of thyroid to try and compensate for that. And you get thyroid tumors.

So that's fairly common. It's one of the mechanisms being looked at as being for special review because it is consistent across this class of compounds. But there's a belief that you would have to see alterations in thyroid hormone levels in humans and over a persistent period of time before you would see anything like this.

And so it's one of these special mechanisms that they're working on to identify and come out with some leads. Some of the Staff may know more about it than I, but I believe that's the --

DR. MACK: The other peculiar thing about this compound was that it wasn't really dropped, it just disappeared. It sounds as though that the disease at the end of the page got cut off. Actually, what happened is, it was no longer in use, and therefore, they didn't feel that they had to do anything about it.

I mean, based on the ethylene thiourea, if I thought that produced carcinomas of the thyroid, I would be concerned about it in my conservative mode, as I was a few moments ago. And I would suggest that it doesn't do any harm to keep it listed. But if, as you say, these are really hormone-induced adenomas, and that ethylene thiourea doesn't produce carcinomas, I'd be inclined to delist it.

DR. ZEISE: Dr. Mack, I believe that ETU does produce carcinomas, and we can confirm that, if you like. We have the bioassay upstairs, the NTP assay. We could bring that down for ETU if you'd like that information to consider.

DR. SANDY: It's actually right here in the document that we provided to you, where ethylene thiourea -- this is according to IARC in 1987 -- "In three studies, ethylene thiourea produced high incidences of follicular carcinomas of the thyroid in rats after oral administration. Animals of each sex were affected, although male rats had a higher incidence. Lower doses produced thyroid follicular hyperplasia.

In mice, oral administration of ethylene thiourea produced liver tumors. The thyroids of these animals were not examined." End quote from IARC.

DR. MACK: Okay. Does anybody else wish to weigh in on this one?

DR. FROINES: Is this material -- did I hear you say the material is not used anymore?

DR. MACK: Yes, that's what I said.

DR. FROINES: It's not used?

DR. MACK: It's de -- it hasn't been registered since 1988; is that not true, John?

DR. FAUST: I'm not exactly sure of the last date on that. I think all -- there's currently no registration for it in California, and tolerances are set to expire, if not now, then shortly.

DR. MACK: Jim?

DR. FELTON: Well, before Jim Coughlin comes up, I'm going to preempt him.

DR. COUGHLIN: I'm not coming up this time.

DR. FELTON: Well, then I'll play your role.

On the timing of this, obviously, what

must have happened was, when the Japanese study came out, then IARC said, "let's look at it again". When they looked at it again, they said, "Huh-uh. There's still nothing there".

DR. FROINES: They didn't look at it again.

DR. MACK: They didn't look at it again.

DR. FELTON: The '87 was a report, though.

DR. FROINES: It was just a summary.

DR. MACK: It's an update, but actually, in the updates, John, to be fair, in the updates, in fact they do draw upon all literature since the original review.

DR. FROINES: No. No. No.

DR. SANDY: Actually, some of the compounds they do, and some they don't. And in this one --

DR. MACK: I was on that particular review, and my recollection on both the fourth and the seventh was that they did that. Now, maybe for that one they didn't. But for all the ones I reviewed, they sure as hell did.

DR. FELTON: But to somebody that has more experience than I do with thyroid tumors,

somebody looked -- obviously, nobody thinks that even after the thyroid tumor study that this was worth giving it higher than a 3.

DR. MACK: Well, my inclination is to suggest delisting on that basis.

DR. FROINES: To suggest?

DR. SPANGLER: Delisting.

DR. MACK: So let's have a vote.

DR. FROINES: I like the fact that -- the selection here for the first time today was C57 black mouse, which was good, because they are cancer resistant. That's different than the B6C3F1 mice.

DR. EASTMOND: The amazing thing is, the Strain A mice did not have an increase, and the C57 blacks did have an increase, which is quite unusual for the lung adenomas, for sure.

DR. FROINES: Before we vote, I'd like to make a policy statement. I have no idea why my time is being taken up and anybody else's on this panel with this compound. Why are we taking this compound? If it hasn't been used in 10 years, why are we doing it? It's a total waste of time.

DR. MACK: Are you finished?

DR. FROINES: Yes.

DR. MACK: Thank You. I think we had the answer to that when we started out, when Martha described why these particular compounds were selected for delisting. I guess I don't know enough to know that that compound won't reappear tomorrow. My guess is it won't.

And I think the delisting issue is different from the prioritization for actual listing. I mean, we've spent a lot of time talking about how common exposure ought to be an important criteria for prioritization for listing. And I think we all agree on that. But I think the delisting is a different issue.

Okay. That's my answer. Maybe Staff has a better answer.

DR. EASTMOND: May I make one comment? I think there's a reasonable chance that this class of compounds will actually come back. Because there's this intensive focus on the unique mechanism of tumorigenesis, and the class seems to work together, typically what happens, why they don't re-register them is

because the testing required in order to get registration is so expensive, they don't think that it's worth the company's while to do that.

If, however, in the meantime, there's this global perspective on how these compounds work, and it's understood mechanistically, and they feel that they can go back with less data, and they know what they're doing, then it may actually come back again. And for this whole class of compounds, the ethylene bisdithiocarbamate compounds, they're all being treated as one type of class, from my understanding. So we could see it, certainly in California, again.

DR. MACK: Okay. Are we ready for -- is there any Staff -- if Jim isn't here, nobody's here.

Okay. Please indicate by a show of hands if in your opinion zineb has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be maintained on the list.

No votes.

Please indicate by a show of hands if in your opinion zineb has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should be taken off the list.

1, 2, 3, 4, 5, 6, and 1 abstention. Correct?

Okay. I think we better forge ahead rather than taking a break. Should we have a one-minute stand and stretch? Wouldn't that be nice? Let's have a one-minute stand and stretch.

I'm sorry. The court reporter needs a break.

How long?

COURT REPORTER: Five minutes, please.

DR. MACK: Five minutes.

(Whereupon a five-minute recess was taken.)

DR. MACK: Okay. We've come to the point that you've all been waiting for. And that is the criteria, the item that was on the beginning of the agenda today. And basically, I have a little monologue to give.

Okay. George wishes to clarify something.

DR. ALEXEEFF: George Alexeeff. This is a clarification of a comment that -- we are responding to a comment that Dr. Coughlin was making on 1,1-dichloroethane. And he was referring to a table he had found on our web site, that it was citing that we had made a conclusion that 1,1-DCA was not carcinogenic, because we were basing our public health goal on a non-cancer endpoint. Okay?

And we were confused, and we thought that he was citing a U.S. EPA finding. Well, as it turns out, that table is reflecting, was reflecting information from a 1988 document that we had, where we did base, not our public health goal, but our MCL at that time, on a non-cancer endpoint.

So that was prior to the HEAST table and prior to the IRIS information. So I just wanted to say that Dr. Coughlin's interpretation was correct that it was a DHS conclusion at that time.

DR. MACK: Okay. Back to the criteria document.

Just to remind my fellow members on the Committee as to the history of this, we have lamented over the course of the last four or five years, the absence of a criteria document, particularly since the other committee, the DART Committee, has had such a criterion. And OEHHA would like us to have had one.

A few years ago, we began by assigning three subcommittees, if you want to think of it that way; one to write an epidemiology document, one to write a animal carcinogenesis document, and one to write a short-term test document. Those were all ultimately produced, although not rapidly. But they really were not in sync. They could not reasonably be integrated into a single document.

So I agreed to spend some time to try and produce a document that included all of the issues that were raised, which I ultimately did, using those three documents, speaking with the people who wrote them, and using the IARC criteria and other available criteria to try and produce something that we might be able to rely upon, historically speaking.

I produced such a document. I circulated it to the other members of the committee and asked for responses and suggestions. I in fact got two such responses. One was an annotated draft, and the other was a verbal set of suggestions, both of which were quite useful, and both of which were ultimately included in the next draft. Then it was circulated to the Committee and to anybody else who wished it, including most of you.

I guess the first thing to mention is the purpose of that document. It cannot and is not meant to be a substitute for individual expertise. It is actually meant to be a sort of a checklist to make sure that when we assess a compound, we think of all the relevant issues and try and put them in perspective.

There are obvious differences of opinion among the members of the committee as to what constitutes an appropriate criteria. And there's no way to resolve those differences.

So the members of the Committee have seen the document. And now, I'm going to ask if any of them have comments or corrections on

the document that they have seen in its most recent version.

Does anybody here on the Committee wish to raise questions about the document that you read in the handout that you got?

Jim?

DR. FELTON: There's just one thing that came up today and we sort of left off our list at the bottom of No. 1 -- I'm sorry. I guess, yeah, "F" at the bottom, just before "2" on the second page.

We don't have anything in here specifically about tumor suppressor genes or oncogenes. It may be a little specific, but it's sort of ignores that specific type of data, which we were getting into on one of the compounds earlier today --

DR. MACK: Could you write a note that suggests what you might wish to see included specifically?

DR. FELTON: Okay. So, I would -- okay. I will do that.

DR. MACK: Thank you.

DR. FROINES: Well, I think that should include looking at mutational spectra and more

sophisticated molecularbiological approaches to looking at genetic changes.

DR. FELTON: I'm sort of saying the same thing. Specifically, we should be looking at data that identifies specific changes in specific genes, and the types of changes that occur.

DR. MACK: Could I ask you, then, check so that you are in agreement about what we should put in, John and Jim?

Are there any others?

DR. SPANGLER: I would just say that it seems to me, I mean, we're approaching this like this is a final document, and we're going to go out and carve this in stone, and we're all going to carry it around with us and bring it to the meetings with us.

And I get the impression that that's not the case, that this is something that is a work in progress. And as the science changes, so will the criteria, so will the so-called criteria. So I would just encourage us to be a little looser about it. And we can talk about these things today. And we can add to them at each meeting.

DR. MACK: Well, the difficulty with that -- first of all, if we're going to have a piece of paper with words written on it, it's not easy in the context of the Government and the State of California to do that.

For example, I thought it was easier than it is. This document was circulated on September 3rd. And it was my intent at that point to take public comment on it at this meeting, and to discuss it and resolve whether or not this represented, if you want to think of it that way, the current version that we could keep and maintain and refer to when needed.

Well, I made a casual comment in a previous meeting, upon being asked by Gary Roberts, if they would have 60 days to look at it. Well, they only had 45 days to look at it. And apparently, Gary needed 60. And so, I was told specifically that I made that promise, and therefore, we couldn't really do that at this meeting, because 60 days had not elapsed.

Furthermore, there is the question of whether or not my circulating that draft to

each of you individuals constituted a hidden meeting. As it happens, I only got two responses, and only one of those was in writing. Had I gotten three responses, we were in violation of the State of California regulations on serial meetings. Okay?

So things are not easy. We cannot be casual about this. We can resolve to change things, but -- well, let me finish, and then we'll see where we stand. But the alteration from time to time is not an easy thing to do. And I will accept any comments from Colleen or Ed or anybody else who wishes to as we go on.

It is not an operational document. It's a reference document, if you want to think of it that way. And yes, of course, we can, from time to time, suggest changes in it. But I think we have to decide exactly what it is when we do that. And let me go on with what I was going to say.

DR. FROINES: Can I make a comment?

DR. MACK: Of course. How am I going to stop you?

DR. FROINES: Am I interrupting you?

DR. MACK: Yes, but go ahead.

DR. FROINES: I think that in here you say, "Thus, if the weight of scientific evidence indicates that a certain chemical causes invasive cancer in humans or that it causes invasive cancer in animals, (unless the mechanism of action is known not to be relevant to humans) the Committee is required to identify that chemical for listing".

It seems to me that someplace in here we should say proactively that mechanistic determinations will aid and enhance and facilitate --

DR. MACK: I think we do say that, proactively.

DR. FROINES: I don't see that. I may have missed it.

DR. MACK: I think you did.

DR. SPANGLER: It's in another -- it's prior to that.

DR. MACK: It's in the earlier section.

DR. FROINES: If I find it, I'll stand corrected.

DR. LANDOLPH: It's on the back of page 2. It says, "Each of the following categories of knowledge may be pertinent to carcinogen

determinations". And then it lists a longer list.

DR. MACK: So there are a couple of other things you might add to that. You can decide later whether you stand corrected. Let me go on.

DR. FROINES: It's not saying what I'm saying.

DR. MACK: Okay.

DR. FROINES: These are specific details that fall from a general point, is my understanding.

DR. MACK: Well, maybe you've got another note to write, then. Okay?

As I said before, I was reminded that I promised 60 days. So we couldn't do anything about it today anyway. And I had hoped that we would have a document that all of you were happy with by today. I was unprepared for the enthusiastic response from the regulated community that came in response to this document. There seems to be a great motion toward a workshop.

A lot of people wanted to talk today coming out of the woodwork. We didn't have

any that came down from Mt. Olympus, but we have one guy from Valhalla, which is probably as close as we're going to get.

DR. FROINES: We did have a meeting to take public comment on this issue.

DR. MACK: Not on this document.

DR. FROINES: Not on this document, but on this issue. Because I remember Michele Corash discussing. So there has been public input.

DR. MACK: There has been repeated discussion of it. You're right, but not this document.

I guess I'd like to say that I find public discussion of individual compounds extremely useful. I can point to Dr. North and Jim Coughlin today. I think both of those contributions to our deliberations were of a very high quality. And I think whenever we're discussing compounds, that's really important.

In my own opinion, that's different from a criteria document. For better or worse, Prop 65 suggested that there be a group of "qualified experts designated by a due process". I don't know what designated expert

means, and I don't know what I'm a designated expert in if it isn't how to decide whether something is a carcinogen.

So it is my opinion that a criteria document produced by the collective efforts of this Committee, and I mean collective over the long run, is just that. It is an effort made by this Committee. And I find it not very useful to have public discussion of it as a means of helping us produce that.

If -- the phobic environmentalists and the regulated community obviously are going to have very different views on what constitutes criteria. And that's neither bad nor good. We are set up to be an objective committee and to have an objective criteria. And I think that means we have to set those criteria ourselves.

That doesn't mean that good suggestions can't come. But it's got to be done in a way that we can accept or reject them easily and not spend a lot of time debating. Therefore, I don't think public discussion of this document at this time is particularly worthwhile.

However, I am told by Ed that California state law demands public discussion. So we'll have some public discussion. It will take a very abbreviated form. We'll have -- I don't know how many cards we've got?

How many do we have? Four. Well, I would suggest we have five minutes each for each of those four people.

Let's see. What else was I going to say here? What we'll do in addition is have anybody who wants to submit a brief document commenting on the criteria to the Staff by the end of the 60 days that Gary demanded. And that date is November 2nd. Those will all be collected and sent to each of us, and we will look at them. Obviously, we will not memorize them. It will be up to us to decide how intensely we look at them, just as one would expect.

And then we will have more deliberation of the same abbreviated nature at the beginning of the next meeting. And perhaps then, we will be able to vote on whether or not we can accept the criteria as a committee.

All right. Does anybody else on the

Committee want to make remarks?

DR. SPANGLER: I would just say that I think that you're being very generous, Mr. Chairman, and that five minutes is generous. I would like to stipulate that it be five minutes of non-repetitive, non-redundant comments.

DR. MACK: I would like to stipulate that too, but I'm not sure how I enforce it.

Anybody else? I have one -- before we have that, I'd like to mention one other thing.

In addition, one person made a request for public documents, to find out, apparently, to find out exactly what had been going on in the preparation of these criteria. I'm a little offended by that.

Gary, had you called me and asked me anything you wanted to about the preparation of the criteria document, I would have been happy to tell you. You will get your public document. It consists of a draft with a bunch of scrawls on it.

I'd like to ask you right now what questions you had when you made that request?

What did you think you were going to find? What did you hypothesize that we were doing that you would so covertly find out?

MR. ROBERTS: I guess the first thing I'd like to say is, I'm a little surprised by what I sense to be a certain anger from the Chair. On behalf of my clients, I want to research appropriate information to make comments on what we consider to be a very important document. And you are a public organization. And I was interested in all of the documents relevant to presenting comments. I don't think that's inappropriate.

DR. MACK: Did you have a hypothesis?

MR. ROBERTS: I was looking for all the relevant information, Mr. Chair.

DR. MACK: Did you ask for my CV, or the rest of the CV's of the rest of us? Presumably, that's equally relevant. Did you ask for any teaching we might have done under the circumstance? I mean, this is a totally expandable question. You could ask for anything you wanted. But if you really want to know something, just call. It's very easy. I really am a pretty open person, and so are

the rest of these people up here. I find this ridiculous.

Okay. You've answered it. I don't see how you could have answered it any other way. Thank you very much.

Now, could I have the four cards.

Joan?

DR. DENTON: I just wanted to add for the record that we received 25 letters on this particular item. Some of them requested a deferral of action or additional time for comment and input. Some of them requested a workshop. And others requested consideration of this item at a separate meeting. And then still others had general comments on the criteria.

So I just wanted to add that we did receive a number of letters which were forwarded on to Dr. Mack, to you, and to the rest of the Committee when we received them.

DR. MACK: Okay. There are five cards. I'd like to remind everybody that they don't really need to speak for five minutes. I'm going to put Dr. North at the end, because he's already spoken a couple of times, if

that's okay with you. Since Gene is sitting right up here in front, why don't you start, Gene. And I'll be responsible for timing.

MR. LIVINGSTON: Thank you Dr. Mack and members. My name is Gene Livingston. I represent a number of clients who are obviously interested in Proposition 65. And I would like to just thank you and the Committee for the work that you've done in trying to develop criteria.

I think Dr. Froines, this morning, indicated how critically important criteria is. He talked about how, in the first decade of Proposition 65, we picked all the low-hanging fruit, fruit where there was plenty of data, good quality data, and good quantity of that data, that we're now in the upper branches of the tree.

One of the things that we saw the Committee struggling with today is how to address situations where you don't have a lot of data. And a lot of times, the quality of that data is questionable. This issue about how you address that, I think, is important to all of us.

And so while it's not exactly what you had in mind, I welcome the opportunity to submit additional comments to this committee and an opportunity to address this after we've had more time to really analyze in more detail the criteria. So I thank you for providing that opportunity.

One of the things that I think is important is that the integrity of the Proposition 65 Program really has rested with the Scientific Advisory Panel and the Identification Committees in the past. There has been a good rigor that has been applied scientifically, and there has been compliance given to the clearly-shown-to-cause-cancer standard.

I would not want to see, as we reach into the upper branches of the tree, any lowering of that bar, any diminution of those standards just because the data is not there. And I sat there today having some concerns about that.

I think your criteria is a very good way to address that kind of problem to prevent that from happening in the future. So we look forward to working with you.

Thank you.

DR. MACK: Thank you, Gene.

DR. FROINES: Can I say one thing, because I appreciate what Gene said.

There is a balance, I think, that we have to achieve. And we haven't really talked about it today. Because let's assume that one of the chemicals that was before us was on the upper branches of the tree, but in terms of public exposure, was very high. Then the issue of what constitutes the criteria from a public health context becomes an important issue.

So that I think that the scientific criteria also sits within a nest. And that nest is a big part of what we do here as well as the science. And that today, we dealt with compounds for which there's virtually no exposure in the State of California for the most part, except for Estragole.

But I foresee that there will come a time when it won't be that simple. And then we'll be wrestling, because we'll have limited data, potentially high exposure; and then how we deal with that seems to me to be the real

challenge that we're going to have to take up. Because we want to maintain the highest quality of science, but also recognize the potential dimensions of significant exposures.

DR. MACK: I think John speaks for all of us.

Thanks again, Gene.

Gary, let's hear from you. We've talked about supplements to the monograph series. And you and I have batted heads on a couple of those.

DR. WILLIAMS: Indeed. For the record, I'm appearing at the invitation of the law firm of Gibson, Dunn, and Crutcher, on behalf of an interested client group. As the Chairman alluded to, I have a long history in chemical carcinogenesis, including writing major chapters on the subject, participating in a number of IARC monograph reviews, including *Volume 71*, which just updated 115 industrial chemicals.

DR. FROINES: Excuse me.

DR. WILLIAMS: Yes?

DR. FROINES: I'm sorry, I don't know you, and Joe didn't either. So could you give

your name?

DR. WILLIAMS: Oh. I didn't want to waste my five minutes. Gary Williams. I'm a Professor of Pathology at New York Medical College, MD, certified in pathology and toxicology. Sorry.

Anyhow, based on my extensive background, I wanted to assure you that the mouse does not retain its urine. It piddles all day, and that's why it's harder to induce bladder cancer in mice than in dogs, for example.

Coming out of the criteria document, which I think is extremely important; it's like buttoning your shirt, if you start in the wrong hole, everything goes wrong afterwards. And I think there's a lot to be commended in this document. In fact, there are things that I wish had been utilized today; for example, purity of the test substance. And I mention that, because I've worked with several of the chemicals that you evaluated today, including 1,1-dichloroethane.

And I know from my experience that the lots of DCE that were used for research in the early days were contaminated by

epichlorohydrin. And you've heard about how nasty that is. And that accounts for a lot of the positive genotoxicity tests that have been reported for 1,1-DCE.

However, in developing these criteria, I mean, I'm mindful of what your purview is, and also of the fact that you're operating under a statute from 1986 that antedated much of what we know about the causation of cancer and the mechanisms pertaining thereto. And that imposes certain limitations. But under those circumstances, I think it's a good idea to maintain a stringent standard for what is an animal carcinogen that should be construed to be a putative human cancer risk.

And I endorse the original wording of the Proposition 65, that is, that the evidence should be clear. And I perceive that in the new draft guidelines, that's been eroded somewhat with the statement about the weight of evidence should "indicate", which seems to me to open the door to less rigorous criteria for evaluating carcinogenesis.

And a couple of other very specific, very specific points I'd like to make with regard

to that, is that in *Item 2b-II,* the term "tumor" is used rather than invasive cancer or cancer. That, then, leads into the use of "only benign tumors" to classify an agent as carcinogenic. And I think that is also a slippery slope that you should think carefully before buying into.

And the way I read the document also, it appears to permit the acceptance of an overall increase in the incidence of tumors in animals as evidence of carcinogenicity as opposed to the induction of a specific tumor type. And I'll tell you that I know of no agent that has ever produced a general increase in cancer that's been associated with a cancer hazard in humans. So I strongly suggest to you that there's certain aspects of this document that need to be reconsidered.

And I would just conclude by pointing out to you that there are several on-going processes that can assist you. The IARC has just published a scientific publication that I participated in on the use of alternative models for assessment of carcinogenicity.

And you've spoken today about the limited

type of data that you have to deal with. And the IARC is facing the same problem, that there are fewer and fewer full-scale bioassays available for evaluation of carcinogenicity. And they've labored now over how to use these other kinds of ancillary pieces of information. And that's included in that document.

And then there's another process under way. The first meeting's taken place. I will be participating in the next meeting at the end of November, where we're looking at specific tumor types for their relevance to human cancer assessment. You agonized over mouse forestomach papillomas and carcinomas. That comes up in the forthcoming November meeting.

To conclude, I would like to just offer you the suggestion that the goal of cancer control is really best served by focusing the public's attention and energy on realistic cancer hazards, and that the use of animal data should lead in that direction. And I wish you the -- I encourage your efforts and wish you the best success in that endeavor.

Thank you.

DR. MACK: Thank you, Gary. That was very helpful. And I'm sure we'll look at your letter very carefully.

The next person is Jay Murray.

DR. MURRAY: Thank you, Mr. Chairman. First, let me thank you for all your hard work that went into these criteria. I know firsthand that it's not easy to write criteria for Prop 65, since I was on the panel at the time we were drafting criteria for developmental and reproductive toxicants.

First, let me respond to something that you said, Mr. Chairman, about there are differences of opinion on what should go into these criteria, and it wouldn't be easy to resolve those differences.

I'd encourage you to try to reach consensus among yourselves on these criteria. And I recognize that that's not an easy thing to do. But we faced that when we wrote the developmental, the DART criteria. We felt that it was important to have consensus so that everybody on the Committee felt like they had some ownership in those criteria.

There were a couple of points in those criteria that we really struggled with to get that consensus. But in the final analysis, we were successful in doing it. So I'm not so sure it isn't possible to do.

I've given you handouts. I'm not going to go through that. You also have written comments from me. I want to comment briefly on the "clearly-shown" standard and how that relates to your criteria.

My main concern is the criteria do not always seem to be consistent with the clearly-shown standard of the statute. Specifically, in *Section 1.d*, on the first page of your criteria, you use the term "indicates", that "the weight of the scientific indicates that the chemicals cause invasive cancer". And I'd encourage you to replace "indicates" with "clearly shows" to be more consistent with the language of the statute.

In addition, Prop 65 applies only to those chemicals known to cause cancer, not those merely suspected to cause cancer. And I think you should include a sentence in *1.d*

which says that specifically.

The second area I'd like to address is relevance to humans. And I want to use an overhead.

I've tried to identify the possible levels of relevance to humans using animal data. And it ranges from No. 1, which is known not to be relevant to humans to No. 5, which is known to be relevant to humans.

As I understand it, the proposed criteria propose to list things that caused cancer in animals unless they're known not to be relevant to humans. That's No. 1. But presumably, 2, 3, 4, 5, would result in listing. And I've been thinking about where I would draw the line.

I'm not sure at this point where I would draw the line. I definitely would not draw it after No. 1. I would for sure at least draw it after No. 2. And I'm not sure how much further, if any, I would go down that list. But to put things on where you feel they're probably not relevant to humans, I think, is inconsistent with the "clearly-shown" standard.

I've also suggested in the handout some specific language for how to deal with this. And the way I would express it is, if the weight of the scientific evidence clearly shows that a chemical causes invasive cancer in animals, I'd include the stuff you've got in humans, but in animals through a mechanism appropriate for extrapolation to humans.

There's also -- the criteria contemplate two possible outcomes. One is you list a chemical, the second is you don't list a chemical. There's a third option, which is presented by Proposition 65. And I'd suggest that you include that third option in your criteria.

That third option is, under Prop 65, the Governor has to publish, at least annually, a list of chemicals that the State's qualified experts -- that's all of you -- have not found to have been adequately tested as required by state and federal regulations. The purpose is so the State can recommend those chemicals for additional testing. So you have the option of putting chemicals on that list.

There is a list out there, but it's

probably the most under-utilized part of Proposition 65. And I'd suggest that you revise your criteria to add a sentence to remind yourselves that that's a third option which is not very often taken but available to you.

In the interest of time, I've got comments on scientifically valid testing. You should make sure that your criteria address that aspect of it. And I have some suggestions in the written comments which you can read. And there are also comments on what amount of testing, the one-species issue, where you draw the lines, things that you should consider there.

So I've tried to highlight some of my comments in five minutes. It's a little frustrating because I think given the experience I've had, I have, you know, a lot of things that I could share with you and offer you. And, you know, to spend 15 minutes on zineb, which John pointed out doesn't really matter to anybody, I mean this -- you're going to have to live with these criteria for a lot of years.

And I'd be the first to say that you need to have flexibility, because the science is going to change. But you want to make sure you get it right. And it's worth spending some time. You don't need to drag this out over, you know, a long period of time. But, you know, there are a lot of people who have things that I think would be of value to you to know about. So I'll stop at this point.

Thank you.

DR. MACK: Thanks, Jay. In fact, we will look at the documents you provided carefully.

Pat Beatty?

DR. BEATTY: Thank you, Mr. Chairman. My name is Patrick Beatty. I'm a toxicologist with Chevron Research and Technology Company. And I'm here today representing the Western States Petroleum Association.

Basically, let me say that in representing WSPA, we are supportive of the idea of generating criteria. They do set a tone for consistency in a body which will change its composition with time. We are also very pleased, I think, to see that the "weight of evidence" approach is incorporated into the

guidelines.

That weight of evidence, as evidenced today by the discussion and the presentations by Staff have included not just the dueling bioassays that sometimes occur, but also the mechanistic, the SAR, and the mutagenistic type of evidence.

However, having said that about weight of evidence, we have some concerns in some of the language of the criteria, which seem to at least be interpreted or could be interpreted in a way that would discourage or even preclude the use of some kinds of data, specifically data the would be negative or would argue against potential identification of a compound.

And it seems to be that a higher hurdle or higher standard of proof is being set for some types of negative data than for more positive data. As a couple of very brief examples, in both the human and animal sections, there is the *II.e* section, where it says that "the plausibility of causation is undiminished or enhanced by detailed characteristics of the observed association as

follows", and then it lists anywhere from 8 to 5 specific characteristics.

The concern there is that these characteristics, if they exist, may enhance the association, but if they do not exist, apparently they have no potential ability to argue against that association. And in the case of some of these, such as a dose response, that is somewhat problematic.

The other example is actually in No. 8 on that one, which says that "an informative negative study must fulfill all criteria". Now it's not quite clear to me in reading this which set of criteria that were previously discussed were being referred to, but there's no equivalent statement made about positive data meeting all criteria.

So sort of in conclusion, and to try to keep this brief, we are somewhat concerned that the guidelines, as written or by the language that has been used, could be interpreted in a way that would undermine the use of a weight of evidence approach. That seems to occur because, again, of setting a different standard for negative data as

opposed to positive data. We're concerned because the effect of this seems to be to rule out certain kinds of data, not based upon the validity of the study from which it comes, but from the type of data that it is, the nature of the results.

We certainly understand that there is uncertainty in scientific data. That's a fact of life for those of us who deal in the realm of science. But there are ways, as already mentioned in the document, the standard statistical methods of dealing with uncertainty to a certain extent.

The residual uncertainty that's left, we think, should not be used to disqualify data a priori, but rather should be reserved to the end and for the very valid exercise of the professional judgement, which is why we have expert panels. So that, we feel, is the more appropriate place for overall consideration of uncertainty and then bring that into the final decision.

And then finally, the language of the Proposition gives, I think, fairly clear guidance in that it says that the basis for

the decisions to list will be based on scientifically valid testing according to generally accepted principles. I think if those criteria are used for the choice of studies, then I think we are well on the way to having the kind of outcome that I think will serve all of us well.

And therefore, thank you.

DR. MACK: Thank you, Mr. Beatty. I presume we're going to have a copy of your suggestions?

DR. BEATTY: Right. I will have more detailed comments and specific wording suggestions with written comments.

DR. MACK: Thank you.

Dr. North?

DR. NORTH: I'm Warner North, with NorthWorks. Since this was not part of my assignment, I believe I'm speaking for myself. And as a former member of the Science Advisory Panel, which preceded the CIC.

I very much applaud your efforts. I believe that my four predecessors, in speaking to you, have also done so. You have a very hard job. In my term, we wrestled with the

issue of how to list carcinogens, and took the position that we would use EPA's criteria for sufficient evidence in animals and sufficient evidence in humans. We did this without a lot of discussion.

I think it's wonderful for you to have this kind of discussion at this time. I applaud your efforts, and I urge you to devote a subsequent meeting to it as well for opportunity for more comment, and frankly, for the group of you to do more polishing of the kind that you've already started to do.

I'd like to briefly endorse Jay Murray's point about changing "indicate" to something to be consistent with "clearly shown", the criteria that's in the law. Next, I'd like to suggest to you something that Jim Swenberg suggested to me on the phone last night -- when we briefly discussed this -- that you pay more attention to some traditional criteria that had been used in evaluating animal studies; for example, dose response, meaning evidence that there is increasing tumor incidence at higher doses, decrease in the latency period, multiplicity of tumors.

Perhaps you think that all of this is obvious. But I think it would be very useful for you to put it the criteria, using language which I believe is fairly standard in toxicology.

The issue of maximum tolerated dose has come up. I didn't find that explicitly set forth in your criteria, and I think that needs to be. The issue of "is it a good study?" often depends on judgement on the maximum tolerated dose.

Finally, I'd like to endorse the theme that John Froines and others of you have discussed today about mechanism. It seems to me that many groups are trying to deal with this issue. EPA certainly is. The National Academy Report, *Science and Judgement*, tried to provide guidance to EPA. And as EPA moves forward to finalize their guidance -- their guidelines -- and then do a series of case studies that illustrate the application of the guidelines, I think they will provide a lot of very interesting insights for you.

I would also commend to you the *Presidential Commission on Risk Assessment and*

Risk Management, which has much discussion on the issue of how to use mechanistic information. I thought Jay Murray had an excellent suggestion for you, actually two of them. One, his viewgraph showing the various levels, and then the question of using this provision in Prop 65 to require more testing. In situations where the mechanism is probable, but shall we say it might be made more certain by additional testing, I think you're in a position to encourage this. I would urge you to incorporate that into the criteria.

Thank you very much.

DR. MACK: Thank you, Dr. North.

Let me first say that all five of you have been very positive and very useful, and we will, in fact, take these remarks very seriously.

Jim?

DR. FELTON: I just wanted to say the same thing. I thought those were all very helpful comments. I just want to put up one caution. As a member of this committee, and I think the other members may believe the same, we were called to serve on this committee

because we using our "expertise" to make decisions. If we make this too specific, and it ends up being like an IRS form, where if you get four out of eight tumors you go to Line 4, and you make another comment, then there's no point in us being here.

And so this is a fine line between having criteria and having us look at it before we make a judgement, and putting so much information and specifics in here that we're really not serving anybody. So, just a caution.

DR. MACK: Thank you. Now we have one more item on the agenda. But before I forget it, I just want to tell the Staff how much we appreciate the work that they did today and that they do each time, because it is an incredible amount of work.

And the degree to which you can succinctly present the material for our edification is really, really helpful. And we really appreciate it. And in fact, privately, we've discussed it among ourselves repeatedly at every meeting. And I just want to make sure we say it to you formally.

Jim, do you want to discuss your beef?

DR. FELTON: Yeah. I can be very quick. But, you know, in thinking about the topic we haven't talked about today, which is selection of chemicals to be listed or to be considered, after the tamoxifen event, I might call it, which took an incredible amount of our time and the State's time, and in looking at it a second time, I just didn't feel that was well served to be putting that much emphasis of our efforts into a prescribed drug.

And then a number of months ago, I was talking to Jay Murray about this, and he made the same suggestion. And I probably wouldn't have said anything to the Committee, but he suggested it might be a good idea to write a letter.

So enclosed in here is a letter that I wrote. And it was my ideas and my letter that you see, but Jay did stir me to write that letter. And so, basically it says that I think we should take prescription drugs that are important but not give them as high a priority as some of the environmental chemicals. And that's all.

DR. MACK: Who wants to speak next? Who do we have to speak next? Is it Colleen or is it somebody on the Staff? Martha. They're looking all back and forth. They all rest on Martha.

DR. FROINES: Is Jim's point -- are we going to talk about that?

DR. MACK: Martha's going to present the Staff's view of that issue.

DR. SANDY: I thought it would be helpful to give you some information. To date, 90 pharmaceuticals have been listed to cause cancer under Proposition 65 by different mechanisms, as shown on this slide. 13 were placed on the list based on the Labor Code, 11 based on Court Order, 43 were listed based on determinations by the State's Qualified Experts, 15 by the authoritative bodies mechanism, and 8 by the Formally Required to be Labeled or Identified mechanism.

Since 1994, this Committee has had brought before it two pharmaceuticals for consideration for listing; tamoxifen, which is prescribed to treat and to prevent breast cancer, and the pediatric sedative, chloral

hydrate. At the Committee's recommendation, tamoxifen was placed on the list, chloral hydrate was not.

If Cindy would just show -- there's several slides just showing you the different pharmaceuticals that are on the list. I'm not going to read through them. You might just flip through.

Next slide. And the next slide.

This just shows the diversity of drugs that are on the list.

Thank you. And now, if you could put the next slide up.

And now, if we turn to prioritization, and we look at the most recent batch of chemicals that we have prioritized with respect to carcinogenicity concern -- that's Batch 3 --out of 60 chemicals randomly selected for prioritization, 12 are drugs. Two of these, estradiol mustard and ICRF-159, appear to have been used only experimentally, however.

In prioritizing chemicals, chemicals of high carcinogenicity concern are placed on the Candidate List, and it is from the Candidate

List that OEHHA selects chemicals to bring before this committee for hazard identification and consideration for a listing as causing cancer.

According to OEHHA's Prioritization procedure, chemicals that are not of high carcinogenicity concern are placed in Category II. As shown here, OEHHA's finalized the priorities of 9 of the drugs in Batch 3. Bleomycin and its salts, isophosphamide, estradiol mustard, and ICRF-159 have been finalized as high carcinogenicity concern and placed on the Candidate List. Still draft -- still to be finalized are lovastatin, methylphenidate and its hydrochloride, and Phenelzine and its salts.

We have finalized and placed in Category II antipyrine, dibromomannitol, diltiazem and omeprazole. And one chemical, 1-butanol, was found to have inadequate data for prioritization.

Thank you.

The last bit of information I wanted to provide was, looking at the chemicals we're currently tracking in our prioritization

database, that have yet to be selected for prioritization, we currently have 73 chemicals, which are pharmaceuticals. That's out of a total of 486 that we're tracking.

Thank you.

MS. HECK: I had a few remarks just on the legal consequences tied up with the prescription drug issue. The long and the short of it is that the lead agency, in its powers as lead agency, has adopted a regulation which provides that for prescription drugs, the labeling approved or otherwise provided under federal law, and the prescriber's accepted practice of obtaining a patient's informed consent shall be deemed to be a clear and reasonable warning.

In other words, some people have looked down the road to what are the consequences of listing a prescription drug. And the net result is, as a function of this regulation, no new warnings are triggered as long as the parties involved are in compliance with the federally required labeling requirements and informed consent provisions.

This is a factor that has been raised in

terms of the prioritization principles. There was recent litigation, in which Mr. Weil represented the State as Deputy Attorney General, that confirmed the vitality of this regulation, if you will, that it says what it says; that is, no matter how obtuse or difficult or technical the federally approved warning language may be, it is sufficient for purposes of complying with Proposition 65.

So I think Mr. Weil has a few follow-up remarks in that regard as the Counsel in that case.

MR. WEIL: Well, what I wanted to suggest to you from that case is that it did say that this regulation, you know, means -- and it's nice the way Colleen put it as confirming the vitality of the regulation. What it meant is that Prop 65 is unenforceable as to prescription drugs that comply with federal law.

But before you use that as part of your hazard identification process, you should be aware that regulations can change, that as a result of that interpretation, the legal validity of that regulation is in question.

You should also know that you do sometimes have prescription drugs that go over the counter. And this regulation does not apply to over-the-counter drugs.

So there are a number of reasons looking down the road why you might want to consider a chemical that's present in a pharmaceutical drug, anyway, and not withstanding the fact that in the short run, there might not be any actual new warning provided out there in the world as a result of it, and keeping in mind that there's a one-year delay.

If you had something where the circumstances changed, and as a result you did want to put it on the list, nothing would happen for a year after that, because you have that one-year grace period built in.

So I know there was some talk among the Committee earlier that they did not want to get into the risk management and other policy aspects in doing the hazard identification. And if that's the Committee's view, it would suggest that you might not want to go too far down the road of deprioritizing pharmaceuticals based on the existence of that

regulatory language.

DR. MACK: Thanks, Ed.

John, you were the first one to say something. You want to say something? Okay. Well, let me say something and you'll get to.

If the motivation for lowering the priority of medicaments is the tamoxifen story, I really don't think it was specific to the pharmaceutical industry, necessarily. We actually passed tamoxifen fairly efficiently. There was very little debate about it. The problem was that the company involved decided that they were going to make a full-court press and prevent that listing in every way they could think of.

Now, it's conceivable that a company that produced another product might do the same thing. I don't have any candidates. But it just happens that that company felt that the listing would do them harm, which I think was in error. But nonetheless, that's the way they felt. And that's what caused the problem.

Now, are we concerned that it's just pharmaceutical manufacturers that would have

that reaction, and do we want to avoid it for that reason? Or, are you concerned that doctors have eminent good sense and always tell patients whether there's a danger in something that they take? I don't believe that. But I do believe that the warning in the drug box is pretty good. The problem is that the doctor very rarely points it out.

So I think for my purposes, the most important thing is the criteria that John keeps harping on, namely the frequency of use and the frequency of exposure. If I look at the list that she put up there, the one that hits my eye is Ritalin. I'd hate to see us lower the priority of Ritalin, just because it's a drug.

On the other hand, in terms of the notification section of Prop 65, as Colleen pointed out, it doesn't make any difference because it's going to be on the label, if FDA has decided it's carcinogenic. But the others up there, I think they can be prioritized depending on their frequency more than anything else.

DR. FELTON: I just want to comment on

that. I think maybe your respect for physicians is different than mine, since you come at it from a different --

DR. MACK: Because I'm a physician. Yes.

DR. FELTON: Yeah. But my feeling along this was really based on that, that I didn't think that us labeling a drug in long term helps the healthcare -- I don't know how to describe this. I guess I trust the physicians more than you do.

The public is not going to get these drugs that we label as carcinogens unless a physician gives it to them. It's just an entirely different situation than an individual that has no concept of what they're consuming or coming in contact with. And so it just seems like a different criteria to me.

And that was the main reason for this. It wasn't the fact that we did go through our prolonged discussion about tamoxifen. It was more, this is controlled by physicians. We're putting another level of control on it, essentially, by putting a label on there.

DR. MACK: I don't have -- what's the word I want -- any illusions about the impact

that Prop 65 has on the average citizen, because it doesn't have much. But if we think it does have something, and we're doing this because we think it has something, what might be the impact, for example, on tamoxifen?

The impact is not going to be on whether doctors spend more time telling women who their prescribing tamoxifen for that there's a danger of endometrial cancer. But the fact is that a lot of doctors have not done that in the past. And if the woman sees in the newspaper or somewhere else that somebody has called tamoxifen a carcinogen, she might ask the doctor, thereby, she might get better informed about what the cons are.

Now, as you know, when we talked about it, we thought, it's a great drug. It does a lot of good for a lot of people. But some women are going to get endometrial cancer. And all women who take it should know about that possibility in advance. And I think if we have any impact on anything, we have that same impact on the pharmaceutical drugs.

DR. FELTON: Tom, can I just say one more thing? I mean, you saw the drug up there,

Bleomycin, that's coming up. To me, that seems like a waste. I mean, we give Bleomycin for a good reason, because it's a great carcinogen. And I don't want to waste my time labeling a good carcinogen that we're using to fight cancer with.

DR. MACK: Well, I think that --

DR. FELTON: Compounds like that, I guess, are different, and they all have different reasons. But these chemotherapeutic drugs that are supercarcinogens look like they're a waste of our time. And I guess the patient may or may not see the thing labeled with the words carcinogen on there, but they're worried about suppressing their cancer. I don't know what impact that would have either. But it just seems like a waste of time to me.

DR. FROINES: I was just going to say I agree with you to a certain extent because -- but that goes to the kind of judgement Staff should make about bringing chemicals forward. I would take a different example.

I would take, say, a blood pressure drug, or even Ritalin, a drug that people tend to

take on a chronic basis. And so therefore, they're average daily dose and their cumulative dose can be very, very high. Where you have circumstances like that, then I think it becomes extremely important for the public to have some sense of awareness that if I'm taking four pills of an antihypertensive drug every day for the next 30 years, I'd like to know if there was a health risk associated with that. I think that's extremely important.

I think the tamoxifen story is a story of success, not failure. And I think that we should pay attention to those chemicals that we think that the public should be informed about if there is a potential for major exposure that could have long-term health consequences. I think that's part of the responsibility that the State has to undertake.

DR. MACK: I think Phenacetin is an example of a drug which has some carcinogenic possibility, and which people are totally unaware of. Another example is estrogens, of course. Now women by and large are pretty

knowledgable. But there was a time when they sure weren't.

DR. FROINES: In fact, one could argue that Phenacetin is one that -- I actually, speaking to the Staff, would like to know where it is in this process, because clearly, Tylenol is a metabolite of Phenacetin and it's not a trivial medication.

DR. EASTMOND: It was listed, I believe.

DR. SANDY: It's listed. Yeah. Phenacetin is listed.

DR. EASTMOND: It comes on the IARC.

DR. FROINES: That's not the point.

MR. WEIL: If I could add a little background on the regulations and some of the enforcement here, partly to show how it can get difficult and complicated, on the chemotherapy drugs; for example, the regulations do provide that a different significant risk standard can be used for certain exposures where there's a countervailing public health interest. So it wouldn't necessarily follow that you would end up requiring cancer warnings for chemotherapy drugs with a 1 in 100,000 risk.

Other examples: Conjugated estrogen; because of the fact that it's on the Proposition 65 list, when the Attorney General received complaints that pharmacists were not providing the federally required labeling and were out of compliance with federal law, we were able to go to the Board of Pharmacy and tell them, "You'd better tell the pharmacists, here's an additional reason why they need to make sure to do this, because they will also be in violation of Prop 65 if they don't".

And finally, the case that got the issue raised in court concerning Lindane, which is the active ingredient in head lice treatment, and is very controversial and in fact the Department of Health Services recommends that it should not be prescribed at all, and very ably analyzed for being over the no significant risk level in normal treatment by the OEHHA Staff, we felt -- and we discovered -- that warnings should be given.

And we discovered that physicians generally, in fact almost exclusively never give warnings about this subject. But that is what led to the Court saying that may all well

be true, but this regulation says they don't have to.

But I would be reluctant to see this Committee get into trying to make all of those judgements down that very long road in deciding what ought to go on the list.

DR. SPANGLER: I don't think -- I agree with Jim. I mean, I think we've gotten, we've branched out here and gotten off the subject. I don't think that we want to do that in any way.

I think what Jim and what I would like to see is that those chemicals have a lower priority, not that they not be on the list. But let's look at some really, let's look at more important things, that the pharmaceutical companies -- there's already a warning, as you've said. There's a mandatory warning for all those compounds.

DR. MACK: Do you want us to take a vote?

DR. SPANGLER: I don't think that we can take a vote in the presence of the Staff. There is a discussion to let them know how the body feels about that particular subject.

I think that the Staff is going to do

what the Staff has to do. And I'm the last one up here that would ever want to do anything to offend or alienate the Staff.

DR. MACK: What Jim is sort of suggesting is that we ask the Staff to deprioritize on the basis of (inaudible) as opposed to their common use and prolonged use. And I think I agree with that, because I would prefer using a criteria that was related to abuse as opposed to --

DR. LANDOLPH: One thing that struck me was, in looking at some prescriptions that are out there, sometimes there's a lot of viable carcinogenicity. And it's blown off. Nobody pays any attention to it. And I think once in a while, in certain cases, it may be in the public's interest to know about that.

Now, I'm not -- chemotherapeutic agents is one thing. People have no choice. They either use these or die from the cancer. That's one thing. I've actually found it surprising how many prescription drugs have a lot of genotoxic activity.

I guess my recommendation would probably be to take a look at those for the reasons

John pointed out, but not all of them.

DR. MACK: You happy with the discussion?

DR. FELTON: No. That's a common problem, obviously. And I have no answer to it. But if I have a drug label, I'll take the drug. It's not my call. As an individual, I guess I'm just having trouble seeing how this label isn't anything more than confusing to the patient rather than a help.

DR. MACK: Isn't that the way complex information is? It's confusing to the patient.

DR. FELTON: I guess I trust physicians more than Tom.

DR. FROINES: I went to a dermatologist, and he gave me a fungal treatment. And I thought, I've seen that someplace before. So I went over to my IARC book. And when I finished reading the IARC book on this particular compound, I went back and asked him for a different prescription. He said, "No problem. It's not a carcinogen". I said, "I think it is, and you're in my window, not yours". And with that, he gave me a different prescription.

DR. MACK: Another example is metronidazole, a drug used to treat amoebic abscesses and other single-celled organisms. It's a very widely used drug. And the women who use it have absolutely no idea that it is carcinogenic.

DR. FROINES: The document says 5:00, which means the meeting must end.

DR. ALEXEEFF: We have listed a number of chemicals, probably most of them that do have warning labels on them and those where there's kind of a dual listing, let's say. But for the ones that we have, for example on the Boards that we are in the process of finally trying to finalize our prioritization, they have not been labeled as carcinogens.

MR. ROBERTS: May I --

DR. MACK: Can you do it in two minutes?

MR. ROBERTS: I can try.

From my perspective, and the perspective of the pharmaceutical companies that I represent, if you all are examining your valuable time, you might want to de-emphasize the examination of pharmaceuticals, because as Ed and Colleen said, the net effect of your

examination is zero in the short term.

Now, Ed points out that circumstances may change. And if circumstances change, certainly you can change them. But in terms of allocating your resources, I think that's something to keep in mind.

I also believe that it's something to keep in mind that FDA, a reliable expert body, is keeping a close eye on the carcinogens that are under its jurisdiction, and all prescription drugs are. All prescription drugs have cancer information in the package insert that is conveyed to the doctor.

And so I disagree with Mr. Alexeeff in his characterization that all pharmaceutical drugs do not have cancer information as conveyed to the doctor.

DR. EASTMOND: I don't believe that counts for anticancer drugs, because a lot of times the testing is not done.

DR. MACK: Okay. That wraps it up. Thank you for your kind attendance. The meeting is hereby brought to a halt.

(Proceedings concluded at 5:05 p.m.)