CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986

(PROPOSITION 65)

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MEETING OF THE SCIENCE ADVISORY BOARD'S

CARCINOGEN IDENTIFICATION COMMITTEE (CIC)

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TUESDAY, DECEMBER 18, 2001

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HELD AT:

California Environmental Protection Agency
Headquarters Building
1001 I Street
Sacramento, California

Reported By: PHYLLIS MANK, CSR No. 5093

ORIGINAL

INDEX

---o0o---

INDEX (Continued)

---o0o---

INDEX (Continued)

---o0o---

SACRAMENTO, CALIFORNIA

TUESDAY, DECEMBER 18, 2001

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DR. DENTON: Good morning to you all. We think there are probably a few more people that probably haven't quite cleared security, but we're going to go ahead and get started.

My name is Joan Denton, and I'm the Director of the Office of Environmental Health Hazard Assessment. This is the official meeting of the Carcinogen Identification Committee.

I would like to introduce the panel members who are here. To my far right is Dr. James Felton. Next to him, Dr. David Eastmond. To my immediate left is Dr. John Peters, and Dr. Peters will be the acting chair for today's meeting. Next to him is Dr. Bill Spangler, and at the end is Dr. Joe Landolph.

Since the last time that the committee met, Dr. John Froines resigned from the committee, so he is no longer on the committee, and Dr. Mack was unable to be here today so he asked Dr. Peters to perform the duties of acting chair, and Dr. Peters graciously accepted the position.

I'd like to welcome everyone to the new building. We've been here a little over a year, and

this is the first time we've had an opportunity to host a meeting of the CIC, and yesterday we had a meeting of the Developmental and Reproductive Toxicant Committee. We hope that in future years we'll be able to at least have some of those meetings in this facility.

I guess that's all I had to say. We have copies of the agenda in the back.

So with that, Colleen.

MS. HECK: I just want to get one procedural issue out of the way before we get into the meat of the meeting; and that is, you'll notice that there's five of you and typically there are seven.

I just want to clarify that OEHHA has received a legal opinion from the Attorney General's Office that this is a properly-constituted quorum, that it is lawful to meet with less than the typical seven.

But there is one additional wrinkle, which is, under the counting rules for votes and what it would take to take action typically to list or de-list a chemical, four votes are still required even though there are only five.

Because typically this committee should consist of seven, a majority of what your normal composition is required, so that's four. So even though there are five of you, it will still take four votes to take any action

by this committee.

DR. DENTON: Thank you. I'll turn it over to Dr. Peters.

CHAIRMAN PETERS: This is my first opportunity to chair this group, and I'm asking Dr. Denton to stay close to my right elbow and prompt me if I make any procedural mistakes.

The first thing we want to consider is the compound allyl isovalerate, and as I understand it, we will first have a staff presentation.

Dr. Faust.

DR. FAUST: Yes, good morning.

The first compound under consideration is allyl isovalerate. Shown here on the first slide are the chemical structure of this branch-chained allyl ester, it's molecular weight and CAS registry number.

The primary use of allyl isovalerate is as a flavoring agent with fruit-like organoleptic properties. The compound is synthetic and is not known to occur naturally.

The Food and Drug Administration has included the compound on a list of chemicals which may be safely used in foods.

Although recent data on levels to which people may be exposed were not located, available data indicate

the concentrations in food in which it is present are frequently in excess of ten parts per million.

Given allyl isovalerate approved use as a flavoring agent and its reported levels in some foods, it is expected that widespread exposure of the general population to low levels of this compound may occur.

This slide summarizes the available data regarding the carcinogenicity of allyl isovalerate. No data were available from humans.

With respect to experimental animals, long-term exposure studies were initiated under the National Cancer Institute's Carcinogenesis Testing Program and later published by the National Toxicology Program.

Briefly, male and female B6C3F1 mice and Fisher 344 rats (50 per group) were treated by oral gavage with two doses of allyl isovalerate in corn oil with an equal number of control animals receiving corn oil alone. Treatments were five days a week for 103 weeks.

The B6C3F1 mice originated from a C3H parental strain with a high degree of variance at one to three genetic loci. However, control and treated groups are expected to have the same degree of genetic heterogeneity.

The slides that follow describe the primary tumor data from these experiments.

Among male rats, a significant increase in mononuclear cell leukemia was observed in the high dose group. This increase showed a significant positive linear trend.

A significant increase in combined adenomas and carcinomas of the preputial gland was also observed in the low dose group, but not in the high dose group, although two such tumors were observed. The test for linear positive trend was not significant.

Among female rats, no significant increases in tumor incidences were observed in allyl isovalerate-treated animals, although a marginally positive linear trend for combined leukemias was observed.

Among male B6C3F1 mice, a marginally positive linear trend was observed for squamous cell papillomas of the gastric mucosa, although the increase was not statistically significant in either of the treatment groups relative to the control group.

In female mice, overall survival was reduced in the low dose group due to what NTP called suppurative lesions in the ovary and uterus.

Among female mice, a significant positive trend was observed for histiocytic malignant lymphomas, although the increase was only marginally statistically

significant in either of the treated groups relative to the control group by Fisher's exact test.

When all lymphomas were combined, there was a marginally significant increase in the incidence in the high dose group relative to the controls and a marginally significant positive linear trend.

Life Table analysis showed the increase in incidence to be statistically significant in the high dose group relative to controls.

This slide summarizes the overall animal data from the NTP studies.

Male rats showed an increased incidence and positive trend in mononuclear cell leukemia. An increase in preputial gland tumor incidence was observed in the low dose group alone.

Female rats showed a marginally significant positive trend in leukemias, primarily mononuclear cell. Male mice showed a marginally positive trend in papillomas of the gastric mucosa, and female mice showed an increase in the incidence of malignant lymphomas with a positive trend.

Allyl isovalerate has been tested in numerous in vitro assays for genotoxicity, including bacterial and mammalian assays. The compound did not induce mutagenicity in several strains of Salmonella, with or

without metabolic activation.

Allyl isovalerate tested positive for increases in both sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells.

A positive finding in a mouse lymphoma cell assay has been reported by the National Toxicology Program and is referred to in a paper by Tennant et al., although primary source for this information was not located.

A positive finding -- allyl isovalerate did not induce morphological transformation in the mouse 3T3 cells, nor did it induce sex-linked recessive lethal mutations in Drosophila.

While allyl isovalerate has not been examined for metabolism in vivo, a metabolic scheme has been proposed for allyl esters and is presented in this slide.

Allyl esters are proposed to be hydrolized to allyl alcohol and a corresponding alkyl ester. Allyl alcohol may then be hydrolyzed to acrolein or glycidol. The alkyl ester, isovaleric acid, may be converted to isovaleryl-Coenzyme A. Allyl alcohol and acrolein may undergo epoxidation to glycidol and glycidaldehyde respectively and then may be further oxidized to glycerol and glyceraldehyde.

The proposed intermediate metabolites, which appear in red, glycidol and glycidaldehyde, are on the Proposition 65 list of chemicals known to cause cancer.

Glycidaldehyde has been shown to produce application site tumors in skin painting and subcutaneous injection studies. Glycidol produces tumors at numerous sites in rats and mice following oral administration.

Two compounds with some structural similarity to allyl isovalerate, both allyl esters, have been tested in long-term exposure studies. They are diallyl phthalate and allyl hexanoate.

NTP reported equivocal evidence for carcinogenicity of diallyl phthalate in male and female mice. Males showed positive increasing trends for lymphoma and lymphoma or leukemia. There were positive trends for forestomach papillomas in both sexes.

Female rats showed equivocal evidence of mononuclear cell leukemia. Positive tests for chromosome aberrations and sister chromatid exchange have been reported for this compound, although there's negative Salmonella assays.

Allyl hexanoate was reported to induce bile duct adenomas in rats treated in diet, although the details available for this study were limited. No genotoxicity

data were located.

Overall, the evidence for the carcinogenicity of allyl isovalerate includes positive findings of hematopoietic tumors in male rats and female mice in long-term gavage studies.

Other relevant evidence include positive findings for genotoxicity, possible metabolic conversion to carcinogenic compounds and structural similarity to other compounds shown to cause tumors.

Two authoritative bodies have assessed the carcinogenicity of allyl isovalerate.

The NTP concluded in their report of the bioassay results that, under the conditions of these studies, allyl isovalerate was carcinogenic for F344/N rats and B6C3F1 mice, causing increased incidences of hematopoietic system neoplasms, mononuclear cell leukemia in male rats, and lymphoma in female mice.

IARC has placed allyl isovalerate in Group 3, not classifiable as to its carcinogenicity to humans, based on limited evidence in experimental animals and no human data.

IARC described the animal evidence as follows. Allyl isovalerate was tested for carcinogenicity by gavage in mice and rats. In mice, it induced squamous cell papillomas of the forestomach in males, and

increased the incidence of lymphomas in females. In rats of both sexes, increases in the incidence of mononuclear cell leukemia were observed.

That concludes the presentation.

CHAIRMAN PETERS: Thank you very much.

Are there any comments or questions from the committee regarding this report?

DR. EASTMOND: I have one.

In the NTP evaluation when they tested -- well, I guess I should back off.

On the diallyl phthalate where they saw the similar sorts of tumors, although they saw the increases, they considered those equivocal. Can you kind of go through the rationale or why you think they came up with that? Any explanation?

DR. FAUST: Well, I think it was because of the trend verses the statistically significant increases in the incidence.

DR. EASTMOND: You mean, the individual doses?

DR. FAUST: As I said, the mice showed positive increasing trends for lymphoma or lymphoma or leukemia in males and positive -- yes. Were you referring to the rats or the mice?

DR. EASTMOND: Well, they're similar in both cases. It seems like it describes there are some

positive trends for an increase, and yet they considered it equivocal. In the parallel way, in this study here we have positive trends are positive trends. Yet, in this case, it's not called positive.

So I'm trying to get a sense of if you know. If you don't know, that's okay.

DR. FAUST: I don't know the answer as to why they called it equivocal, but I think it would rest with the significance of the increase in the treated group versus control.

CHAIRMAN PETERS: Are there any other comments or questions from our committee?

Dr. Spangler.

DR. SPANGLER: I believe this compound is also responsible for a decrease in several forms of neoplasms in rats. How do you deal with that in your analysis of the --

DR. FAUST: We presented the increases -- or decreases in tumor incidence in the description of the studies. We generally consider that an increase in tumor incidence is a cause for concern, so it didn't add --

DR. SPANGLER: In other words, it doesn't impact your decision at all as to how you approach it?

DR. FAUST: No.

DR. SANDY: The purpose of the hazard identification document is to present the evidence of carcinogenicity to you, the committee, to make a decision.

If you're referring to how we do a dose response assessment, then that's a different question, and there we're looking at the dose response and tumor response.

DR. SPANGLER: I was just thinking philosophically, if you have a compound that maybe marginally increases one type of hematopoietic neoplasm in one sex, in rats for instance, but this compound causes a dramatic decrease in four or five tumors that normally occur in a population of rats, would that bring any weight to bear on your decision at all as to how to evaluate the compound?

DR. SANDY: Again, I think we summarize all the data and present the data for your committee for the decision as to whether it's been clearly shown to cause cancer.

CHAIRMAN PETERS: Dr. Landolph.

DR. LANDOLPH: There is a precedent for what I think Dr. Spangler is alluding to, and I'm thinking of dioxin, which has hormonal antagonistic properties, but it's pretty widely accepted now as a carcinogen, a tumor promoter, but it does decrease the incidence of tumors

at other sites. It just has hormonal antagonistic properties, so there is precedent for that in other situations.

CHAIRMAN PETERS: Dr. Felton.

DR. FELTON: The one thing that we hadn't really talked about before, which I'd like to ask a question about is, looking at these large control studies that NTP did -- in one case there was seven sites in the rat, and I think in six different locations in the mouse -- is this really -- this was in the data that you gave us to look over -- is this really a good way to do this?

I mean, what you really want is to control data from the same location where the tumor studies were done, and yet the NTP took six or seven sites and got large numbers, but I'm not convinced that's the best comparison to use.

Now, you didn't use the argument of these large control studies in your discussion, but I was trying to use them in my mind, and I have trouble using that data. I just wanted your comment on that.

DR. FAUST: Well, we included the information because NTP had done so in their report. As far as how you might weight it, that is your judgment. It's there for you to use or not to use.

DR. FELTON: I think the data gives us a pretty

good background on that particular strain, but what you really want to look at in controls is whether there's some environmental impact in the location where the particular tumor study went on, whether it's the feed or the air or -- I don't know -- the cages.

So I have a hard time using that particular data when we're so close on deciding whether there's statistical significance here.

DR. EASTMOND: I have a minor question. With regards to the historical control coincidence, I think it's actually very important to the compound to look at those and evaluate the responses in that context. In some respect, a lot of these strike me as frequent -- in some cases, they're outside of the historical range and sometimes within it.

If you look at the historical range given for the same laboratory methods, the tests, which is on one page, and then put that -- apparently that's a subset of what's in the tables, so -- the information on the bottom of page seven, for example, talks about historical control incidences and gavage studies at Southern Research Institute, it's a subset of what's found on Table 4, the information on Table 4, but it seems like some of them are outside of the range.

So the range reported on female mice was between

ten and 22 percent incidence in this particular institute, and that's supposed to be a subset of this other group, and yet the range in the other only goes to 18 percent.

So I didn't know if these were covering different periods of time, or if this was just a minor somehow discrepancy between -- it's a minor thing, but I'm trying to get a feel for historical control frequencies.

Does everyone follow what I'm saying? It's a minor discrepancy, but it's fairly important when you start looking at these because you are looking at fairly high control frequencies, and then the treatment is increased but it's not a great increase. So I'm trying to get a feeling for that.

CHAIRMAN PETERS: Any response from the staff?

Any further questions from our committee?

DR. DENTON: Lauren, did you want to say something?

DR. ZEISE: Well, the historical control range I don't know with respect to this particular report, but it's frequently a three-year window for the historical control range that is used for comparison in the NTP studies.

As you suggest, it is quite possible that the

Southern Research Institute's historical control covers a broader time period and that might explain that discrepancy.

DR. EASTMOND: It seems to me in this case, if we're looking at -- this is in the female B6C3F1 mice. The control incidence in this case for malignant lymphomas is 22 percent, and that is the highest control incidence that they've seen.

So we're looking at a test in which controls have the highest, for instance, they've seen in this particular institute and among the highest that's been seen historically.

So an increase in tumors in a group that's always having a very, very high incidence for some unknown reason certainly plays a factor in the way I look at the data.

CHAIRMAN PETERS: Okay.

DR. FELTON: Can I ask David, so what you're saying is, your feeling from this data is that the Southern Institute had higher controls than the overall controls for the other locations based on the average?

DR. EASTMOND: What it says is the range is from ten to 22 percent, which is presumably a subset of what's in Table 4. But the range in Table 4 only goes to 18 percent, so there's a little bit of discrepancy

there.

But, in context, this is the study which had the highest control frequency that they've seen in actually probably any of these. So you're looking at an increase in the specific study in which the control frequency was the highest that had been seen in any of the -- not only this study and -- those studies conducted at Southern Research Institute, but apparently those also conducted at these other sites, the six study locations.

CHAIRMAN PETERS: Okay. If I understand the procedure, we're now ready for any public comments.

I see the name Jay Murray.

DR. MURRAY: Thank you, Chairman Peters. I'm Jay Murray. I'm here today on behalf of two organizations: the Flavor and Extract Manufacturers Association, and the Fragrance Materials Association. I'm only going to take one minute, literally.

I submitted written comments which I believe you all have and have read, and I'm not going to run back through everything that I had in the written comments. I'll just make a couple of very brief comments.

One is you've been talking a little bit about the female mouse lymphoma and some of the controversial aspects of the interpretation of the female mouse lymphoma, and it's not clear -- although we know what

the conclusions of the NTP bioassay were in 1983, it's doubtful that NTP would come to that same conclusion today, specifically with respect to lymphoma in female mice.

We've got an example from earlier this year of another compound that went through an NTP bioassay where there was an even more clear example of a statistically significant increase in lymphoma in female mice where NTP called that equivocal evidence in female mice.

Probably more importantly, NTP, as you all know, publishes its Report on Carcinogens, and they are compelled to include chemicals where they believe there is sufficient evidence of carcinogenicity in animals, and allyl isovalerate is not in the Ninth Edition of the Report on Carcinogens, which is the current edition. Also, remember, it hasn't been in any of the previous editions of the Report on Carcinogens.

So it looks to me like NTP, for whatever reason, didn't consider their own bioassay in '83 to be sufficient evidence to have allyl isovalerate be in the NTP Report on Carcinogens.

Finally, as Dr. Faust has already pointed out, IARC has also looked at this one, initially in 1985, more recently in 1999, and concluded that allyl isovalerate was not classifiable, gave it a Group 3.

And both NTP today and IARC, when it did its evaluation in 1999, is dealing with the same set of data that you're dealing with today. There's nothing that you're looking at, to my knowledge, that they didn't consider.

Thank you.

CHAIRMAN PETERS: Do we have any committee questions on the public comments? Please come back in case there are any questions. Does anybody have any questions?

I had one. I understood your arguments in the letter you provided except for one, and that was the old style NTP assays were two level and nowadays they're three.

Seems like the argument you made is reversed; that is, if you find something with two levels, you're more likely to have found it with three.

So could you comment on that, please?

DR. MURRAY: Yes. My point on that is that this is really one of the earlier NTP studies, and it was when NTP was using two dose levels of the test material rather than the three that they currently use.

My concern with that is that it's harder to look at a dose response relationship if you only have two dose levels rather than three.

So I thought -- that by itself is not a critical flaw in an NTP bioassay, but it certainly -- certainly you have more evidence if you have three dose levels because you can start to look at dose response. It also gives you another opportunity to know how much variability you're seeing in various tumor types within that current study. But that's the nature of the early NTP studies.

The other thing I remember about that is, remember, this is before NTP had its current classification system. This is before we had clear evidence, some evidence, equivocal evidence and so on.

In '83, NTP used the term "positive," it called this a positive study, but it was before the current classification system was in place.

CHAIRMAN PETERS: Thank you.

Dr. Eastmond.

DR. EASTMOND: As I recall, your document indicated there was no evidence for hematopoietic toxicity from this compound. Yet, in the document apparently there with some relatively minor effects seen in a follow-up study.

Did you notice that difference, and would you like to elaborate on that?

DR. MURRAY: The study you're referring to is

the NTP follow-up study where they were specifically looking for effects on the hematopoietic system --

DR. EASTMOND: I saw an increase in spleen weight and some changes in --

DR. MURRAY: They did, but my understanding is they didn't see the histologic changes that they were looking for that would give them a better sense that the hematopoietic system was a target.

The reason for NTP's doing the study, as I understand it, was NTP was having some trouble interpreting the study, and that was the trigger to go back and to look at the hematopoietic system to see if that was a target organ for toxicity. That was a study of much shorter duration than the two-year study.

But the idea was that if the hematopoietic system were a target, it would likely show up even in a study of shorter duration; and if that was a target, it would give increased confidence that this compound might cause hematopoietic tumors; but if it didn't show up, it would give less confidence that allyl isovalerate was really causing tumors of the hematopoietic system.

DR. EASTMOND: Your take is they didn't see any overt signs of hematopoietic toxicity, but they did see, using some subtle sorts of tests, changes in the spleen weight and colony forming units? They did see some

possible effects? Is that kind of the summary?

DR. MURRAY: That is correct. My understanding is their interpretation of that was that it was less likely that tumors of the hematopoietic system would be caused by allyl isovalerate because they didn't see more in their follow-up study.

CHAIRMAN PETERS: Dr. Felton.

DR. FELTON: I wanted a little more data, if it's possible, on the infection in the female mice. You describe it in your letter as a general infection. Did that ever get defined by the investigators as a specific agent? And how -- I mean, you also describe in there that animals died before their normal time. How sick were they? It would be interesting to know just more detail, if you had it.

DR. MURRAY: Dr. Felton, I don't remember what the specific cause was, and I'm not sure -- I just don't recall whether it was in the NTP report or not.

I do remember it was a high incidence, there were a number of early deaths, but it was seen in all three groups in female mice.

I know some people have looked at that and said, well, it's not such a problem because it was at least seen across the board, it's in the controls, the low and the high dose.

But I also think it's important to take into account you had something else going on at the time this study was done in the female mice, such that more than 50 percent of the female mice had died from the bacterial infection in all three groups.

CHAIRMAN PETERS: Okay. As I understand it, it's now the committee's opportunity to have our lead reviewers present their findings, and in this -- sorry.

DR. SANDY: I wonder if we might respond to some of the points?

CHAIRMAN PETERS: Absolutely.

DR. FAUST: In regard to the concern regarding its lack of appearance in the Report on Carcinogens, I did want to mention that the technical report process for NTP and the Report on Carcinogens are separate processes in that there are numerous compounds which have been tested in NTP protocols which have not entered into the report on carcinogen consideration. So that's there.

I also wanted to call your attention to an issue that you brought up before regarding the historical control incidence.

It appears that there is a transposition error in the table -- Table 4 in the document that, for those incidences -- the range of incidences reported at the

different test sites, the male and females were transposed there. So the true range for females is 4.2 to 34.7 percent, and among males, 0 to 18.2 percent.

CHAIRMAN PETERS: Thank you. That explains at least one puzzle.

DR. SPANGLER: I have another comment for Jim. I think he was asking about the NTP report does make specific mention of the reproductive tract pathology in the female mice.

But I think, typical for this kind of study, they really didn't investigate that to the fullest extent. I mean, they were characterized as suppurative lesions of the ovaries and the uterus, but they didn't culture the organism.

Presumably it was a bacteria, and they mentioned Klebsiella bacteria that is known to be associated with this type of change -- or has been associated with this type of change in mouse colonies in other studies.

CHAIRMAN PETERS: Okay. Now, back to the committees's presentations.

Dr. Landolph and Dr. Spangler have been asked to provided reviews, and we'll go to Dr. Landolph first.

DR. LANDOLPH: Okay. I read this data very carefully.In fact, I read Dr. Murray's critique first, and then I read the data just to make sure I looked

through everything.

I guess that's seeing chemicals as a function of time -- I think we're getting things which are less carcinogenic than others; i.e., we're working down towards scraping the bottom of the barrel as a function of time, so some of these data are not as clear-cut.

When I looked at Table 1, the mononuclear cell leukemia was dose responsive. The tumors went from 1 to 4 to 7, and the trend was statistically significant, and so I weighed dose responsiveness. Malignant lymphomas were 0, 0 and then 2 at the high end.

I looked at the female data, and certainly the control is highest, as pointed out, but the mononuclear cell leukemia goes 4, 6 and 8 out of roughly 50. The trend was not significant, but there is a dose response there. And the leukemias combined went from 4 to 6 to 9, and that trend was statistically significant.

In the mice studies, the gastric mucosa, that's the benign tumor, the squamous cell papilloma, that went from 0 to 1 to 3, and the trend was statistically significant.

All malignant lymphomas had a high background in the males, but they went from 4 to 6 to 8. The trend wasn't statistically significant, but there was evidence of a dose response there.

I also looked at the malignant lymphomas, histiocytic, and they went from 0 to 1 to 4, and that trend was statistically significant. All malignant lymphomas certainly had a horrendously high background, as was pointed out, but at the high dose, that was statistically significant, 11 versus 18, and "f" indicates that the trend was significant.

So I found it a little bit difficult to accept a null hypothesis, that there was no positivity here, even though the studies certainly are not perfect that the background was high. It's difficult for me to ignore that positive data.

The genotox, I think, adds a little bit in terms of the mutagenicity in the mouse L5178Y lymphoma system without S9 metabolic activation. And the chromosomal aberrations with S9 metabolic activation gives a tenfold increase, so there's some evidence that this compound caused mutations in chromosomes as well.

The business end of the molecule is certainly the dangerous part. It seems to be the allyl alcohol part which can be metabolized to acrolein and to other genotoxic molecules.

So when I integrated this data together, yeah, it's not perfect, but it led me to the conclusion that I would view this compound as a carcinogen.

I'd sure like to see NTP re-test it with their present tiering and their present skills, but I think, based on the data which we have here, I would vote positively in favor.

CHAIRMAN PETERS: Do we want any questions at this point or Dr. Spangler present his and then have a discussion?

Go ahead, Dr. Spangler.

DR. SPANGLER: I basically agree with Joe in the way he approached the problem. All of the analysis and data that -- I think overall I guess I have more doubts.

The summary of the peer review -- this study was peer reviewed by a group of people who came in and looked at the data and actually looked at the mice and rats, and they had -- these people had some serious doubts about -- well, they were ambivalent, I guess, and that probably sums up my feelings about this particular compound.

I agree that the weight of the evidence suggests it's probably a carcinogen, but I think -- to me, I think the data does not rise to the occasion that we use on this panel, and that is that this compound clearly causes cancer.

Based on all of the data that we have here, I can't myself say that I think this compound clearly

causes cancer. I think there is some equivocal data, and I think there's room on both sides of the fence. So that's my position on the compound.

CHAIRMAN PETERS: Okay. The subject is now open to discussion. Any questions from other committee members?

Dr. Felton.

DR. FELTON: You know, I looked this over. Joe's opening remark is the best part. You know, we're down to these toughies. If they were easy, I guess we wouldn't even be talking about them.

You bring in all the little factors about historical controls and infection and weak dose response in some cases, one decent dose response in another case, the lack of genotoxicity, obviously, it's so much on the edge, you could go either way on this one. It's really on the edge.

I guess I would be more inclined to go with the latter comments. It's just so close to being equivocal that there's no way -- at least I couldn't convince myself that this was really a solid case, so I probably would vote no on this one.

CHAIRMAN PETERS: Any other comments?

DR. EASTMOND: I'll echo a few of the things Jim said. Obviously, we're looking at a compound that does

have some general patterns and tendencies that makes it a little uncomfortable. It would certainly make me uncomfortable.

But on the other hand, when I look at these in context with the historical controls for those particular tumor types in those tissues, a lot of those -- these trends fall within the historical control range, which weakens the argument, from my perspective.

In addition, when we talk about statistical significance, certainly a number of them -- the increases are statistically significant using one particular type of test and another one it's not. We're really working right on the edge.

As far as the genotoxicity data, certainly with the positive structural chromosomal aberration, it seems to me that those concentrations are really very, very high. Probably -- it's 300 to 500 micrograms, which strikes me as a really high concentration. So that could be simply a high dose phenomenon in this particular assay.

As far as the mechanism, there are some postulated mechanisms going through that make some sense; but if, indeed, that was taking place -- well, if you can mimic that in vitro, you would expect them probably to be positive in the Ames test. The lack of

that in the Ames test is a little bit of concern. However, you probably do not get those metabolites formed given the complexity of the metabolic pathway.

So I have kind of mixed feelings about it, but as Bill indicated, my concern is the charge to the committee is really clear evidence and, to me, this falls into this much more fuzzy -- in the realm where I don't think it is quite as clear as I would be comfortable with.

CHAIRMAN PETERS: Any other comments?

I wish we had a clearer definition of "clear."

Any comments on that that might help this process?

DR. SPANGLER: I think my comment from the historical point of view is that it's clear that we're not going to get a clear definition of "clear."

CHAIRMAN PETERS: So, Joe, do you have anything further, or are we ready to vote?

DR. LANDOLPH: I think we're pretty much ready to vote. I also was struck by the positive carcinogenicity of the allyl chloride and the allyl hexanoate and the fact that you have positives in the two species.So that worried me about this compound.

Regardless, if we vote negatively on it overall, I would like to see perhaps Dr. Denton and staff

recommend to NTP to get a better animal carcinogenicity test, however this comes out.

CHAIRMAN PETERS: Any other comments or issues?

I assume somebody will make a motion. I have two scripts.One says: Please indicate by a show of hands if, in your opinion, allyl isovalerate has been clearly shown.And the other one is: Has not been clearly shown. Which one should I read? Okay.

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

We have one vote, and that ends it, doesn't it? The record should reflect one vote was cast to add allyl isovalerate to the Proposition 65 list as causing cancer. The majority, which in this case is four, of the appointed members is required to add a chemical to the list. Accordingly, allyl isovalerate is not added to the Proposition 65 list.

With enough coaching, I could get this right.

Okay, let's move on to the compound N-carboxymethyl-N-nitrosourea, and we're ready for the staff presentation.

Dr. McDonald.

DR. McDONALD: Hello, everyone. My name is Tom

McDonald, and I'll be presenting the evidence of carcinogenicity for N-carboxymethyl-N-nitrosourea, which throughout my presentation I'll abbreviate as CMNU.

The structure of CMNU as well as its molecular weight and CAS number are shown on the first slide.

CMNU is a naturally occurring N-nitrosourea compound with no known commercial uses. CMNU is formed primarily from the reaction of glycocyamine and nitrite.

Glycocyamine is a direct metabolic precursor of creatin and is present in muscle. In other words, it's present in meat and meat products. Nitrite is a compound produced endogenously, is added to cured meat as a preservative and color enhancer and is a common drinking water contaminant. CMNU may also form from reaction of nitrite and hydantoic acid, which is found in some plants.

The typical daily dose of CMNU received by humans is unknown, but is expected to vary widely depending primarily on nitrite and meat intake.

The available carcinogenicity studies of CMNU are as follows.

In humans, OEHHA is not aware of any studies directly examining the potential associations of CMNU and cancer.

In experimental animals, the carcinogenicity of

CMNU has been investigated in two drinking water studies.

Buley et al. in 1979 treated male Wistar rats with CMNU in drinking water five days a week for 74 weeks and then followed them until death.

Maekawa et al. in 1983 dosed female Donryu rats with CMNU in drinking water on a daily basis for 68 weeks and then sacrificed the animals after dosing ceased.

CMNU has not been tested for carcinogenicity in mice.

With respect to the actions taken by authoritative bodies, none of the authoritative bodies shown on this slide have evaluated CMNU. Thus, to my knowledge, this committee is the first to evaluate this chemical for determination as a carcinogen.

The tumor findings among male rats from the Buley study are shown on this slide. Increases of adenocarcinomas of the large and small intestines were significantly increased relative to vehicle and untreated control animals.

These findings are important since in the next slide I will show intestinal tumors were also observed among female rats treated with CMNU.

Marginal increases in the incidences of squamous

cell carcinomas of the tongue and forestomach combined were also observed.

CMNU treated rats exhibited significantly increased incidence of squamous cell papillomas and carcinomas combined of the skin compared to vehicle or untreated controls.

This slide and the next describe the studies conducted by Maekawa et al. in female rats.

Increased incidences of intestinal hyperplasia, adenoma and adenocarcinoma were observed in the two highest groups compared to controls. Strong dose-related trends were observed for all three endpoints. Fibromas, fibrosarcomas and myosarcomas of the intestine were also observed in a few animals in the two highest dose groups.

Also, squamous cell tumors of the oral cavity were significantly increased with dose, significant by trend test only.

The findings of Maekawa et al. for the female CMNU treated rats continue on this slide.

The incidences of mammary fibroadenoma and total mammary tumors among CMNU treated rats were significantly increased in the low and mid dose groups, but not in the high dose group relative to controls.

The number of mammary tumors per tumor-bearing

rat was also elevated above controls for all treatment groups. However, the lack of increased incidence of mammary tumors in the high dose group questions whether the observation of increased rates in the lower dose groups are truly treatment related.

Also, among CMNU treated females, squamous cell tumors of the Zymbal's gland were significantly increased with dose, significant by trend test but not pairwise comparisons with controls.

Thus, to summarize the tumors findings, CMNU administered in the drinking water induced malignant cancers of the intestines in two independent studies, one in male Wistar rats and another in female Donryu rats. Treatment related increases in malignant cancers of the skin were also observed in male rats.

Increases in tumors of the Zymbal's gland were significant by trend test in female rats and increased tumors of the oral cavity were significant by trend test in females and marginally significant among males.

It is worth noting that the tumors of the skin, Zymbal's gland and oral cavity were all of the same cell type, squamous cell tumors. Findings of mammary tumors among female rats are unclear. CMNU, as I said before, has not been tested in mice.

Other relevant data with respect to CMNU's

carcinogenic potential include genotoxicity, structure activity, as well as mechanistic data.

Genotoxicity of CMNU is summarized in this slide. CMNU is a direct acting mutagen and clastogen. In bacterial assays, CMNU caused mutations in Salmonella, strains TA98, 100 or 1537, but not in 1535. CMNU caused mutations in E. coli in either a wild type or pair deficient strain.

In mammalian cells in vitro, CMNU caused mutations and chromosomal aberrations in Chinese hamster lung fibroblast cells.

No in vivo genotoxicity studies of CMNU were located.

CMNU bears strong structural resemblance to other N-alkyl-N-nitrosourea compounds such as the model carcinogens, methyl- and ethyl-nitrosourea, which are carcinogenic to rodents, pigs and primates.

Maekawa and his colleagues compared CMNU to other alkylnitrosourea compounds in rat drinking water studies conducted in their laboratory.

CMNU, like methyl-, ethyl-, propyl-, butyl- and isobutyl-N-nitrosourea caused tumors of the intestines or oral cavity.

Although the precise mechanism of carcinogenesis is not known, CMNU likely causes cancer through a

genotoxic mechanism. As mentioned earlier, CMNU caused mutations and chromosomal damage in short-term test systems.

CMNU is a carboxymethylating agent which likely gives rise to carboxymethyl-DNA adducts, which was reviewed by Harrison in 1997, although these adducts have not been directly measured.

Other carboxymethylating agents are carcinogenic and mutagenic.For example, azaserine and N-nitrosoglycocholic acid are compounds known to form carboxymethyl adducts with DNA in vivo.

Azaserine has been the subject of more than 50 publications demonstrating its ability to induce pancreatic cancer in animals. N-nitrosoglycocholic acid, when administered orally to rats, resulted in increases in stomach and liver cancer.

N-nitrosated peptides which contain glycine on the C-terminus, such as the ones shown here, are also expected to be carboxymethylating agents and have been observed to be carcinogenic in rodents.

Thus, a genotoxic mechanism is likely responsible for the observed carcinogenic effects of CMNU.

To summarize the evidence, CMNU induced intestinal tumors in two independent drinking water

studies: one in male rats and one in female rats.

CMNU also induced squamous cell carcinoma of the skin in male rats, and induced squamous cell tumors of the oral cavity and Zymbal's gland in female rats.

Other relevant evidence includes observations that CMNU is mutagenic and clastogenic in vitro. CMNU is also structurally similar to well-recognized carcinogens such as ENU. Also, other carboxymethylating agents, like CMNU, cause cancer in rodents.

Thank you, and I'd be happy to answer any questions.

CHAIRMAN PETERS: Do we have some questions? If not, we will go to public comments. If not, we'll go to committee presentations --

DR. EASTMOND: Can I ask a question?

CHAIRMAN PETERS: Yes.

DR. EASTMOND: I realize some of the primary articles you were looking at were difficult to tease out some of the information. There were some tumors in the adrenal gland that were mentioned, and according to the article they were statistically significant, but it was impossible to detect what the control incidence had been.

DR. McDONALD: That's correct. The author of the Buley study claimed that adrenal gland tumors were

significantly increased. Although, as I mentioned in the document, in the untreated controls there was also a relatively high incidence.

But the way -- the reporting being so poor, we couldn't tell if those tumors were in female or male rats because this was a study of many chemicals and also used females as controls for other nitrosourea compounds.

So I felt uncomfortable stating that this was truly a treatment related effect when we don't know what the true incidence in the controls are.

CHAIRMAN PETERS: I'd like to make one minor comment before we go on to the committee presentations; and that is, you should check the document for the spelling of the name Buley because it's spelled two different ways throughout.

DR. McDONALD: Thank you. I'll check that.

CHAIRMAN PETERS: In this case, we've assigned Dr. Eastmond and Dr. Felton to comment, and Dr. Eastmond will go first.

DR. EASTMOND: This is a compound that would be interesting to discuss on the committee. In contrast from the last compound, this is from a class of compounds which are widely recognized as being mutagenic and carcinogenic, although the specific compound has

much less data.

As I looked at this, there were really two animal studies, the two studies in different strains of rats, and there were some similarities between the two studies.

There were a lot of tumors increased -- well, there was an increase in tumors seen in both studies in the gastrointestinal tract. Depending on how you combine tumors together, you can get significant increases or not.

The ones I found to be probably the most convincing were the adenomas and the adenocarcinomas of the large and small intestines in which there was a significant dose-related increase in the Wistar rats and also in the Donryu female rats -- in fact, there was a very strong response in that particular strain of rats -- in which the tumor incidence increased from very low frequencies of 0 out of 36 animals to -- for adenomas, it was 23 out of 34, and adenocarcinomas increased in a dose-related fashion to 19 out of 34.

So that, I thought, was a very strong response, and there was consistency between these two different strains of rats.

There was also an increase in skin tumors seen in the male rats and not in the female rats. There was

a really strong increase in mammary tumors seen in the middle doses in the female rats, but not at the high dose. A very peculiar sort of dose response relationship. In addition, there were some other tumor types that were increased.

I also considered that this was -- the results were consistent with known chemical properties, it's a direct alkylating agent and similar carcinogenic and genotoxic results have been seen with other nitrosoureas and other carboxymethylating agents.

In addition, I looked at the mutagenicity data, and it appears to be fairly mutagenic. It also causes chromosomal aberrations.

I might point out, also, that I believe the concentration in which increases in structural chromosomal aberrations were seen in the Chinese hamster lung fibroblast cells may be incorrect in the document.

The table is a little confusing to read, but I believe, rather than being 12.5 micromoles, it's actually about 850 micromoles. That should be checked. The table heading is confusing to read, but I believe it's a higher concentration.

Anyway, the assessment really is that it's a mutagenic agent. It appears to be -- the DNA adducts seem to be fairly rapidly repaired. And this may be

consistent with some of the effects in some of the organs being relatively weak.

In my opinion, the real challenge here is that we have what I think is consistent data in two different strains of rats, but no data from the mouse.

DR. FELTON: Well, I don't have much to add. I mean, we're being asked to make the decision on this because we don't have the mouse data. If we had the mouse data, we wouldn't be discussing this compound.

My background and feeling on this is sort of similar to David's in that with this class of compounds, there's no reason to suspect that it's not going to be also a major dose dependent carcinogen in the mouse. We just don't have the data.

We're being asked to make a decision based on the genotoxicity, which is strong and expected for a class of compounds like this, and the results from the other relatives of this compound, which are also strong mutagenic carcinogens, and then we also have the strong -- I consider this strong rat data, but we don't have the mouse data.

So that's what we're being asked to make the decision on, and I guess I'm really leaning toward saying yes just because I have a hard time believing this isn't going to be a carcinogen in the mouse, and

the other data really supports it pretty strongly.

There's no negative data to suggest that it's -- the other compound we looked at earlier this morning was very equivocal, that is, positive and negative data. Everything here is positive. It's just that we don't have as much as we'd like to see.

So with the interpretation of the structure activity relationships and the genotoxicity, this looks like it's probably one we should worry about.

CHAIRMAN PETERS: Any other comments or questions from committee members?

DR. LANDOLPH: While you do have the genotoxicity data, as you point out, it does fit into the nitrosamine class, all those are carcinogenic, and yet the carcinoma data I found particularly compelling -- 0 to 1 to 9 to 19 tumors in the trend is pretty significant -- and you've got two different experiments in rats, although the first one didn't have extensive dosing data, just one dose, it all looks pretty positive to me.

CHAIRMAN PETERS: Anything?

DR. SPANGLER: Yeah, I think from the perspective of the pathologists this probably is a study that can be looked on with some positivity because you are producing a high level of significance in a tumor --

or an organ system that is not normally involved a great deal or which there's not a large background of cases of these intestinal lesions, which I think are fairly compelling evidence in this particular case.

CHAIRMAN PETERS: Any further comments?

Then do we have a motion?

Please indicate by show of hands if, in your opinion, N-carboxymethyl-N-nitrosourea has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Okay. The record should reflect four votes were cast to add N-carboxymethyl-N-nitrosourea to the Proposition 65 list as causing cancer.

A majority, which in this case is four, of the appointed members is required to add a chemical to the list. Accordingly, N-carboxymethyl-N-nitrosourea is added to the Proposition 65 list.

Oh, I didn't know that the chairman was supposed to vote. I should have asked about that. I don't know whether we can do things retroactively. If we can, there would be two votes on the first one and there would be five votes on this one.

MS. HECK: You just took care of that by clarifying that on the record that you would like to clarify that your abstention the last time wasn't an

abstention, you didn't know you could vote, if I'm correctly capturing your thoughts here, and you would have cast a no vote.

CHAIRMAN PETERS: I would have cast a yes vote. So there would have been two votes in favor.

MS. HECK: It doesn't change the listing status, but clarifies the record as to your vote. And then you wish to cast a vote for yes on this compound, which means it's five votes rather than four. And, again, the outcome is the same, it is added to the list.

CHAIRMAN PETERS: Correct.

We move on to Roman numeral III, and we have a presentation of possible removal, and we'll have to have some explanation on this, but I assume we'll get it and Colleen Heck will provide that.

MS. HECK: Thank you, Dr. Peters.

This is a nonsubstantive presentation, to be sure. The possible removal is not from the list of chemicals known to the State to cause cancer; rather it's a much lesser known list that we also have in regulation.

In Title 22, Section 14000, there's a list of chemicals that are required by state or federal law to have been tested for their potential to cause cancer but which have not been adequately tested as determined by

this committee.

This is a statutory duty that's in Proposition 65 that we have not made highly visible or brought to this committee's attention as currently constituted for some ten years or so. We're now bringing it back to you because this is a task assigned to you.

But, again, because nothing is ever quite that simple, it seems, we're not asking you to weigh in on whether or not all these three compounds have been adequately tested.

The way the regulation reads, a chemical cannot simultaneously be placed on the list of chemicals to cause cancer and on the list of chemicals which you find not to be adequately tested.

We did a manual check, if you will, side by side, and all three of these chemicals are on the Proposition 65 list as known to the State to cause cancer.

This is largely a housekeeping detail, an administrative matter, and we would like you at this time to direct us, if you would, if it's appropriate, to remove these three chemicals from the Section 14000 list of chemicals that are not adequately tested.

In the future, there may be more significant or substantive matters where you may actually be delving

into whether or not the chemical has been adequately tested, but we're not asking for that kind of input from you today.

CHAIRMAN PETERS: Is the committee clear on what we're being asked to do?

DR. LANDOLPH: No. If I understand this right, it's listed on the Proposition 65 list, but you also have it listed as it's not been adequately tested?

MS. HECK: That's correct.

DR. LANDOLPH: So what do you believe is true?

MS. HECK: I certainly wouldn't want to weigh in, but I can tell you this. The regulation on the list of not yet adequately tested says there cannot be on the list, as a matter of law, those -- under the heading of not adequately tested, anything that's on the list of known to cause.

DR. LANDOLPH: I understand that, and that's one of the better laws I've heard of in a long time.

My question is now: Why is it on both lists?

MS. HECK: We haven't gone through to clean up the list of not adequately tested to keep it current with the known to cause. There's just been a lag. We're trying to fix that by this action today.

DR. LANDOLPH: Does your staff feel that it was adequately tested?

MS. HECK: They made no substantive review because there was none called for. It's a mutually exclusive proposition to be on both lists, so there was no superficial review even of the carcinogenicity of any of them.

DR. LANDOLPH: So you're asking the committee for guidance; is that correct?

MS. HECK: No, I'm asking you to take the action as only this committee can take, which is to direct us to take the administrative task of actually pulling these three off the list of those not adequately tested.

We're asking for an affirmative vote, if you will, of, yes, it's true that it's on both lists, but it can't be on both lists, so take it off the list of those not yet adequately tested.

CHAIRMAN PETERS: Any other comments or questions from the committee before we try to deal with this?

Joe.

DR. LANDOLPH: This is odd, to be blunt.

CHAIRMAN PETERS: I think that the issue is clear -- it is odd, but the issue is clear.

DR. SPANGLER: It is odd, but there's only one course of action.

CHAIRMAN PETERS: Any public comments? Hearing none, seeing none, seeing no blue slips, are we ready to make a motion or vote?

DR. LANDOLPH: Can I ask one more question?

How did it get onto the Proposition 65 list? Was that by deliberation, prior addition by this committee, or was it by an authoritative body listing?

MS. HECK: We have three, and I'm going to have to defer to either Martha Sandy or the Proposition 65 implementation folks as to how they got on.

DR. SANDY: I wasn't prepared for this, but I know propachlor is a recent listing by an authoritative body. Maneb, I believe, is a U.S. EPA authoritative body listing.PCP, I'm not sure, it may have been a committee listing. It's an older listing. I don't know if Cindy can help me. If you give us ten minutes, we can give you the answer.

CHAIRMAN PETERS: But they're clearly constituted compounds on the lists somehow or another, right?

DR. SANDY: That's right.

CHAIRMAN PETERS: I think that's all we need to know.

Let's have a motion.

DR. FELTON: Okay.

CHAIRMAN PETERS: Motion to approve the removal of these three items from the 14,000 list. Is there a second?

DR. SPANGLER: I'll second.

CHAIRMAN PETERS: Any discussion on the motion? Let's vote.In favor, please raise your hand. Opposed, none. It carries unanimously.

Staff updates.

MS. OSHITA: I would like to take a few moments to brief the committees members on the status of the administrative listings under Proposition 65. Since the Carcinogen Identification Committee met last November, OEHHA has administratively added 19 chemicals to the Proposition 65 list. Nine were added as causing cancer, nine were also added as causing reproductive toxicity, and we added one for both endpoints, as causing reproductive toxicity and cancer.

There is a complete current list of these chemicals within your binders of meeting materials, and we have highlighted each of the newly-added chemicals for your reference.

In addition to these, we have several other chemicals for which we have received comment and they are still under consideration for administrative listing, and we hope to make some final decisions on

those in the very near future.

CHAIRMAN PETERS: Thank you. Anybody have any questions? Thank you.

The next presentation, prioritization process/ random selection, Colleen Heck.

MS. HECK: Thank you.

Just briefly -- this is really combining the two items -- I have no litigation in the classic sense, court suits, to report on.

But there was an administrative challenge filed with the Office of Administrative Law, actually some almost three years ago now, asserting that the prioritization process that we follow for working up chemicals that ultimately make their way to this committee and your counterpart committee is what's known as an underground regulation. That is, it should have been adopted as a regulation but it was not.

As you may know, we have engaged in the past in three random selections, which is the first step toward the ultimate more substantive review of chemicals for potential listing, most recently in the fall of this year, and it is that practice that was challenged.

The Chemical Industry Council filed documents with the Office of Administrative Law asking that agency to deem that practice unlawful until adopted as a

regulation. We filed papers with the OAL asserting that the practice was not a regulation and, therefore, did not need to be adopted as such.

A decision is expected within the next two to six weeks.There's basically only two outcomes that can happen:

Either the challenge is correct and our agency will be charged with adopting a prioritization process, whether it's the current one or some other version, in regulation;

Or OEHHA is correct, it's not a regulation, and we're free to continue using the current practice without reg or would be free to change it internally without going through this full regulation adoption process.

So we'll keep you apprised when we next see you as to the outcome of that challenge.

That's all I have.

DR. DENTON: Colleen, do you want to mention about the random selection?

MS. HECK: I'm not sure what you --

DR. DENTON: We underwent a random selection for carcinogens in, I think, September of --

CHAIRMAN PETERS: Would somebody describe that process? I think it would be useful for us to know.

DR. SANDY: I can tell you that random selection -- the results were published on November 9th and -- Dr. Peters, can you repeat --

CHAIRMAN PETERS: The process by which you do a random selection.

DR. SANDY: Yes. As we've done in the past, we have a pool of chemicals that we are tracking for carcinogenicity concern, and we select from a subset of that pool a group. This time we had 100 chemicals. We randomly order them using a seed from the California Lotto and the top 50, after randomly ordering them, were selected and we will now prioritize them.

For chemicals which receive a priority of high carcinogenicity concern, we will then place those on the final candidate list and bring to you chemicals from that list in the form of a hazard identification document for your consideration.

This process has evolved over time. We've given you a few presentations over the years. There's a document that was finalized in May 1997 that discusses the prioritization procedures. This random selection was discussed in there as a pilot process that we've been using.

CHAIRMAN PETERS: Thank you.

DR. EASTMOND: Can I ask a question?

Martha, if I get this process correct, the top 100 chemicals that you are tracking, 50 are randomly selected for placing on this list. The other 50 are just held in some sort of reserve until later.

It would seem to me that you could have a chemical which would be of significant concern from a public health point of view which would randomly fall in into that second half of the list and would sit there for a long period of time without being considered.

It strikes me as an unusual way to do this. I would think at some level you would be prioritizing all of these 100 and bringing forward those which are of most concern to the people potentially of the State of California and acting upon those in as practical a fashion as possible.

Can you comment on that?

DR. SANDY: I should let you know that I spoke of a pool of 100 that we randomly selected from. However, to create that pool, as we discussed in the notice, we randomly selected from a larger pool, so there are more than 100.

Of this pool of 100, we made no determination as to whether they're of the highest concern or not. They're just the randomly selected group.

CHAIRMAN PETERS: That's a requirement, right?

DR. DENTON: Maybe I could pitch in here, too.

Dr. Eastmond, this is a process, using the lotto system and so forth, that was worked out over a period of years for selection of these chemicals.

And you're right that some chemicals may or may not be selected which would be of more concern than others, but we are subject to the random selection.

We look upon this committee as an advisory committee to OEHHA. If you would want to be briefed on this process, would want to have some input into this process, that would certainly be within your authority and responsibility as the committee.

The history goes back, but it was designed to be completely random without any really kind of pre-selection, so to speak.

So depending upon the desire of the committee, you could look at it or not.

DR. EASTMOND: I would guess the intention is that a particular group wouldn't want to feel like they were being unfairly targeted, so it does bring some sort of fairness to the process.

Counterbalancing that, though, is we want to use your staff's time and the committee's time as efficiently as possible to protect the people of California.

I would think, under those circumstances, it would be wise to try to identify a way to use some sort of judgment to prioritize -- to bring things forward, because something could sit in this larger list, even greater than 100, for many, many years that might be of significant concern to the State of California that would never rise to the upper list.

I think it's probably worth looking at that. Maybe we should go through this another time and talk about it some more.

DR. DENTON: It looks like George wants to say something.

DR. ALEXEEFF: George Alexeeff here.

You make a good point, Dr. Eastmond. Actually, the panel, or specifically the chair, has a role of embarking on that process. The chair, in consultation with the director, can propose chemicals of specific concern.

So if there was a chemical that either you in your work or you somehow became aware was something you felt needed to be looked at carefully because of public health interests, that could be brought up to the forefront. So there is a way of addressing those public health issues.

DR. EASTMOND: George, is that from within the

list or is that just where --

DR. ALEXEEFF: Any chemical.

CHAIRMAN PETERS: The mechanism would be a committee member could go through the --

DR. ALEXEEFF: The chair. I presume the committee member could talk to the chair.

The other point is the administrative listing process also is, in part, a prioritization process as well because chemicals are administratively listed.

But if a chemical doesn't quite make it through the listing process, without getting into technicalities, it makes it to a notice of intent to list, but then evidence is brought forward that brings that information into question, then that comes to the committee as well. So it's sort of a prioritization process.

That has actually been the most common method chemicals have gone to the DART committee in the last couple of years, is through the administrative -- almost-administratively-listed process.

So there are really three ways chemicals can come to the committee. In the past few years, it has been mainly through this random selection prioritization process.

CHAIRMAN PETERS: Are there any public comments?

I see no blue slips, so I assume none.

Then at this point Dr. Denton is going to summarize what we did.

DR. DENTON: Before I summarize, maybe to go back to the last item, is this something the committee would like to see on their next agenda, to review how chemicals are brought forward to them or --

DR. FELTON: I don't think it's necessary to go through the process. I think David, Dr. Eastmond, is the newest member of the panel and hasn't been through this in the past.

But I think what would be nice is communication with this panel from the staff in reminding us that when we do hear about compounds that are not on the list through some research, or whatever the context, that we get some communication about it. I think that would be a nice thing, to have a reminder to do that, because I have one in mind.

DR. LANDOLPH: I remember, Dr. Denton, your predecessor in the period of time this random prioritization started, I thought it was a little odd at the time, to be honest with you.

I guess my druthers would be, if you see something, your staff sees something that they think is pretty genotoxic or looks like it might be carcinogenic,

my recommendation would be to move it up as fast as you can and don't wait for all these things to take place.

But I don't want to interfere with your machinery that obviously has been polished over a five- or six-year period. I would like to see you use your judgment if you think something needs to be moved faster, you have my vote to move it faster.

DR. DENTON: With that, I will summarize the actions of the committee today.

Allyl isovalerate was not added to the Proposition 65 list. I also am -- Dr. Landolph requested, and I assume that the committee is in agreement, that we ask NTP to do a chronic animal bioassay on that chemical.

N-carboxymethyl-N-nitrosourea was added to the Proposition 65 list of carcinogens.

The committee also voted to remove the three chemicals that are listed on the agenda from Section 14000, the list of chemicals that have not been adequately tested, an administrative action, as Colleen mentioned.

I guess, finally, regarding chemicals and how chemicals come to this committee, the committee expressed the interest that if the staff at OEHHA see chemicals which are genotoxic or carcinogenic, that we

communicate with the panel as well as expedite those chemicals, if possible. So that's my summation.

I turn it back to you, Dr. Peters. Dr. Peters, thank you for being acting chair today.

CHAIRMAN PETERS: I would just say thank you to the committee members, thank you to the staff for your usual excellent work, and thank you to the audience for at least one participant who came forward, and thanks to Dr. Denton for trying to keep me under semi-control.

(Meeting concluded at 11:35 a.m.)

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REPORTER'S CERTIFICATE

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STATE OF CALIFORNIA)
) ss.
COUNTY OF SACRAMENTO)

I, PHYLLIS MANK, certify that I was the Official Court Reporter and that I reported in shorthand writing the foregoing proceedings to the best of my ability; that I thereafter caused my shorthand writing to be reduced to typewriting, and the pages numbered 1 through 64, inclusive, constitute a complete, true and correct record.

In witness whereof, I have subscribed this certificate at Sacramento, California, on this 7th day of January, 2002.

PHYLLIS MANK, CSR No. 5093