

MEETING
STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
PROPOSITION 65
CARCINOGEN IDENTIFICATION COMMITTEE

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Catherine Crespi, PhD, MS

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Joseph Landolph, PhD

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PROCEEDINGS

CHIEF DEPUTY DIRECTOR EDWARDS: Welcome. Welcome to everyone joining this meeting of the Carcinogen Identification Committee. This, the meeting, is being held in person and virtually.

My name is Dr. David Edwards. I am the Chief Deputy Director of the Office of Environmental Health Hazard Assessment or OEHHA. I am filling in today for Dr. Kris Thayer, our Director, who is unable to attend.

OEHHA is a department within the California Environmental Protection Agency and is the lead State agency for the assessment of health risks posed by environmental contaminants.

As we get started, just a couple of housekeeping items for those attending in the room here in Sacramento. The emergency exits are the double doors directly behind you, and at the front of the room to the left and the right. You can access the restrooms by going out the back double doors, turning left, and walking to the end of the hall. If we were to get a fire drill, which I'm not expecting today, we would go out through the exit doors and walk down the stairs. Please don't take the elevator.

Great. Our main agenda item for today is the consideration of N-methyl-N-formylhydrazine for listing as a carcinogen under Proposition 65. After the

1 N-methyl-N-formylhydrazine agenda item, the Committee will
2 take up a consent item on the Section 27000 list of
3 chemicals for which testing has been required, but has
4 been inadequate. The is different from the Proposition 65
5 list. For the third and final agenda item, staff will
6 present updates on various Proposition 65 regulatory and
7 other activities.

8 We'll take a 45-minute break for lunch around
9 noon and a take a short 15-minute sometime in the
10 afternoon. This meeting is being recorded and
11 transcribed. The transcript will be posted on OEHHA's
12 website.

13 All right. So now, a little bit on the public
14 comment part

15 (Slide presentation).

16 CHIEF DEPUTY DIRECTOR EDWARDS: During this
17 meeting there will be an opportunity to provide oral
18 public comment on the N-methyl-N-formylhydrazine item.
19 Individuals who are in person and wish to make an oral
20 comment at today's meeting are asked to fill out a blue
21 comment card and give them to OEHHA staff. Blue comment
22 cards area located in the back of the room on the table.

23 If you wish to provide a comment anonymously, you
24 may fill out a blue comment card, but leave the name and
25 affiliation sections blank. Instead, please write a

1 unique identifier of your choice, such as nickname,
2 initials, or a number in the top corner of the card. This
3 will be used to call on you without revealing your
4 identity. When called by the Chair, please approach the
5 microphone. We encourage you to state your name and
6 affiliation and then provide your comment. However,
7 there's no obligation to identify yourself and you are
8 free to comment anonymously, if you wish.

9 When called by the Chair -- oh, sorry.

10 Those who are joining us virtually and wish to
11 make an oral comment at today's meeting are asked to join
12 the Zoom webinar. Please make sure that you join under
13 the name you would like to be identified as when
14 commenting, including if you would like to remain
15 anonymous.

16 Information on how to join via Zoom is shown on
17 the slide. Go to bit.ly/4hapalg and register for today's
18 Zoom webinar. You will receive a link to join the webinar
19 at the end of the registration process, and if you
20 provided a working email address, you will also receive an
21 email with a link to join the webinar. Zoom users can
22 also access closed captioning by clicking on the "CC"
23 button on the bottom panel of the screen. Those of you
24 watching by CalEPA webcast will be able to watch the
25 meeting, but you need to join the meeting by Zoom to

1 speak. When requested by the Chair, individuals on Zoom
2 may queue to provide oral comment by using the "Raise
3 Hand" function.

4 When you are called during the -- during the
5 opportunity for public comment, you will be prompted to
6 unmute yourself. Please unmute yourself, state your name
7 and affiliation, if you are willing to provide that
8 information, and provide your comment. Again, anonymous
9 comments are also welcome. If you would like to present
10 slides during your public comment and have not already
11 sent them, please email them now to
12 p65public.comments@oehha.ca.gov. Public comment will be
13 limited to five minutes per commenter.

14 Now, I'm pleased to introduce the members of the
15 Committee that are present today. And I will note that
16 Dr. Felsher is not able to join us today. As I introduce
17 you, please state your name and affiliation.

18 Dr. Ludmil Alexandrov.

19 COMMITTEE MEMBER ALEXANDROV: Ludmil Alexandrov,
20 University of California, San Diego.

21 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. Ahmad
22 Besaratinia.

23 COMMITTEE MEMBER BESARATINIA: Ahmad Besaratinia,
24 Keck School of Medicine (inaudible).

25 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. Jason Bush.

1 COMMITTEE MEMBER BUSH: Good morning. Jason
2 Bush, California State University, Fresno.

3 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. Catherine
4 Crespi.

5 COMMITTEE MEMBER CRESPI: Catherine Crespi,
6 University of California, Los Angeles.

7 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. David
8 Eastmond.

9 COMMITTEE MEMBER EASTMOND: David Eastmond,
10 University of California Riverside.

11 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. Joseph
12 Landolph.

13 COMMITTEE MEMBER LANDOLPH: Hi. Joe Landolph.
14 University of Southern California at the Norris
15 Comprehensive Cancer Center and Research Institute, and
16 the Department of Molecular Microbiology and Immunology
17 and Department of Pathology.

18 CHIEF DEPUTY DIRECTOR EDWARDS: Thank you. Our
19 Committee Chair, Dr. Dana Loomis.

20 CHAIR LOOMIS: Dana Loomis, retired. Most
21 recently from the Plumas County Public Health Agency, and
22 before that from IARC.

23 CHIEF DEPUTY DIRECTOR EDWARDS: Dr. Sophia Wang.

24 COMMITTEE MEMBER WANG: Hi. I'm Dr. Wang --
25 Sophia Wang, City of Hope Comprehensive Cancer Center.

1 CHIEF DEPUTY DIRECTOR EDWARDS: And now, I'll
2 turn to Dr. Mariana Stern who's on Zoom.

3 COMMITTEE MEMBER STERN: Oh, apologies. I was
4 muted.

5 CHIEF DEPUTY DIRECTOR EDWARDS: Whoops. I think
6 she froze for a moment. I'll call that as here. I heard
7 her speak a little bit.

8 TINA COX: Dr. Stern, can you repeat yourself,
9 please. We -- you froze for a second.

10 COMMITTEE MEMBER STERN: Oh, yes. Can you hear
11 me now?

12 CHIEF DEPUTY DIRECTOR EDWARDS: Yes.

13 TINA COX: Yes.

14 COMMITTEE MEMBER STERN: Okay. I'm Mariana Stern
15 at the University of Southern California.

16 CHIEF DEPUTY DIRECTOR EDWARDS: Great.

17 COMMITTEE MEMBER STERN: Good morning, everyone.

18 CHIEF DEPUTY DIRECTOR EDWARDS: All right.
19 Welcome. We really appreciate you taking the time to
20 provide your advice and judgment at this meeting.

21 All right. Now, I'd like to introduce OEHHA
22 staff. For those in the room, I invite them to raise
23 their hand. For those joining via Zoom webinar, I invited
24 them to turn on their cameras. Dr. Kim Gettmann, Deputy
25 Director for Scientific Programs. And then from the

1 Reproductive and Cancer Hazard Assessment Branch, Dr.
2 Martha Sandy who's the Branch Chief. Staff of the Cancer
3 Toxicology and Epidemiology Section that are joining us
4 today: Drs. Isabel Alvarado, Jordan Aron, Vanessa Cheng,
5 Sarah Elmore, Kate Li, Homa Sadeghi -- okay got it -- all
6 right -- and Feng Tsai.

7 Then Office of External and Legislative Affairs,
8 Proposition 65 Implementation Program: Amy Gilson, Deputy
9 Director of External and Legislative Affairs; Tina Cox,
10 Senior Environmental Scientist, Section Chief of the
11 Proposition 65 Implementation Program; Esther
12 Barajas-Ochoa, Analyst, Proposition 65 Implementation
13 Plan; Julia Dolloff, Senior Environmental Scientist,
14 Proposition 65 Ombudsperson. And then from OEHHA Legal,
15 Corey Friedman.

16 CHIEF DEPUTY DIRECTOR EDWARDS: All right. Now,
17 I'll ask Corey Friedman for some introductory remarks
18 about Bagley-Keene and other legal issues related to
19 today's meeting.

20 COREY FRIEDMAN: Good morning, everyone. I met a
21 number of you at our last meeting, but I am Corey, one of
22 the attorneys here at OEHHA. And I'm going to give the
23 usual spiel, although many of you have heard it more than
24 once. But please feel free to ask me questions if you
25 have any legal concerns at any point during (inaudible)

1 afterwards. I will be here the whole time.

2 A reminder that the Bagley-Keene Open Meetings
3 Act applies to this meeting, the goal of which is to --
4 for transparency. So for the Committee members, please
5 remember that all discussions and deliberations about
6 agenda items need to be conducted during the open meeting,
7 not during breaks or lunch, not with individual members of
8 the Committee via phone, or email, or text, or chats. The
9 goal is for the business to all be conducted in public.

10 Next, all experts serving on this Committee have
11 participated in mandatory ethics training and have
12 disclosed any actual or potential conflicts of interest,
13 including any relevant ex parte communication about the
14 subject matter. If any potential conflict of interest
15 question comes up in the future at any time, not
16 necessarily during a meeting, please give me a call or
17 contact my colleague Kristi.

18 At today's meeting, you will be considering
19 whether to place an additional chemical on the Proposition
20 65 list as a carcinogen. It is your decision, not the
21 decision of OEHHA staff, but staff are obviously available
22 to answer your questions or to locate information, if you
23 need it.

24 The Governor appointed you because of your
25 scientific expertise to be the State's qualified experts

1 on carcinogenicity. There is no need for you to feel
2 compelled however to go outside that charge. For example,
3 you need not consider whether a Prop 65 warning may be
4 required for an exposure to a chemical or any other
5 consequences of the listing.

6 According to guidance adopted by this Committee,
7 you have maximum flexibility in evaluating all pertinent
8 scientific information in making a determination. You can
9 consider all evidence bearing on the issue of
10 carcinogenicity shown through scientifically valid
11 testing, according to generally accepted principles. That
12 is a direct quote from the adopted guidance. And that may
13 include human, animal, mechanistic, or other data.

14 If you need more information, or more time to
15 consider the evidence, or to discuss it further before you
16 vote, there is no requirement that you make a decision
17 today. For example, you could decide to table the
18 decision and take it up at a future meeting.

19 Again, please feel free to ask any clarifying
20 questions of me or the other OEHHA staff during the
21 meeting. And if we do not know the answer, we will do our
22 best to find it and report it to you.

23 Do you have any questions?

24 If not, then I will give this back to you.

25 CHIEF DEPUTY DIRECTOR EDWARDS: Great. Thanks,

1 Corey. All right. I will now turn the meeting over to
2 Dr. Loomis the Committee Chair.

3 CHAIR LOOMIS: Thank you, Dave. And I'd like to
4 take this opportunity to extend a welcome to all members
5 of staff who are here who have prepared the background
6 material, members of the public - although I don't see any
7 in the room - and all of the Committee members who are
8 with us today in the room and on Zoom.

9 So, with that, I'll move on to the main agenda
10 item, which is consideration of N-methyl-N-formylhydrazine
11 as known to the State of California to cause cancer. And
12 to start us off on that topic, I'll turn it over to Dr.
13 Sandy for a staff presentation

14 (Slide presentation).

15 DR. MARTHA SANDY: Thank you, Dr. Loomis. And
16 good morning to everyone. I think we're all going to need
17 to talk closely to the mic, so that this is transcribed
18 properly. So just a little background on this chemical
19 that we're bringing to you today.

20 N-methyl-n-formylhydrazine was placed in the medium
21 priority group by your Committee back in 2010 for future
22 listing consideration. And OEHHA selected this chemical.
23 And in November 2024, we solicited public information
24 relevant to the assessment of the evidence of its
25 carcinogenicity from the public. No information was

1 received. Staff went ahead and conducted literature
2 searches and prepared the document that you have with you
3 now.

4 And we'll now hear from staff a brief
5 presentation of the evidence. And we'll start with Dr.
6 Li.

7 DR. KATE LI: Good morning. Our presentation
8 today will summarize the evidence on the carcinogenicity
9 of N-methyl-N-formylhydrazine, or MFH for short.

10 [SLIDE CHANGE]

11 DR. KATE LI: Oh, yeah. I need to point that.
12 Here is an outline of what our team will cover
13 today. I will begin with background information on the
14 occurrence of and exposure to MFH. After that, we will
15 present the evidence for carcinogenicity. I will start
16 with the animal carcinogenicity data. I should note that
17 there are no human carcinogenicity data for MFH.

18 For the mechanistic and other relevant data, Dr.
19 Elmore will present information on pharmacokinetics and
20 metabolism, and Dr. Alvarado will present data related to
21 the key characteristics of carcinogens, and structural
22 activity considerations, and then wrap up with a summary
23 of the evidence.

24
25 [SLIDE CHANGE]

1 DR. KATE LI: MFH is a hydrazine compound with a
2 nitrogen-nitrogen covalent bond, as shown in the figure on
3 the top right. MFH is soluble in water and in organic
4 solvents. It's also volatile. It occurs naturally in
5 wild edible mushrooms of the genus Gyromitra. These
6 mushrooms, commonly known as "false morels", are shown
7 here, along with real morels. The false morel is the
8 first mushroom pictured on the right.

9 Other toxic chemicals are also present in
10 Gyromitra mushrooms, including the hydrazone compound
11 Gyromitrin, and other hydrazines, such as
12 monomethylhydrazine, or MMH for short.

13 In addition to its natural occurrence in these
14 wild mushrooms, MFH is synthesized for use in production
15 of Marboflaxcin, and antibacterial agent used in
16 veterinary medicine, and for use in research. Humans may
17 be exposed to MFH, mainly from consumption of fresh or
18 dried Gyromitra mushrooms. Exposure to MFH may also occur
19 in some occupational settings, for example heat processing
20 during preparation of Gyromitra mushrooms, synthesis, and
21 use of MFH.

22 [SLIDE CHANGE]

23 DR. KATE LI: Now, we'll present the available
24 evidence on carcinogenicity for MFH.

25 [SLIDE CHANGE]

1 DR. KATE LI: In cancer hazard identification,
2 evidence of carcinogenicity is integrated across multiple
3 evidence streams to characterize a chemical. As shown
4 here, we identify and analyze data from human and animal
5 carcinogenicity studies, and collect the mechanistic and
6 other relevant data, including information on
7 pharmacokinetics and metabolism, key characteristics of
8 carcinogens, and structure-activity relationships.

9 In the case of MFH, we did not identify any
10 cancer epidemiological studies. In animals, OEHHHA
11 identified multiple carcinogenicity studies in mice and
12 hamsters.

13 [SLIDE CHANGE]

14 DR. KATE LI: In the following slides, I will
15 present the findings from animal studies.

16 [SLIDE CHANGE]

17 DR. KATE LI: This table gives an overview of the
18 available studies. A total of 14 studies were reported,
19 with 12 in Swiss mice and two in Syrian golden hamsters.
20 All animal studies were conducted in Dr. Bela Toth's
21 laboratory at the University of Nebraska Medical Center.
22 The Toth Laboratory conducted and published chemical
23 carcinogenesis studies for over 40 years.

24 Among the mouse drinking water studies, the Toth
25 Laboratory tested a range of MFH concentrations in males

1 or females, as noted by M and F in the table. As you can
2 see, these researchers started by administering high doses
3 of MFH in the studies published in 1978. Because of early
4 mortality associated with MFH toxicity, reduced
5 concentrations of MFH were tested in subsequent studies.
6 A total of seven concentrations of MFH in drinking water
7 were tested and reported in four publications between 1978
8 and 1982.

9 Four subcutaneous, or SC, injection studies were
10 conducted in mice. There were two single injection
11 studies and two 40-weekly injection studies in males or
12 females, respectively. In addition, two drinking water
13 studies were conducted in male and female hamsters.

14 In each of the studies shown on this slide, 100
15 animals were used for the control group and 50 animals
16 were included in each treated group. All treatments
17 started at six weeks of age with lifetime exposure for
18 drinking water studies or started at six weeks of age for
19 single SC injection or multiple injection studies, then
20 observed for life.

21 [SLIDE CHANGE]

22 DR. KATE LI: This table presents the summary of
23 tumor findings in mouse drinking water studies, organized
24 by administered concentration of MFH from high to low and
25 tumor sites. I will refer to statistically significant

1 findings as "significant increase" in this presentation.

2 The pathology evaluations for each study involved
3 full necropsies and histopathological examinations of
4 numerous tissues, including all organ sites shown here.
5 Each checkmark indicates tumor incidence with a
6 significant increase. The blank cells indicate there were
7 no significant increases in tumor incidence at that site
8 and administered dose. And "r" represents a rare tumor
9 type.

10 When animals were treated with 0.0156 percent
11 MFH, the highest concentration, there was high early
12 mortality at 30 weeks of age, 84 percent in males and 78
13 percent in females. Few animals lived long enough at this
14 dose for tumors to be detected. Indeed, the only
15 significant tumor findings were liver tumors in females.

16 When animals were treated with a series of
17 decreasing concentrations of MFH, significant tumor
18 findings were observed in several organ sites in males and
19 females. Lung tumors were observed in males and females
20 in all dosed groups, except in the highest concentration.
21 Tumor of liver, gallbladder, bile duct, and blood vessels
22 were seen in mice receiving MFH in drinking water at
23 several concentrations.

24 In males, tumors were also observed at other
25 sites, including the seminal vesicles, forestomach,

1 glandular stomach, and subcutis. The tumor types observed
2 in each organ site are listed in the next slide. Tumor
3 incidence data from mouse drinking water studies are
4 presented in Table 3 through Table 10 in the HID document.
5 I won't go through each table here due to time of
6 constraints. I will walk you through one study which
7 tested two of the concentrations as an example, after the
8 next slide.

9 [SLIDE CHANGE]

10 DR. KATE LI: This slide provides more detail on
11 the tumor sites and types observed in MFH-treated mice in
12 drinking water studies. In the respiratory system, lung
13 adenoma, adenocarcinoma, or adenoma and adenocarcinoma
14 combined were observed in studies of males and studies of
15 females. MFH significantly increased a number of benign
16 and malignant tumors in organs of the digestive, vascular,
17 and integumentary systems, and in the male reproductive
18 system. As noted, several of these tumor types are rare
19 tumors.

20 [SLIDE CHANGE]

21 DR. KATE LI: Now, I will show you an example of
22 the tumor findings from one of the drinking water studies.
23 In this study, female mice were treated with two
24 concentrations of MFH, at 0.001 and 0.002 percent. Tumor
25 incidences are summarized in the table.

1 A significant increase in tumor incidence in a
2 treatment group compared to the control group by pairwise
3 comparison is noted with the asterisk's symbol.

4 In the lung, you can see that the increases of
5 adenoma, adenocarcinoma, and the combination of two are
6 significant by pairwise comparison in both dose groups
7 with significant dose-related trends.

8 In gallbladder, there was a significant increase
9 in adenoma and adenocarcinoma combined in the high-dose
10 group. Gallbladder tumors are rare.

11 In blood vessel, incidences of angioma and
12 angiosarcoma were significantly increased in the high-dose
13 group and the incidence of angioma and angioma --
14 angiosarcoma combined was significantly increased in both
15 dose groups with significant trends.

16 [SLIDE CHANGE]

17 DR. KATE LI: Among the four SC injection
18 studies, different doses were used in the single and
19 multiple injection studies in male and female mice, with
20 much lower MFH doses administered in the 40-weekly
21 injection studies.

22 In males, lung tumors were seen in mice treated
23 with 40-weekly injections of MFH. In the male single
24 injection study, rare preputial gland tumors were observed
25 in both doses. In females, lung tumors were observed in

1 both the multiple injection and single injection study.

2 We will look at the lung tumor types in one of
3 the SC studies in the next slide.

4 [SLIDE CHANGE]

5 DR. KATE LI: Here is an example showing tumor
6 incidences in female mice administered 180 mg per kilogram
7 body weight MFH by a single SC injection at six weeks of
8 age. Significant increases in lung adenoma,
9 adenocarcinoma, and adenoma and adenocarcinoma combined
10 were observed.

11 [SLIDE CHANGE]

12 DR. KATE LI: Now, let's look at a summary of the
13 hamster studies. Hamsters were administered one
14 concentration or 0.0078 percent of MFH in drinking water
15 starting at six weeks of age and observed for life. In
16 males, significant tumor findings were observed in the
17 liver, gallbladder, and bile duct. In females, tumor
18 findings were also observed in the liver. Two different
19 types of liver tumors occurred in these studies:
20 hepatocellular tumors and malignant histiocytomas, also
21 referred to as Kupffer cell sarcomas. Each of these tumor
22 types are rare in hamsters.

23 [SLIDE CHANGE]

24 DR. KATE LI: This is an example table showing
25 the tumor findings from the male hamster study. In the

1 liver, hepatocellular tumors, including adenoma,
2 carcinoma, and the combination of the two, were
3 significantly increased. In addition, a significant
4 increase in a different tumor type, malignant
5 histiocytoma, or Kupffer cell sarcoma, was observed in the
6 liver. In gallbladder, papillary adenoma, or papillary
7 adenoma and adenocarcinoma combined were significantly
8 increased. In bile duct, significant tumor findings
9 include cholangiocarcinoma or cholangioma and
10 cholangiocarcinoma combined. Again, all the significant
11 tumors are rare tumor types in hamsters.

12 This concludes our summary presentation with
13 examples of tumor findings from several of the
14 carcinogenicity studies conducted in mice and hamsters.

15 Now, Dr. Elmore will present the pharmacokinetics
16 and metabolism of MFH as part of the mechanistic evidence
17 stream.

18 [SLIDE CHANGE]

19 DR. SARAH ELMORE: Thank you, Dr. Li.

20 We are now switching to a short summary of the
21 pharmacokinetics and metabolism of MFH. Data on the
22 pharmacokinetics and metabolism of MFH are sparse.

23 However, information may be inferred from in vivo
24 animal studies investigating the toxicity of MFH, reports
25 on the onset and poisoning symptoms in humans following

1 the ingestion of the Gyromitra mushrooms, and from studies
2 on the MFH metabolite, monomethylhydrazine or MMH.

3 Following ingestion or inhalation, MFH is
4 absorbed and distributed throughout the body. MFH or its
5 metabolites may be excreted in expired air as carbon
6 dioxide and methane, in urine, and feces.

7 [SLIDE CHANGE]

8 DR. SARAH ELMORE: And now we will discuss the
9 proposed metabolism of MFH. Here, MFH is shown in red.
10 MFH is hydrolyzed to MMH under acidic conditions, or
11 enzymatic hydrolysis by cytochrome P-450 monooxygenases,
12 or CYPs, or flavin adenine dinucleotide-containing
13 monooxygenases, or FMO, may also occur.

14 MMH is oxidized to methyl or formyl free radicals
15 via CYP, FMO or myeloperoxidase. While these products
16 have been identified in various in vitro/in vivo studies,
17 the intermediate steps have yet to be characterized.
18 These radicals can either go on to form adducts directly
19 or through the formation of formaldehyde and acetaldehyde.

20 There.

21 As previously mentioned, methane and carbon
22 dioxide are also produced as end products. Little is
23 known about the detoxification pathways for MFH, both
24 acetylation and glutathione reactions have been proposed.

25 And that concludes the pharmacokinetics and

1 metabolism section for MFH. And now, Dr. Alvarado will
2 continue with the key characteristics of carcinogens.

3 [SLIDE CHANGE]

4 DR. ISABEL ALVARADO: Thank you, Dr. Elmore.

5 We organized the mechanistic data for MFH by the
6 ten key characteristics of carcinogens, or KCs, that were
7 identified by IARC based on a comprehensive review of
8 mechanistic information on agents known to cause cancer in
9 humans. The KCs have been applied by IARC and other
10 agencies, including NTP and U.S. EPA in their evaluations
11 of carcinogenicity evidence. As detailed in the HID,
12 there is evidence on MFH for two of the 10 KCs, KC1 and
13 KC2. A brief overview of the evidence for each will be
14 presented.

15 [SLIDE CHANGE]

16 DR. ISABEL ALVARADO: For KC1, is electrophilic
17 or can be metabolically activated, the evidence for MFH is
18 based on several studies of its hydrolysis metabolite,
19 MMH.

20 First, let's look at the in vivo evidence. The
21 O6MeGu adduct was detected in mice exposed to MMH in DNA
22 from liver and kidney. The N7MeGu adduct was observed in
23 mice exposed to MMH in DNA from liver and large intestine,
24 and in RNA from the liver, large intestine, and kidney.
25 The same adduct was also observed in rats exposed to MMH

1 in DNA from liver.

2 In vitro studies, MMH bound covalently to nucleic
3 acids in rat liver slices and bound covalently to proteins
4 in rat liver microsomes and S9. In the spin trapping
5 studies of MMH, electrophilic methyl radicals were
6 observed in rat hepatocytes, neutrophils, and liver
7 microsomes. And the electrophilic metabolites,
8 acetaldehyde and formaldehyde, were observed in rat liver
9 microsomes incubated with MMH.

10 [SLIDE CHANGE]

11 DR. ISABEL ALVARADO: Evidence for genotoxicity
12 comes from MFH and its metabolite MMH. In the studies of
13 MFH, a dose-dependent increase in mutations was observed
14 in the Salmonella TA100 strain in one study. No increases
15 were observed in other studies or strains. MFH did not
16 induce unscheduled DNA synthesis in vitro in rat or mouse
17 hepatocytes.

18 The genotoxicity of MMH has been evaluated in
19 multiple test systems. In studies of MMH in vivo, DNA
20 adducts were found in the tissues of mice and rats, as
21 discussed in the context of KC1. No induction of
22 unscheduled DNA synthesis was observed in rat liver and no
23 induction of dominant lethal mutations were observed.

24 [SLIDE CHANGE]

25 DR. ISABEL ALVARADO: Continuing with the

1 evidence in vitro, MMH induced unscheduled DNA synthesis
2 in mouse and rat hepatocytes, mutations in Chinese hamster
3 lung fibroblasts, and binds covalently to nucleic acids in
4 rat liver slices. In bacteria, MMH increased mutations in
5 some strains of Salmonella and E. coli, and also increased
6 SOS response and DNA repair in E. coli. In addition, MFH
7 and MMH can form the genotoxic and carcinogenic
8 metabolites acetaldehyde and formaldehyde.

9 [SLIDE CHANGE]

10 DR. ISABEL ALVARADO: Now, Let's move to the
11 structure activity considerations. Five structurally
12 related hydrazine or hydrazone compounds were identified
13 for consideration and tumor site and type comparison with
14 MFH, using findings from mouse and hamster cancer
15 bioassays. They are Gyromitrin, MMH, hydrazine,
16 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine.

17 This table shows the chemical names and
18 structures. As you can see, all of them have a
19 nitrogen-nitrogen covalent bond. All of the comparator
20 chemicals are Proposition 65 carcinogens. And their
21 cancer classification by IARC and NTP are also noted in
22 the table.

23 In mice, treatment-related tumor sites and types
24 observed in common with MFH were: Lung, observed with all
25 five comparator chemicals; liver hepatocellular, observed

1 with three of the chemicals; blood vessel, also observed
2 with THREE of the chemicals.

3 In hamsters, treatment-related tumor sites/types
4 observed in common with MFH were: liver hepatocellular,
5 observed with two of the chemicals; and liver malignant
6 histiocytoma, or Kupffer cell sarcoma, observed with one
7 of the chemicals.

8 [SLIDE CHANGE]

9 DR. ISABEL ALVARADO: The evidence of MFH
10 carcinogenicity comes from multiple evidence streams and
11 includes animal evidence of carcinogenicity from studies
12 in mice and hamsters, and mechanistic and other relevant
13 data. Information from this evidence stream consists of
14 information relevant to two key characteristics of
15 carcinogens, KC1 and KC2, information on pharmacokinetics
16 and metabolism, and structure activity considerations.
17 This information needs to be integrated across that --
18 across these evidence streams, in making an overall
19 evaluation of the carcinogenicity of MFH.

20 [SLIDE CHANGE]

21 DR. ISABEL ALVARADO: In the next two slides,
22 we're going to provide a short summary of the
23 carcinogenicity data for MFH.

24 From animal bioassays, treatment-related
25 increases in tumors were seen at multiple sites and in

1 multiple studies in male and female mice administered MFH
2 in drinking water. Tumors were also seen in male and
3 female mice exposed to MFH by subcutaneous injection. In
4 hamsters, treatment-related increases in multiple types of
5 tumors were seen in males and females administered MFH in
6 drinking water.

7 [SLIDE CHANGE]

8 DR. ISABEL ALVARADO: This slide -- this slide
9 presents highlights of mechanistic considerations and
10 other relevant data.

11 The ADME review indicates that MFH undergoes
12 non-enzymatic hydrolysis to form MMH, which can be
13 enzymatically oxidized to form reactive metabolites and
14 DNA adducts. Regarding the Key Characteristics of
15 carcinogens, for KC1, MFH forms MMH and is further
16 metabolized to electrophilic species, which form RNA and
17 DNA adducts in vivo, and protein adducts in vitro.

18 For KC2, MFH induced mutations in one Salmonella
19 strain. More evidence of genotoxicity comes from studies
20 of MMH. MMH formed DNA adducts in vivo and in vitro, and
21 increased mutations and induced unscheduled DNA synthesis
22 in mammalian cells in vitro. In bacteria, increases in
23 mutations, and induction of SOS and DNA repair were
24 reported with MMH exposure. Formaldehyde and acetaldehyde
25 are two genotoxic metabolites of MFH and MMH.

1 In structure activity considerations common
2 treatment-related tumors were observed between MFH and
3 five comparator hydrazine or -- and hydrazone compounds.
4 In mice, lung, hepatocellular and blood vessel tumors were
5 common. In hamsters, liver hepatocellular and liver
6 malignant histiocytoma were common between MFH and some of
7 the comparator chemicals.

8 [SLIDE CHANGE]

9 DR. ISABEL ALVARADO: And this concludes our
10 presentation on the carcinogenicity evidence of MFH. We
11 are happy to take any questions.

12 Thank you.

13 CHAIR LOOMIS: Thank you very much. At this
14 point, we will turn to the Committee to ask clarifying
15 questions. I see Dr. Eastmond is eagerly moving toward
16 the microphone, so please go ahead, David.

17 COMMITTEE MEMBER EASTMOND: Thank you for the
18 overview. It's not critical, but as I look at the
19 structures of these, I think the acetaldehyde is formed
20 from the Gyromitrin and the conversion. And I don't think
21 it's formed from MFH, because you only have --
22 essentially, you have two carbons and you end up with one
23 carbon, so you can only lose one carbon in that process.
24 So acetaldehyde, from my point of view, has to come
25 previously from an earlier reaction.

1 That being said, it doesn't really matter because
2 you have formaldehyde formed, which is an aldehyde
3 combined DNA, and you get the other radicals, but it was
4 just something I noticed in looking at this scheme. I
5 thought I'd mention it.

6 CHAIR LOOMIS: Very good. Let's -- yeah, we'll
7 just go down this side of the table.

8 Go ahead, please.

9 COMMITTEE MEMBER BESARATINIA: Thank you. Thank
10 you for the presentation. Just quick question regarding
11 the biotransformation of these compound for Dr. Elmore.
12 Are there any in vivo data regarding the biotransformation
13 of these compounds? What proportion of the original
14 compound undergoes detoxification and what proportion of
15 it is converted (inaudible) reactive agent.

16 DR. SARAH ELMORE: Thank you for the question.
17 So as I stated, the data was fairly sparse a lot. We had
18 to infer, but there was one study, oral gavage in mice,
19 where actually they excise mouse stomach and they saw that
20 both MFH and MMH were present after exposure to MFH. And
21 they thought -- they said that 25 percent of the original
22 compound was hydrolyzed, but that wasn't clear how they
23 came up with that value.

24 But to your second part of the question in terms
25 how much of that is bound to DNA, we don't know just based

1 on the multiple studies and the difference between them
2 dosing directly with MFH, MMH. So we don't have that
3 information, but that's something that we could try and
4 calculate for you, if that's something you're interested
5 in.

6 CHAIR LOOMIS: Go ahead.

7 COMMITTEE MEMBER EASTMOND: Another clarifying
8 question. This is probably for Dr. Li. So I noticed --
9 and this is just for my own education, but on some of
10 the -- the same study in different tumor types, the animal
11 numbers would vary based on presumably when the first
12 tumor showed up, at some point. So you have -- and that
13 seemed unusual to me, so that it was -- when the first
14 tumor within that tissue appeared, that's when you started
15 the -- that's the denominator, so that's why it varies
16 from tissue to tissue the number of animals, is that
17 correct?

18 You've got to put on your thing.

19 DR. KATE LI: Dr. Eastmond, yeah, I do mention
20 about high mortality. We -- actually, can we open our
21 backup slide file. One of the studies, what we do for --
22 about the denominators, yeah. Because of the high
23 mortality, we don't do our usual way of always count the
24 number of live animals at the time first tumor occurs. We
25 actually try to honor a balanced point when we observe

1 enough number of animals and there are enough number of
2 tumors.

3 Backup slide number five, I believe. Five.

4 COMMITTEE MEMBER EASTMOND: And I might mention,
5 I went to some of these studies and I was impressed with
6 how you were able to tease out the information, because
7 they were pretty challenging, it seemed me. So
8 congratulations to you for really the work you did on it.

9 DR. KATE LI: So we can look at this slide. As
10 you can see, what we present in our HID is in the first
11 part, the number of tumors. And then if we go by the
12 number of animals alive at 20 weeks. The reason is
13 because, as in the case of -- in this case in the bile
14 duct tumors, we select 20 weeks instead of 30 weeks.
15 Thirty week is the first tumor occurrence week. So what
16 the report has is they do not have the first occurrence
17 number of counts, but they do present the survival
18 information at 10 week intervals. So, the closest we can
19 capture for some of the 33 week is 30 week.

20 So, in this case, the survival was pretty poor at
21 30 weeks. I can read out a percent of animals -- percent
22 of survival for the low dose, which is 0.0078 at 30 weeks,
23 only 58 percent alived and see in the second half of our
24 table if we cutoff by 30 week -- 29, because total is 50
25 animals. And there are 16 -- only 16 percent of animals

1 are lived in the high-dose group.

2 So when we summarize our data, we decide we need
3 to have enough number of animals. And then in this case
4 when we look at both tables, we don't change the
5 significant values, if you are agree. And I can also show
6 you one more study, which it's more seen give you --
7 probably slide number six.

8 DR. MARTHA SANDY: And this is Martha Sandy.
9 Just to modify what you just said, we don't change the
10 findings that -- the level of significance may change, the
11 p-value, but yeah, basically the message is the same. Go
12 ahead with this, Kate.

13 DR. KATE LI: Sensitivity may change. In this
14 table, this is another slide. This is in females in these
15 high-dose studies, because the top dose you can see very
16 toxic, the animal -- and then when we -- just choose, for
17 example, gall bladder, so you're asking about first tumor
18 occurrence. When we apply first tumor occurrence, weak
19 for something -- for gall bladder in the bottom, 59 weeks.
20 Then that's 50 weeks -- at 50 weeks in this high dose, and
21 low dose only -- like high dose, only five animals or 10
22 percent animals are lived. And then for the low dose,
23 it's 23, 46 percent animals are lived. Instead, in our
24 HID, we present the denominator used the number of and
25 animals lived at 20 weeks, which we do have about 80

1 percent, or close to 80 percent, animals we can look at
2 when -- alived animals we can look at.

3 We do not change the overall conclusion, because
4 we see here there's a significant in one out of five in
5 the gall bladder. However, we can see the same occurrence
6 in the lower dose, so we know we captured this site, just
7 a little bit different dose level.

8 COMMITTEE MEMBER EASTMOND: Thanks. I'd kind of
9 guessed that way had done, because I went to some of the
10 papers and I'd saw they'd reported every 10 weeks. I
11 thought this must have been how they did it. So anyway,
12 thank you. And it was actually very clear in the
13 presentation. So much clearer in your presentation than
14 in the papers than I might say.

15 Thank you.

16 CHAIR LOOMIS: Okay. Let's go on down the table
17 there. Dr. Wang, question from you.

18 COMMITTEE MEMBER WANG: I guess I'm not sure if
19 this is a question, but I Guess I would appreciate a
20 little bit of context for this compound. You know, I
21 appreciate that there's no human studies on the topic and
22 there seems to be very sparse data in general. And I just
23 wanted maybe for some of the more seasoned and -- of you
24 who are here for the animal studies, I mean, I guess how
25 worried or how concerned should we be that all of the

1 animal studies came from one author or one lab. I mean,
2 you know, in human studies, we want, you know,
3 replication, you know, from outside collaborators or
4 investigators. So I'm just wondering, it seems like a lot
5 of studies, and they seem compelling, but I just wonder,
6 you know, should we be concerned that it's only from one
7 lab and what is the context? Why is only one lab studying
8 this?

9 DR. KATE LI: Thank you, Dr. Wang, for the
10 question. Answer some. And Toth Laboratory has only
11 published (inaudible), they have many -- I mentioned about
12 40 years publication we can search from PubMed and not
13 only study carcinogenesis (inaudible) regulation area. So
14 I would say the lab has been presenting pretty solid
15 studies in various areas (inaudible). Many of those
16 studies are in animals. So that's one part we can look
17 at.

18 And another part we can look is when we present
19 the tumor sites, for some lung tumors that's been observed
20 in all the (inaudible) of the highest when the mortality
21 is high. And then lung tumors, it's not the -- what I it,
22 site of entry (inaudible) study. So that give us enough
23 confidence. This is not like an ingestion site or -- or
24 contact site kind of tumor. But however, we do recognize
25 there are many study limitations in the Toth Laboratory.

1 I, yeah, appreciate you suggest we should put more context
2 on that. So the study limitations I try to, yeah, make a
3 short number for example. That's also you talk about only
4 from one lab. That's limitations. And then we also
5 have -- couldn't find information or absence of
6 information about how pathologist was -- whether they're
7 blinded to the treated or controlled groups when it is
8 pathological evaluations.

9 And then also another thing, if you (inaudible)
10 hamster studies, they actually have pretty poor survival
11 in the controls. So those are kind of thing we are also
12 aware of. And then of course, Dr. Eastmond mentioned that
13 they published 10-week interval survival information. So,
14 we have no place to find a time to tumor data of this
15 animal study -- what we call animal bioassays. And
16 (inaudible).

17 DR. MARTHA SANDY: Well, thank you for that
18 Kate -- Dr. Li. I'll also say that it -- so we tried to
19 address this on page 11 and 12 of our document. The Toth
20 Laboratory is well known for their 40 years of experience
21 in publishing and they did look at a number of hydrazines.
22 They also looked at urethane. They looked at DMBA,
23 benzo(a)pyrene and other PAHs. So they have a real track
24 record of doing animal bioassays at the University of
25 Nebraska in the Eppley Institute.

1 So they're a well-respected laboratory. And
2 these studies, you know, they were doing multiple studies.
3 So it's -- at different doses. It's not one study at one
4 time with all these dose levels. So, we're pretty
5 confident that what they're finding, especially for lung
6 tumors in all these studies, in all these doses in males
7 and female mice is valid, but there may be other opinions
8 there.

9 CHAIR LOOMIS: Okay. Thank you. It seems to me
10 this is an appropriate topic for Committee discussion, an
11 important one. And maybe Dr. Bush and Dr. Eastmond will
12 want to come back it when we get to that portion of the
13 meeting. So, Dr. Bush, any questions from you, just
14 clarifying questions? Nothing.

15 COMMITTEE MEMBER BUSH: Nothing.

16 CHAIR LOOMIS: All right. Let's go to Dr. Stern
17 online, so that she's not forgotten. Any questions from
18 you?

19 We can't hear you.

20 We can't hear you.

21 You might be muted.

22 It looks like you're frozen now, so I will
23 come -- oh, there you are. Okay. Go ahead, please.

24 COMMITTEE MEMBER STERN: Yes. Okay. Yes, so I
25 guess my question follows Dr. Besaratinia's question.

1 What I'm curious about it looks like MFH hydrolyzes to
2 MMH, and then that leads to formation of compounds that
3 have already been listed in Prop 65, like formaldehyde,
4 acetaldehyde. So I guess my question is whether we feel
5 we have a good understand of what proportion of the MFH
6 leads to the formation of these compounds? Because in my
7 reading of the document, it looks --

8 CHAIR LOOMIS: Unfortunately, you have frozen
9 again. So you may need to repeat that.

10 COMMITTEE MEMBER STERN: Okay. Yeah. So can you
11 hear me?

12 Can you hear me now?

13 CHAIR LOOMIS: Yes.

14 COMMITTEE MEMBER STERN: Okay.

15 CHAIR LOOMIS: It's happened again.

16 It happened again. So we didn't hear your
17 question. Maybe -- some people are suggesting turning
18 your video off, if you don't -- if you're losing bandwidth
19 there. That might help.

20 COMMITTEE MEMBER STERN: Okay.

21 CHAIR LOOMIS: Go ahead and ask your question.

22 COMMITTEE MEMBER STERN: Yes. My question -- can
23 you hear me?

24 CHAIR LOOMIS: Yes.

25 COMMITTEE MEMBER STERN: Okay. My question has

1 to do whether we understand what proportion of the MFH
2 leads to the formation of formaldehyde and acetaldehyde,
3 even that those are compounds already listed in
4 Proposition 65?

5 COREY FRIEDMAN: Just before you all answer that,
6 I'm just noting that the speaker has turned off her video
7 camera, because she's having some technical difficulties.
8 And doing so allows the audio to come through, just making
9 a record of that.

10 Thanks.

11 CHAIR LOOMIS: Would you like her to turn her
12 camera back on at this point?

13 COREY FRIEDMAN: I think that -- that no, that's
14 fine. It's just that we're -- people are appear remotely
15 are required -- or at least members, not members of the
16 public, but members of the Committee, who appear remotely,
17 are generally required to have their cameras on. And if
18 they need to turn it off for some reason, or they lose
19 video are required to explain why.

20 DR. SARAH ELMORE: Okay. So if I'm understanding
21 your question correctly, you're acknowledging that the
22 metabolites that we presented are prop -- or a few of them
23 are Prop 65 carcinogens and you want to know what portion
24 of those occur based on MFH exposure, is that correct?

25 I'm going to -- I'm going to answer based on

1 that.

2 So my answer is we don't know the exact
3 proportions. However, we do have DNA binding studies, so
4 that we know that it's not just broken down and mainly
5 expired as carbon dioxide or methane. And some of those
6 studies are spin trapping agents. And so they're able to
7 capture those adducts and identify them. I think Isabel
8 was going to answer or address that as well.

9 DR. ISABEL ALVARADO: Yeah. It's just part of
10 the KCs' evidence, where in vivo evidence showed the
11 formation of adducts in animals administered MFH directly.

12 CHAIR LOOMIS: Thank you. Okay. Before we --
13 all right. Another question -- another answer.

14 DR. MARTHA SANDY: This is Martha Sandy. Just to
15 follow up on Dr. Eastmond's question or comment on
16 acetaldehyde. Is it or is it not a presumed metabolite of
17 MFH? And so in our summary of the metabolism section, we
18 were reading a lot of papers and trying to summarize that.
19 If you look at Gannett at el., 1991, they are saying that
20 MFH yields formaldehyde and acetaldehyde. It's MFH
21 oxidation through -- the formation of acetaldehyde
22 requires the oxidation of MFH to a diazonium ion, or a
23 diazine, and fragmentation to form formal n-methyl
24 radicals. So this is -- you know, in -- we didn't
25 summarize all the details in the HID, but that's the

1 Gannett et al. and that --

2 COMMITTEE MEMBER EASTMOND: The problem is is MMH
3 has one carbon.

4 DR. MARTHA SANDY: I understand.

5 COMMITTEE MEMBER EASTMOND: So you're degrading
6 it and you're coming out with a product with two carbons.

7 DR. MARTHA SANDY: So it's --

8 COMMITTEE MEMBER EASTMOND: That's the issue.

9 DR. MARTHA SANDY: Yeah. And we could get you
10 that paper, if you'd like

11 COMMITTEE MEMBER EASTMOND: I mean, there's --
12 you could evoke that, you know, they're some sort of
13 combination occurring, but it would be very unusual
14 chemistry from my point of view.

15 DR. MARTHA SANDY: There's a number of theories
16 of the unusual chemistry, and this is one of them. And so
17 we -- if you'd like, we could provide you Figure 3 of
18 Gannett, et al. 1991 is where you'd want to look for that
19 schema.

20 COMMITTEE MEMBER EASTMOND: Yeah, it would be
21 interesting, but not -- it's not critical in my mind,
22 because you have other DNA reactive metabolites that
23 the -- and the evidence from the animal studies is pretty
24 convincing --

25 DR. SARAH ELMORE: Exactly.

1 COMMITTEE MEMBER EASTMOND: -- even independent
2 of our knowledge of the mechanism, but that's fine.

3 CHAIR LOOMIS: Let's move on then. I see a hand
4 raised on the other side of the table. But before we go
5 that way, I have a couple of questions that I want to ask
6 as well. Do we have any information about which of the --
7 any -- which of these species occur in California?
8 Mushrooms I'm talking about, not the chemical species.

9 DR. FENG TSAI: Hi. My name is Feng Tsai from
10 OEHHA. So MFH or -- and Gyromitrin are found in many wild
11 mushroom in the Gyromitra genus. And there are many, many
12 subspecies. And there are studies found that there are --
13 this kind of -- this group of mushroom may be in
14 California, but mostly in Montana or Michigan.

15 But we found out that you could purchase the
16 dried false more morel from the Etsy or eBay. I just
17 checked yesterday. So even if we don't have fresh
18 mushroom available in California, people could still
19 purchase online, and to get their dried false morel.

20 CHAIR LOOMIS: That leads to my next question is,
21 is there any information about the amount of consumption
22 of these mushrooms?

23 DR. FENG TSAI: I think -- I believe from the
24 literature it said it's more popular in European
25 countries, especially the Scandinavia countries. Like in

1 Finland, they do have some safety cooking guidelines that
2 you need to boil the mushroom twice and change the boiling
3 water, et cetera.

4 In the U.S., I think mushrooms are consumed by
5 some people. They are mushroom hunters and professional
6 mushroom so -- but we don't have the data. The only data
7 we got was very old, in 1970s or 80s.

8 Yes, and -- but there are some mushroom poisoning
9 reports from the U.S. and many -- I think many -- most of
10 the cases are in *Gyromitra esculenta*. That's the most
11 studied species, but there also other species that's
12 available. So we do know that the people eat mushroom,
13 wild mushroom especially, but we do not -- we don't know
14 how many, how much.

15 CHAIR LOOMIS: Okay. Thanks. Yeah. No, we have
16 at least one of these in California, Montana I think.
17 *Gyromitra Montana*. So my other question is essentially
18 for curiosity. So, given that there are a number of
19 compounds in these mushrooms that are already listed and
20 some that are IARC Group 2 agents. I'm just curious about
21 why the decision was made to list this chemical and not
22 the plant? I know that was done by the Committee some
23 years ago, but there is precedent for listing entire
24 plants as carcinogens.

25 DR. MARTHA SANDY: Well, I wish you'd been here

1 when we were prioritizing this a few years back.

2 (Laughter).

3 CHAIR LOOMIS: Well, I wasn't. That's why I'm
4 asking.

5 DR. MARTHA SANDY: Right. So it came to us in
6 our prioritization process. You know, we track different
7 chemicals as a chemical, not as a plant. But I know IARC
8 has listed some plants, some genuses as well. Yeah. Good
9 idea.

10 CHAIR LOOMIS: What's done is done. Let's go
11 down this side of the table. Dr. Landolph, questions.

12 COREY FRIEDMAN: I can also answer that to some
13 extent, which is that we have different listing mechanisms
14 and OEHHHA has listed substances, as opposed to chemicals.
15 But usually when that is done, it is through a different
16 mechanism in this committee, in part because of the way
17 that the language of the law is written, in terms of when
18 you can list a substance versus a chemical.

19 CHAIR LOOMIS: Thanks.

20 COMMITTEE MEMBER LANDOLPH: (Inaudible). Thank
21 you -- cholangiomas of the liver and cholangiocarcinomas
22 of the liver, which occur in Thailand and which I just got
23 back from, caused by liver flukes. So they're very
24 unusual tumors. And I see Table 6 angiomas and
25 angiosarcomas and they're also sentinel tumors, because

1 they're so rare. They're these bloody tumors (inaudible)
2 blood vessels. So as well as your lung tumors, liver
3 tumors, gall bladder tumors, et cetera. So, I think
4 (inaudible).

5 CHAIR LOOMIS: Okay. Dr. Alexandrov, questions
6 of clarification.

7 COMMITTEE MEMBER ALEXANDROV: Yes. Thank you so
8 much for the very -- well, very extensive and clear
9 report. I will reserve my comments when it comes to the
10 one lab generating the mouse data for discussion
11 session -- section of this meeting. I do have two related
12 questions to the mouse studies, which were unclear to me
13 from the publications, and perhaps you have greater
14 clarity. Did they say that they're only the detecting
15 primary disease. So is it possible some of the actual
16 tumors are metastatic tumors?

17 DR. KATE LI: (Inaudible) studies, they did not
18 talk about metastatic tumor. But by the time when
19 multiple tumors might -- observed in one animals, we are
20 not sure, but --

21 DR. MARTHA SANDY: So, Dr. Li, I think I can step
22 in here. So it's clear from their mechanistic -- their
23 methods section in many, many papers -- I mean, several
24 people on staff and colleagues -- co-authors of these
25 papers are pathol -- were pathologists. So, it was common

1 procedure, if you see metastasis to say that. They -- and
2 they did not. So these are all primary tumors that are
3 seen. You know, there's different stains and
4 characteristics of a me -- you know, a liver metastasis
5 into the lung, you'd be able to identify that. And so if
6 that had happened, they would have reported that.

7 COMMITTEE MEMBER ALEXANDROV: Understood. Thank
8 you. That wasn't clear to me. The other thing that I
9 found striking, and again it will be great to clarify,
10 there seems to be mice where you see the hepatocellular
11 adenomas and mice where you see the hepatocellular
12 adenocarcinomas, but not both at the same time. When you
13 add up the numbers, they seem to be always mutually
14 exclusive.

15 And I did want to -- again, I couldn't see it in
16 their methods where if they see adenocarcinoma, they would
17 just say there is adenocarcinoma and no presence of
18 adenoma.

19 DR. MARTHA SANDY: So I believe for all these
20 publications, we were able to see that the authors had
21 presented the benign tumors and the malignant tumors
22 separately and then combined as benign or malignant.
23 If -- in some publications where we can't tell the
24 difference, we don't combine them. But in all of these I
25 think we were able to combine benign and malignant. And

1 sometimes they add up. No animal had both, but other
2 times they don't, because one animal had a benign tumor
3 and a malignant tumor. So it's counted only once in the
4 combined incidence. So we're pretty confident we were
5 able to get that from the publications.

6 COMMITTEE MEMBER ALEXANDROV: Understood. Thank
7 you.

8 CHAIR LOOMIS: Over to you, Dr. Crespi for any
9 questions of clarification.

10 COMMITTEE MEMBER CRESPI: I don't have any
11 questions of clarification. Thank you very much for the
12 well done report and the clear presentation.

13 CHAIR LOOMIS: Very good. At this point, we will
14 move on with the agenda. Oh, there's another question
15 bubbling up over here. Go ahead, please.

16 COMMITTEE MEMBER BESARATINIA: Well, actually, I
17 have two. Probably one would be discussed during the
18 panel discussion, but --

19 CHAIR LOOMIS: Let's save it then.

20 COMMITTEE MEMBER BESARATINIA: Okay. Yeah. But
21 just one general comment, toxin levels in these
22 (inaudible) very well known that the level of toxins in
23 those mushrooms collected at different times of the year
24 are very different, at different regions, as well as at
25 different altitude -- higher altitude, higher toxins and

1 (inaudible) information probably helpful for the reader
2 (inaudible).

3 DR. MARTHA SANDY: I believe it is in the -- in
4 section 1. I'll find you the page number in a minute.

5 CHAIR LOOMIS: Yeah, it's there. All right. Any
6 more last minute questions of clarification for the staff?

7 Okay. At this point, we're going to move on to
8 the Committee discussion. The agenda says break for lunch
9 by 12. So, let's see how it goes. If we're close to
10 being ready to vote by 12 or a little after, we may go
11 ahead and do that, if it's okay with everybody. If not,
12 we'll break at the appropriate -- at the scheduled time.

13 So first, we'll ask the assigned discussants to
14 present on the animal carcinogenicity data beginning with
15 Dr. Bush.

16 COMMITTEE MEMBER BUSH: Thank you, Dr. Loomis. I
17 want to thank Dr. Sandy and the team for putting together
18 a great document. I do understand that there are no
19 public comments for -- at this time for the particular
20 chemical. In all honesty, I appreciate that, because that
21 often reduces the confounding factors that we need to
22 consider when evaluating the data.

23 I do appreciate part of the discussion talking
24 about the limitations coming from a single lab. I concur
25 with what has been said that the Toth Lab does have a

1 long, you know, reputable history of producing quality
2 research. So, while there are some, you know, perceived,
3 you know, deficiencies -- minor deficiencies, I looked at
4 this from a more macro view and, you know, looking at
5 outcomes.

6 And I don't think when we consider the tumor
7 burden outcomes, that the limitations substantively
8 detract from that. And so, when evaluating that, I still
9 viewed the data with, you know, medium to high confidence.

10 So with that, I'll kind of give a snapshot and a
11 macro view in the interests of time. Of course, we've got
12 these mushrooms that have this, you know, toxicity. So
13 the sublethal effect is really what we're looking at. And
14 the 14 lifetime studies, I think, paint a compelling
15 picture.

16 The 12 studies in the albino mice, the two
17 studies in the golden hamsters, the exposure to drinking
18 water and subcutaneous injection. And these were, of
19 course, lifetime exposure studies, so with the full
20 necropsy and histopathology.

21 To the -- to the mouse studies and with respect
22 to the drinking water, we do see a consistent increase in
23 the tumors at multiple sites and across doses in both
24 sexes. Pardon me. I've got some lingering congestion, a
25 little bit of a runny nose. You know, the major tumor

1 types we see, the data was presented in those beautiful
2 tables. Thank you for that, lung, liver, gallbladder. We
3 see those common sites, particularly lung across all
4 systems.

5 We see a dose -- a clear dose response observed
6 when we combine those lung tumors. In liver, we see the
7 both benign and malignant forms, and combined again
8 painting a persistent dose effect, even at lower doses.
9 The fact that we're seeing rare tumors like gallbladder
10 that we don't see in controls is -- excuse me, again --
11 compelling evidence. The vascular system tumors that we
12 see across the sexes is again even in low dose, because
13 when we look at the 1982 paper, the low dose experiments
14 that Toth did, we are still seeing some cancers there or
15 evidence of carcinogenicity.

16 Moving on to the subcutaneous studies, regardless
17 of whether it's a single dose or the multiple dose, we
18 still see tumor burden, again particularly in lung,
19 between the adenomas and the adenocarcinomas. We see it
20 significantly increased in both sexes across both those
21 protocols. And then this rare preputial gland squamous
22 tumors that we see after the single high dose.

23 In the hamsters -- hamster studies, we see
24 similar lifetime drinking studies. And the common liver,
25 gallbladder, bile duct again these rare tumors that we are

1 seeing in both sexes and then this -- another rare tumor,
2 the Kupffer cell tumor that we saw in males and females,
3 which we don't historically see in controls.

4 So again, this paints this picture across all
5 species, sexes, exposure routes. We see that MFH produces
6 this consistent, multi-organ response, including these
7 rare tumors. The findings are particularly strong for
8 lung, liver, bile duct, and gallbladder. And this mirrors
9 the tumor burden that we're seeing in the related
10 hydrazine compounds.

11 So my final statement I would say that these
12 studies collectively support again a compelling picture of
13 carcinogenicity.

14 CHAIR LOOMIS: Great. Thank you, Dr. Bush.

15 Dr. Eastmond, anything to add to what we've just
16 heard?

17 COMMITTEE MEMBER EASTMOND: You know my thoughts
18 are similar and appreciate the OEHHA staff for the
19 presentation and also preparation of the documents.

20 My reading, significant tumors both benign and
21 malignant were seen in multiple studies, in multiple
22 tissues in both male and female mice, as well as in
23 hamsters. A lot of these studies you might see a
24 significant increase only in one, at the intermediate
25 dose, but there are dose-related increases in many of the

1 studies. There -- that's a large amount of information
2 indicating that this chemical causes cancer in these
3 laboratory animals. And there are these (inaudible) rare
4 tumors that are seen as well.

5 The -- I guess the issue that came back with this
6 comes -- these all come out of one laboratory. However,
7 that's the only laboratory that's ever done the studies,
8 so that's -- and it's a well-regarded laboratory. These
9 increases are really substantial in most cases. So it's
10 not likely to be an error from my reading of this.

11 And, you know, you're looking at studies that are
12 40 to 50 years old. Certainly, these are not ideal
13 studies and the reports are not ideal, but I think they
14 are sufficient and adequate to make a decision based upon
15 the reports that have been made. So I think the evidence
16 is pretty compelling that it causes cancer.

17 CHAIR LOOMIS: Thank you, both.

18 All right. Now, we'll move on to discussion of
19 the key carcinogenesis -- key characteristics of
20 carcinogens and other mechanistic data starting with Dr.
21 Landolph.

22 COMMITTEE MEMBER LANDOLPH: Yeah. The
23 mechanistic data is pretty clear. These are -- this is
24 an electrophilic compound. There's structure activity
25 correlations to it. The compounds metabolize through

1 cytochrome P450 and FMO enzymes. You get DNA adducts with
2 it, so it's both electrophilic and leads to DNA adducts.
3 It's kind of a classical carcinogen and so are its
4 metabolites. And it's metabolized to many metabolites,
5 which are genotoxic, carcinogenic. So I think this is a
6 fairly straightforward case. There's nothing that would
7 cause me to hesitate in moving forward with its listing.

8 So I think the staff again did a great job
9 writing this up and looking at the characteristics of
10 carcinogens, which were published in a review article a
11 while back and fits a number of those criteria for
12 carcinogens. And it's kind of a classical genotoxic
13 carcinogen. Very straightforward, causes tumors in a
14 number of organs, and being some of those, which are
15 sentinel tumors, i.e. they're very rare in animals. And
16 when you see them, you start to get worried, because they
17 actually cause these sentinel tumors, which are otherwise
18 not very common. And I'm thinking of the
19 cholangiocarcinomas, and cholangiomas, and also the tumors
20 of the blood vessels, the very interesting tumors,
21 angiosarcomas and angiomas.

22 So altogether, this story hangs together pretty
23 well. The mechanistic data is pretty straightforward and
24 the staff again did a great job writing it up very
25 clearly, so it's easy to read. It's a nice document to

1 read. And it's got a plethora of data in it. So to me,
2 it looks like it's a -- MFH is clearly a genotoxic
3 carcinogen, which has metabolites that are genotoxic.

4 So, I think it will be relatively straightforward
5 to list this as a carcinogen without too many problems.

6 Thank you.

7 CHAIR LOOMIS: Thank you.

8 Dr. Alexandrov, your turn.

9 COMMITTEE MEMBER ALEXANDROV: Thank you so much
10 and thank you again for the well-written report.

11 I should say I very much disagree with what was
12 just said about this specific carcinogen. So, at the
13 onset, it's important to know that from the 10 key
14 characteristics that we have for carcinogens, we have some
15 evidence for one key -- K -- well, key carcinogen -- key
16 characteristic 1, which is the metabolic activation and
17 key characteristic 2, which is the genotoxicity.

18 And even when we look at those two
19 characteristics, I find the evidence to be somewhat
20 limited, indirect. And it's largely based on the
21 surrogates not the compound itself.

22 I think the report did a very good job to
23 summarize the available mechanistic data and the database
24 available for us to consider MFH is actually very sparse.
25 And there are actually very few studies that have directly

1 evaluated these compounds. Indeed, there is a lot of
2 mechanistic information available for parent compounds or
3 for the hydrolysis products, such as MMH.

4 But again, now we're are relying on surrogates to
5 infer mechanistic conclusions. And I personally found
6 that to be somewhat of a weaker evidence.

7 And just going briefly to Key Characteristic 1,
8 the metabolic activation. So MFH, again you have proposed
9 to hydrolyze to MMH, which can form reactive methyl/formyl
10 radicals and then you get formaldehyde and acetaldehyde.
11 And the story there is clear, we know that they cause DNA
12 adducts. We know that they cause cancer.

13 However, again, we have reliance on this specific
14 set of steps and we don't have any direct demonstration
15 that actually, as far as I can see, that MFH derived
16 electrophilic intermediates are actually doing that.

17 From a genotoxicity perspective, again I find
18 evidence personally to be quite limited. We have reversal
19 of mutations in one single assay, but we have another --
20 and I'm sorry. I don't have that in my notes, another
21 several assays that you do not -- we do not see the
22 effect. And we do not have any induction of unscheduled
23 DNA synthesis for the actual compound.

24 Now, again, if we go to the parent compound, we
25 have quite a lot of evidence of unscheduled DNA synthesis.

1 We have a number of additional -- we have a number of
2 additional evidence. But again, that's for the parent
3 compound.

4 So this is for the two characteristics. There is
5 another eight key characteristics. And again, there was
6 not particularly much evidence found from -- for them.
7 When it comes to the toxicokinetic information, again we
8 have mostly inferential evidence from the absorption. We
9 have formal absorption in humans which is inferred from
10 the mushroom poisoning cases. We have some animal studies
11 that provide direct evidence of absorptions, but again, we
12 don't have quantitative kinetic pedometers for these
13 studies.

14 We have some animal studies for the distribution,
15 some animal studies using radiolabeled MMH and Gyromitrin,
16 but again not MFH. And again, when we look at the
17 metabolism, we have very good evidence for MFH. Well, we
18 have -- sorry. We have very good evidence for the parent
19 compound, but not that good evidence for MFH itself. And
20 then last, but not least, when it comes to the
21 elimination, again we can see the elimination based on the
22 poisoning cases, which takes a typical two to five days.
23 But again, this is an indirect suggestion that how MFH
24 will be eliminated from the system.

25 So overall, at least from my perspective, there

1 is some limited evidence and some indirect mechanistic
2 evidence that MFH put just on two key characteristics,
3 specifically the electrophilic activation and the possible
4 genotoxicity. But however, I find that the overall body
5 of mechanistic data is just fragmented, indirect and it
6 just doesn't give us the evidence for this specific
7 compound to suppose -- to support a clear carcinogenic
8 mode of action.

9 CHAIR LOOMIS: Okay. Thank you. It looks like
10 Dr. Landolph wants to respond.

11 COMMITTEE MEMBER LANDOLPH: When you take the
12 totality -- when I take the totality of the data here,
13 there's a lot of dose response data. There's
14 multi-species, multi-organ carcinogenicity. So, I don't
15 view this as inferential at all. I view this as pretty
16 strong data and that the metabolites are also genotoxic.
17 So this, for me, is one of the easiest ones I've ever
18 dealt with, so I think we disagree strongly here.

19 Thank you.

20 CHAIR LOOMIS: All right. Well, it is time for
21 Committee discussion. And I'd like to first -- I'll come
22 back to. I know you want to respond. So what I'd like to
23 do first is allow the Committee members to ask questions
24 of the discussants about their presentations and then
25 we'll move on to a more general discussion. So let's

1 focus on questions first. Dr. Alexandrov, I guess you'd
2 like to respond to Dr. Landolph's remarks.

3 COMMITTEE MEMBER ALEXANDROV: Well, perhaps a bit
4 yes. I think we definitely do disagree on the
5 interpretation. I think one thing is to consider the
6 mechanistic part by itself, you can combine that with the
7 actual mouse or model organism data. And again, from my
8 perspective, something that was raised by another
9 Committee member, the biggest concern there is this is
10 coming from one lab. And this could be -- this is a
11 respected -- a very well-respected lab, and it could be
12 the best people to do that experiment, but the fact that
13 you have one lab that did the experiment 40, 50 years ago
14 and no one repeated that in the last 40, 50 years is at
15 least telling how important that is for the rest of the
16 community, and again brings up the concern of what if they
17 made some mistake? I know they have multiple studies, but
18 we have zero reproducibility of this experiment --
19 independent reproducibility.

20 And again, that's my biggest concern with the
21 mouse data. Other than that, the mouse studies are very
22 convincing. They're very clear. If they were coming from
23 three or four groups, I think I'll have a very different
24 opinion. But they're coming from one group without any
25 subsequent follow-up.

1 CHAIR LOOMIS: Okay. More questions for the
2 discussants first. Looking to my left. Okay. Dr. Wang.

3 COMMITTEE MEMBER WANG: So given the sparse
4 amount of data and that a lot of the data came quite a
5 while ago, is it the opinion that there will be very
6 little data in the future, thereby the decision we have to
7 make is based on the data that we already have in hand? I
8 mean, that's basically all the data we're going to get.

9 DR. MARTHA SANDY: This is Martha Sandy. It
10 looks like you're asking us? Yes. We don't anticipate
11 seeing any more data on this chemical.

12 COMMITTEE MEMBER WANG: That's helpful to know
13 that there's no more -- other data. This is what we have,
14 so we have to make a decision based on what we have.

15 CHAIR LOOMIS: Okay. Other questions for the
16 discussants?

17 This way.

18 Microphone.

19 COMMITTEE MEMBER BESARATINIA: Just a general
20 question. I understand that this was decided to be
21 considered. Looking at a broad picture, I'm trying to
22 find out what additional value we get by naming this
23 compound as a carcinogen, considering that the parent
24 compound has already been classified as a carcinogen.
25 Metabolites, MMH, and acetylaldehyde, and others have

1 already been classified as carcinogen. The data with
2 regard to this particular compound in terms of
3 pharmacokinetic is very sparse.

4 And in terms of the magnitude of the problem,
5 when I look at the national data, it doesn't seem like a
6 pressing public health issue at least at this time. For
7 example, the report indicates that over the course of 18
8 years, there have been over 118 cases of mushroom
9 poisoning. That amounts to seven cases per year. And
10 when I look at the national data, this is more or less
11 consistent with that. And the data, like six or seven
12 cases per year, come from Michigan, which is a large scale
13 with a population of over 10 million.

14 So, I'm trying to find out -- of course, I do
15 understand that this was proposed many, many years ago.
16 What is the public health relevance of identifying and
17 classifying this compound as a carcinogen at this time?

18 CHAIR LOOMIS: An interesting question. I don't
19 know who is in a position to answer that, if anyone?
20 Martha is going to give it a attempt. But let me just say
21 first, it seems to me that we're already moving to very
22 general discussion leading to a vote, and that's great.
23 We need to do that, but if there are questions that are
24 specific to the data that have been presented, I'd like to
25 deal with those first.

1 So, let me put your -- park your question with
2 Martha and then see if there any other questions about
3 clarifications regarding the data before we move on.

4 COMMITTEE MEMBER BESARATINIA: That was just a
5 perspective. It was not really a question.

6 CHAIR LOOMIS: Not a question. It's a comment,
7 yeah.

8 (Laughter).

9 CHAIR LOOMIS: I recognize that. Mariana, there
10 on Zoom, if you have a question you'd like to ask, please
11 wave at me, because I can see you, but I don't know if
12 you're trying to raise your hand or anything.

13 No. Okay. This way, questions, anything?

14 Yes. Cate.

15 COMMITTEE MEMBER CRESPI: Yeah, if I could ask a
16 question of the discussants who focused on the animal
17 studies. And that is, this lab did a whole series of
18 studies where they, you know, assessed at one dose and
19 then a lower dose, and then a lower dose. And was that
20 series just -- was it motivated because of the high
21 toxicity or were there other reasons? I just wonder
22 whether you might have any insights into why there was
23 such a series of studies. And it's just a little
24 surprising that they put so much -- so many people found
25 this one particular compound, so -- so many repeated

1 studies.

2 COMMITTEE MEMBER BUSH: Thank you, Dr. Crespi. I
3 can speculate. My take from reading the papers and this
4 data is that it was exactly that. Initially, they found
5 this high toxicity and were trying to titrate it down.
6 And so, you know, get to a point where you've got kind of
7 a minimal low dose that may still have a carcinogenic
8 effect. And that's why we see that progression in the --
9 in the papers.

10 Beyond that, I didn't note any alternative
11 rationale for doing this, but there were separate studies,
12 yeah.

13 CHAIR LOOMIS: Thank you. Any other questions
14 for the discussants?

15 Yes.

16 COMMITTEE MEMBER ALEXANDROV: Perhaps one
17 question. I mean, we have like epidemiological data. And
18 one of the questions I'd like -- I do wonder is whether
19 that's -- it's even possible to have epidemiological data
20 for the specific compound or am I going outside of the
21 purview of the committee?

22 CHAIR LOOMIS: No. I think that's a legitimate
23 question.

24 COMMITTEE MEMBER ALEXANDROV: Yeah, because I
25 didn't -- like just trying to think who are you going --

1 control studies -- you can think of controls, but who did
2 the cases exposed to this would be the people who get
3 mushroom poisoning, like the eight per year or something
4 like that. It's -- that's one of the things. Is it even
5 possible to have epidemiological data for this specific
6 compound?

7 CHAIR LOOMIS: Well, there are other
8 epidemiologists present, but I'll try to answer that. And
9 I'd say it's possible, but not likely to have very
10 definitive data on this kind of exposure. Most likely, it
11 would come from dietary epidemiology studies involving
12 questionnaires. And typical questionnaires are not that
13 specific about the kind of mushrooms that people eat. If
14 the studies were done in the United States, I think there
15 wouldn't -- probably wouldn't be enough information to
16 work with, because, consumption of these plants -- these
17 particular plants doesn't seem to be common here.

18 Other epidemiologists may know more about this
19 than I do, but I think that kind of study would be
20 unlikely.

21 COMMITTEE MEMBER WANG: I don't know any more
22 about this than you do, but I mean I would probably go to
23 Scandinavia, right? They have levels that they've
24 already -- safety levels that they've already initiated,
25 then presumably they have human population data that led

1 to those specific levels.

2 CHAIR LOOMIS: Okay. I'm not seeing any more
3 questions for the discussions -- discussants. So at this
4 point, I think we can move on to a more general
5 discussion, leading to a decision on listing this agent.
6 So, we've heard a question about public health relevance.
7 Martha was already to answer and I asked to put that on
8 hold, but perhaps go ahead at this point.

9 DR. MARTHA SANDY: So thank you. So we have
10 tracked chemicals that have some evidence of
11 carcinogenicity and we follow them over the years, and
12 we'll do updates of the literature to see if there's any
13 new evidence that's published on them. And we welcome
14 nominations from the public, from all of you for chemicals
15 that we should be keeping track of. And periodically, we
16 bring those chemicals to your Committee, the CIC, for
17 ranking in our prioritization process.

18 And so back in 20 -- 2009, '10, and '11, we
19 brought a total of around a hundred chemicals for those
20 three years and asked you all to rank them. And this was
21 one of those chemicals that was ranked at that time. And
22 the Committees, both the Carcinogen Identification
23 Committee and the Developmental and Reproductive Toxicant
24 Identification Committee met years ago to advise us and
25 help us develop a prioritization process. And there it

1 was determined that the Committees really want us to focus
2 on chemicals that have the potential for exposure in
3 California, and potential for toxicity - either
4 carcinogenicity or reproductive or developmental toxicity,
5 depending upon the Committee.

6 So, when we bring you these chemicals in the
7 prioritization process to rank, we give you information on
8 exposure and we give you information on toxicity. And the
9 consideration for public health - sometimes there's low
10 level exposure to the general population, sometimes there
11 could be significant exposure to small portions of the
12 population.

13 And the public -- I think in this case, that's
14 what you have. You have people that may be exposed,
15 either through occupational exposure -- we mentioned that
16 this is also synthesized and used to make a veterinary
17 drug. It's used in research, also preparing the dried
18 mushrooms and boiling the mushrooms, you can be exposed,
19 and then people that consume these mushrooms.

20 So it's a small group and we know from
21 experience, exposure can change and exposure patterns can
22 change. Now, you can get these online and you can, you
23 know, be -- hear about, oh, here's this wonderful tasty
24 mushroom, and, you know, who knows what's going to happen
25 down the line in the future. But I think that's -- I hope

1 that gives you some feeling for how this was prioritized.

2 COREY FRIEDMAN: I can also just -- just as a
3 reminder as already mentioned, we did confirm that these
4 are available online. And so -- (inaudible) online as a
5 (inaudible) recipes, and are available to Californians
6 (inaudible) not have been in the past.

7 CHAIR LOOMIS: Come back to you.

8 COMMITTEE MEMBER BESARATINIA: Yes. Just
9 probably Corey would be the right person to ask. Just out
10 of curiosity, so assuming that these products have already
11 been labeled, let's say this mushroom that contains
12 Gyromitrin that is the parent compound, I'm assuming that
13 Prop 65 requires manufacturers or producers to put a label
14 on the mushrooms that are being sold in the market.

15 So now, if we classified this other intermediate
16 as a carcinogen, what are they supposed to do, supposed to
17 specify what ingredients of this mushroom is causing
18 cancer or is it going to be a double labeling, how does it
19 work?

20 COREY FRIEDMAN: Well, I can't -- I can answer
21 that. But just as a reminder, that does go beyond the
22 purview of the Committee, so your listing decisions should
23 not be based on, you know, any evaluation of what the
24 effects would be in terms of warnings, no warnings. If a
25 warning is required, then there needs to be a warning on

1 products when sold to -- in -- to California.

2 The -- in terms of what that warning contains,
3 there has been a recent change in regulations, so that
4 ultimately all the warnings will need to list at least one
5 chemical per endpoint. They do not need to list multiple
6 chemicals, although some companies choose to put multiple
7 chemicals in their warning.

8 However, I cannot say whether these mushrooms
9 that are currently being sold, whether they have warnings
10 or not when they're sold. I haven't looked into that, so
11 I don't know if people are selling them with the
12 Proposition 65 warnings or not. I just don't have any
13 information about that.

14 DR. MARTHA SANDY: Just to underscore what Corey
15 said at the beginning of the meeting, your task is to do
16 hazard identification. That does not involve
17 consideration of exposure. That is just: "Is this a
18 cancer hazard?"

19 CHAIR LOOMIS: And I think that's the critical
20 point. The question before the Committee is whether this
21 compound meets the criteria for listing as a cancer
22 hazard. Downstream considerations are not really for us.

23 COREY FRIEDMAN: Right. That should be the basis
24 of the vote. If there's another conversation that
25 wants -- that people want to have about prioritization,

1 that would be a different conversation than the question
2 about whether or not to list this specific chemical.

3 CHAIR LOOMIS: Okay. Any other general
4 discussion and the mindset for a decision?

5 I'm not seeing anything. Mariana online? You're
6 good? Give me a wave if you're okay.

7 You're okay.

8 Okay over here.

9 Okay. At this point, we would take public
10 comment, but I understand there is no public comment in
11 the room, is that correct?

12 TINA COX: Correct, there's none.

13 CHAIR LOOMIS: Is there any public comment on
14 Zoom?

15 TINA COX: I'm looking now to see if anyone is
16 raising their hand on Zoom.

17 No, I'm not seeing any raised hands.

18 CHAIR LOOMIS: Okay.

19 So we are not having any public comment, which
20 means that we can move to a vote. The agenda says I
21 should ask if there's any further Committee discussion,
22 but I think we've had that, but this is the last chance.

23 Any burning discussion?

24 Not seeing any.

25 Yes, go right ahead.

1 COMMITTEE MEMBER EASTMOND: I may just make one
2 comment. It's hard telling these older papers, but at
3 least one of them said these studies were funded by the
4 National Cancer Institute. And it could be that the
5 funding just ended and that's why there are no additional
6 studies that went on. And others may have reviewed this
7 and considered the evidence sufficient and so they didn't
8 feel the need to do additional studies, but that's --
9 we're dealing with what we have.

10 CHAIR LOOMIS: Very good. Last chance. This is
11 it.

12 Okay. Hearing nothing, we will move to a vote.
13 So the question before the Committee in formal language
14 is, "Has N-methyl-N-formylhydrazine been clearly shown
15 through scientifically valid testing, according to
16 generally accepted principles to cause cancer?"

17 So I'm going to go down the list in alphabetical
18 order and ask each of us -- each of you for your "yes" or
19 "no" vote. You don't need to explain your vote or justify
20 it. Just say "yes" or "no".

21 Dr. Alexandrov?

22 COMMITTEE MEMBER ALEXANDROV: No.

23 CHAIR LOOMIS: Dr. Besaratinia?

24 COMMITTEE MEMBER BESARATINIA: Yes.

25 CHAIR LOOMIS: Dr. Bush?

1 COMMITTEE MEMBER BUSH: Yes.

2 CHAIR LOOMIS: Dr. Crespi?

3 COMMITTEE MEMBER CRESPI: Yes.

4 CHAIR LOOMIS: Dr. Eastmond?

5 COMMITTEE MEMBER EASTMOND: Yes.

6 CHAIR LOOMIS: Dr. Landolph?

7 COMMITTEE MEMBER LANDOLPH: Yes.

8 CHAIR LOOMIS: He said yes.

9 COMMITTEE MEMBER LANDOLPH: Yes.

10 CHAIR LOOMIS: Dr. Loomis, yes.

11 Dr. Stern?

12 COMMITTEE MEMBER STERN: Yes.

13 CHAIR LOOMIS: Yes.

14 Dr. Wang?

15 COMMITTEE MEMBER WANG: Yes.

16 CHAIR LOOMIS: Very good. We have five "yes"
17 votes -- no, eight "yes" votes and one "no" vote, which
18 means that the chemical will be listed.

19 So at this point, I think we can decide whether
20 we want to break for lunch now or move on to the consent
21 item and anything else on the agenda that may come after
22 that. What's the Committee's pleasure on that?

23 Keep going?

24 Keep going. Keep going. Okay.

25 We'll keep going. So, consent item, update of

1 the California Code of Regulations, Title 27, Section
2 27000, a list of chemicals which have not been adequately
3 tested as required.

4 (Slide presentation).

5 CHAIR LOOMIS: So we'll go ahead and take up this
6 consent item. The Committee is being asked to affirm
7 changes in response to submissions from the Department of
8 Pesticide Regulation. U.S. EPA's Office of Pesticide
9 Programs have indicated there are no changes, so -- and no
10 response was received from the U.S. EPA. So, this is a
11 ministerial duty only, in that we rely on information
12 provided to OEHHA by the Department of Pesticide
13 Regulation and the federal EPA in order to identify the
14 chemicals that needed to be added or removed to Section
15 27000.

16 So I will now invite Senior Environmental
17 Scientist Tina Cox to give the staff presentation on this
18 item. Tina.

19 TINA COX: Thank you, Dr. Loomis and thank for
20 the Committee to be here -- for being here today. So as
21 Dr. Loomis mentioned, Proposition 65 requires the State to
22 publish and update annually a list of chemicals that are
23 required to be tested under State or federal law for
24 carcinogenicity or reproductive toxicity and that have not
25 yet been adequately tested or -- as required. This list

1 can be found in Title 27, Section 27000 of the California
2 Code of Regulations and is commonly known or is referred
3 to as the Section 27000 list. It is a separate and
4 distinct item from the Proposition 65 list, and it is
5 chemicals known to cause cancer -- were -- sorry.

6 Separate from -- distinct from the Proposition 65 list of
7 chemicals known to cause cancer or reproductive toxicity.

8 The Section 27000 list has no regulatory impact.
9 It does not require that any testing be done. Rather, it
10 is a source of information concerning chemicals that need
11 further testing pursuant to State or federal law. To
12 update the list, OEHHA requests information from the
13 California Department of Pesticide Regulation and the U.S.
14 Environmental Protection Agency's Office of Pollution
15 Prevention and Toxics and Office of Pesticide Programs
16 each year.

17 This year, OEHHA staff reviewed the responses
18 received and identified four recommended changes to the
19 Section 27000 list, which are the removal of butoxy
20 polypropoxy polyethoxy ethanol - iodine complex,
21 chlorophacinone, sodium chlorate, and tetraglycine
22 hydroperiodide. Based on information received from DPR,
23 the data requirements for these chemicals have been
24 fulfilled.

25 Next slide, please.

1 [SLIDE CHANGE]

2 TINA COX: The letter from DPR, along with
3 additional background, a response letter from OPP, and a
4 mock-up of the proposed change are available in the staff
5 report provided to the Committee and posted online on
6 October 8th. The proposed change is also shown on the
7 slide. As Dr. Loomis mentioned, this is a consent item
8 and ministerial duty of the Committee, in that the DARTIC
9 and CIC committees used the information to provide by --
10 they are -- they are used to -- the information to --
11 provided by DPR and U.S. EPA to identify the chemicals
12 that need to be added or removed from the Section 27000
13 list.

14 We now ask the Committee members to vote in favor
15 of the proposed changes, so that OEHHA can update this
16 list. I'll now turn it back over to Dr. Loomis and we'll
17 be happy to take any questions that you may have.

18 CHAIR LOOMIS: Right. So are there any
19 questions? Just noting this is a consent item. I expect
20 it to be non-controversial, but clarifying questions are
21 welcome. This way? Mariana, any questions?

22 Nope.

23 This way.

24 Very good. So we'll move to a vote. And the
25 question we vote on is, "Should Section 27000 of the Title

1 27 of the California Code of Regulations be amended as
2 indicated?" And I don't turn the page and read out all
3 the things that were on there, but maybe you remember
4 them. So I'll now call your names again. Vote "yes",
5 "no", or "abstain". And again, you don't need to explain
6 your vote.

7 Dr. Alexandrov?

8 COMMITTEE MEMBER ALEXANDROV: Yes.

9 CHAIR LOOMIS: Dr. Besaratinia?

10 COMMITTEE MEMBER BESARATINIA: Yes.

11 CHAIR LOOMIS: Dr. Bush?

12 COMMITTEE MEMBER BUSH: Yes.

13 CHAIR LOOMIS: Dr. Crespi?

14 COMMITTEE MEMBER CRESPI: Yes.

15 CHAIR LOOMIS: Dr. Eastmond?

16 COMMITTEE MEMBER EASTMOND: Yes.

17 CHAIR LOOMIS: Dr. Landolph?

18 COMMITTEE MEMBER LANDOLPH: Yes.

19 CHAIR LOOMIS: Dr. Loomis votes yes.

20 Dr. Stern?

21 COMMITTEE MEMBER STERN: Yes.

22 CHAIR LOOMIS: Dr. Wang?

23 COMMITTEE MEMBER WANG: Yes.

24 CHAIR LOOMIS: Very good. The changes affirmed.

25 So, again I'll ask the question, we have staff

1 updates, which might last 30 minutes or so, maybe less.

2 Tina says maybe less. Take them now or stop for lunch?

3 Let's do it. Let's do it. Everybody says: let's
4 do it. Okay. Let's do it.

5 So the next item is update on Proposition 65
6 listings regulations and litigation since the last
7 meeting.

8 (Slide presentation).

9 CHAIR LOOMIS: Tina, that is back to you, I
10 believe.

11 TINA COX: All right. Make sure my mic is on.

12 All right. Thank you again, everybody.

13 So I'll be providing you with an update on
14 important Proposition 65 developments since the last CIC
15 Committee meeting. I'll start by going over the chemicals
16 or endpoints added to the Proposition 65 list, or under
17 consideration for potential listing. Then, I'll review
18 the safe harbor levels that have been adopted or proposed.

19 After that, I'll turn it over to our counsel,
20 Corey Friedman, to provide a brief update on other
21 regulatory actions.

22 Next slide.

23 [SLIDE CHANGE]

24 TINA COX: Following the Committee's last
25 meeting, the male reproductive endpoint was added to the

1 listing of Bisphenol S for reproductive toxicity.

2 And last month, the Developmental and
3 Reproductive Identification Committee considered listing
4 BPS for developmental toxicity. The DARTIC voted yes on
5 the question, "Has Bisphenol S been clearly shown through
6 scientifically valid testing, according to generally
7 accepted principles to cause developmental toxicity." And
8 so the developmental endpoint will be added to the list of
9 this chemical.

10 Next slide.

11 [SLIDE CHANGE]

12 TINA COX: Recently, OEHHA listed a -- or issued
13 a data call-in on para, para-bisphenol' -- or sorry, para,
14 para'-bisphenol chemicals to solicit information related
15 to their reproductive toxicity. The comment period ends
16 December 1 of 2025.

17 Next slide.

18 [SLIDE CHANGE]

19 TINA COX: Since the Committee's last meeting,
20 we adopted a No Significant Risk Level for Titanium
21 Dioxide (airborne unbound particles of respirable size)
22 where both of the following intake levels must be met: 440
23 micrograms per day for airborne, unbound titanium dioxide
24 particles with diameters of 10 micrometers or less, and 44
25 micrograms per day for airborne, unbound titanium dioxide

1 particles with diameters of 0.8 micrometers or less. The
2 effective date for the adopted -- the adoption of the NSRL
3 was October 1 of 2025.

4 Next slide.

5 [SLIDE CHANGE]

6 TINA COX: Also, since the last -- since the
7 Committee's last meeting, we proposed to adopt a No
8 Significant Risk Level for 1-Bromopropane and
9 Diethanolamine. For 1-Bromopropane, the proposed NSRL is
10 54 micrograms per day. For Diethanolamine, the proposed
11 NSRL is 6.4 micrograms per day for dermal exposures. We
12 are still in the regulatory process for this proposed --
13 these proposed NSRLs.

14 And so now, I will turn it over to Corey to
15 provide a regulatory update.

16 COREY FRIEDMAN: Thank you very much. So onto
17 the next slide.

18 [SLIDE CHANGE]

19 COREY FRIEDMAN: So first, we would like to
20 present this proposal to the Committee for your -- oh. Is
21 that better? Am I more audible?

22 Okay. For your consideration, this is a fairly
23 technical regulatory change that OEHHA is considering.
24 Essentially, it would change existing law, existing
25 regulation, so that once the Committee has a quorum what

1 is required for a vote is a majority of the members
2 present. So, if not everyone can attend, a vote can still
3 be taken, as long as the quorum is met, which is usually
4 the purpose of quorum requirements in the first place.
5 For most committees, once you make quorum, then you
6 therefore have enough for a vote. But because of this
7 quirk in the existing language, sometimes that would not
8 be the case, because anyone who is not present would
9 essentially be counted as a "no" vote, rather than just
10 not counted at all. So, we wanted to let you all know
11 about this and see if anyone has any comments or
12 questions.

13 CHAIR LOOMIS: Sounds like a good idea to me.

14 COREY FRIEDMAN: Thank you. That's appreciated.
15 Okay. Well, if no one has anything else --

16 COMMITTEE MEMBER EASTMOND: I have a question.
17 So, your letting us know about this and for input, but who
18 ultimately will make this decision on?

19 COREY FRIEDMAN: Well, in order for it to be
20 actually-done, we would need to do a rulemaking, a formal
21 rulemaking, because it's in regulation right now. So
22 OEHHA would propose the regulation. There would be a
23 public comment period. Of course, the Committee members
24 would be able to comment on that point as would anyone,
25 and then it's -- it goes through the same sort of

1 processes as any other regulation. It would have to be
2 submitted to the Office of Administrative Law, et cetera,
3 et cetera. We'd have -- yeah. All right then, we can go
4 on to --

5 [SLIDE CHANGE]

6 COREY FRIEDMAN: -- a update on litigation. It
7 has been a fairly eventful year.

8 The first item on that list is California Chamber
9 of Commerce versus Bonta. This one is the acrylamide
10 case. It may be familiar to you, as it has been going on
11 for a number of years. It was up at the Ninth Circuit
12 earlier on an earlier stage of this case. But
13 essentially, the issue was whether a Proposition 65
14 warning requirement for acrylamide in food violated
15 businesses' First Amendment Rights, because it was
16 compelled commercial speech. And the rule is that the
17 State may compel commercial speech, if it is factual and
18 non-controversial. That's the key phrase.

19 And essentially, the plaintiff, the California
20 Chamber of Commerce, argued that there was a scientific
21 debate about whether the amount of acrylamide in food
22 actually poses a risk of cancer. And the district court,
23 the trial court, agreed with the Chamber and found that it
24 did -- the Proposition 65 warnings did violate the First
25 Amendment rights of the Chamber's members.

1 So, the Attorney General's office has filed
2 notice of appeal and we will see what happens from there.

3 The second case on the list is essentially the
4 same issue, somewhat different facts, as there were
5 different -- there was different warning language at issue
6 in both of these cases. But, Personal Care Products
7 Council versus Bonta was again a First Amendment challenge
8 to Proposition 65 warnings for Titanium Dioxide, unbound
9 airborne particles of respirable size. That's what the
10 listing was for specifically in cosmetics and personal
11 care products. And there, the trial judge also agreed
12 with the plaintiffs and found that the First Amendment was
13 violated. That one was not appealed.

14 The third one on that list from OEHHA's
15 perspective has a -- had a better outcome. Physicians
16 Committee for Responsible Medicine versus OEHHA. This is
17 the only one on the list in which OEHHA was itself a
18 party. And that was a dispute over the fact that OEHHA
19 did not list processed meat, quote/unquote, as a
20 carcinogen.

21 As mentioned earlier in this meeting, there are
22 multiple ways of adding things to the Proposition 65 list.
23 And one of those is that under certain circumstances, IARC
24 designations can result in a listing. IARC listed --
25 found that processed meat was a carcinogen, but OEHHA

1 argued that based on the monograph we could not really
2 determine what it was that had been actually listed. We
3 could not tell what constituted "processed" or what they
4 were including as "meat". So, it was therefore not
5 something that we could list, because it was not
6 identifiable essentially.

7 And there, the trial judge did agree with OEHHA
8 that this -- that judgment was entered fairly recently, so
9 it is still within the time period where PCRM could decide
10 to appeal, so we don't know if they will choose to do that
11 or not.

12 Finally, a California appellate court case
13 Consumer Advocacy Group versus Walmart. The question here
14 is whether agreement to compelled arbitration could apply
15 to a Prop 65 claim. You may have heard about compelled
16 arbitration specifically in the context of employment
17 disputes that it's fairly common, sometimes in personal
18 injury. But here, it was an online agreement that
19 allegedly would compel the plaintiff to arbitration, thus
20 giving up their right to appear in civil court.

21 But the appellate court explained that the
22 penalties for Prop 65 are essentially for the public.
23 It's not a private right that can be given up. It is a
24 public right. There are penalties and a plaintiff is
25 entitled to 25 percent of those penalties, as a sort of

1 finder's fee to encourage people to bring these claims.
2 And they're entitled to attorney's fees, but what they are
3 doing essentially is enforcing a public right, not -- it's
4 not a -- not so much a personal injury to themselves, but
5 something that benefits everyone, and therefore it could
6 not be given up by the plaintiff and is a part of a
7 compelled arbitration agreement.

8 And that is it for my litigation update. If
9 anyone has any questions, I can answer them.

10 Not seeing any, so I think that is it.

11 CHAIR LOOMIS: Very good. Thank you, Corey and
12 Tina.

13 Well, there is a question.

14 COMMITTEE MEMBER EASTMOND: A question. It seems
15 like these First Amendment claims may become more common.
16 Is that possible?

17 COREY FRIEDMAN: I mean, we're certainly
18 concerned about that. So far, these claims have been
19 brought -- brought for specific chemicals. These are not
20 facial challenges to Proposition 65 warning requirements,
21 but we are -- we are definitely cognizant of First
22 Amendment risks and trying to evaluate possible responses
23 to them. It's -- one thing to note is that these are
24 essentially action seeking injunction against enforcement.
25 That's part of why OEHHA is not a party. There are suits

1 against the Attorney General's office saying no one can
2 enforce this requirement.

3 So, that's one way you might see these claims.
4 You could also see it as a defense to litigation. And
5 those would be individual suits. We haven't heard about
6 that. I mean, we've heard about people raising that as a
7 defense, but not really actively pursuing it. It's
8 possible that they are somewhere or that that could happen
9 as well. But these are sort of businesses actively
10 seeking an order from the court that nobody can enforce
11 the warning requirement.

12 CHAIR LOOMIS: Any other questions?

13 Seeing none, I will ask Dave to summarize the
14 Committee actions today.

15 CHIEF DEPUTY DIRECTOR EDWARDS: Thank you, Dana.

16 All right, so today the Committee considered and
17 deliberated on whether to add N-methyl-N-formylhydrazine
18 to the Proposition 65 list as a carcinogen. By a vote of
19 eight yeses and one no, the Committee approved to list
20 N-methyl-N-formylhydrazine.

21 The Committee also voted on a consent item to
22 remove butoxy polypropoxy polyethoxy ethanol - iodine
23 complex, chlorophacinone, sodium chlorate, and
24 tetraglycine hydroperiodide from the Section 27000 list
25 that's published in the California Code of Regulations.

1 The vote was unanimous yes nine, zero. And so the
2 chemicals will be removed from that list.

3 I want to give thanks and acknowledgment for the
4 work that the Committee did to prepare for this meeting.
5 We really appreciate your effort and preparation. And, of
6 course, I want to add my thanks for the staff for all of
7 their work to put the document together and also for the
8 audience and commenters today, and just general feedback
9 that we had. It was a good discussion overall.

10 I will now turn it back to Dr. Loomis to adjourn
11 the meeting.

12 CHAIR LOOMIS: Thank you, Dave. I'd like to
13 reinforce the thanks to the staff for excellent work
14 preparing the background material. I really appreciate
15 that, to all the Committee members for their review prior
16 to the meeting and very interesting discussion today.

17 And with that, it falls to me to adjourn the
18 meeting. You know they don't give me a gavel her, but I
19 could -- if I had one, I'd smack it down and say
20 "Adjourned", but we are adjourned.

21 (Thereupon the Carcinogen Identification
22 Committee adjourned.)
23
24
25

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, do hereby certify:

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, Carcinogen Identification Committee was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed under my direction, by computer-assisted transcription;

I further certify that I am not of counsel or attorney for any of the parties to said workshop nor in any way interested in the outcome of said workshop.

IN WITNESS WHEREOF, I have hereunto set my hand this 5th day of February, 2026.



JAMES F. PETERS, CSR
Certified Shorthand Reporter
License No. 10063