Response to Comments Pertaining to the Notice of Intent to List Furfuryl Alcohol as Causing Cancer under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
September 2016

The Office of Environmental Health Hazard Assessment (OEHHA) has determined that furfuryl alcohol meets the criteria for listing under Proposition 65[1] via the authoritative bodies mechanism based on conclusions by the US Environmental Protection Agency (US EPA) that furfuryl alcohol causes cancer, and on the scientific evidence relied on by US EPA[2]. US EPA is designated as an authoritative body for purposes of listing chemicals as causing cancer pursuant to Title 27, Cal. Code of Regulations, section 25306[3]. Furfuryl alcohol will therefore be added to the Proposition 65 list as a chemical known to cause cancer.

OEHHA made this determination after reviewing public comments on the proposed listing of furfuryl alcohol. On July 31, 2015, OEHHA issued a Notice of Intent to List[4] (NOIL) furfuryl alcohol under Proposition 65 as a chemical known to the state to cause cancer. The action was based on Proposition 65 statutory requirements[5] and on the authoritative bodies provision of the Proposition 65 implementing regulations, Section 25306. This document responds to public comments received on the Notice of Intent to List furfuryl alcohol under Proposition 65.

Under Section 25306, a chemical has been "formally identified" as causing cancer by an authoritative body if: (1) the chemical has been included in a list of chemicals causing cancer published by the authoritative body; is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer; or has been "otherwise identified" as causing cancer by the authoritative body in a document that indicates that the identification is a final action; and (2) if the list, report, or document meets specified criteria in Section 25306(d)(2).

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.) hereinafter referred to as Proposition 65 or the Act.
[2] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[3] All further references are to sections of Title 27 of the California Code of Regulations, unless otherwise indicated.
[4] Notice of Intent to List: Furfuryl Alcohol. Available at http://oehha.ca.gov/proposition-65/crnr/notice-intent-list-furfuryl-alcohol
[5] Health and Safety Code section 25249.8(b)

OEHHA has reviewed the data and conclusions in the US EPA 2014 report entitled *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol*[6]. OEHHA has determined that these conclusions and statements satisfy the Section 25306(d)(1) requirement. Specifically, furfuryl alcohol is the subject of a report published by the authoritative body that concludes that furfuryl alcohol causes cancer and it has otherwise been identified as causing cancer in a document that indicates that such identification is a final action. Further, OEHHA has determined that the report meets the Section 25306(d)(2) requirements. Thus the 2014 US EPA Document satisfies the formal identification criteria in the Proposition 65 regulations for furfuryl alcohol. In the 2014 US EPA Document, US EPA concludes that furfuryl alcohol is "Likely to be Carcinogenic to Humans" based on sufficient evidence of carcinogenicity from studies in experimental animals[7]. OEHHA is relying on US EPA's discussion of data and conclusions in the report that furfuryl alcohol causes cancer. Evidence described in the report includes studies showing that furfuryl alcohol increased the incidence of rare nasal epithelial squamous cell carcinomas and combined nasal epithelial carcinomas and epithelial squamous cell carcinomas in male rats, and rare renal carcinomas and combined renal carcinomas and adenomas in male mice:

> "(i) Treatment-related nasal tumors (adenomas, carcinomas and/or squamous cell carcinomas observed in male rats[)];
>
> (ii) Treatment-related kidney tumors (adenomas, carcinomas and/or combined adenomas/carcinomas observed in male mice[)]"[8].

The evidence cited by US EPA[9] in support of these conclusions was reviewed by OEHHA with regard to the sufficiency of evidence criteria in Section 25306(e)(2). Based on US EPA's conclusions and the data relied on by US EPA in reaching those conclusions, OEHHA has determined that furfuryl alcohol meets the sufficiency of evidence criteria in Section 25306.

The July 31, 2015 notice initiated a 30-day public comment period that was scheduled to close on August 31, 2015. OEHHA extended the public comment period to September 30, 2015 after receiving a request for extension from the Flavor Extract

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[6] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[7] *Ibid.*
[8] *Ibid.*
[9] *Ibid.*

Manufacturers Association. Three sets of comments on the Notice of Intent to List furfuryl alcohol were submitted, as shown in the table below.

Commenter	Date	Affiliation
James Simonelli	September 30, 2015	California Metals Coalition (CMC)
Gary Roberts and Jay Murray	September 30, 2015	The Flavor and Extract Manufacturers Association of the United States (FEMA)
Jennifer Wagar	September 30, 2015	toXcel, on behalf of Illovo Sugar Ltd. ("Illovo") and its USA representative Harborchem LLC, IFC North America Inc., Pennakem LLC, TransFurans Chemicals BVBA and Agriguard Company LLC

OEHHA reviewed all of the comments and accompanying materials submitted in the context of the regulatory criteria for listing chemicals under the authoritative bodies mechanism in Section 25306.

Comments relevant to the NOIL are summarized, grouped, and numbered by topic, and responses follow below.

1. Formal identification criteria

Comment:
"Furfuryl alcohol should not be listed as a carcinogen because…US EPA did not "formally identify" furfuryl alcohol as causing cancer…" (FEMA, p.1)

Response:
OEHHA has reviewed the 2014 US EPA report and determined that US EPA has formally identified furfuryl alcohol as causing cancer. Specifically, US EPA has "classified furfuryl alcohol as 'Likely to Be Carcinogenic to Humans.'" US EPA went on to state: "This determination was based on the following:

> (i) Treatment-related nasal tumors (adenomas, carcinomas and/or squamous cell carcinomas observed in male rats[)];

(ii) Treatment-related kidney tumors (adenomas, carcinomas and/or combined adenomas/carcinomas observed in male mice[)]"[10].

1.1 *The 2014 US EPA report*

1.1.1 Comment:
"The Carcinogen Assessment Review Committee (CARC), a committee within the US EPA's Office of Pesticide Programs ("OPP") only made a *recommendation* that furfuryl alcohol be classified as 'Likely to Be Carcinogenic to Humans.' The report containing the CARC recommendation, was not a final action of the Agency, and there is evidence that US EPA has not accepted this recommendation." (FEMA, p. 1)

"The role of the CARC is advisory. According to the US EPA website, the CARC ***recommends*** a cancer classification…" (FEMA, p. 3)

"The CARC Report does not satisfy any of the requirements of 25306(d). It is not a list, and it is not a published report. The report does not state that it is the final action of OPP or of the USEPA. It is not reviewed by an advisory committee in a public meeting, made subject to public review, published in a publication such as the federal register, signed by the chief administrative officer or a designee, adopted as a final rule, or set forth in an official document utilized for regulatory purposes. To the contrary, the CARC Report simply makes a recommendation, which has not been adopted by the US EPA." (FEMA, p. 5)

Response:
OEHHA disagrees and has determined that the 2014 US EPA report entitled *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol* [11] satisfies the requirements of Section 25306(d), as it is a final US EPA report which concludes that furfuryl alcohol is "Likely to be Carcinogenic to Humans".

Under Proposition 65[12], chemicals are required to be listed via the authoritative bodies listing mechanism as known to cause cancer if they meet certain criteria specified in Section 25306. The regulation provides that a chemical is known to the state to cause cancer if a body considered to be authoritative has "formally identified" the chemical as

[10] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014, p. 43.
[11] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[12] Health and Safety Code section 25249.8(b)

causing cancer and if certain scientific criteria are met. The regulation sets out three alternative bases for determining that a chemical has been "formally identified" as causing cancer or reproductive toxicity in Section 25306(d)(1): 1) "the chemical has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body;" 2) the chemical "is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer or reproductive toxicity;" or 3) the chemical "has otherwise been identified as causing cancer or reproductive toxicity by the authoritative body in a document that indicates such identification is a final action".

As discussed in more detail below, the 2014 US EPA report satisfies the Section 25306(d)(1) requirement because furfuryl alcohol is the subject of a report published by the authoritative body that concludes that furfuryl alcohol causes cancer[13], and it has otherwise been identified as causing cancer in a document that indicates that such identification is a final action[14]. A document must satisfy only one of the six criteria in subsection (d)(2) in order for it to be used as the basis for the lead agency's determination that a chemical has been "formally identified" by any authoritative body.

- The document is clearly a final US EPA report: (i) the title page of the report includes the word "FINAL" just above the date of the report, (ii) the header on each page of the report reads: "FURFURAL AND FURFURYL ALCOHOL FINAL CANCER ASSESSMENT DOCUMENT".
- The cancer classification of furfuryl alcohol in this report is not merely a 'recommendation'. The EXECUTIVE SUMMARY and Section VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL of the 2014 US EPA report[15] clearly indicate that furfuryl alcohol has been classified by the Cancer Assessment Review Committee (CARC) as "Likely to be Carcinogenic to Humans" based on findings of tumors in animals.
- Recommendations of the CARC are presented in later sections of the 2014 US EPA Report (Sections VII and VIII), and are recommendations for the approach to quantifying furfuryl alcohol (and furfural) human cancer risk, and for additional carcinogenicity testing of furfural.

US EPA describes its process for reviewing pesticides for carcinogenic potential on its website:

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[13] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014
[14] *Ibid.*
[15] *Ibid*., pages 6, 41, 42.

> "The Health Effects Division of the Office of Pesticide Programs performs an independent review of studies conducted in mice and rats to evaluate the carcinogenic potential of pesticides. The results of the independent review are peer-reviewed by the Cancer Assessment Review Committee. This committee recommends a cancer classification. The classification will determine how the Agency regulates the pesticide and will include methods for quantification of human risk"[16].

Thus the classification by the Cancer Assessment Review Committee is used by US EPA in other documents to regulate the pesticide. For example, the cancer classification for imazalil, as presented in the Cancer Assessment Document on that chemical[17], was used in the Reregistration Eligibility Decision for imazalil[18].

OEHHA has determined that the 2014 US EPA report also meets the Section 25306(d)(2) requirements.

The 2014 US EPA document meets multiple criteria in subsection (d)(2):

- It was reviewed by an advisory committee:
  - The US EPA Cancer Assessment Review Committee [subsection (d)(2)(A)].
- It was published by the authoritative body:
  - This report is published as a final Cancer Assessment Document by the US EPA [subsection (d)(2)(C)].
- It is an official document utilized by the authoritative body for regulatory purposes:
  - The Cancer Assessment Document is a final US EPA document that establishes the cancer classification of furfuryl alcohol, which will be

[16] US Environmental Protection Agency (2016). Evaluating Pesticides for Carcinogenic Potential. Available at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluating-pesticides-carcinogenic-potential

[17] US Environmental Protection Agency (1999). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Imazalil (Third Review). Final Report. Health Effects Division, Office of Pesticide Programs. December 7, 1999. Available at: https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:7:::NO:1,3,31,7,12,25:P3_XCHEMICAL_ID:2562

[18] US Environmental Protection Agency (2003). Reregistration Eligibility Decision for Imazalil, Chemical List B, Case No. 2325. Office of Pesticide Programs. Available at: https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:31:::NO:1,3,31,7,12,25:P3_XCHEMICAL_ID:2562

utilized by the US EPA, including for regulatory purposes, e.g., evaluating petitions for pesticide new use patterns[19] [subsection (d)(2)(F)].

Thus the 2014 US EPA report satisfies the formal identification requirements of Section 25306(d).

1.1.2 Comment:
"The US EPA Office of Pesticide Programs is free to choose whether it accepts or does not accept the recommendation of the CARC. In the case of furfuryl alcohol, there is evidence that the US EPA Office of Pesticide Programs has not accepted the recommendation of the CARC." (FEMA, p. 3)

"It appears that the US EPA Office of Pesticide Programs did not adopt the recommendation of the CARC with respect to furfuryl alcohol. The US EPA Office of Pesticide Programs publishes an Annual Cancer Report, which contains a list of all of the chemicals evaluated for carcinogenic potential by the Office of Pesticide Programs, including the cancer classification of each chemical. The most recent Annual Cancer Report was published by the Office of Pesticide Programs on October 2, 2014, and furfuryl alcohol is not listed as "Likely to Be Carcinogenic to Humans" or mentioned in this report. There is no indication that the Office of Pesticide Programs accepted or agreed with the recommendation of the CARC." (FEMA, pp. 3-4)

"The absence of furfuryl alcohol from the most recent Annual Cancer Report dated October 2, 2014 is not explained by an issue with timing. The final CARC Report is dated February 6, 2014. As such, there was about 8 months between the date of the final CARC Report and the publication of the Annual Cancer Report. Of note, another chemical, furfural, was also evaluated at the same time (and in the same CARC Report as furfuryl alcohol), and, unlike furfuryl alcohol, the CARC's recommended classification is recognized and listed in the Annual Cancer Report dated October 2, 2014. Therefore, it appears that the Office of Pesticide Programs has not accepted the CARC's recommendation for furfuryl alcohol, and as such, the CARC recommendation for furfuryl alcohol has not been adopted or used for regulatory purposes." (FEMA, p. 4)

Response:
The 2014 US EPA *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol* [20], which serves as the basis for this

[19] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014, see p. 4.

authoritative body listing, evaluates the carcinogenic potential of two chemicals, furfural and furfuryl alcohol; however, only furfural is a pesticide active ingredient. Because furfuryl alcohol is a major degradation product of furfural, and furfuryl alcohol contamination of drinking water could occur as a result of a proposed new use of furfural, the 2014 US EPA report presents cancer classifications for both the pesticide active ingredient furfural, and the degradation product, furfuryl alcohol.

The commenter refers to an October 2, 2014 list of pesticide chemicals and cancer classifications published by the US EPA Office of Pesticide Programs as the Annual Cancer Report 2014. Page one of this report, under the heading "What is this list?", states:

> "The following list provides an overview of *pesticide chemicals* evaluated for carcinogenic potential by EPA's Pesticide Program through October 2012. The evaluation of many of these chemicals is an ongoing process. Therefore, the information in this list may be subject to change as new and/or additional data are submitted to EPA"[21] (emphasis added).

The commenter is correct that furfuryl alcohol is not included on the list in the October 2, 2014 document. However, as noted above, furfuryl alcohol is not a pesticide active ingredient.

As discussed in detail in the response to comment 1.1.1, the US EPA document which serves as the basis for the listing of furfuryl alcohol (i.e., *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol* [22]) is a final US EPA report which concludes that furfuryl alcohol is "Likely to be Carcinogenic to Humans". Thus, furfuryl alcohol meets the criteria for listing, including the formal identification requirements of Section 25306(d), based on the findings of the 2014 US EPA *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol* [23].

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[20] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[21] US Environmental Protection Agency (US EPA, 2014). Annual Cancer Report, Chemicals Evaluated for Carcinogenic Potential, Office of Pesticide Programs. October 2, 2014.
[22] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[23] *Ibid*.

1.2 *US EPA report vs. NTP technical report conclusions*

Comment:
"The NTP study has been publicly available since 1999, and we are unaware of any other authoritative body that has reviewed the results and come to the same conclusions as the review group within the EPA." (toXcel, p.1)

"The NTP study authors interpreted the study results differently than the CARC, and concluded that there was 'some' evidence of carcinogenic activity of furfuryl alcohol in male F344/N rats, 'equivocal' evidence of carcinogenic activity in female F344/N rats, 'some' evidence of carcinogenic activity of furfuryl alcohol in male B6C3F1 mice and 'no' evidence of carcinogenic activity in female B6C3F1 mice exposed to 1, 8, or 32 ppm furfuryl alcohol." (toXcel, p. 6)

"The data suggesting carcinogenic activity for furfuryl alcohol come from National Toxicology Program (NTP) Technical Report No. 482 (TR-482). Yet, the recommended classification by the CARC conflicts with the conclusions of the NTP, the authoritative body that actually conducted the cancer bioassay of furfuryl alcohol on which the CARC relied. OEHHA's scientific review of the CARC report pursuant to section 25306(e) of the regulations should conclude that there is not sufficient data to list furfuryl alcohol for the scientific reasons noted below. Moreover, there is no question that the NTP's analysis of furfuryl alcohol was far more detailed and more thorough. Since the less thourough [*sic*] CARC analysis contains analytical flaws and does not explain why the CARC came to a different conclusion from the NTP, OEHHA should decline to list furfuryl alcohol based on the CARC report. If OEHHA were to list furfuryl alcohol based on the CARC report, we believe it would break new ground by basing a listing on a weaker analysis that is not subject to any outside review which differs with a clearly more detailed, more thorough analysis by the entity that undertook the study upon which the listing is proposed, with no new or additional data." (FEMA, pp. 1-2)

"NTP's conclusions regarding the results of its own cancer bioassay of furfuryl alcohol fall far short of meeting the requirements of "sufficient evidence" in animals, as detailed in Section 25306(e)(2). Thus, furfuryl alcohol cannot be listed as a carcinogen via the authoritative bodies listing mechanism based on NTP's conclusions about the results of its own study." (FEMA, p. 7)

"We are aware OEHHA has maintained that conflicting opinions of authoritative bodies do not matter as long as one authoritative body "formally identifies" a substance "as causing cancer." However, OEHHA should be cautious about listing a chemical based on the statement in a CARC Report about a study conducted by another authoritative

body, which has concluded that the evidence from its study is inadequate to meet the "sufficient evidence" criteria. One would think that the authoritative body that conducted the study would be in the best position to interpret the results of its own study. This is especially true for an NTP cancer bioassay, since the review process at NTP includes a more thorough and rigorous overall evaluation and a more extensive internal and external peer-review of its own study than does the CARC." (FEMA, pp. 9-10)

Response:
As detailed in response to comment 1.1 above, US EPA has formally identified furfuryl alcohol as causing cancer, and OEHHA is therefore required to list it under Proposition 65 if the chemical meets the criteria in the regulations. The authoritative bodies regulation does not require agreement among the various authoritative bodies, so conclusions by the National Toxicology Program (NTP) do not affect the listing of furfuryl alcohol as causing cancer based on the conclusions of the US EPA in the 2014 cancer assessment document[24], which formally identifies furfuryl alcohol as causing cancer. There is no indication that the analysis by US EPA was less thorough than the analysis conducted by NTP.

1.3 *US EPA report did not evaluate non-pesticide uses*

Comment:
"The US EPA report did not evaluate other use scenarios with different use and exposure characteristics, and specifically did not evaluate use in foundries. US EPA has a mechanism for evaluating potentially carcinogenic chemicals more broadly, the Integrated Risk Information System (IRIS). IRIS has not evaluated furfuryl alcohol carcinogenicity. Since the report did not include a broad evaluation of use scenarios and specifically did not evaluate a use scenario applicable to some California users of furfuryl alcohol, we believe the report fails to qualify as a report by an authoritative body for listing purposes." (CMC, p. 3)

Response:
As discussed in response to comment 1.1 above, US EPA has formally identified furfuryl alcohol as causing cancer, and OEHHA is therefore required to list it under Proposition 65 if the chemical meets the criteria in the regulations. The authoritative bodies regulation does not require the report by the authoritative body to evaluate uses specific to California, nor is the use of a chemical a factor in the determination of whether a chemical meets the criteria for listing under Proposition 65 authoritative

[24] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

bodies listing process (see response to Comment 1.1.1 for details about why the 2014 US EPA report meets the criteria specified in Section 25306).

2. Sufficiency of evidence criteria

2.1 *US EPA criteria and sufficiency of evidence criteria are not identical*

Comment:
"The [Cancer Assessment Review] Committee claimed that it relied upon the classification criteria identified in the US EPA's 2005 Guidelines for Carcinogen Risk Assessment (the "Guidelines"). According to the Guidelines, "This descriptor [Likely to Be Carcinogenic to Humans] is appropriate when the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor 'Carcinogenic to Humans.'" The Guidelines further state: "Adequate evidence consistent with this descriptor covers a broad spectrum." The Guidelines proceed to provide a number of examples that represent "supporting data for this descriptor." And the Guidelines further state: "The examples below are meant to represent the broad range of data combinations that are covered by this descriptor; they are illustrative and provide neither a checklist nor a limitation for the data that might support use of this descriptor." In contrast, the Proposition 65 regulations provide highly specific criteria for the determination of 'sufficient evidence of carcinogenicity.'" (FEMA, p. 8)

"…EPA's criteria for the descriptor "Likely to Be Carcinogenic to Humans" and the criteria of "sufficient evidence" under the Proposition 65 regulations are not identical. Therefore, OEHHA is required to carefully evaluate the data on furfuryl alcohol relied upon by the CARC to determine whether it meets the "sufficient evidence" criteria of Section 25306(e)(2)" (FEMA, p. 9).

Response:
It is true that OEHHA must determine if the data relied on by US EPA in formally identifying furfuryl alcohol as causing cancer meet the sufficiency of evidence criteria in Section 25306(e).

As was made clear in the *ExxonMobil v OEHHA* case[25], OEHHA must evaluate the evidence in the scientific record before the authoritative body and determine if there is sufficient evidence that the chemical meets the criteria for listing in OEHHA's implementing regulations. The criteria for finding that there is "sufficient evidence" that

[25] *ExxonMobil v OEHHA* (2009) 169 Cal.App.4th 1264.

a chemical causes cancer are contained in Section 25306(e). These criteria are the basis for OEHHA's decisions, regardless of the criteria that may be used by a given agency in developing its own documents. As was noted in the *Western Crop v Davis* case[26], it is up to OEHHA to determine whether the criteria in its own regulations have been met, notwithstanding the criteria that may be applied by the authoritative body in reaching its conclusion.

OEHHA has evaluated the evidence cited in the 2014 US EPA report[27] for the carcinogenicity of furfuryl alcohol against the sufficiency of evidence criteria for "as causing cancer," as laid out in Section 25306(e)(2) and determined that the criteria are met. Specifically, US EPA[28] concluded that furfuryl alcohol is "likely to be carcinogenic to humans" based on studies showing that furfuryl alcohol increased the incidence of rare nasal epithelial squamous cell carcinomas and combined nasal epithelial carcinomas and epithelial squamous cell carcinomas in male rats, and rare renal carcinomas and combined carcinomas and adenomas in male mice. Thus, US EPA[29] found that furfuryl alcohol causes increased incidences of malignant tumors and combined malignant and benign tumors in multiple species (rats and mice), and these findings meet the sufficiency of evidence criteria in Section 25306(e)(2) (e.g., "…studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species….") .

2.2 *Sufficiency criteria for human data*

Comment:
"We are unaware of any epidemiological studies where exposure to furfuryl alcohol can be directly correlated with health effects because of the presence of other, more toxic, chemicals in the same studies." (toXcel, p. 8)

Response:
Epidemiology studies in humans are not required to satisfy the sufficiency of evidence criteria, as detailed in Section 25306(e), which reads as follows:

> "(e) For purposes of this section, "as causing cancer" means that **either** of the following criteria has been satisfied *[emphasis added]*:

[26] *Western Crop Protection Assn. v. Davis* (2000) 80 Cal.App.4th 741.
[27] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[28] *Ibid.*
[29] *Ibid*.

(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, "sufficient evidence" means studies in humans indicate that there is a causal relationship between the chemical and cancer.
(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, "sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset."

Thus in order to meet the sufficiency of evidence criteria of section 25306(e), a chemical must satisfy the requirements of *either* 25306(e)(1) or 25306(e)(2), not both. As indicated in response to comment 2.1 above, it is US EPA's discussion in the 2014 report[30] of data and conclusions from studies in experimental animals that meets the sufficiency of evidence criteria in Section 25306(e).

2.3 *Sufficiency criteria for animal data*

Comment:
"The referenced NTP study included only two species (mouse and rat), three dose levels, one route of administration (inhalation), and gave an inconsistent site of tumor occurrence between species. Therefore, the NTP study was insufficient for making a cancer determination based on the first part of §25306 (e) (2)." (toXcel, p. 2)

Response:
The sufficiency of evidence criteria in Section 25306(e)(2) reads as follows:

> "Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, "sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset."

[30] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014

The data relied on by the US EPA in classifying furfuryl alcohol as "Likely to be carcinogenic to humans" includes studies showing that furfuryl alcohol increased the incidence of nasal epithelial squamous cell carcinomas and combined nasal epithelial carcinomas and epithelial squamous cell carcinomas in male rats, and renal carcinomas and combined carcinomas and adenomas in male mice. Nasal tumors are rare in F344 rats[31] and renal tubule adenomas and carcinomas are rare in B6C3F1 mice[32,33]. These tumor findings (i.e., increased incidence of malignant tumors or combined malignant and benign tumors) observed in male rats and male mice (i.e., multiple species) satisfy the sufficiency of evidence criteria in Section 25306(e)(2). In addition, since the types of tumors induced by furfuryl alcohol in male rats are rare, and the types of tumors induced in male mice are rare, both experiments satisfy the alternative criterion in Section 25306(e)(2) of an observed increase in a single experiment of tumors that are unusual with regard to site or type.

Induction of tumors at the same site across species is not expected of carcinogens by the US EPA, or other authoritative bodies. Nor is tumor site concordance across species required in order to meet the sufficiency of evidence criteria in Section 25306(e)(2).

2.3.1 *Evidence in male rats*

2.3.1.1 Comment:
"One of the critical requirements of scientifically valid carcinogenicity testing in rodents is the proper selection of dose levels. In male rats, the high dose level of furfuryl alcohol exceeded the Maximum Tolerated Dose (MTD). None of the male rats exposed to the highest concentration of furfuryl alcohol (32 ppm) survived until the end of the study. Clearly, a high dose associated with 100% mortality before the end of the study represents an excessively high dose. Thus, the only evidence of carcinogenicity in rats administered furfuryl alcohol was observed at an inappropriate dose level that exceeded the MTD." (FEMA, p. 16)

[31] Haseman JK, Hailey JR, Morris RW (1998). Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. *Toxicol. Path*. **26**:428-441.
[32] *Ibid*.
[33] NTP (1999). Historical control tumor incidence summary in B6C3F1 mice exposed via inhalation for years 1984-1994. Available at https://ntp.niehs.nih.gov/ntp/research/database_searches/historical_controls/path/m_inhar.txt

"The CARC did not consider the possibility that the excessively high dose may result in tumor effects that are secondary to the toxicity rather than directly attributable to the agent, as described by the US EPA Guidelines (2005)." (FEMA, p. 2)

"Whereas the CARC stated that the doses used in the NTP study were adequate and not excessive, we maintain that the high dose likely exceeded the maximum tolerated dose in both the rat and mouse studies. Findings at these dose levels may be confounded by excessive toxicity." (toXcel, p. 3)

Response:
According to the US EPA Guidelines for Carcinogen Risk Assessment[34], "The high dose [for animal carcinogenicity testing]… is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity…"

In evaluating the tumor findings of the F344/N male rat study of furfuryl alcohol, the US EPA was aware of the mortality at the end of the study in the high dose group, and took this information into consideration in evaluating the adequacy of dosing used in the male rat study, and in classifying the weight of evidence for furfuryl alcohol, as shown by the following:

- "The CARC determined that the concentrations tested in the study were adequate … to assess the carcinogenic potential of furfuryl alcohol. This was based on the presence of non-neoplastic and neoplastic lesions of the nasal cavity."
- "Mean body weights of 32 ppm males were less than those of the chamber controls beginning at week 19 (94% of control values); by week 91, the body weights of 32 ppm males were 76% of those of the chamber controls. Mean body weights of 2 and 8 ppm male groups…were similar to those of the chamber controls, throughout the study."
- "Although there was 100% mortality at the high dose, the CARC did not consider this concentration to be excessive, since survival was 80% at 18 months and 32% at week 91 which met the test guideline requirement (i.e., survival no less than 50% at 18 months for rats). Additionally, all rats were available for histopathological examination (i.e., no more than 10 percent of any group was

[34] US Environmental Protection Agency (US EPA, 2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F.

lost due to autolysis, cannibalism, or management problems, as required by the test guideline)." (US EPA, 2014[35], p. 23)

- "The highest dose tested [in rats] was considered to be adequate, but not excessive, in both sexes to assess the carcinogenic potential of furfuryl alcohol." (US EPA, 2014[36], p. 41)

The Statement of Reasons for Section 25306 states: "It is not the intention of the Agency to substitute its scientific judgment for that of the authoritative body. The Agency's inquiry will be limited to whether the authoritative body relied upon scientific data in an amount sufficient to conclude that the chemical causes cancer." OEHHA cannot substitute its scientific opinion for that of US EPA. In this case, US EPA weighed the evidence and did not consider the highest dose to be excessive in rats.

2.3.1.2 Comment:
"If there is no increase in kidney tumors in male mice attributable to furfuryl alcohol, the only other tumor type considered to be increased by the CARC is nasal tumors in male rats. In the absence of any other tumor type, an increase in nasal tumors resulting from inhalation exposure to furfuryl alcohol would strongly suggest a direct local effect of furfuryl alcohol on the nasal tissues. Such a local effect at the site of entry would be consistent with a carcinogen that is route-specific (i.e., carcinogenic by inhalation only). However, in fact, the nasal tumor data in male rats do not provide sufficient evidence to conclude that furfuryl alcohol causes cancer. If OEHHA concludes otherwise, OEHHA should only list furfuryl alcohol via the inhalation pathway." (FEMA, pp. 13-14)

Response:
OEHHA does not agree that the kidney tumors in male mice should be discounted (see response to Comment 2.3.2.1 below). US EPA concluded that furfuryl alcohol induces kidney tumors in male mice and nasal tumors in male rats. Thus, two types of rare tumors were observed following exposure to furfuryl alcohol.

The US EPA classified furfuryl alcohol as "Likely to be carcinogenic to humans," with no limitation on route of exposure. Thus, there is no basis for limiting or qualifying the listing of furfuryl alcohol via the authoritative bodies listing mechanism to only the inhalation pathway.

[35] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[36] *Ibid*.

2.3.1.3 Comment:
"Regarding the nasal lesions in the rat study, it is considered that repeated local tissue damage at the portal of entry over time leads to an adaptive proliferation of cells and subsequent tumor formation (Weiler, 1997) resulting from chronic continued exposure. The non-neoplastic lesions of furfuryl alcohol including increased inflammation, hyperplasia of the lateral wall, atrophy and metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium are similar to those described for other nasal toxicants, demonstrating the likelihood of a similar, threshold mode of action." (toXcel, p. 4)

Response:
Specific dose response issues, such as the presence of a threshold, are addressed once a chemical has been placed on the Proposition 65 list, during the development of a "No Significant Risk Level."

With respect to cancer dose response assessment for furfuryl alcohol, the 2014 US EPA report recommended "quantification of human cancer risk using a linear approach since no mode of action data are available to support a non-linear mode of action for the tumor types seen with … furfuryl alcohol"[37].

2.3.1.4 Comment:
"The OEHHA Notice description of male rat nasal tumors differs from the description in the CARC report. In fact, the CARC Report never describes the nasal tumors in male rats in the furfuryl alcohol bioassay as "rare" tumors. This distinction is important because the Proposition 65 regulations indicate that the criteria for "sufficient evidence" in animals may be met if there is an increased incidence "to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset." The CARC Report did not state that the nasal tumors in male mice are rare or unusual with respect to high incidence, site or type of tumor. OEHHA has provided no scientific data that would support the proposition that these tumors are rare, a conclusion that neither US EPA nor NTP made." (FEMA, p. 14)

"The issue of the historical control data on male rat nasal tumors arose during the peer review of the NTP cancer bioassay of furfuryl alcohol by the NTP's Board of Scientific Counselors Technical Reports Review Subcommittee. Dr. Joseph Haseman, one of the authors of the NTP furfuryl alcohol cancer bioassay said that although there were no squamous cell carcinomas of the nose in the chamber control groups for inhalation

[37] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

studies, there have been one or two in some control groups in other concurrent studies." (FEMA, pp. 14-15)

"While the CARC recognizes the treatment-related nature of the tumors they do not characterize them as 'rare'." (toXcel, p. 2)

"In the body of the report, the CARC did not identify any of the nasal effects in the NTP furfuryl alcohol rat study as being rare; they have been observed with a number of substances which are known to be irritant, but are an uncommon background finding in untreated animals." (toXcel, p. 3)

Response:
As discussed above in the response to comment 2.3, the findings that furfuryl alcohol increased the incidence of tumors in multiple experiments (i.e., malignant tumors of the nasal epithelium in male rats, and malignant and combined malignant and benign kidney tumors in male mice in the NTP (1999)[38] studies) satisfy the Section 25306(e) criteria for "sufficient evidence" in experimental animals. The nasal tumor findings in male rats were statistically significant; therefore, it is not necessary to make a determination that these tumors are rare.

However, the 2014 US EPA report presented the laboratory historical incidence of nasal tumors in chamber control male F344/N rats as the following:

- Adenoma Total: 1/897 (0.1%), SD *[standard deviation]* 0.5%;
- Carcinoma: 0/897;
- Squamous Cell Carcinoma: 0/897[39].

Therefore, although the US EPA report[40] did not use the word 'rare' to describe the tumors, the laboratory historical control data cited by the US EPA clearly indicate that nasal tumors are rare in male F344/N rats. NTP historical control data also indicate that nasal tumors are rare[41] (See the response to Comment 2.3, pg. 13-14.)

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[38] NTP (1999). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (Inhalation Studies).* NTP-TR-482. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
[39] *Ibid*.
[40] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.
[41] Haseman JK, Hailey JR, Morris RW (1998). Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. *Toxicol. Path*. **26**:428-441.

As stated by the NTP (2015), "Historical controls should resemble the concurrent controls with respect to species, sex, strain, diet and other factors influencing tumor response"[42]. The most appropriate controls for comparison are those fed the same diet, with the same exposure conditions (i.e., the same route of administration). Thus the appropriate historical control database for the furfuryl alcohol inhalation studies is comprised of data from other inhalation studies employing the same diet (NIH-07 diet) and conducted during the same approximate time period, preferably in the same laboratory. Consistent with this guidance, the NTP maintains a database of tumor incidences, growth curves and survival curves for control animals from the two-year carcinogenesis studies[43] and these historical control data are summarized by species, sex, and route of administration and vehicle (e.g., inhalation air).

2.3.1.5 Comment:
"The CARC did not rely on a sufficient amount of data to conclude that furfuryl alcohol causes nasal tumors in male rats because it combined histologically different types of nasal tumors." (FEMA, p. 15)

"There is a scientific issue regarding whether it is appropriate to combine nasal epithelial adenomas, epithelial carcinomas, and squamous cell carcinomas. Squamous cell carcinoma is a histologically distinct form of cancer. It arises from the uncontrolled multiplication of cells of epithelium, or cells showing particular cytological or tissue architectural characteristics of squamous cell differentiation, such as the presence of keratin, to no filament bundles, or desmosomes, structures involved in cell-to-cell adhesion. Usually tumors are combined when they are within the same family. For example, it is appropriate to combine adenomas and carcinomas when the adenomas have the potential to progress to carcinomas of the same origin. In the case of the furfuryl alcohol bioassay, there is no evidence in the record that epithelial carcinomas and squamous cell tumors have a common histological origin. Accordingly, these tumors should not be combined. OEHHA presented no analysis of this issue, nor did US EPA." (FEMA, p. 15)

"The issue of the appropriateness of combining epithelial carcinomas and squamous cell carcinomas is important because the combined incidence was barely statistically significant (p=0.044) in male rats at the high dose level in the NTP cancer bioassay. Neither the incidence of epithelial carcinomas nor the incidence of squamous cell

[42] NTP (2015). National Toxicology Program. Handbook for preparing report on carcinogens monographs. US Department of Health and Human Services. Available at ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf
[44] NTP (1999). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (Inhalation Studies).* NTP-TR-482. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

carcinomas was statistically significantly increased compared to controls at any dose level in the NTP cancer bioassay. Only by combining these two different types of carcinomas was it possible to demonstrate a statistically significant effect. There is no indication in the CARC Report whether the histological difference in the two types of carcinomas was considered." (FEMA, pp. 15-16)

Response:
Both the US EPA and NTP found it appropriate to combine the nasal tumors. According to the pathology section of the NTP study, all of the nasal neoplasms were of epithelial origin[44]. US EPA states that there was a statistically significant trend for nasal epithelial squamous cell carcinomas, and a significant trend and a significant pair-wise comparison of the high dose group with the controls for combined nasal lateral wall adenomas, epithelial adenomas, epithelial carcinomas and epithelial squamous cell carcinomas. The tumors were "corroborated by the presence of non-neoplastic lesions" of the olfactory and respiratory epithelium[45]. US EPA considered the nasal tumors in male rats to be treatment-related.

As explained in the response to comment 2.3.1.1, OEHHA cannot substitute its scientific judgment for that of the authoritative body. In this case, US EPA found it appropriate to combine the nasal tumors, all of which were of epithelial origin.

2.3.2 *Evidence in male mice*

2.3.2.1 Comment:
"…the CARC considered the kidney tumors in male mice to be rare when compared to the historical control incidence. But, the CARC did not consider that the furfuryl alcohol study employed an extended evaluation of the kidneys that included approximately 8 additional sections; in contrast, the historical control studies typically used only a single section. Compared to the historical controls, the methodology used to evaluate the kidneys in the furfuryl alcohol study provided a greater opportunity to detect kidney tumors." (FEMA, p. 2)

"Initially, the kidneys were examined using single sections, i.e., the standard evaluation in NTP cancer bioassays. The standard evaluation of the kidneys revealed no

[44] NTP (1999). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (Inhalation Studies).* NTP-TR-482. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
[45] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

statistically significant increase in adenomas, carcinomas or combined adenomas or carcinomas at any dose level." (FEMA, p. 11)

Subsequent to the standard evaluation, NTP performed an "extended evaluation" which consisted of making step sections through the kidneys in order to look for tumors that might have been missed by the single section evaluation. According to the NTP, "Kidney step sections provide approximately eight additional sections per animal that may have additional proliferative lesions." Like the standard evaluation, the results of the extended evaluation revealed no statistically significant increase in adenomas, carcinomas, or combined adenomas or carcinomas at any dose level." (FEMA, p. 11)

"Finally, NTP combined the results of the standard evaluation with the results of the extended evaluation. By making this combination, the NTP reported a statistically significant (p=0.036) increase in adenoma or carcinoma combined (but not adenoma alone or carcinoma alone) at the high dose only." (FEMA, p. 11)

"There is no indication that the CARC was aware of or took into consideration the different results obtained with the different evaluation methods (i.e., the standard evaluation, the extended evaluation, and the combined standard and extended evaluations)." (FEMA, p. 12)

"US EPA noted "kidney tumors are rare among historical controls and the incidences of the combined tumors in this study (10%) were 25-fold higher than the historical control incidence (0.4%)." However, this reveals that the authors of the CARC Report did not understand that the methods of kidney evaluation in the furfuryl alcohol study are atypical of the kidney evaluation employed in most NTP cancer bioassays…it is not NTP's usual practice to conduct extended evaluations (step sections) of the kidneys in its cancer bioassays. …Therefore, the CARC's comparison of the 10% incidence of kidney tumors with single and step sections at the high dose cannot be compared directly against the results of a historical control database that did not use the same rigorous procedures. Unlike the CARC, NTP recognized this important distinction, and when NTP compared the kidney tumors results from its furfuryl alcohol cancer bioassay against the historical controls, it compared only the standard evaluation (single section) results against the historical controls, since the historical control studies used single section evaluations." (FEMA, pp. 12-13)

"It should be noted that the statistical increase was only apparent after the NTP had conducted a second evaluation of the kidneys which involved examining an additional 8 sections. This practice was not followed for the control animals (neither concurrent nor

historical) and it was only possible to attain statistical significance by combining the adenoma and carcinoma results from the first and second evaluations." (toXcel, p. 5)

Response:
Step sectioning of the kidney is commonly performed to provide additional tissue sections that may reveal previously undetected tumors and provide additional information about the pathology of the kidney. It is appropriate to combine the tumors from the standard evaluation and the step sectioning to find the total incidence of tumors. In the case of the furfuryl alcohol study in male mice, an extended evaluation with step sections was conducted to determine whether additional tumors were present in the kidneys, since "renal tubule neoplasms are uncommon in male $B6C3F_1$ mice, and their presence in four 32 ppm males is consistent with an exposure-related carcinogenic response"[46]. The NTP report indicates that each tumor was only counted once in the combination analysis, and that step sectioning was conducted on both the control and treated animals in the study[47]. Step sectioning revealed one additional adenoma, which was observed in the high-dose group.

Kidney tumors are rare in untreated male B6C3F1 mice. The combined standard and step-section tumor incidence data from the concurrent controls in the NTP male mouse furfuryl alcohol study (i.e., 0%) is consistent with standard kidney section incidence data from laboratory historical controls from chamber studies with male mice (i.e., 0.4%).

2.3.2.2 Comment:
"The total number of pair-wise statistical comparisons for adenomas, carcinomas or combined adenomas or carcinomas of the kidney, given three dose levels and three combinations of evaluation methods, was 27. With the selected p value of $p<0.05$, a false positive rate of 1 out of 20 is considered to be acceptable. In other words, with 27 pair-wise statistical comparisons of the male mouse kidney tumor data, more than one statistically significant difference from controls would be expected due to chance alone. In fact, only one statistically significant difference was observed among the 27 pair-wise statistical comparisons of the kidney tumor data in the NTP cancer bioassay. This raises doubt about whether the one difference observed among the 27 different pair-wise differences is due to treatment with furfuryl alcohol or simply due to chance." (FEMA, pp. 11-12)

[46] NTP (1999). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (Inhalation Studies).* NTP-TR-482. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
[47] *Ibid*.

Response:
In concluding that the kidney tumors observed in furfuryl alcohol-treated male mice are treatment related, US EPA considered a number of other factors, in addition to the results of statistical tests. Specifically, US EPA took into consideration the following:

- Statistical tests for trend
- Statistical tests for pairwise comparison with controls
- Kidney tumors are rare in untreated male mice, as demonstrated by historical control incidence data
- Non-neoplastic kidney lesions were observed in furfuryl alcohol-treated male mice and in a study of furfuryl alcohol treated female mice
- The severity of the non-neoplastic kidney lesions increased with increasing dose of furfuryl alcohol in males, but not in females[48]

Regarding the findings from pairwise comparisons, US EPA considered the pairwise comparison of the 32 ppm dose group with the controls to be statistically significant at $p < 0.05$ for renal tubule adenomas and/or carcinomas combined. In considering multiple comparisons, US EPA Guidelines for Carcinogen Risk Assessment state the following:

> "Considerations of multiple comparisons should also be taken into account. Haseman (1983) analyzed typical animal bioassays that tested both sexes of two species and concluded that, because of multiple comparisons, a single tumor increase for a species-sex-site combination that is statistically significant at the 1% level for common tumors or 5% for rare tumors corresponds to a 7–8% significance level for the study as a whole. Therefore, animal bioassays presenting only one significant result that falls short of the 1% level for a common tumor should be treated with caution"[49].

Since renal tubule adenomas and carcinomas are rare according to historical control data (renal tubule adenomas: 0.3%; carcinomas: 0.1%; combined adenomas and carcinomas: 0.4%[50]), significance at the 5% level is considered acceptable according to the US EPA guidelines.

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[48]US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014, page 5.
[49] US Environmental Protection Agency (US EPA, 2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F.
[50] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

2.3.2.3 Comment:
"The mouse renal tumors are the result of an exacerbated pathology that does not occur in humans" (toXcel, p. 5)

"Chronic progressive nephropathy (CPN) is an age-related disease of spontaneous origin commonly observed and well characterized in rats (Hard 2004). A spontaneous chronic nephropathy is also a common occurrence in mice as noted in the furfuryl alcohol inhalation study where 49/50 control males and 41/50 control females were diagnosed with nephropathy. Frazier and Seely (2013) state '*while the classical and most studied presentation of CPN occurs in the rat, a similar but pathologically distinct renal lesion also occurs in the mouse. The clinical relevance of CPN in the mouse is thought to mirror CPN in rats, including a relationship to increased tubular epithelial proliferation in the kidney in chronic studies*'." (toXcel, p. 5)

"There is growing evidence and consensus that advanced CPN is a risk factor for development of a background incidence of atypical tubule hyperplasia and renal tubule tumors (RTT) where this association has been extensively studied in rats…. Since the clinical implications of nephropathy in mice mirror CPN in rats as mentioned above (Frazier and Seely, 2013), the implication of exacerbated CPN and enhanced tubular epithelial proliferation for renal tumor development in rats is relevant for understanding tumor development in mice. Since there is no counterpart to rodent CPN in humans (Hard 2013), renal tumors in rodents resulting from chemical enhancement of this spontaneous rodent pathological syndrome are not considered as a relevant indication of human risk." (toXcel, p. 6)

Response:
Scientific consensus on the validity of the hypothesis that chronic progressive nephropathy (CPN) can lead to renal tumor formation (RTT) has not been reached for either rats or mice. Melnick et al. (2012) reviewed 58 NTP carcinogenicity studies associated with CPN, and showed that many chemicals that induce severe CPN do not induce renal tumors. Further, the hypothesized sequence of events "lacks the fundamental requirement needed to judge biological plausibility: the mechanism(s) of chemically exacerbated CPN and of RTT development are complex and generally not known. …A limited number of select studies reporting correlations between increased CPN severity and induction of RTTs in male rats do not provide proof of a causal relationship nor insight into the mechanistic events involved in renal carcinogenesis" [51].

[51] Melnick RL, Burns KM, Ward JM, and Huff J (2012). Chemical exacerbated chronic progressive nephropathy not associated with renal tubular tumor induction in rats: an evaluation based on 60 carcinogenicity studies by the National Toxicology Program. *Toxicol Sci* **128**(2):346-356.

Thus, this proposed mode of action does not meet the US EPA guidelines regarding use of mechanistic data to determine a mode of action for carcinogenesis[52].

Additionally, the pathology findings observed in this study are inconsistent with the hypothesis that treatment-related CPN results in the development of renal tumors. Specifically, the majority of the male mice in the study, including the controls, developed nephropathy. The average severity of the observed nephropathy was slight in all treatment groups, with a minimal difference between the control and treated groups. The average severity grade of nephropathy was 1.2 in controls and 1.8 in the high-dose group (1=minimal, 2=mild, 3=moderate, 4=marked)[53]. These data suggest that RTTs can form when advanced CPN is not present, and that additional mechanisms may contribute to the carcinogenicity of furfuryl alcohol.

2.3.2.4 Comment:
"…the CARC noted that the presence of kidney tumors is rare in historical controls; however, the CARC report did not state whether the tumor type was a rare occurrence in treated mice such as in this study, for which multiple renal step sections were evaluated." (toXcel, p. 3)

Response:
US EPA first compared the combined standard and step-section incidence of kidney tumors observed in furfuryl alcohol treated male mice with the combined standard and step-section incidence in concurrent controls, which is the most appropriate comparator group, and second, with the incidence in historical controls.

When determining whether the occurrence of a particular tumor type is rare or uncommon in a particular species/strain/sex, the key issue is how often that tumor type is observed in untreated/control animals. Rare and uncommon tumors are very infrequently observed in untreated/control animals. The frequency with which a particular tumor type is observed in treated animals (e.g., animals administered chemicals in carcinogenesis studies) has no bearing on whether a particular tumor type is considered rare or uncommon. Thus, in discussing the rare nature of kidney tumors in male mice, US EPA referred to the rare incidence of kidney tumors observed in historical controls.

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[52] *Ibid.*
[53] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

2.4 *Genotoxicity of furfuryl alcohol*

Comment:
"The CARC report reviewed a battery of genetic toxicology assays deemed acceptable for regulatory purposes, and summarized them saying*, "The data indicate that furfuryl alcohol is not mutagenic in bacteria and does not cause chromosome aberrations or SCE induction in mammalian cells. These in vitro data are supported by the results of whole animal studies showing that furfuryl alcohol was not clastogenic, aneugenic or genotoxic in mouse bone marrow, cytogenetic, micronucleus or SCE assays."* Thus, the CARC concluded that furfuryl alcohol does not present a genotoxic or mutagenic concern. Therefore the mode of action for tumour development is non-genotoxic and the result of some other mode of action." (toXcel, p. 3)

Response:
US EPA states that "[b]ased on the available NTP genetic toxicology data, there is no mutagenic concern for …furfuryl alcohol"[54]. However, the 2014 US EPA report does not discuss or speculate as to the possible carcinogenic modes of action of furfuryl alcohol. In any case, evidence of genotoxicity is not required in order for a chemical to be identified as causing cancer, either by the scientific community at large, or under Section 25306 for purposes of listing carcinogens under Proposition 65. Indeed, a number of carcinogens are known to act via non-genotoxic mechanisms in addition to or instead of genotoxicity.

3. Human cancer risk at anticipated exposure levels

3.1 Comment:
"When mulled, the binder coats the grain of sand. This process is done in a closed system within the manufacturing facility. CMC is unaware of a situation where this process presents an exposure risk to the general public. And since the furfuryl alcohol is consumed in the binder process, it is not present in the final product—commonly a steel or iron casting." (CMC, p. 1)

"Within the facility, California foundries commonly provide high rates of general exhaust ventilation to further reduce employee exposure to molding emissions and other sources of airborne contaminants. Within the facility, potential worker exposure to furfuryl alcohol during the molding process primarily occurs during the molding process

[54] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014, p. 5.

when the workers are tamping the coated sand into the pattern, and striking off the mold. Although furfuryl alcohol is relatively volatile and some furfuryl alcohol emissions are generated, the total losses are actually quite small because the chemical hardener quickly polymerizes the furfuryl alcohol creating an infusible solid." (CMC, p. 2)

"Emissions from the mixing, molding and curing process have been quantified, and totaled 0.34% by weight (*Castings Emissions Reduction Program, 2005*). Furfuryl alcohol exposure was also documented in studies in the 1960's and 1970's, and averaged roughly 5 mg/m^3 (*NIOSH Publication No. 79---133, 1979*). CMC believes worker exposure levels have decreased significantly since that time. Conservatively estimated, at a 5 mg/m3 *[sic]* average exposure rate, an adult male at 70 Kg with a workday inhalation rate of 20 m^3/day would be exposed to roughly 1.4 mg/Kg body weight. None of the studies cited in the EPA report found carcinogenic effects at similar exposure levels." (CMC, p. 2)

"The data US EPA Office of Pesticide Programs used in its cancer assessment have been subject to more broad evaluation by companies making submittals to the EU as part of the REACH program, and those assessments have specifically considered foundry use exposure scenarios…. We believe the information and conclusions developed by those companies is important to understanding whether use of furfuryl alcohol in foundry binder applications warrants a Proposition 65 listing." (CMC, p. 3)

"OEHHA proposes to rely on a report by an authoritative body, in this case US EPA Office of Pesticide Programs, as the basis for listing furfuryl alcohol. The cited report evaluated furfuryl alcohol use as a soil fumigant, a use with very different exposure characteristics than use in foundry binders." (CMC, p. 3)

"The CARC assessment is based on studies conducted by NTP (1999) in the rat and mouse via the inhalation route; this is a route of exposure which is relevant to some industrial and agricultural uses but of less relevance to consumer exposure." (toXcel, p. 2)

"The Joint FAO/WHO Expert Committee on Food Additives (JECFA), published a draft monograph (WHO, 2001) on its evaluation of a group of 15 furfuryl derivatives including the parent furfuryl alcohol and its structurally related analogs and derivatives. These flavoring agents were grouped on the basis of the criterion that all are hydrolyzed and/or metabolized to furoic acid or a substituted furoic acid. Based on the predicted metabolism of these substances and data on their toxicity (including review of the NTP carcinogenesis studies) the Committee concluded that consumption of furfuryl alcohol

and the 14 related substances at the current levels of intake would not raise concern for safety." (toXcel, p. 7)

Response:
The level of anticipated exposure and the route of exposure to a chemical is not a factor in the determination of whether a chemical meets the criteria for listing under the Proposition 65 authoritative bodies listing process[55]. Listing of a chemical as causing cancer under this process involves only identification that the chemical can cause cancer as specified in Section 25306.

Dose-response assessment under Proposition 65 is carried out after a chemical is listed[56]. Pharmacokinetic issues related to route of exposure are addressed in dose-response assessments. The dose-response assessment analysis is used as the basis for deriving a "No Significant Risk Level" (NSRL), which is the level that poses no significant risk of cancer assuming daily exposure to that level for a lifetime (i.e., 70 years). No significant risk is defined in regulation as risks of one per 100,000 and less, per Section 25703(b)[57]. If a given exposure does not pose a significant risk, the warning and discharge-prohibition provisions of Proposition 65 would not apply[58].

3.2 Comment:
"US EPA provides additional clarification on the meaning of the descriptor "Likely to Be Carcinogenic to Humans." The Guidelines state: "Although the term 'likely' can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether a chemical is carcinogenic. This is because the data that support cancer assessments generally are not suitable for numerical calculations of the probability that an agent is a carcinogen." This raises the possibility that US EPA may describe a substance as "Likely to Be Carcinogenic to Humans" when the probability that it is carcinogenic to humans is low. If listed, such a substance might be required to carry a warning that it is "known to the State of California to cause cancer" when, in fact, there is only a low probability that it causes cancer." (FEMA, p. 9)

Response:
The level of cancer risk posed by an exposure to a given carcinogen is, not a factor in the determination of whether a chemical meets the criteria for listing under the

[55] Title 27, Cal. Code of Regulations, Section 25306.
[56] See *ExxonMobil v OEHHA* (2009) 169 Cal.App.4th 1264, see also *Western Crop Protection Assn. v Davis* (2000) 80 Cal.App.4th 741.
[57] Title 27, Cal. Code of Regulations, Section 25703.
[58] See Section 25701 *et seq*.

Proposition 65 authoritative bodies listing process[59]. Listing of a chemical as causing cancer under this process involves only identification that the chemical can cause cancer as specified in Section 25306.

Cancer risk is a function of the level of exposure and the estimated cancer potency for the carcinogen in question. Dose-response assessment must be performed to estimate the cancer potency of furfuryl alcohol. As described in response to Comment 3.1 above, dose-response assessment takes place after a chemical is listed[60]. The estimated cancer potency, sometimes called a cancer slope factor, is used to develop a NSRL for chemicals listed as causing cancer. Where such a level has not been adopted by OEHHA, the implementing regulations provide guidance for businesses to calculate their own. If a given exposure does not pose a significant risk, the warning and discharge-prohibition provisions of Proposition 65 would not apply[61].

4. Request for referral to Carcinogen Identification Committee (CIC)

Comment:
"The California Metals Coalition (CMC) proposes that instead of relying on the "authoritative body" approach to listing furfuryl alcohol, OEHHA should employ its Carcinogen Identification Committee (CIC) to evaluate the claims by the chemical producers in Europe, and other available data, to determine whether the data on use as a foundry binder supports identification of furfuryl alcohol as a carcinogen on the Proposition 65 list." (CMC, p. 3)

Response:
Listings by the CIC are just one of the ways a chemical can be listed under Proposition 65. The statute's four listing mechanisms are not hierarchical. Proposition 65 requires the listing of a chemical if it meets the criteria for any of the four listing mechanisms. US EPA has been designated by the CIC as an authoritative body for the purpose of identifying chemicals as causing cancer under Proposition 65 (Section 25306(m)(4)). OEHHA has determined that US EPA has formally identified furfuryl alcohol as causing cancer and that the evidence meets the scientific criteria specified in the regulation. Because of US EPA's formal identification of furfuryl alcohol as a carcinogen, and because it meets the scientific criteria for listing, there is no reason for OEHHA to refer the chemical to the CIC. Furfuryl alcohol will be listed under Proposition 65 via the authoritative bodies listing mechanism.

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[59] Title 27, Cal. Code of Regulations, Section 25306.
[60] See *ExxonMobil v OEHHA* (2009) 169 Cal.App.4th 1264, see also *Western Crop Protection Assn. v Davis* (2000) 80 Cal.App.4th 741.
[61] See Section 25701 *et seq*.

5. Reviews by other regulatory bodies

Comment:
"A similar interpretation [to the NTP report] was made by the German Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission)…. In 2008, the MAK Commission (2012a) conducted a comprehensive formal review and evaluation of the 1999 NTP studies. The Commission determined that the available information is insufficient to classify furfuryl alcohol as a likely human carcinogen and assigned a classification of '3B' in the carcinogenicity category." (toXcel, p. 7)

"Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures includes furfuryl alcohol and classifies the chemical as 'Carc Cat 2, H351' which is defined as a 'Suspected human carcinogen…not sufficiently convincing to place the substance in Category 1A or 1B.'" (toXcel, pp. 7)

Response:
US EPA has been designated as authoritative under Proposition 65, and its determination regarding the carcinogenicity of furfuryl alcohol[62] serves as the basis for the proposed listing. Neither the MAK Commission nor the European Parliament have been identified as one of the authoritative bodies for the identification of chemicals as causing cancer, which are listed in Section 25306(m). Moreover, the information provided by the commenter regarding the conclusions of the MAK Commission and the European Parliament do not provide substantial evidence that the sufficiency of evidence criteria of Section 25306(e) have not been met for furfuryl alcohol.

6. Development of Safe Harbor Levels

Comment:
"In the event that OEHHA CIC determines furfuryl alcohol warrants listing, then we believe OEHHA should publish safe harbor levels for furfuryl alcohol at the same time as its listing, allowing the supplier and user communities to determine whether the warnings can be omitted for specific uses such as foundry binder applications within the manufacturing facility." (CMC, p. 3)

[62] US Environmental Protection Agency (US EPA, 2014). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Furfural and Furfuryl Alcohol. Final Report. Health Effects Division, Office of Pesticide Programs. February 6, 2014.

Response:
The Office's general practice is to propose a No Significant Risk Level, when sufficient data and resources are available, for chemicals listed under Proposition 65 within the 12-month grace period before the warning requirement takes effect. This assists businesses in determining whether they must provide a warning for exposures to the chemical their products or activities may cause. Where such a level has not been adopted by OEHHA, the implementing regulations provide guidance for businesses to calculate their own.

7. Other comments

Comment:
CMC states that furfuryl alcohol is a better option than petroleum-based alternatives.

"Foundry binders formulated with furfuryl alcohol are an ideal choice when compared to other chemical binder systems, primarily those formulated from synthetic organic chemicals. The binders that are displaced are ultimately derived from oil, and their principal component ingredients include phenol, formaldehyde, MDI, and petroleum naphtha." (CMC, p. 2)

"California Air Resources Board (CARB), Cal---EPA, and the California Legislature have been leading advocates for eliminating, and/or substituting, petroleum products. Moreover, many in the environmental community argue that society should be sourcing an increasing number of chemicals from biologically derived materials, and particularly those which (like furfuryl alcohol) do not divert food crops or land used for production of food crops to production of chemicals or fuels. Development of such biologically---derived base chemicals is a field of great scientific interest and rapid development." (CMC, p. 2)

"Emissions from furfuryl alcohol based binders have been compared to those from conventionally formulated binders. As compared to a conventional phenolic urethane no-bake binder, furfuryl alcohol-containing binders emitted 81% less organic carbon emissions, and 46% less hazardous air pollutants (*Castings Emissions Reduction Program, 2001*)." (CMC, p. 2)

Response:
OEHHA acknowledges the importance of considering the use of furfuryl alcohol in comparison to alternatives. While issues related to the benefits of using the chemical and the potential consequences of listing it under Proposition 65 cannot be considered

in the listing process, an exemption is provided for carcinogen exposures that do not pose significant cancer risk. OEHHA's general practice is to propose a No Significant Risk Level when sufficient data and resources are available, for chemicals listed under Proposition 65, within the 12-month grace period before the warning requirement takes effect. This assists businesses in determining whether they must provide a warning for exposures to the chemical their products or activities may cause. Where such a level has not been adopted by OEHHA, the implementing regulations provide guidance for businesses to calculate their own.

Proposition 65 does not ban chemicals, and a Proposition 65 listing does not preclude furfuryl alcohol's use as a petroleum substitute. At least one gasoline substitute, methanol, is on the Proposition 65 list.

For a particular, well-defined use of a listed chemical, interested parties may request that OEHHA issue a "safe use determination," as described in Section 25204. A safe use determination is issued by OEHHA for a carcinogen when the specified use is found to pose no significant risk of cancer. A safe use determination is advisory only, and is specific to the requester and the facts presented in the request.