Response to Comments Pertaining to the Notice of Intent to List β-Myrcene as Causing Cancer under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
March 2015

On February 7, 2014, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List[1] β-myrcene under Proposition 65[2] as a chemical known to the state to cause cancer. The action was based on Proposition 65 statutory requirements[3] and on the authoritative bodies provision of the Proposition 65 implementing regulations, Title 27, Cal. Code of Regulations, section 25306[4]. OEHHA found that β-myrcene meets the criteria for listing via this mechanism based on conclusions by the National Toxicology Program (NTP) that β-myrcene causes cancer, and on the scientific evidence relied on by the NTP[5]. NTP is designated as an authoritative body for purposes of listing chemicals as causing cancer pursuant to Section 25306. This document responds to public comments received on the Notice of Intent to List β-myrcene under Proposition 65.

A chemical has been "formally identified" as causing cancer by an authoritative body pursuant to Section 25306(d) if: (1) the chemical has been included on 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).

OEHHA has reviewed the conclusions and statements in the NTP 2010 report entitled *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*[6], and determined that these conclusions and statements satisfy the Section 25306(d)(1) requirement that β-myrcene is the subject of a report published by the authoritative body that concludes that β-myrcene causes

[1] Notice of Intent to List: Beta-Myrcene. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilpkg44betamyrcene.html
[2] 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.
[3] Health and Safety Code section 25249.8(b)
[4] Title 27, Cal. Code of Regulations, section 25306; all further references are to sections of Title 27 of the California Code of Regulations, unless otherwise indicated.
[5] NTP (2010). *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
[6] *Ibid*

cancer; and that the report meets the section 25306(d)(2) criteria, thus satisfying the formal identification criteria in the Proposition 65 regulations. NTP's conclusions in the report on which OEHHA relies include the following:

NTP stated in the "Abstract" and "Discussions and Conclusions" sections of the report:

> "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms. … There was *clear evidence of carcinogenic activity* of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma." (NTP, pp. 9, 63)[7]. (emphasis in original)

In the "Conclusions" section of the "Summary", NTP stated:

> "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice." (NTP, p. 5) [8].

Based on the NTP's conclusions and the data relied on by the NTP in reaching those conclusions, OEHHA has determined that β-myrcene meets the sufficiency of evidence criteria in Section 25306.

Comments on the Notice of Intent to List were submitted by individuals on behalf of several organizations:

Commenter	**Date**	**Affiliation**
John Guerard	March 24, 2014	Responsible Farmers Coalition (RFC)
John Paul Maye	March 24, 2014	S.S. Steiner, Inc. (Steiner)
F. Jay Murray and Gary M. Roberts	March 24, 2014	Flavor and Extract Manufacturers Association; Consumer Healthcare Products Association; International Fragrance Association, North America; Juice Products Association; Personal Care Products Council; Renewable Citrus Products Association (hereafter this group of commenters are referred to as "the associations")

[7] NTP (2010). *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
[8] *Ibid*.

Several comments were similar to those submitted in response to the earlier Request for Relevant Information published on February 10, 2012[9]. OEHHA's responses to those comments[10] are included in the administrative record and incorporated herein by reference. Comments from the individuals and organizations listed above are grouped and numbered by topic, and responses follow below.

1. Formal Identification Criteria

1.a. NTP TECHNICAL REPORT

1.a.1. Comment:
The associations object to listing β-myrcene, stating that:

> "OEHHA lacks the authority to list β-myrcene as a carcinogen because the NTP did not 'conclude' that β-myrcene 'causes cancer' in animals." (p. 2)

Response:
A similar comment was submitted by the associations during the earlier informal "Request for Relevant Information" comment period. As OEHHA noted previously in response to those comments,[11] under Proposition 65 chemicals are required to be listed via the authoritative bodies listing mechanism as known to cause cancer if they meet the criteria specified in Section 25306. That 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 causing cancer and certain scientific criteria are met. OEHHA has determined that an authoritative body, NTP, has formally identified β-myrcene as causing cancer in its Technical Report, *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies)* (NTP, 2010).

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[9] Available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/DCIABPkg44_021012.html

[10] OEHHA (2014). *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf

[11] OEHHA (2014). *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf

The NTP Technical Report on β-myrcene[12] concludes that the chemical causes cancer. On page 9 the NTP concludes that there is clear evidence of carcinogenic activity of β-myrcene in male rats and male mice:

> "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms. … There was *clear evidence of carcinogenic activity* of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma." (emphasis in original)

On page 5 of the NTP Technical Report in the "Conclusions" section of the Summary, NTP states: "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice."

These conclusions by NTP regarding the carcinogenic activity of β-myrcene, and the data in the report supporting the conclusions, are the basis for OEHHA's determination that β-myrcene meets the criteria for listing pursuant to the authoritative bodies mechanism set out in Section 25306.

The formal identification requirements of Section 25306 are met because β-myrcene is the subject of a report[13] published by the authoritative body (NTP), which concludes that the chemical causes cancer and the report was (1) reviewed by an advisory committee in a public meeting, (2) subject to public review and comment, and (3) formally published by the NTP.

The conclusions of the NTP Technical Report on β-myrcene also satisfy the "sufficiency of evidence" criteria set out in Section 25306 (see Topic 2 below for discussion of the sufficiency of evidence criteria).

<u>1.a.2. Comment:</u>

The associations argue that the three statements bulleted below from the NTP Technical Report "do not demonstrate that NTP 'concluded' β-myrcene 'causes' cancer in animals for purposes of the authoritative bodies listing process because: (1) the clause in the Summary is inaccurate and not scientifically reliable, (2) None of the three

[12] NTP (2010). *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

[13] NTP (2010). *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

passages.reflect the necessary overall evaluation of animal carcinogenicity that is the bare minimum for a legally adequate 'sufficient evidence' conclusion, and (3) the overall context of the NTP Report, reporting on discrete studies it sponsored rather than assessing the larger picture of what 'studies in experimental animals indicate' does not support a listing." (pp. 3-4)

- "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice." (NTP, p. 5)
- "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms." (NTP, p. 9)
- "There was *clear evidence of carcinogenic activity* of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma." (NTP, p. 63)

<u>Response:</u>
OEHHA disagrees with the commenters. The conclusions quoted above from the NTP Technical Report on β-myrcene were made by NTP and specifically address the carcinogenicity of β-myrcene.

In the Summary, NTP summarizes key aspects of the scientific report, including its conclusions, in plain English. The Summary states:

> "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice."

This statement is consistent with NTP's conclusions presented in more technical language in later sections of the report. For example:

> "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms."
>
> "There was *clear evidence of carcinogenic activity* of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma."
> (NTP, p. 9).

Regarding the second and third points raised in this comment, OEHHA has determined that the conclusions of the NTP Technical Report on β-myrcene also satisfy the

"sufficiency of evidence" criteria set out in Section 25306 (see Topic 2 below for discussion of the sufficiency of evidence criteria).

1.a.3. Comment:

The associations reiterate a comment they made during the earlier informal request for relevant information comment period and express their disagreement with OEHHA's response:

> "The Technical Report warns that its conclusions are not to be extrapolated 'to other species, including characterization of hazards and risks to humans' because doing so would require 'analyses beyond the intent of the Report' " (p. 15)
>
> "We respectfully disagree with OEHHA's interpretation of NTP's statement in the Forward (sic) to the Technical Report." (p. 21)
>
> "NTP clearly communicates that both human hazard identification and human risk assessment are beyond the scope of these reports. Nothing in the levels of evidence passage noted by OEHHA is inconsistent with NTP's clear statement that the assessment of 'hazards to humans' is beyond the scope of the Technical Report." (p. 22)
>
> "NTP indicates that it is not considering all the available information, including existing data on the relevance of specific animal tumors to human hazard identification, in its Technical Reports. NTP is simply reporting the results of its animal study 'under the conditions of the study' nothing more." (p. 23)

Response:

OEHHA disagrees with the commenters' interpretation of the sentence from the Foreword to the NTP Technical Report which they partially quote, and which reads in full:

> "Extrapolation of these *results* to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports." (*emphasis added*)

As noted previously in OEHHA's response to comments on the Request for Relevant Information on β-myrcene[14], listing under Proposition 65 is based on the identification of

[14] OEHHA (2014). *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at

chemicals that cause cancer, as provided in Section 25306. It is not necessary for the authoritative body to identify the chemical as causing cancer in humans[15]. The NTP report identified β-myrcene as causing cancer in male rats and male mice. This satisfies the criteria for listing under Section 25306.

1.b. NTP REPORT ON CARCINOGENS

1.b.1. Comment:
The associations assert:

> "If NTP had *actually* identified β-myrcene as causing cancer in the Technical Report, it would have been obligated to nominate it for and include it in the RoC. The absence of the chemical in the RoC [*Report on Carcinogens*] indicates that NTP did not identify the chemical 'as causing cancer'." (pp. 24-25)

Response:
OEHHA disagrees with the assertion that NTP is obligated to nominate for the Report on Carcinogens all chemicals that it has identified as causing cancer in NTP Technical Reports. No such obligation exists. The NTP Report on Carcinogens process for nominating and selecting candidate substances for consideration for inclusion in the Report is laid out in the document entitled "Process for Preparation of the Report on Carcinogens"[16]. It is clear from this process document that the NTP Technical Report Series development process is a separate and distinct activity from the NTP Report on Carcinogens. There is no requirement that chemicals identified as causing cancer in NTP Technical Reports be nominated for possible inclusion in the Report on Carcinogens.

The NTP Technical Report on β-myrcene satisfies the "formal identification" criteria (see responses to comments 1.a.1 and 1.a.2 above) and the data in the report satisfies the "sufficiency of evidence" criteria set out in Section 25306[17] (see Topic 2 below for discussion of the sufficiency of evidence criteria).

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www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf

[15] See *AFL-CIO v Deukmejian* (1989) 212 Cal. App. 3d. 425; *Exxon Mobil Corp v OEHHA* (2009)169 Cal.App.4th 1264

[16] NTP (2012). *Process for Preparation of the Report on Carcinogens*. Office of the Report on Carcinogens, U.S. Department of Health and Human Services, National Toxicology Program. Available at http://ntp.niehs.nih.gov/ntp/roc/thirteenth/process/finalrocprocesswithfig.pdf

[17] *Exxon Mobil Corp v OEHHA* (2009)169 Cal.App.4th 1264 ;*Western Crop Protection Assn. v. Davis* (2000) 80 Cal.App.4th 741

Sufficiency of Evidence Criteria

2.a. APPLICATION OF SUFFICIENCY OF EVIDENCE CRITERIA

2.a.1 Comment:
The associations assert:

> "The NTP Technical Report at issue (NTP TR-557 or 'Report') does not make a 'sufficient evidence' finding concerning animal carcinogenicity, and OEHHA cannot analyze the data to make its own 'sufficient evidence' finding in support of a listing." (p. 1)
>
> "The authoritative bodies listing mechanism may be employed by OEHHA only when a chemical has been 'formally identified by an authoritative body as causing cancer' in a report which 'concludes' that '[s]ufficient evidence of carcinogenicity exists from studies in experimental animals.' To constitute a 'sufficient evidence' finding, the authoritative body's formal 'report' must 'conclude[]' (sic) that 'studies in experimental animals indicate that there is an increased incidence of' malignant or combined tumors under certain circumstances. OEHHA is not authorized to substantively evaluate the data on β-myrcene and conclude on its own that 'sufficient evidence' of carcinogenicity exists. OEHHA's role is limited by regulation to the 'ministerial' task of reviewing the authoritative body's formal reports and determining whether the authoritative body has, itself, issued a qualifying sufficient evidence 'conclu[sion']." (pp. 2 – 3)
>
> "None of the NTP statements OEHHA cites reflect a 'sufficient evidence' conclusion by NTP and thus OEHHA is not authorized to list β-myrcene through the authoritative bodies listing process." (p. 11)
>
> "NTP did not formally identify β-myrcene 'as causing cancer' because it did not express any opinion about whether 'sufficient evidence of carcinogenicity exists' from 'studies' (plural) in 'experimental animals' (plural)." (p. 12)

The associations further commented that the final statement of reasons for section 25306(e)

> "confirm[s] that the California Health and Welfare Agency, which wrote the regulation, expected the sufficient evidence standard would be 'applied' *by the authoritative body* to 'conclude that the chemical causes cancer.'" (emphasis in original) (p. 14)

Response:
The associations have incorrectly summarized the authoritative bodies listing criteria laid out in Section 25306. Under Section 25306(a) the mechanism may be employed "…if the *lead agency* [OEHHA] determines that an authoritative body has formally identified the chemical as causing cancer… as specified in this section." (emphasis added). As detailed in the previous section, an authoritative body, namely the NTP, has indeed formally identified β-myrcene as causing cancer pursuant to Section 25306. The regulation does not include a requirement that the report by the authoritative body conclude that sufficient evidence of carcinogenicity exists. As described earlier in this response, once an authoritative body has formally identified a chemical as causing cancer, OEHHA, as the lead agency, must make a determination as to whether the sufficiency of evidence criteria specified in its own regulations are met for the chemical in question.[18]

2.a.2. Comment:
The associations assert:

> "OEHHA has identified three NTP statements that OEHHA claims represent a 'sufficient evidence' conclusion within the meaning of section 25306. None of these three statements, however, satisfy the section 25306 requirement that NTP, rather than OEHHA, articulate a 'sufficient evidence' conclusion in order to support an authoritative body conclusion." (p. 3)
>
> "OEHHA further argues at page 6 of its 2014 Response to Comments that it is sufficient for OEHHA to stitch together the separate and limited findings that NTP made in its Technical Report and call that a 'sufficient evidence' finding that satisfies section 25306. This assertion defies standard rules of statutory construction, does not address the interpretive points made above, and fails to explain the Final Statement of Reasons statements that NTP must make the sufficient evidence finding. This constitutes OEHHA asserting it is authorized to make the ultimate 'sufficient evidence' determination. OEHHA does not have that authority." (p. 25)

Response:
The Final Statement of Reasons accompanying Section 25306, and relevant case law interpreting Proposition 65, make clear that OEHHA is the entity that makes the determination whether these chemicals have been formally identified as causing cancer

[18] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264

for purposes of Proposition 65[19] [20]. That determination need not be made by the authoritative body, in this case NTP[21].

Further, the authoritative body's report or document need not make the findings described in Section 25306. Rather, *OEHHA* must conclude that the authoritative body's formal identification of the chemical as causing cancer meets the criteria in Section 25306. OEHHA can make its determination based on the document issued by the authoritative body. OEHHA can also make its determination on the entire scientific record on which the authoritative body relied; including the scientific literature relied on by the authoritative body and OEHHA's knowledge of the authoritative body's methodology.[22] The FSOR for Section 25306 indicates that, because an entity has been designated as an authoritative body, "…there is a presumption that the authoritative body properly applied the criteria."[23] In making its determination that β-myrcene has been formally identified by NTP as causing cancer, OEHHA relied on the NTP Technical Report, as well as OEHHA's knowledge of the NTP's methodology.

As discussed in response to comments 1.a.1 and 1.a.2 above, the statements referred to by the commenters are conclusions made by NTP in the 2010 Technical Report on β-myrcene[24] regarding the chemical's carcinogenic activity. OEHHA has found that these statements meet the criteria for identification in section 25306.

<u>2.a.3. Comment</u>
The associations assert:

> "...the two separate and limited conclusions OEHHA cites about carcinogenic activity in one strain of mice and one strain of rats *under the conditions of NTP's experiment* are not 'sufficient evidence' conclusions either." (emphasis in original) (pp. 11-12)
>
> "Two separate, limited conclusions about male rats and male mice are not a "sufficient evidence" conclusion that can support an authoritative body listing." (p. 19)

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[19] OEHHA has been designated by Executive Order of the Governor as the Lead Agency pursuant to Health and Safety Code section 25249.12 and Title 27, Cal. Code of Regs., section 25102(o).
[20] Title 27, Cal Code of Regs, section 25306(c).
[21] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264
[22] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1280-1281
[23] Final Statement of Reasons for Section 25306 (formerly 12306), page 25 and *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1283
[24] NTP (2010). *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

Response:
As was made clear in *Exxon* Mobil Corp v OEHHA [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 Section 25306(e) criteria. 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 *Western Crop v Davis*,[26] OEHHA determines 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.

Section 25306(e) states:

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

The conclusions of the NTP Technical Report on β-myrcene regarding clear evidence of carcinogenic potential in the study in male rats and the study in male mice was based on findings of increased incidences of combined benign and malignant kidney (renal tubule) neoplasms in male rats and increased incidences of liver (hepatocellular) adenoma and carcinoma, and hepatoblastoma. The scientific data satisfy the 25306(e)(2) sufficiency of evidence criteria.

2.b. EVIDENCE IN MALE RATS

2.b.1. Comment:
In discussing the language in the NTP report's Summary section on kidney tumors, the associations states:

[25] See *ExxonMobil Corp v OEHHA* (2009) 169 Cal. App. 4th 1264
[26] *Western Crop Protection Association, et al. v. Gray Davis*, (2000) 80 Cal.App.4th 741

> "...the Summary also asserted that β-myrcene caused more than one type of cancer – 'cancers.' The use of the plural in this sentence also was clearly mistaken." (p. 6)

Response:

The language referred to by the commenters occurs in the Summary of the 2010 NTP Technical Report on β-myrcene, which summarizes key aspects of the scientific report in language intended to be understandable to the general public, including the NTP's conclusions regarding the carcinogenicity of β-myrcene. The phrase in question in the Summary reads: "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice...". The use of the plural 'cancers' refers to the kidney neoplasms, in this case renal tubule neoplasms. It is a simplification of NTP's conclusion of "*clear evidence of carcinogenicity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms".

2.b.2. Comment:

The associations assert:

> "The Summary section incorrectly states that β-myrcene 'caused kidney cancers in male rats.' β-myrcene caused a statistically significant increase in *benign* kidney tumors, not malignant kidney tumors (i.e. kidney cancer) in male F344/N rats. OEHHA does not have the authority to list a chemical through the authoritative bodies process based on benign tumors. Recognizing this, OEHHA normally does not list a chemical as a carcinogen unless it has sufficient evidence of increases in malignant tumors." (pp. 4-5)

> "Proposition 65 requires that a chemical be demonstrated to 'cause cancer,' not just benign tumors, before listing. The data indicates that the male rat 'clear evidence' statement by NTP may not have been materially influenced by the very few malignant tumors observed in the study. ...NTP conducted statistical analyses on the incidences of benign (only), malignant (only), and combined malignant and benign renal tubule tumors among both male and female rats. A statistically significant increase in benign renal tubule tumors (but not malignant renal tubule tumors) was observed in male rats exposed to β-myrcene. The incidence of combined malignant and benign renal tubule tumors was also increased among male rats, but this was accounted for by the statistically significant increase in benign tumors. If there had been no carcinomas among the male rats, there would have still been a marked, statistically significant increase in combined malignant and benign renal tubule tumors." (pp. 17-19)

Response:
Section 25306(e)(2) states:

> "… '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…" (emphasis added).

As noted by the commenters, the NTP reported a statistically significant increase in combined malignant and benign renal tubule tumors in the study of male rats exposed to β-myrcene. Indeed, both renal tubule adenomas and renal tubule carcinomas were observed in the low- and mid-dose male rats. The increased incidences of combined malignant and benign kidney tumors in male rats, taken together with the increased incidences of malignant and combined malignant and benign liver tumors in male mice in the NTP studies, satisfy the sufficiency of evidence criteria in Section 25306(e)(2)[27].

2.b.3. Comment:
The associations assert that male rat kidney tumors may not be relevant to humans:

> "The human relevance of male rat kidney tumors is suspect, so these tumors cannot *per se* be the basis for OEHHA to conclude that clear evidence of male rat kidney tumors supports a sufficient evidence of carcinogenicity finding." (p. 28)

> "…even if α2u-globulin is not the sole mechanism of action, the other most likely mechanism of action involves chronic progressive nephrophathy (CPN). NTP discussed the likelihood that CPN may play a role in the induction of rat kidney tumors. ...the kidney tumor data in rats in the NTP bioassay of β-myrcene are consistent with CPN playing a significant role in kidney tumor induction. But CPN, like α2u-globulin, is a mechanism of action considered by many not to be relevant to humans [Hard *et al*., 2013]." (p. 29)

Response:
OEHHA's previous responses to comments received during the "Request for Relevant Information" public comment period[28] contained a detailed discussion of issues related to the mechanism of action of β-myrcene-induced male rat kidney tumors, including the

[27] Title 27, Cal. Code of Regulations, Section 25306(e).
[28] OEHHA (2014). *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf

possible involvement of α2u-globulin, and how these issues were addressed by the NTP in the 2010 NTP Technical Report on β-Myrcene. In short, NTP noted the induction of nephrosis in both male and female β-myrcene-exposed rats and the increased incidence of renal tubule adenomas in female rats, and concluded "the mechanism of β-myrcene-induced renal carcinogenesis in male and female rats is not clear".

The associations cite Hard *et al.* (2013)[29] in their comments regarding chronic progressive nephropathy (CPN) and the relevance of male rat kidney tumors to human cancer risk assessment. Hard *et al.* (2013) propose a set of criteria for considering exacerbation of CPN as a mode of action (MOA) for renal tubule tumors in rats. A scientific consensus on the validity of this proposed MOA has not been reached. However, the NTP male rat kidney data do not meet at least four of the seven elements of these proposed criteria. The proposed criteria elements are:

1. Lack of genotoxic activity based on overall evaluation of *in vitro* and *in vivo* data
2. Tumor incidence is low, usually < 10%
3. Tumors are found toward the end of 2-year studies
4. Lesions are usually ATH [atypical tubular hyperplasia] or adenomas (carcinomas can occasionally occur)
5. Chemical exacerbates CPN to most advanced stages, including end-stage kidney
6. ATH and tumors occur in rats with advanced CPN and in CPN-affected tissue
7. Absence of cytotoxicity in CPN-unaffected tubules, in rats with lower grades of CPN, and in subchronic studies

The incidence of renal tubule adenomas or carcinomas (single and step section) in the low-dose (0.25 g/kg) and mid-dose (0.5 g/kg) β-myrcene treatment groups in the two-year NTP study in male rats was 28% and 26%, respectively. These data do not fit proposed criteria element 2. The first incidence of renal tubule adenomas or carcinomas (single and step section) in the mid-dose (0.5 g/kg) β-myrcene treatment group in the two-year NTP study in male rats was observed at 551 days, which was approximately 75% of the study length. These data do not fit proposed criteria element 3. NTP reported a renal tubule carcinoma incidence (single and step section) of 6% and 2% for the low-dose (0.25 g/kg) and mid-dose (0.5 g/kg) β-myrcene treatment groups in the two-year NTP study in male rats, respectively. These data do not fit proposed criteria element 4. NTP conducted 23-day and 90-day studies of β-myrcene in male and female rats receiving doses of 0, 0.25 g/kg, 0.5 g/kg, 1 g/kg, 2 g/kg, or 4

[29] Hard GC, Banton MI, Bretzlaff RS, Dekant W, Fowles, JR, et al. (2013). Consideration of rat chronic progressive nephropathy in regulatory evaluations for carcinogenicity. *Toxicol Sci* 132(2):268-75.

g/kg. In the 90-day studies both males and females exhibited renal tubule necrosis in all β-myrcene treatment groups and nephrosis in the 1 g/kg and 2 g/kg treatment groups. In the 23-day studies significant renal tubule degeneration was observed in the male rat 2 g/kg treatment group and the female rat 1g/kg and 2 g/kg treatment groups. NTP stated that the renal tubule degeneration was similar to the nephrosis seen in the rats exposed for 90 days. These data do not fit proposed criteria element 7.

To summarize, based on the proposed criteria laid out in the reference cited by the commenters, CPN exacerbation is not a valid MOA for the male rat kidney tumors observed after β-myrcene exposure.

2.c. EVIDENCE IN MALE MICE

2.c.1. Comment:
The associations assert:

> "The human relevance of mouse liver tumors is suspect, so these tumors cannot *per se* be the basis for OEHHA to conclude that clear evidence of mouse liver tumors supports a sufficient evidence of carcinogenicity finding." (p. 25)
>
> "...the European Food Safety Authority and Commonwealth of Australia have taken a consistent approach to considering such liver tumors not relevant to humans." (pp. 25-26)
>
> "OEHHA's response [to previous comments] is not adequate to establish that clear evidence of mouse liver tumors for a non-genotoxic chemical is *per se* adequate to establish one positive experiment or one positive strain for purposes of a 'sufficient evidence of carcinogenicity' determination *in the view of NTP*. First, OEHHA cites no support for its statement that the NTP considers mouse liver tumors relevant for cancer hazard identification without any 'discounting'...Second, 'relevance' alone is not necessarily adequate for a sufficient evidence finding...OEHHA has offered no basis to conclude that NTP considers all mouse liver tumors adequate to support one half of a 'sufficient evidence' conclusion." (emphasis in original) (pp. 26-27)
>
> "Absent a clear basis for OEHHA to conclude that *NTP* considers *all* mouse liver tumors adequate to support one-half of a sufficient evidence conclusion, and absent NTP affirming that view as it relates to β-myrcene, the listing of β-myrcene cannot proceed pursuant to the authoritative bodies listing process." (emphasis in original) (p. 27)

Response:
A detailed discussion of OEHHA's position on NTP's conclusion regarding male mouse liver tumors is provided in OEHHA's previous responses to comments received during the "Request for Relevant Information" public comment period, which are included in the administrative record for this listing[30]. In short, mouse liver tumors are considered relevant for cancer hazard identification by the NTP and other bodies designated as authoritative for purposes of identifying chemicals as causing cancer under Proposition 65 (*e.g.*, International Agency for Research on Cancer, US Environmental Protection Agency).

Further, neither NTP nor other bodies designated as authoritative for purposes of identifying chemicals as causing cancer under Proposition 65 (e.g., US EPA) consider mouse liver tumors induced by nongenotoxic carcinogens as irrelevant for human risk assessment, absent clear evidence of a mode of action not relevant to humans[31]. NTP did not identify the mechanisms by which β-myrcene induced liver tumors in mice, stating:

> "Further studies are needed to understand the mechanism of action of β-myrcene-induced toxicity and carcinogenesis in rats and mice. β-Myrcene and *d*-limonene are not mutagenic or clastogenic… β-Myrcene may be metabolized by P450 to an epoxide, which may have the ability to alkylate DNA."

NTP has been designated as "authoritative" under Proposition 65 (Section 25306 (l)(3)), and its determination regarding the carcinogenicity of β-myrcene serves as the basis for the proposed listing. Neither the European Food Safety Authority nor the National Industrial Chemical Notification Assessment Scheme of Australia are identified as "authoritative bodies" under Proposition 65.

2.d. GENOTOXICITY FINDINGS

2.d.1. Comment:
Steiner asserts that it would be inappropriate to list β-myrcene, given the absence of positive genotoxicity findings.

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[30] OEHHA (2014) *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf

[31] U.S. Environmental Protection Agency (U.S. EPA, 2005a). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Benthiavalicarb-isopropyl. Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. October 18, 2005.

Response:
Lack of genotoxicity does not equate with lack of carcinogenicity and evidence of genotoxicity is not part of the sufficiency of evidence criteria in Section 25306[32]. As discussed above, the sufficiency of evidence criteria are met by the NTP studies by increased incidences of combined malignant and benign tumors in multiple species.

Also, as described in OEHHA's previous responses to comments received during the "Request for Relevant Information" public comment period, OEHHA agrees that NTP did not find evidence of genotoxicity in its own testing, which consisted of tests for mutation in *Salmonella typhimurium* and *Escherichia coli,* as well as tests for increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. NTP states that the mechanism of β-myrcene-induced carcinogenesis is not clear and discusses a number of possible non-genotoxic modes of action for β-myrcene in rats and mice.

2. Other Comments

3.a. HUMAN EXPOSURE TO β-MYRCENE

3.a.1. Comment:
Steiner and RFC assert that β-myrcene exposure to humans from hops used in beer would be low (Steiner) and from carrots would be negligible (RFC).

Response:
OEHHA acknowledges the information provided on the levels β-myrcene in carrots, hops, and beer. The level of anticipated exposure to a chemical is not a factor in the determination of whether a chemical meets the criteria for listing under Proposition 65 authoritative bodies listing process[33].

Listing of a chemical under Proposition 65 involves only identification that the chemical can cause cancer as specified in Section 25306[34]. It should be noted that a Proposition 65 warning is not required if the cancer risk is insignificant. Proposition 65 exempts from its requirement to warn about listed chemicals "an exposure for which the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer"[35].

[32] OEHHA (2014). *Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65*, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf
[33] Title 27, Cal. Code of Regulations, Section 25306.
[34] Title 27, Cal. Code of Regulations, Section 25306.
[35] Health and Safety Code Section 25249.10(c)

No significant risk is defined in regulation as risks of one per 100,000 and less, per Section 25703(b)[36]. Thus, lifetime exposures to agricultural products associated with risks of one per 100,000 or less would not require warning. Additionally, food products in which β-myrcene occurs naturally would not require warning, e.g. carrots and hops as discussed below.

3.b. NATURAL OCCURRENCE OF β-MYRCENE

3.b.1. Comment:
Steiner and RFC noted that β-myrcene occurs naturally in hops and several fruits, vegetables and tree nuts, and argue that, as a naturally occurring chemical, it should not be listed as causing cancer under Proposition 65.

Response:
OEHHA agrees that β-myrcene occurs naturally in several plant-based foods. As stated in the Notice of Intent to List, β-myrcene is a "natural constituent of food plants, such as *hop*, bay, verbena, lemongrass, citrus, pomegranate, and *carrot*, and of their juices and essential oils"[37]. (emphasis added)

The provisions governing the evaluation of Proposition 65 exposures to naturally occurring chemicals are contained in the implementing regulations, specifically, Title 27, Cal. Code of Regs., section 25501, which states:

> "Human consumption of a food shall not constitute an "exposure"…to a listed chemical in the food to the extent that the person responsible for the exposure can show that the chemical is naturally occurring in the food."

Section 25501(a)(1) provides,

> "A chemical is 'naturally occurring' if it is a natural constituent of a food, or if it is present in a food solely as a result of absorption or accumulation of the chemical which is naturally present in the environment in which the food is raised, or grown, or obtained."

Section 25501(a)(3) provides,

> "A chemical is naturally occurring only to the extent that the chemical did not result from any known human activity. Where a food contains a chemical, in part naturally occurring and in part added as a result of known human activity,

[36] Title 27, Cal. Code of Regulations, Section 25703.
[37] NTP 2010. *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

> "exposure" can only occur as to that portion of the chemical which resulted from such human activity"[38].

Thus, while the natural occurrence of a chemical in a food does bear on the question of whether or not warning is required for the food, it does not bear on whether or not the chemical meets the regulatory criterion for listing as "causing cancer" under Proposition 65.

Thus, the listing of a chemical under the authoritative bodies provision of Proposition 65 involves only a determination by OEHHA that the chemical meets the regulatory criteria[39]. The extent to which a given level of exposure to a listed chemical is exempt from Proposition 65 warning requirements is governed by the level of a given exposure and, in the case of the natural occurrence of β-myrcene in food, the application of Section 25501 to that exposure[40].

3.c. PLAIN LANGUAGE SUMMARY SECTION OF THE NTP TECHNICAL REPORT

<u>3.c.1. Comment:</u>
The associations assert:

> "The Summary section of the [NTP] Report, including the clause OEHHA cites in its Notice, did not receive *any* external peer-review, whether by the NTP Board of Scientific Counselors (BSC) or otherwise. Moreover, it does not appear that the Summary section received any internal peer review either. 'We concluded that the chemical caused kidney cancers in male rats and liver cancer in male mice…' does not appear anywhere in the draft Technical Report reviewed by the public and the BSC Technical Reports Review Subcommittee." (pp. 8-9)
>
> "The Summary section is not published in a publication such as the Federal Register, signed, set forth in an official document used for regulatory purposes, or adopted as a final rule. Thus, none of the indicia of reliability discussed in section 25306(d)(2) apply to the Summary section." (p. 9)
>
> "The Summary section must receive no weight." (p. 11)

[38] Title 27, Cal. Code of Regulations, Section 25501(a).
[39] Title 27, Cal. Code of Regulations, Section 25306.
[40] Title 27, Cal. Code of Regulations, Section 25501.

Response:
OEHHA agrees that the Summary of the 2010 NTP Technical Report on β-myrcene was not included in the draft report released for public comment and peer review by NTP's advisory committees. However, as part of the NTP Technical Report, the Summary meets the "formal identification" requirements of Section 25306 specifically (d)(2)(c), since it is part of a report that is formally published by the authoritative body (NTP).

3.c.2. Comment:
The associations highlight a typographical error in the NTP Technical Report:

"[The Summary section of the NTP Technical Report] wrongly states that 'liver tumors in female **rats** may have been related to β-myrcene administration.'" (p. 7)

Response:
The commenters correctly note what appears to be a typographical error in the Summary of the NTP report; the phrase in question should have read: 'liver tumors in female **mice** may have been related to treatment.'

The specific phrase in question refers to NTP's conclusion regarding equivocal evidence of carcinogenic activity in female mice. This finding of equivocal evidence of carcinogenic activity in female mice is not part of the basis for OEHHA's determination that β-myrcene meets the criteria for listing pursuant to Section 25306. As indicated in the Notice of Intent to List β-Myrcene[41], OEHHA's determination is based on findings that can be found in the body of the report that there is clear evidence of carcinogenic activity of β-myrcene in male rats and male mice[42]. The typographical error has no bearing on the listing of β-myrcene.

3.c.3. Comment:
The associations state:

> "The β-myrcene Technical Report is not the only example of a significant inconsistency between the conclusions in the Summary and those in the main body of a NTP Technical Report… For example, the Summary section of the Technical Report (TR-538) for methyl isobutyl ketone (MIBK) contains a sentence similar to the sentence that appears in the Summary section of the Technical Report on β-myrcene:

[41] Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf_zip/021012DCIABPkg44.pdf
[42] NTP 2010. *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies*). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

> ‘We conclude that methyl isobutyl ketone caused cancer of the kidney in male rats and of the liver in male and female mice.’
>
> Yet, there was no ‘clear evidence of carcinogenic activity’ in male rats, female rats, male mice or female mice in the conclusions in the Abstract and Conclusions sections of the Technical Report[.]” (pp. 9-10)

Response:
According to NTP’s *Definition of Carcinogenicity Results*[43], two categories exist to describe positive results, namely ‘clear evidence’ and ‘some evidence’. NTP defined these categories as follows:

> “*Some Evidence of Carcinogenic Activity* is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.”

The studies in MIBK showed increases in tumors of the kidney in male rats and increases of liver tumors in male and female mice, each of which NTP determined to be treatment-related, and each of which NTP concluded provided *some evidence of carcinogenic activity*. Thus, the conclusion in the Summary section of the Technical Report for MIBK (TR-538) is consistent with the NTP’s conclusions elsewhere in that report, and with NTP’s definition of ‘positive evidence’.

3.d. REQUEST FOR REFERRAL TO THE CARCINOGEN IDENTIFICATION COMMITTEE (CIC)

3.d.1. Comment:
The RFC objects to the listing and asserts that the CIC should review the issue:

> “Before beta-myrcene is added to the list of carcinogens under Proposition 65, OEHHA should request that the Carcinogen Identification Committee (CIC) review the issue. The CIC is the primary authoritative body for reviewing candidate carcinogens. The NTP did not give equivocal [*sic*] evidence that the chemical causes cancer in humans. The CIC, therefore, should be consulted before OEHHA makes its final decision.”

[43] NTP (2013). *Definition of Carcinogenicity Results*. U.S. Department of Health and Human Services, National Toxicology Program. Available at http://ntp.niehs.nih.gov/index.cfm?objectid=07027D0E-E5CB-050E-027371D9CC0AAACF#CARCDEF

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.

NTP 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)(3)). OEHHA has determined that NTP has formally identified β-myrcene as causing cancer and that the evidence meets the scientific criteria specified in the regulation[44].

3.e. PRODUCT LABELING

3.e.1. Comment:
The RFC objects to listing β-myrcene because it would place an unfair burden on products containing the chemical, especially food products such as carrots that naturally contain β-myrcene.

Response:
Under Proposition 65, OEHHA cannot consider economic impacts or burdens that might be associated with the listing of a chemical. A chemical must be added to the Proposition 65 list if it meets the criteria for listing contained in the statute and the implementing regulations.

While the commenter did not specify exactly how a listing would be burdensome or unfair, it would be reasonable to interpret the comment as a statement of concern over the impact of warnings on carrots and other foods containing naturally occurring β-myrcene. As discussed above in responses to comment 3.b.1, food products in which β-myrcene occurs naturally would not require a warning.

[44] OEHHA (2014). Response to Comments Pertaining to the Request for Relevant Information on β-Myrcene as Causing Cancer under Proposition 65, February 2014. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/pdf/020714B-myrceneResponse.pdf