

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

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

The Office of Environmental Health Hazard Assessment (OEHHA) has determined that styrene meets the criteria for listing under Proposition via the authoritative body mechanism based on conclusions by the National Toxicology Program (NTP) that styrene causes cancer, and on the scientific evidence relied on by NTP¹. NTP is designated as an authoritative body for purposes of listing chemicals as causing cancer pursuant to Section 25306. Styrene 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 styrene under Proposition 65. On February 27, 2015, OEHHA issued a Notice of Intent to List² (NOIL) styrene under Proposition 65³ as a chemical known to the state to cause cancer. The action was based on Proposition 65 statutory requirements⁴ and on the authoritative bodies provision of the Proposition 65 implementing regulations, Title 27, Cal. Code of Regulations, section 25306⁵. This document responds to public comments on the Notice of Intent to List styrene 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).

¹ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

² Notice of Intent to List: Styrene. Available at http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilstyrene2015.html

³ The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified in Health and Safety Code section 25249.5 et seq.) herein after referred to as Proposition 65 or the Act.

⁴ Health and Safety Code section 25249.8(b)

⁵ All further references are to sections of Title 27, California Code of Regulations unless indicated otherwise.

OEHHA has reviewed the conclusions and statements in the 2011 NTP *Report on Carcinogens, Twelfth Edition*⁶, and determined that these conclusions and statements satisfy the Section 25306(d)(1) requirement. Specifically, styrene has been included in a list of chemicals causing cancer published by the authoritative body; *and* it is the subject of a report published by the authoritative body that concludes that styrene causes cancer; *and* the NTP *Report on Carcinogens* indicates this identification is a final action. Further, OEHHA has determined that the report meets the Section 25306(d)(2) requirements, thus the NTP *Report on Carcinogens* satisfies the formal identification criteria in the Proposition 65 regulations for styrene. In the 2011 *Report on Carcinogens*, NTP concludes that styrene is “reasonably anticipated to be a human carcinogen” based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis⁷. OEHHA is relying on NTP’s discussion of data and conclusions in the report that styrene causes cancer. Evidence described in the report includes studies showing that styrene increased the incidence of combined malignant and benign lung tumors in two strains of male mice (CD-1 and B6C3F1) and increased the incidence of malignant and combined malignant and benign lung tumors in female CD-1 mice:

“Styrene caused lung tumors in several strains of mice and by two different routes of exposure. The most robust studies are two-year studies of inhalation exposure in CD-1 mice (Cruzan *et al.* 2001) and oral exposure (by stomach tube) in B6C3F1 mice (NCI, 1979). Inhalation exposure caused benign lung tumors (alveolar/bronchiolar adenoma) and increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in CD-1 mice of both sexes; in females it also increased the separate incidence of malignant lung tumors. In male B6C3F1 mice, oral exposure to styrene increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma), and a positive dose-response trend was observed (NCI, 1979).”⁸

The evidence cited by NTP⁹ in support of these conclusions was reviewed by OEHHA with regard to the sufficiency of evidence criteria in Section 25306(e)(2). Based on NTP’s conclusions and the data relied on by NTP in reaching those conclusions,

⁶ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁷ *Ibid.*

⁸ *Ibid.*

⁹ *Ibid.*

OEHHA has determined that styrene meets the sufficiency of evidence criteria in Section 25306.

The February 27, 2015, notice initiated a 30-day public comment period that was scheduled to close on March 30, 2015. OEHHA extended the public comment period to April 29, 2015 after receiving a request for extension from the Expanded Polystyrene (EPS) Industry Alliance. Thirteen sets of comments were submitted by the following organizations and private citizens:

- American Chemistry Council (ACC), submitted by Mike Levy and Steve Russell
- American Coatings Association (ACA), submitted by Stephen Wieroniey and Javaneh Nekoomaram
- APTCO LLC (APTCO), submitted by Harry Grant and Margaret Cerrato-Blue of Riddell Williams PS
- Ashland Inc. (AI), submitted by Theodore Harris
- California Grocers Association (CGA), submitted by Timothy James
- Center for Environmental Health (CEH), submitted by Caroline Cox, and the Natural Resources Defense Council (NRDC), submitted by Veena Singla.
- EPS Industry Alliance (EPSIA), submitted by Lynn Bergeson of Bergeson and Campbell PC
- Nicolette Good, private citizen
- Komatsu America Corp (Komatsu), submitted by Taimoor Khan
- National Marine Manufacturers Association (NMMA), submitted by Jeffrey Gabriel
- North American Meat Institute (NAMI), submitted by Mark Dopp
- Styrene Information Research Center (SIRC), submitted by John Snyder
- The Art and Creative Materials Institute (ACMI), submitted by Ann Grimaldi of Grimaldi Law Offices

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 from individuals and groups listed above are summarized, grouped and numbered by topic, and responses follow below.

1. In support of listing

Comment:

The Natural Resources Defense Council and the Center for Environmental Health support the listing of styrene under Proposition 65. NRDC and CEH note that the

proposed listing meets the requirements of the Proposition 65 regulations. An authoritative body, NTP, has formally identified styrene as a carcinogen in the *Twelfth Report on Carcinogens*. NTP found that there was sufficient evidence in animals to make this determination, thus satisfying the regulation's scientific sufficiency criteria. The scientific basis of the determination by NTP has been confirmed by the National Research Council.

Response:

OEHHA agrees with NRDC's and CEH's comments that an authoritative body, NTP, has formally identified styrene as a carcinogen in the 2011 NTP *Report on Carcinogens, Twelfth Edition*¹⁰ and that the basis for NTP's findings of sufficient evidence of carcinogenicity from studies in experimental animals meets the sufficiency of evidence criteria in Section 25306.

OEHHA also agrees that the National Research Council of the National Academy of Sciences, in its 2014 report *Review of the Styrene Assessment in the National Toxicology Program*¹¹, confirmed the scientific basis of the NTP's determination that styrene is a carcinogen:

"Literature published by June 10, 2011, provided sufficient evidence that "there is an increased incidence of . . . a combination of malignant and benign tumors" in experimental animals induced by styrene administered by multiple routes of exposure (inhalation and oral gavage). The most informative experimental animal studies that support that conclusion are studies in mice (NCI 1979; Cruzan et al. 2001)." (p. 9)¹²

The National Research Council also found that:

"compelling evidence exists to support a listing of styrene as, at a minimum, *reasonably anticipated to be a human carcinogen*. That conclusion is based on credible but limited evidence of carcinogenicity in traditional epidemiologic

¹⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹¹ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

¹² *Ibid.*

studies, on sufficient evidence of carcinogenicity in animals, and on convincing evidence that styrene is genotoxic in exposed humans.” (p. 17)¹³

2. Formal identification criteria are not met

Comment:

Ashland Inc. comments that NTP’s 2011 *Report on Carcinogens* serves as an inappropriate basis by which to list styrene, and the 2011 *Report on Carcinogens* alone does not satisfy the data sufficiency requirements of the authoritative bodies listing mechanism.

Response:

OEHHA disagrees and has determined that NTP has formally identified styrene as causing cancer in its 2011 *Report on Carcinogens, Twelfth Edition*¹⁴.

Under Proposition 65¹⁵, 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 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) that the chemical “has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body;” 2) if 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) if 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.”

The 2011 NTP *Report on Carcinogens, Twelfth Edition*¹⁶ meets all three of the bases for establishing formal identification. More specifically, the report meets the criteria in

¹³ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

¹⁴ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁵ Health and Safety Code section 25249.8(b)

¹⁶ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page

Section 25306(d)(1) since styrene is included on a list of chemicals causing cancer issued by NTP, is the subject of a report that was published by NTP which concludes that styrene is reasonably anticipated to be a human carcinogen, and the NTP Report on Carcinogens indicates this identification is a final action. The report meets the criteria in Section 25306(d)(2) since styrene is specifically and accurately identified, and the report was reviewed by an advisory committee in a public meeting, was subject to public review and comment, and was formally published by the NTP.

OEHHA has evaluated the evidence cited by the 2011 NTP *Report on Carcinogens, Twelfth Edition*¹⁷ for the carcinogenicity of styrene against the sufficiency of evidence criteria for “as causing cancer,” as laid out in Section 25306(e)(2) and determined that the basis for the formal identification is satisfied. The regulation 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, 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.”

NTP¹⁸ concluded that styrene is reasonably anticipated to be a human carcinogen based on studies showing that styrene increased the incidence of combined malignant and benign lung tumors in two strains of male mice (CD-1 and B6C3F1) and increased the incidences of malignant and combined malignant and benign lung tumors in female CD-1 mice. Thus, NTP¹⁹ found that styrene causes increased incidences of combined malignant and benign lung tumors in two strains of male mice, exposed by different routes of administration (i.e., oral and inhalation), and increased incidences of malignant and combined malignant and benign lung tumors in female mice.

383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁸ *Ibid.*

¹⁹ *Ibid.*

3. Sufficiency of evidence criteria are not met

3.1 Sufficiency criteria for animal data

Comment:

The Styrene Information Research Center (SIRC) and APTCO LLC comment that the sufficiency criteria for listing styrene under Section 25306(e)(2) are not met. Specifically, the sufficiency criteria for animal data are not met because one of the two male mouse studies does not demonstrate an increased incidence of tumors, and there is only limited evidence in humans. They note that in 2002 the International Agency for Research on Cancer (IARC) concluded that the same two animal studies the NTP Report on Carcinogens relied on to list styrene did not constitute sufficient evidence, because the National Cancer Institute (NCI) study was negative. The commenters state that NTP reconstructed the original NCI male mouse study by replacing the control incidence with historical control data from other laboratories and that NTP's subsequent analysis and findings regarding the NCI study (increased lung tumors in male mice) is incorrect. The commenters conclude that there is only one valid animal study and hence the criteria for listing are not met. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC's comment.

Response:

OEHHA disagrees with these comments.

NTP²⁰ identified three key animal cancer studies in which exposure to styrene increased lung tumors: the inhalation exposure studies of styrene in male and female CD-1 mice (Cruzan *et al.*, 2001)²¹, and the oral exposure study of styrene in male B6C3F1 mice (NCI, 1979)²².

NTP²³ analyzed NCI's tumor incidence data from the male B6C3F1 mouse study²⁴ and concluded that styrene increased the combined incidence of benign and malignant

²⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

²¹ Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA, Bevan C, Hardy CJ, Coombs DW, Mullins PA and Brown WR (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol* **21**(3):185-198.

²² National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

²³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

²⁴ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

tumors in male mice, based on a statistical comparison with the concurrent, not historic, controls. In doing so NTP followed scientifically accepted standard procedures^{25,26}, as well as its own procedures (now described in NTP's *Handbook for Preparing Report on Carcinogens Monographs*²⁷ which states: "... the concurrent controls are considered the most relevant comparison group for evaluating potential exposure-related tumor effects").

OEHHA has concluded that NTP's²⁸ analysis and conclusion regarding the NCI male mice study²⁹ is correct, and that the study clearly shows a statistically significant increase in combined malignant and benign lung tumors in male mice. Together with the lung tumor findings from the male and female mouse studies of Cruzan *et al.*³⁰, the animal evidence clearly shows an increased incidence in malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments. Thus, styrene meets the requirements for listing "as causing cancer" as defined in Section 25306(e)(2) based on sufficient evidence in experimental animals.

3.2 Use of historical control data

3.2.1 Comment:

SIRC and APTCO comment that NTP ignored NCI's conclusions regarding the outcome of the 1979 oral gavage study in male mice; departed from accepted science by using historical controls from another laboratory in its analysis of the study; and included external historical control data leading to the conclusion that sufficient evidence of carcinogenicity exists in mice following oral administration of styrene. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC's comment.

²⁵ International Agency for Research on Cancer (IARC, 2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, World Health Organization, Lyon, France, p 14. Available online at: <http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf>

²⁶ US Environmental Protection Agency (US EPA, 2005). Guidelines for carcinogen risk assessment. US EPA, Washington, DC. Document number EPA/630/P-03/001F, pp 2-20 to 2-21

²⁷ National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. Office of the Report on Carcinogens, Division of the NTP, National Institute of Environmental Health Sciences, US Department of Health and Human Services. Available online at <http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html>

²⁸ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

²⁹ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

³⁰ Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA, Bevan C, Hardy CJ, Coombs DW, Mullins PA and Brown WR (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol* **21**(3):185-198.

Response:

This assertion is incorrect. NTP³¹ did not ignore NCI's conclusion regarding the outcome of the 1979 male mouse study³² nor did it use historical control data from another laboratory to reach its conclusion that male mice exposed to styrene had a significant increase in combined malignant and benign lung tumors as compared to concurrent controls. NTP³³ interpreted the outcome of the NCI study³⁴ that styrene exposure led to an increase in combined malignant and benign lung tumors in male mice based on comparison with the *concurrent vehicle* control used in the study. In making this determination, NTP³⁵ followed standard scientific procedures (e.g., US Environmental Protection Agency [US EPA], 2005^{36,37}), as well as its own procedures (now described in NTP's *Handbook for Preparing Report on Carcinogens Monographs*³⁸ which states: "... *the concurrent controls are considered the most relevant comparison group for evaluating potential exposure-related tumor effects*").

The original NCI (1979) report of the male mouse study³⁹ noted some uncertainty regarding the absence of lung tumors in the concurrent controls. NCI's uncertainty reflected the limited *historical vehicle* control population available at that time, which NCI considered too small to provide a useful perspective on tumor rates in the concurrent controls. NCI also considered data from a larger number of *historical*

³¹ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

³² National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

³³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

³⁴ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD

³⁵ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

³⁶ US Environmental Protection Agency (US EPA, 2005). Guidelines for carcinogen risk assessment. US EPA, Washington, DC. Document number EPA/630/P-03/001F, pp 2-20 to 2-21

³⁷ International Agency for Research on Cancer (IARC, 2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, World Health Organization, Lyon, France, p 14. Available online at: <http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf>

³⁸ National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. Office of the Report on Carcinogens, Division of the NTP, National Institute of Environmental Health Sciences, US Department of Health and Human Services. Available online at <http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html>

³⁹ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

untreated controls from the same laboratory, in which the average lung tumor incidence was 12 percent. These considerations led the NCI study authors to conclude that the evidence of carcinogenicity in the male mouse study was suggestive but not convincing⁴⁰.

The 2011 NTP *Report on Carcinogens, Twelfth Edition*⁴¹ did not mention any controls, other than concurrent controls, with respect to the tumor findings observed in the 1979 NCI male mouse study⁴². This is consistent with standard scientific procedures in evaluating tumor incidence data – US EPA's carcinogen risk assessment guidelines were published in 2005, and NTP's most recent handbook recommending the use of concurrent controls was published in 2015. Thus, the 2011 NTP *Report on Carcinogens, Twelfth Edition*⁴³ followed accepted practices in relying on concurrent controls and did not rely on considerations of historical control data in concluding: “In male B6C3F1 mice, oral exposure to styrene increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma), and a positive dose-response trend was observed (NCI 1979)”.

In criticizing NTP's use of historical control data in reinterpreting the results of the NCI study, the commenters appear to be referring to an additional analysis of historical vehicle controls that was presented in the Report on Carcinogens Background Document for Styrene, which was published by NTP in 2008⁴⁴. This analysis used data from the laboratory historical vehicle controls identified by NCI from two studies, combined with data from 12 additional NCI studies conducted with a similar study duration, with animals from the same source, and within 3 years of the NCI styrene male mouse study, but in a different laboratory. The incidence of lung tumors in vehicle control male mice from these 14 studies was four percent. The 2008 NTP document⁴⁵

⁴⁰ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

⁴¹ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁴² National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

⁴³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁴⁴ National Toxicology Program (NTP, 2008). Report on Carcinogens Background Document for Styrene. US Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC. Available at: http://ntp.niehs.nih.gov/files/styrene_background_document_%289-29-08%29f%5B1%5D.pdf

⁴⁵ *Ibid.*

concluded from this additional analysis that the incidence of lung tumors in the vehicle control group in the 1979 NCI male mouse study⁴⁶ was not unusually low.

While the findings of the 2008 NTP document⁴⁷ are informative, the document nevertheless is separate and distinct from the 2011 NTP *Report on Carcinogens, Twelfth Edition*⁴⁸. Furthermore, the 2011 NTP *Report on Carcinogens, Twelfth Edition*⁴⁹ did not cite the 2008 document⁵⁰.

3.2.2 Comment:

SIRC and APTCO state that historical controls can be used to further evaluate the outcome of a particular study and note that historical controls are the same species and strain of animal, and should be from the same laboratory to assure that all the controls were subject to the same circumstances. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC's comment.

Response:

OEHHA agrees that historical controls should be of the same species and strain of animal as the study in question, and that incidence data from such historical controls can be useful in some instances. For example, additional insight about statistical and biological significance can come from an examination of historical control data and can add to the analysis. In particular, examination of historical control data can be useful in the identification of uncommon tumor types or high spontaneous incidence of a tumor in a given animal strain.

⁴⁶ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

⁴⁷ National Toxicology Program (NTP, 2008). Report on Carcinogens Background Document for Styrene. US Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC. Available at:

http://ntp.niehs.nih.gov/files/styrene_background_document_%289-29-08%29f%5B1%5D.pdf

⁴⁸ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL:

<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁴⁹ *Ibid.*

⁵⁰ National Toxicology Program (NTP, 2008). Report on Carcinogens Background Document for Styrene. US Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC. Available at:

http://ntp.niehs.nih.gov/files/styrene_background_document_%289-29-08%29f%5B1%5D.pdf

Laboratory historical controls are preferred over historical controls from other laboratories, as indicated by the US EPA in its Guidelines for Carcinogen Risk Assessment⁵¹:

“The most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with extreme caution.”

However, OEHHA concurs with US EPA⁵² and NTP⁵³ that the standard for determining statistical significance of tumor incidences from studies in animals comes from comparisons with *concurrent* controls.

3.3 *Studies of limited design used as supportive evidence of animal carcinogenicity.*

Comment:

“The NTP also claimed in its summary table that the 2001 and 1979 studies *are supported by findings* in other studies. It left out the fact that within its report, it in fact concluded that this “supporting” evidence was limited. *Id.* The Styrene Expert Panel for the 12th RoC concluded in 2008 that [*most of the rodent cancer bioassays summarized [in the Draft Report on Carcinogens Background Document for Styrene] had design flaws and other limitations.* NTP Styrene Expert Panel Report, Part A, p. 14 (2008). The Expert Panel emphasized in its report that the additional supporting studies (e.g., Ponomarev and Tomatis 1978) were *limited in their ability to detect carcinogenic effects because of study design (low doses, short treatment, short study duration, small group size), high early mortality, or limited reporting (tumor diagnosis).* *Id.*, Part B at 3. The NTP included a similar explanation in its 2008 Final Background Document: *Many of the studies were severely limited in their ability to detect carcinogenic effects.* 2008 Final Background Document at 214.” (APTCO)

Response:

First, it is the NTP *Report on Carcinogens, Twelfth Edition*⁵⁴ which serves as the basis for the listing of styrene, not the Styrene Expert Panel Report Part A⁵⁵, or the Draft or

⁵¹ US Environmental Protection Agency (US EPA, 2005). Guidelines for carcinogen risk assessment. US EPA, Washington, DC. Document number EPA/630/P-03/001F.

⁵² *Ibid.*

⁵³ National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. Office of the Report on Carcinogens, Division of the NTP, National Institute of Environmental Health Sciences, US Department of Health and Human Services. Available online at <http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html>

⁵⁴ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page

Final Report on Carcinogens Background Document for Styrene⁵⁶. Second, the commenter confuses identification of limitations in experimental study design with evaluation of study findings. As noted in the comment, studies of limited experimental design are often limited in their ability to detect carcinogenic effects, i.e., it is more difficult to observe an increase in tumors in such studies. Thus when carcinogenic effects are detected in such studies, this is particularly noteworthy.

It bears reiterating that the NTP *Report on Carcinogens, Twelfth Edition*⁵⁷ cites the inhalation exposure studies of styrene in male and female CD-1 mice (Cruzan *et al.*, 2001)⁵⁸, and the oral exposure study of styrene in male B6C3F1 mice (NCI, 1979)⁵⁹ as “the most robust studies” demonstrating that styrene causes lung tumors in mice. It is these three studies which meet the sufficiency of evidence criteria in Section 25306(e)(2).

The NTP *Report on Carcinogens, Twelfth Edition*⁶⁰ cites the studies by Ponomarkov and Tomatis (1978)⁶¹ as *supporting* evidence. The NTP *Report on Carcinogens, Twelfth Edition*⁶² notes the findings in these studies of lung tumors in both sexes of O20 mice exposed to styrene after a single dose to dams on gestational day 17, and subsequent exposure of pups orally once a week for 16 weeks after weaning. The NTP

383-391. [Most recent edition of the Report on Carcinogens available at URL:
<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁵⁵ National Toxicology Program (NTP, 2008) Styrene Expert Panel Report Part A – Peer Review of the draft background document on styrene, available at
http://ntp.niehs.nih.gov/ntp/roc/twelfth/2008/expertpanelmtgs/styrene_panelreportparta_508.pdf

⁵⁶ National Toxicology Program (NTP, 2008) Final Report on Carcinogens Background Document for Styrene September 29, 2008, available at
http://ntp.niehs.nih.gov/ntp/roc/twelfth/2010/finalbds/styrene_final_508.pdf

⁵⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL:
<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁵⁸ Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA, Bevan C, Hardy CJ, Coombs DW, Mullins PA and Brown WR (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol* **21**(3):185-198.

⁵⁹ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

⁶⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL:
<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁶¹ Ponomarkov V and Tomatis L (1978). Effects of long-term oral administration of styrene to mice and rats. *Scand J Work Environ Health* **4**(Suppl 2):127-135.

⁶² National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL:
<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

*Report on Carcinogens, Twelfth Edition*⁶³ further notes that a significantly increased incidence and earlier onset of combined benign and malignant lung tumors was observed in both sexes as early as 16 weeks after weaning. Thus, despite the low doses, short treatment, short study duration, high early mortality and small group size, increases in tumors were observed. While these limitations in study design ordinarily would make it more difficult to observe increases in tumors (a tumorigenic effect of treatment), an increase in tumors was observed in these studies.

3.4 *Genotoxicity of styrene*

3.4.1 Comment:

SIRC and APTCO state that there is no convincing evidence that styrene is genotoxic *in vivo* and that studies in workers exposed to styrene and *in vitro* studies using human cells provide conflicting results. The commenters note that about 30 studies where workers are exposed to styrene have exhibited micronucleus and/or chromosomal aberrations but that there does not seem to be a correlation between styrene exposure and micronucleus formation. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC's comment.

Response:

OEHHA disagrees with the commenters' statement that there is no convincing evidence of genotoxicity for styrene (and its metabolites). On the contrary, there is substantial evidence for the genotoxicity of styrene and also its metabolite, styrene-7,8-oxide, as reviewed by NTP⁶⁴, *inter alia*. NTP states: "Detection of styrene-7,8-oxide-DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action"⁶⁵.

It is important to note that the formation of micronuclei is only one of many possible indicators of genotoxicity. In discussing the cytogenetic effects observed in occupationally exposed humans, NTP⁶⁶ concluded: "The most consistent cytogenetic effects in styrene-exposed workers were single-strand DNA breaks and chromosomal aberrations (Anwar and Shamy 1995, Bonassi *et al.* 1996, Lazutka *et al.* 1999, Somorovská *et al.* 1999, reviewed by Cohen *et al.* 2002)."

⁶³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁶⁴ *Ibid.*

⁶⁵ *Ibid.*

⁶⁶ *Ibid.*

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. In classifying styrene as “reasonably anticipated to be a human carcinogen”, NTP⁶⁷ specifically noted that the proposed mechanisms of carcinogenicity of styrene include both genotoxic and non-genotoxic pathways.

3.4.2 Comment:

SIRC and APTCO acknowledge that exposure to styrene results in DNA adduct formation in mice, rats and humans, but argue that these DNA adducts are not sufficient to cause tumors, based on levels of DNA adducts/gram tissue in mouse liver versus mouse lung, and levels in rat lung versus mouse lung. APTCO further states that DNA adducts involving chemicals may reflect chemical exposure but are not a measure of mutagenic changes or cancer risk. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC’s comment.

Response:

Evidence that DNA adduct formation resulting from exposure to styrene is sufficient to cause tumors is **not** required in order for a chemical to be identified as causing cancer under Proposition 65 via the authoritative bodies mechanism⁶⁸. Nonetheless, OEHHA provides the following in response to this comment on styrene-induced DNA adducts:

Different types of DNA adducts may vary in their degree of mutagenic effect due to differences in chemical stability, repair rates, impact on the fidelity of DNA replication, and general target area within the genome. All of these factors may vary between chemicals, target tissues and dose regimes. However, as stated by the National Research Council⁶⁹, the presence of DNA adducts in target tissues following exposure to styrene reflects the formation of reactive metabolites that bind covalently to DNA and to proteins. The presence of these structurally modified DNA bases greatly increases the probability that polymerase errors during DNA synthesis will create mutations in genes that may lead to cancer.

⁶⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁶⁸ Section 25306

⁶⁹ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

As noted by NTP⁷⁰, a variety of DNA adducts are induced by styrene and the styrene metabolite styrene-7,8-oxide and have been detected in human and other mammalian cells exposed *in vitro*, experimental animals exposed *in vivo*, and occupationally exposed workers. In humans, levels of some adducts were five- to seven-fold higher in occupationally exposed workers compared to controls. While some DNA adducts can be efficiently removed by endogenous repair mechanisms and hence are considered to have weak mutagenic potential, several styrene-7,8-oxide-DNA adducts are considered to be more strongly pro-mutagenic because they can interfere with base-pairing and lead to miscoding during DNA replication. NTP⁷¹ states, “The major styrene-7,8-oxide adduct (at N7-guanine) may also be pro-mutagenic, because it can undergo spontaneous or glycosylase-mediated depurination, thus creating abasic sites that promote coding errors during DNA replication”.

Hence, DNA adducts resulting from exposure to styrene are indicative of an enhanced probability of mutagenic change and therefore of increased cancer risk.

3.5 *Claims that styrene does not present a cancer risk to humans*

Comment:

SIRC and APTCO comment that styrene’s mechanism of action causing lung tumors is unique to mice. Mode of action research indicates that mouse lung tumors are caused by mouse-specific metabolism by the enzyme CYP2F2, resulting in cytotoxicity and regenerative hyperplasia, which result in tumor formation. The mechanism involves metabolism by mouse lung CYP2F2, which does not occur in humans and rats. Mice carrying the human CYP2F1 enzyme do not experience cytotoxicity when exposed to styrene. Thus, the animal data are irrelevant to human cancer risk. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC’s comment.

Response:

The authoritative body, NTP⁷², considered the issues raised by the commenters and concluded that the animal carcinogenicity data for styrene are relevant to humans. Briefly, NTP reviewed and considered information on the pharmacokinetics and metabolism of styrene in mice, rats, and humans and on mechanisms of action, including studies of genotoxicity, lung cytotoxicity in mice, and immunosuppression. NTP reached the following conclusions regarding the relevance of the animal tumor findings to humans:

⁷⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁷¹ *Ibid.*

⁷² *Ibid.*

“Although styrene disposition differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard. Detection of styrene-7,8-oxide-DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action”⁷³.

OEHHA concurs with NTP’s assessment of the evidence⁷⁴, and notes the following:

- Both mice and humans metabolize styrene to styrene-7,8-oxide and other mutagenic metabolites, thus making genotoxicity a highly likely contributing mechanism in both species.
- Cytotoxicity caused by styrene is not restricted to mouse lung tissue. As noted by the National Research Council⁷⁵, (i) studies in rodents indicate that in addition to the lung, the liver is a target for styrene and its metabolites, and (ii) studies in occupationally exposed humans indicate additional targets for styrene and its metabolites in the lymphohematopoietic, gastrointestinal, and urinary systems.

“The evidence pertaining to cytotoxicity indicates that this mode of action and later proliferation at injured sites depends on the cellular, metabolic, and chemical processes involved in different organs, and how their interactions modulate the toxic response.”⁷⁶

“The toxic responses of multiple organs may play a role in modulating the circulating concentrations of styrene, its metabolites, and other key

⁷³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁷⁴ Under Proposition 65 and its implementing regulations, OEHHA does not substitute its scientific judgment for that of the authoritative body or re-weigh the evidence. OEHHA simply reviews the authoritative body’s record to confirm there was sufficient evidence in the record to meet the identification criteria in the regulation. See *Exxon Mobil Corp. v. Office of Environmental Health Hazard Assessment*, (2009)169 Cal.App.4th 1264

⁷⁵ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

⁷⁶ *Ibid.*

compounds, such as glutathione, and in affecting the toxic response of other organs in the same individual.”⁷⁷

- The presence of cytochrome P450 (CYP) enzymes is tissue and species-specific. While studies using CYP2F2 knockout mice demonstrated that metabolism by the CYP2F2 isozyme plays an important role in the production of bronchiolar cytotoxicity in the lungs of mice, other species and tissues contain different cytochrome P450 enzymes that are involved in generating cytotoxic metabolites from styrene. For example, in mice, Cyp2e1 predominates in the liver and Cyp2f2 in the lung. In humans, CYP2A13, CYP2F1, CYP1A2, CYP2C8, CYP2A6, and CYP2E1 metabolize styrene in the lung, and CYP2B6 and CYP2E1 are active in the liver. The human equivalent of the mouse CYP2f2, the CYP2F1, has been shown to metabolize styrene *in vitro*⁷⁸. The contribution of specific metabolites to the genotoxic and cytotoxic effects of styrene may be organ-specific and the metabolites primarily responsible for cytotoxicity may not be the same in all organs or species⁷⁹.

4. Data not considered by NTP indicate the criteria of 25306(e) are not met

Comment:

SIRC said: “Authoritative bodies listing proposals require OEHHA to consider new scientific data and data not considered by NTP. A listing may not proceed if it is established that the sufficiency of evidence criteria were not met.” ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC’s comment.

Response:

OEHHA agrees with the commenter. Section 25306(f) requires that “the lead agency shall find that a chemical does not satisfy the definition of “as causing cancer” if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (e), paragraph (1) or subsection (e), paragraph (2).” The commenters describe several studies as having relevant data that were not considered by the authoritative body. Comments specific to

⁷⁷ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

⁷⁸National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁷⁹ *Ibid.*

the new data and data not considered by the authoritative body will be discussed in the remainder of this section.

4.1 Comment:

APTCO asserts that NTP did not consider the original NCI (1979) animal study on styrene which concluded there was no convincing evidence of increased incidence of malignant tumors. “Because the NTP did not consider the scientifically valid NCI animal study on styrene which concluded there was no convincing evidence of increased incidence of malignant tumors, there is insufficient evidence of carcinogenicity in experimental animals for OEHHA to list styrene.”

Response:

This is factually incorrect. The NTP *Report on Carcinogens, Twelfth Edition*⁸⁰ explicitly cites the NCI study⁸¹ in the discussion of evidence of the carcinogenicity of styrene in experimental animals: “In male B6C3F1 mice, oral exposure to styrene increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma), and a positive dose-response trend was observed (NCI 1979).” Moreover, this statement by NTP⁸² is consistent with what NCI⁸³ reported regarding comparison of the dosed groups to the concurrent control group and conducting a test for trend among the dosed groups and the concurrent control group.

4.2 Comment:

Four of the human studies discussed in the 2011 *Report on Carcinogens* were updated following the NTP report’s publication (Collins *et al.* 2013, Coggon *et al.* 2014, Ruder *et al.* 2014, Kolstad *et al.* 2014). The updated information demonstrates that the human evidence is inadequate, and not limited, thus the requirement of sufficient evidence in humans is not satisfied. These studies also demonstrate that styrene is not carcinogenic. (ACA, SIRC and APTCO) ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC’s comment.

⁸⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁸¹ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

⁸² National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁸³ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

Response:

A finding of ‘sufficient evidence in humans’ is not a requirement for listing a chemical as causing cancer under the Proposition 65 authoritative bodies listing mechanism⁸⁴, and NTP’s conclusion⁸⁵ that there is limited evidence in humans for the carcinogenicity of styrene is not part of the basis for OEHHA’s determination that styrene meets the criteria for listing pursuant to Section 25306.

Section 25306(e) reads as follows:

“(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.”

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 OEHHA’s Notice of Intent to List⁸⁶, it is NTP’s discussion of data and conclusions from studies in experimental animals that meets the sufficiency of evidence criteria in Section 25306(e), not NTP’s discussion of data and conclusions from studies in humans. Thus the NTP *Report on Carcinogens, Twelfth Edition*⁸⁷ meets the sufficiency of evidence criteria of Section 25306(e)(2).

⁸⁴ See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.

⁸⁵ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

⁸⁶ Notice of Intent to List: Styrene. Available at http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilstyrene2015.html

⁸⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

The commenters characterize the four recent updates to the human studies discussed in the NTP report as new information demonstrating that styrene is not carcinogenic. OEHHA notes that two of these ‘updates’ (Kolstad *et al.* 2014⁸⁸, Ruder *et al.* 2014⁸⁹) are posters presented at an epidemiology conference, and not peer-reviewed scientific articles. The other two ‘updates’ (Collins *et al.* 2013⁹⁰, Coggon *et al.* 2014 [2015]⁹¹) are published scientific articles. The findings from these two published articles are briefly discussed below.

Collins *et al.*⁹² is an update of the US reinforced-plastics industry cohort mortality study first reported by Wong *et al.* (1994)⁹³, with an additional 19 years of follow-up. Collins *et al.*⁹⁴ employs different exposure metrics and exposure metric groupings than did Wong *et al.*⁹⁵ Limitations noted by the National Research Council⁹⁶ for both Wong *et al.* and Collins *et al.*⁹⁷ included (i) limited exposure assessment for styrene, (ii) 24% of the cohort was employed for <1 year and 27% for >5 years, and (iii) the absence of information on smoking, alcohol use or other lifestyle factors. As noted by the National Research Council⁹⁸, neither Wong *et al.*⁹⁹ nor Collins *et al.*¹⁰⁰ reported any positive

⁸⁸ Kolstad *et al.* (2014) 24th International Epidemiology in Occupational Health (EPICOH) Conference, “Challenges for Occupational Epidemiology in the 21st Century”. 24-27 Jun 2014, Chicago, IL. *Occup Environ Med* 2014; v. 71, Suppl 1; pp A82-A83.

⁸⁹ Ruder *et al.* (2014) 24th International Epidemiology in Occupational Health (EPICOH) Conference, “Challenges for Occupational Epidemiology in the 21st Century”. 24-27 Jun 2014, Chicago, IL. The Ruder poster was published in *Occup Environ Med* 2014; v. 71, Suppl 1; pp A74-A75.

⁹⁰ Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

⁹¹ Published in 2015, as Coggon D, Ntani G, Harris EC, Palmer KT (2015). Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med* 72(3):165-170.

⁹² Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

⁹³ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

⁹⁴ Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

⁹⁵ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

⁹⁶ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at: <http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

⁹⁷ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

⁹⁸ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at:

associations between styrene exposure and mortality due to leukemia, non-Hodgkin lymphoma, or the broader category of lymphohematopoietic cancer. With respect to kidney cancer, Wong *et al.*¹⁰¹ found no association, while Collins *et al.*¹⁰² “observed an increased and positive association between styrene exposure and kidney cancer (proportional hazards ratio = 1.009, 95% CI 1.000-1.017) and exposure response trends for cumulative exposure (ppm-months) ($p = 0.045$) and for number of peak exposure days ($p = 0.054$)”¹⁰³. With respect to pancreatic cancer, Wong *et al.*¹⁰⁴ found no association, while Collins *et al.*¹⁰⁵ “found a significantly increased proportional hazard ratio of 1.008 (95% CI 1.002 -1.015) that was based on cumulative exposure and a monotonic “increasing risk with increasing average exposure...with SMRs of 0.75, 0.83, 1.46, and 1.52” (Collins et al. 2013, p. 201)”¹⁰⁶. With regard to lung cancer, “the Wong et al. (1994) and Collins et al. (2013) studies found statistically significant increases in their combined cohort on the basis of 162 and 556 cases, respectively. In the analysis by Wong et al. (1994), the most highly exposed subgroup, which consisted of people who worked in open-mold processing for at least 2 years, did not have an excess SMR [*standardized mortality ratio*] (eight cases)...Collins et al. (2013) observed an increased SMR for lung cancer (SMR = 1.34, 95% CI 1.23-1.46) but reported inverse linear trends for cumulative exposure ($p < 0.001$). The proportional hazard ratio was below 1.0, and the 95% CI included 1.0”¹⁰⁷. The National Research Council¹⁰⁸ considered the findings

<http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

⁹⁹ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

¹⁰⁰ Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

¹⁰¹ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

¹⁰² Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

¹⁰³ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at:

<http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

¹⁰⁴ Wong O, Trent LS, Whorton MD (1994). An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396.

¹⁰⁵ Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

¹⁰⁶ National Research Council (NRC, 2014). Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. National Research Council of the National Academies. The National Academies Press. Washington, D.C. Available online at:

<http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens>

¹⁰⁷ *Ibid.*

¹⁰⁸ *Ibid.*

of Collins *et al.*¹⁰⁹ to contribute to credible but limited evidence from epidemiologic studies that styrene exposure is associated with kidney and pancreatic cancer.

Coggon *et al.*¹¹⁰ is an update of a British reinforced-plastics industry cohort mortality study comprised of workers at eight facilities during 1947 - 1984, that was first reported by Coggon *et al.* (1987)¹¹¹. This British cohort was also part of the United Kingdom subcohort included in the combined European retrospective cohort study of reinforced-plastics industry workers from six countries reported by Kogevinas *et al.* (1994)¹¹². In reviewing the initial report on the eight British reinforced-plastics facilities published in 1987, IARC^{113,114} noted the following: (i) there was no minimal period of employment required in order to be included in the cohort; (ii) of the 7949 men and women in the cohort, 5434 had jobs entailing exposure to styrene, and of those, only 2458 had worked such jobs for at least one year; (iii) follow-up of cohort members was variable, ranging from 99.7 – 61.9%; (iv) for one of the facilities only a low proportion of subjects could be traced; and (v) no information was available on smoking habits. IARC¹¹⁵ went on to say “The main analysis was restricted to seven facilities where a satisfactory proportion of the cohort had been traced (average, 96.7%). A total of 100 deaths from cancer were observed (SMR, 93 [95% CI, 76-113]), including one from Hodgkin’s disease (SMR, 78), one from myeloma (SMR, 89), one from leukaemia (SMR, 22) and 51 from cancers of the lung, pleura and mediastinum (SMR, 126 [94-166])...The excess of lung cancer was concentrated particularly among workers who had had one to nine years of exposure to styrene, but risk did not increase with time since first exposure.”

The combined European cohort study of Kogevinas *et al.*¹¹⁶ included the eight British reinforced-plastics facilities of Coggon *et al.*¹¹⁷ as one of eight subcohorts, and

¹⁰⁹ Collins JJ, Bodner KM, Bus JS (2013). Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 24(2):195-203.

¹¹⁰ Coggon D, Ntani G, Harris EC, Palmer KT (2015). Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med* 72(3):165-170.

¹¹¹ Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, Acheson ED (1987). Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health*. 13:94-9.

¹¹² Kogevinas M, Ferro G, Andersen A, Bellander T, Biocca M, Coggon D, et al. (1994). Cancer mortality in a historical cohort of workers exposed to styrene. *Scand J Work Environ Health* 20:251-61.

¹¹³ International Agency for Research on Cancer (IARC, 1994). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 60, Some Industrial Chemicals. IARC, World Health Organization, Lyon, France, pp. 233-320.

¹¹⁴ International Agency for Research on Cancer (IARC, 2002). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 82, Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC, World Health Organization, Lyon, France, pp. 437-550.

¹¹⁵ International Agency for Research on Cancer (IARC, 1994). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 60, Some Industrial Chemicals. IARC, World Health Organization, Lyon, France, pp. 233-320.

¹¹⁶ Kogevinas M, Ferro G, Andersen A, Bellander T, Biocca M, Coggon D, et al. (1994). Cancer mortality in a historical cohort of workers exposed to styrene. *Scand J Work Environ Health* 20:251-61.

extended the follow-up through 1991. As discussed by IARC¹¹⁸, the Kogevinas *et al.*¹¹⁹ update of this British subcohort reported 13 deaths in the subcohort due to lymphatic and haematopoietic cancer (SMR, 88; 95% CI, 47-151) and 77 deaths due to lung cancer (SMR, 106; 95% CI, 84-132).

The most recent update by Coggon *et al.*¹²⁰ extends the follow-up of the workers at the eight British reinforced-plastics facilities through December 2012, and includes a nested case-control analysis of 122 incident or fatal cases of lympho-haematopoietic cancer and 1,138 matched controls. No increases in deaths from lympho-haematopoietic cancer or non-Hodgkin lymphoma/chronic lymphocytic leukaemia were observed in the cohort analyses, and no association between lympho-haematopoietic cancer and styrene exposure was found in the case-control analysis. The authors¹²¹ reported that “Mortality from lung cancer was significantly elevated, and risk increased progressively across exposure categories, with an SMR of 1.44 (95% CI 1.10-1.86) in workers highly exposed for ≥ 1 year.” The authors also reported that mortality from cancer of the brain and nervous system was significantly elevated in exposed workers (SMR 1.55, 95% CI 1.02-2.28), and especially in those who had worked as laminators for ≥ 1 year (9 deaths v 4.1 expected – see Table 4). Because this is the first reported association of styrene exposure and cancer of the brain and nervous system, the authors¹²² suggested the association “may have occurred simply by chance.” In summary, the 2015 updated findings by Coggon *et al.*¹²³ of an association of styrene exposure with lung cancer, but not with lympho-haematopoietic cancer are consistent with previous analyses of this cohort^{124,125}.

¹¹⁷ Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, Acheson ED (1987). Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health*. 13:94-9.

¹¹⁸ International Agency for Research on Cancer (IARC, 1994). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 60, Some Industrial Chemicals. IARC, World Health Organization, Lyon, France, pp. 233-320.

¹¹⁹ Kogevinas M, Ferro G, Andersen A, Bellander T, Biocca M, Coggon D, et al. (1994). Cancer mortality in a historical cohort of workers exposed to styrene. *Scand J Work Environ Health* 20:251-61.

¹²⁰ Coggon D, Ntani G, Harris EC, Palmer KT (2015). Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med* 72(3):165-170.

¹²¹ *Ibid.*

¹²² *Ibid.*

¹²³ *Ibid.*

¹²⁴ Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, Acheson ED (1987). Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health*. 13:94-9.

¹²⁵ Kogevinas M, Ferro G, Andersen A, Bellander T, Biocca M, Coggon D, et al. (1994). Cancer mortality in a historical cohort of workers exposed to styrene. *Scand J Work Environ Health* 20:251-61.

4.3 Comment:

SIRC and APTCO claim that new mechanistic information on mouse lung tumors not considered by the 2011 NTP *Report on Carcinogens, Twelfth Edition* undermines the NTP's conclusion that styrene is reasonably anticipated to be a human carcinogen, since the new information indicates that toxicity is dependent on the presence in the mouse lung of types and concentrations of cytochrome P450 (CYP) enzymes not found in the human lung. Studies they referred to were: the published studies on styrene by Cruzan *et al.*, 2012; 2013, 2015¹²⁶, Carlson 2012, and reportedly on naphthalene by Shen *et al.* 2014, and an unpublished 4-week styrene inhalation study using knockout, wild type, and transgenic mouse models. ACA, ACC, ACMI, AI, CGA, EPSIA, NAMI, and NMMA support SIRC's comment.

Response:

OEHHA disagrees with the assertions in the comments that (i) these new mechanistic studies indicate that [*styrene*] toxicity is dependent on the presence in the mouse lung of types and concentrations of cytochrome P450 enzymes not found in the human lung, and (ii) these studies undermine the NTP's conclusion¹²⁷ that styrene is reasonably anticipated to be a human carcinogen. Indeed, for the most part, these studies (i.e., Cruzan *et al.*, 2012¹²⁸; 2013¹²⁹, Carlson 2012¹³⁰, Shen *et al.* 2014^{131,132}, and the unpublished 4-week inhalation study in mice¹³³) are an extension, and in some cases a

¹²⁶ The comments submitted by SIRC (see pages 9, 12, 17) describe a publication in volume 144 of the journal *Toxicological Sciences* by Cruzan *et al.* 2015 as a genomics analysis of styrene in the lungs of mice; however, the article does not appear as cited in *Toxicological Sciences*. Moreover, OEHHA was not able to locate the article through a search of the US National Library of Medicine's searchable online database PubMed, using the list of authors and the title of the article indicated on page 17 of the comments submitted by SIRC.

¹²⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹²⁸ Cruzan G, Bus J, Hotchkiss J, Harkema J, Banton M, Sarang S (2012). CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors. *Regul Toxicol Pharmacol* **62**: 214-220.

¹²⁹ Cruzan G, Bus J, Hotchkiss J, Sura R, Moore C, Yost G, Banton M, Sarang S (2013). Studies of styrene, styrene oxide and 4-hydroxystyrene toxicity in CYP2F2 knockout and CYP2F1 humanized mice support lack of human relevance for mouse lung tumors. *Regul Toxicol Pharmacol* **66**: 24-29.

¹³⁰ Carlson GP (2012). Modification of the metabolism and toxicity of styrene and styrene oxide in hepatic cytochrome P450 reductase deficient mice and CYP2F2 deficient mice. *Toxicology* **294**(2-3):104-108.

¹³¹ The comments submitted by SIRC (see page 13) characterize Shen *et al.* (2014) as a study demonstrating that "toxic naphthalene metabolites are generated in the lung....", when in fact this study investigates the metabolism of styrene in mouse lung and liver microsomes.

¹³² Shen S; Li L; Ding X; Zheng J (2014). Metabolism of styrene to styrene oxide and vinylphenols in cytochrome P450 2F2- and P450 2E1-knockout mouse liver and lung microsomes. *Chem Res Toxicol* **27**: 27-33.

¹³³ The 4-week styrene inhalation study using knockout, wild type, and transgenic mouse models submitted by SIRC (i) is an unpublished study report, (ii) has not undergone scientific peer-review, and

reiteration, of earlier work considered by NTP¹³⁴. While findings from these studies indicate that lung toxicity occurs in mice exposed to styrene, none of these studies establish that the toxicity is either necessary or sufficient for the carcinogenicity of styrene. As discussed in detail below, this new information does not undermine NTP's conclusion¹³⁵ that styrene is *reasonably anticipated to be a human carcinogen*, nor does it provide substantial evidence that the sufficiency of evidence criteria of Section 25306(e)(2) (i.e., sufficient evidence of carcinogenicity exists from studies in experimental animals) have not been met.

As noted above, much of the new mechanistic information provided in the comments reiterates and expands upon earlier work on styrene metabolism and toxicity in mouse lung *in vivo* and *in vitro*, using various mouse models (e.g., wild type mice, CYP2F2 or CYP2E1 knockout mice, and mice expressing human forms of CYP enzymes in place of mouse CYP enzymes, such as human CYP2F1 instead of mouse CYP2F2). The bulk of this new mechanistic work has been performed with mice of a different strain (C57BL/6) than the male and female CD-1 mice used in the two-year styrene inhalation cancer bioassays of Cruzan *et al.* (2001)¹³⁶ or the male B6C3F1 mice used in the oral gavage study by NCI¹³⁷. These strain differences raise uncertainty regarding the degree to which the findings from mechanistic studies carried out in C57BL/6 mice are directly applicable to the lung tumor findings in CD-1 and B6C3F1 mice. For example, CD-1 mice are an outbred strain, whereas C57BL/6 mice are an inbred strain¹³⁸, and genetic differences between these strains, and even within C57BL/6 substrains are recognized¹³⁹.

Much of this new mechanistic work is based on the premise that the induction of tumors in mouse lung by styrene is a result of mouse-specific metabolism of styrene in the lung

(iii) is of short exposure duration (4 weeks), and thus of limited usefulness in assessing the effects of lifetime exposures (2 years) in the mouse lung.

¹³⁴ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL:

<http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹³⁵ *Ibid.*

¹³⁶ Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA, Bevan C, Hardy CJ, Coombs DW, Mullins PA and Brown WR (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol* 21(3):185-198.

¹³⁷ National Cancer Institute (NCI, 1979). Bioassay of Styrene for Possible Carcinogenicity. Technical Report Series No. 185. Bethesda, MD.

¹³⁸ Zwemer CF, Song MY, Carello KA, D'Alecy LG (2007). Strain differences in response to acute hypoxia: CD-1 versus C57BL/6J mice. *J Appl Physiol* 102(1):286-293.

¹³⁹ Zwemer CF, Song MY, Carello KA, D'Alecy LG (2007). Strain differences in response to acute hypoxia: CD-1 versus C57BL/6J mice. *J Appl Physiol* 102(1):286-293.

Zurita E, Chagoyen M, Cantero M, Alonso R, González-Neira A, López-Jiménez A, López-Moreno JA, Landel CP, Benítez J, Pazos F, Montoliu L (2010). Genetic polymorphisms among C57BL/6 mouse inbred strains. *Transgenic Res* DOI 10.1007/s11248-010-9403-8.

via CYP2F2. However, after reviewing information on styrene metabolism in the mouse lung and information on styrene metabolism and in a number of tissues in the human, including the lung, liver, lymphocytes, and hematopoietic stem cells, as well as the formation of protein and DNA adducts by the carcinogenic styrene metabolite styrene-7,8-oxide in various human tissues, the NTP¹⁴⁰ reached the following conclusions:

“Although styrene disposition differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard.” (emphasis added)

“Detection of styrene-7,8-oxide-DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action.” (emphasis added)

In discussing information on styrene metabolism, the NTP¹⁴¹ noted the following regarding major and minor pathways of styrene metabolism:

“Styrene is metabolized primarily (over 90%) to the genotoxic metabolite styrene-7,8-oxide, which can be detoxified by glutathione conjugation or conversion to styrene glycol by microsomal epoxide hydrolase. “

“A second, minor pathway of styrene metabolism involves oxidation of the aromatic ring resulting in formation of 4-vinylphenol, presumably via the arene intermediate styrene-3,4-oxide, which has been detected in humans (Pfäffli *et al.* 1981, Manini *et al.* 2003) and rats (Bakke and Scheline 1970) and whose occurrence in mice *in vivo* was implicated by indirect measures (Boogaard *et al.* 2000).”

In discussing the involvement of cytochrome P450 enzymes in styrene metabolism in different species and tissues, the NTP¹⁴² noted the following:

“The initial step in styrene metabolism is catalyzed by cytochromes P450, and there are tissues-specific differences in the enzymes responsible for styrene oxidation.”

¹⁴⁰ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁴¹ *Ibid.*

¹⁴² *Ibid.*

“In mice, Cyp2e1 predominates in the liver, and Cyp2F2 in the lung (Carlson 1997, 2004, Vodicka *et al.* 2006a).”

“In humans, CYP2A13, CYP2F1, CYP1A2, CYP2C8, CYP2A6, and CYP2E1 are active in metabolizing styrene to styrene glycol in the lung, and CYP2B6 and CYP2E1 are most active in the liver (Nakajima *et al.* 1994, IARC 2002, Fukami *et al.* 2008). Human CYP2F1 (equivalent to Cyp2f2 in mice and CYP2F4 in rats) has been shown to metabolize styrene in vitro (Nakajima *et al.* 1994).”

“CYP2B6 is expressed in human [*lung*] Clara cells..”

“CYP2E1 is also expressed in [*human*] lymphocytes (Siest *et al.* 2008), and CYP2E1 protein and activity were detected in human hematopoietic stem cells (Kousalova *et al.* 2004).”

The lungs are composed of more than 40 different cell types, and the NTP¹⁴³ noted the following differences between mice and humans in the distribution of cytochromes P450 in the lungs:

“In mice, the Clara cell is regarded as the major lung-cell type in which styrene is activated to styrene-7,8-oxide following inhalation exposure (Hynes *et al.* 1999).

“In mice, Cyp2e1 predominates in the liver, and Cyp2f2 in the lung (Carlson 1997, 2004, Vodicka *et al.* 2006a).”

“In general, **expression of CYP enzymes is more widely distributed in the human lung** than in the lungs of experimental animals, where expression is concentrated in Clara cells, type II alveolar cells, and alveolar macrophages.” (emphasis added)

“CYP2B6 is expressed in human Clara cells, and CYP2E1 in human bronchial, bronchiolar, and alveolar epithelium, alveolar macrophages, and lung tumors (Kivistö *et al.*, 1995, Hukkanen *et al.* 2002).”

Thus, a number of different human tissues and cell types are capable of catalyzing the initial step in styrene metabolism (i.e., styrene oxidation to either styrene-7,8 oxide or styrene-3,4-oxide).

¹⁴³ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

The NTP¹⁴⁴ noted that the presence of the styrene metabolite styrene-7,8-oxide is not limited to a specific tissue, citing evidence for the systemic distribution of this metabolite in humans:

“Systemic distribution of styrene-7,8-oxide in workers has been demonstrated from measurements of styrene-7,8-oxide-based hemoglobin adducts in erythrocytes and DNA adducts in lymphocytes (Tornero-Velez *et al.* 2001, Vodicka *et al.* 2003, 2006a).”

The NTP¹⁴⁵ further noted that differences between individuals in enzyme activity may contribute to inter-individual differences in susceptibility to the toxic effects of styrene:

“Because many of the enzymes involved in styrene metabolism are polymorphic, individuals may differ in their susceptibility to styrene-induced toxicity.”

“Some studies have found that polymorphisms in glutathione S-transferase mu 1 influence excretion of styrene metabolites (De Palma *et al.* 2001, Haufroid *et al.* 2002, Teixeira *et al.* 2004); however, studies evaluating genotoxicity and polymorphisms in genes involved in either styrene metabolism or DNA repair have not clearly identified specific polymorphisms related to genotoxic effects (Godderis *et al.* 2006, Migliore *et al.* 2006, reviewed by Vodicka *et al.*, 2006a).”

In discussing studies on mechanisms of styrene carcinogenesis, the NTP¹⁴⁶ noted the following:

“The mechanisms of styrene carcinogenesis are not fully understood.”

“The primary metabolite of styrene, styrene-7,8-oxide, is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*, based on sufficient evidence in experimental animals. Oral exposure to styrene-7,8-oxide caused forestomach tumors in rats and mice and liver tumors in male mice (see the profile for styrene-7,8-oxide, NTP 2004b).”

“The proposed mechanisms for the carcinogenicity of styrene include both genotoxic and non-genotoxic pathways, which are not necessarily mutually exclusive.”

¹⁴⁴ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁴⁵ *Ibid.*

¹⁴⁶ *Ibid.*

“Most of the mechanistic studies have focused on either general genotoxicity or issues considered relevant to the mouse lung tumors, and **there has been little research on mechanisms specific to lymphohematopoietic cancer in humans.**” (emphasis added)

“Possible modes of action for styrene-induced carcinogenicity involve (1) genotoxicity (**relevant to all types of cancer**), (2) cytotoxic effects of styrene metabolites in the mouse lung, and (3) immunosuppression (**relevant to lymphohematopoietic cancer**).” (emphasis added)

In discussing the observation that styrene causes lung tumors in mice but not in rats, the NTP¹⁴⁷ noted three known human carcinogens that like styrene either form epoxides or are epoxides, and induce lung tumors in mice but not rats:

“The induction of lung tumors [*by styrene*] in mice but not rats has also been observed in studies of exposure to epoxides and other epoxide-forming chemicals, including the known human carcinogens vinyl chloride, 1,3-butadiene, and ethylene oxide (NTP 2004a,b; see the profiles for those substances).”

Thus, given all of the above, including in particular the evidence that

- (i) humans metabolize styrene to styrene-7,8 oxide and styrene-3,4-oxide,
- (ii) human metabolism of styrene can occur through the enzymatic activity of a number of different cytochromes P450,
- (iii) human metabolism of styrene can occur in multiple tissues, including the lung, liver, lymphocytes, and hematopoietic stem cells, and
- (iv) styrene-7,8-oxide, which itself is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*, is distributed throughout the body, as evidenced by measurement of styrene-7,8-oxide-based hemoglobin adducts in erythrocytes and DNA adducts in lymphocytes,

the new mechanistic studies discussed in the comments do not undermine NTP’s conclusion¹⁴⁸ that styrene is *reasonably anticipated to be a human carcinogen*, nor do they provide substantial evidence that the sufficiency of evidence criteria of Section 25306(e)(2) (i.e., sufficient evidence of carcinogenicity exists from studies in experimental animals) have not been met. This is because the new mechanistic studies discussed in the comments focus on styrene metabolism, changes in gene expression,

¹⁴⁷ National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391. [Most recent edition of the Report on Carcinogens available at URL: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.]

¹⁴⁸ *Ibid.*

and toxicity in the mouse lung, and regardless of the particular cytochromes P450 expressed in the experimental mouse models used in those studies, the studies do not challenge or contradict the evidence that humans metabolize styrene to styrene-7,8-oxide and styrene-3,4-oxide, that this metabolism can occur in various sites and tissue types in humans, and that biomarkers of DNA damage (i.e., styrene-7,8-oxide-DNA adducts at base-pairing sites) and genotoxicity associated with increased risk of cancer¹⁴⁹ (i.e., chromosomal aberrations) are detected in lymphocytes of styrene-exposed workers.

5. Styrene is a naturally occurring compound

Comment:

APTCO comments that styrene is naturally occurring and is naturally present in many fruits, vegetables, and spices.

Response:

Styrene may be formed naturally in some fruits and vegetables and the portion formed naturally in these foods may not be considered an exposure under Proposition 65¹⁵⁰. Under Proposition 65, the fact that a chemical may be naturally occurring or naturally present in foods is not part of the criteria for listing. Lead and arsenic are examples of listed Proposition 65 chemicals that occur naturally and may be found in foods.

6. Safety of polystyrene

6.1 Comment:

The ACC, AI, APTCO, EPSIA, and the CGA point out that polystyrene is different from its monomer, styrene. Styrene is used in the production of polystyrene for uses in food packaging, insulating materials, art materials, and as a component of other products. ACC, AI, APTCO and CGA further note that food packaging uses have been deemed safe by the US Food and Drug Administration (FDA) and NTP has indicated that styrene exposure from polystyrene food service items is not an issue.

¹⁴⁹ Bonassi S, Norppa H, Ceppi M, Strömberg U, Vermeulen R, Znaor A, Cebulska-Walsilewska A, Fabianova E, Fucic A, Gundy S, Hansteen IL, Knudsen LE, Lazutka J, Rossner P, Sram RJ, Boffetta P (2008). Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22358 subjects in 11 countries. *Carcinogenesis* 29(6):1178-83.

¹⁵⁰ Title 27, Cal Code of Regs., section 25501 (Exposures to a Naturally Occurring Chemical in a Food

Response:

OEHHA agrees that styrene is not the same as polystyrene and points out that polystyrene is not the subject of the proposed listing. OEHHA is aware of the multiple uses of polystyrene, including in food containers and food packaging materials. In its regulations of food packaging and food contact materials – including styrene and polystyrene – FDA considers that these materials may contain substances or unreacted monomers that can migrate in trace amounts to foods or beverages. FDA reviews safety data and sets regulatory specifications for these materials, including styrene and polystyrene, and requires sufficient scientific information to demonstrate that the intended uses of these materials are safe. Food contact materials meeting FDA's standards are considered safe for food use.

OEHHA notes that under Proposition 65 regulations, a warning for styrene would not be required for exposures where there is no significant risk of cancer. OEHHA can provide compliance assistance for affected industries through the adoption of a safe harbor level for styrene and via Safe Use Determinations for certain products where requested¹⁵¹.

6.2 Comment:

APTCO expressed concern that a listing of styrene could negatively impact California's styrene and agricultural industries. Polystyrene packaging is vital for the packaging and shipping of California's agricultural products.

Response:

OEHHA is listing styrene, not polystyrene. While free or unreacted styrene may be present in such products, only styrene exposures that pose a significant cancer risk would require a warning. Businesses are exempted from the Proposition 65 warning requirement if the exposures they cause are so low as to create no significant risk of cancer¹⁵². The potential economic impact of the listing is not relevant to the criteria for listing a chemical under Proposition 65. However, it should be noted that the listing of styrene does not ban or restrict the use of the product. A listing can trigger two separate provisions of law. First, under Health and Safety Code section 25249.5, a person is prohibited from releasing a significant amount of the listed chemical into sources of drinking water. This requirement becomes effective automatically 20 months after the chemical is listed. The second provision of law that is triggered by a listing is Health and Safety Code section 25249.6 which requires businesses that expose people to a significant amount of the chemical to first provide a clear and reasonable warning. This requirement becomes effective automatically 12 months after the listing. OEHHA's

¹⁵¹ See Section 25204 and the OEHHA Safe Use Determination fact sheet available at: http://www.oehha.ca.gov/prop65/CRNR_notices/safe_use/pdf_zip/SUDfacts081809.pdf

¹⁵² Health and Safety Code section 25249.10(c)

general practice is to propose a No Significant Risk Level¹⁵³ when sufficient data and resources are available, for chemicals listed under Proposition 65, within the 12-month grace period established by the law. 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 regulations¹⁵⁴ provide guidance for businesses to calculate their own no significant risk level.

6.3 Comment:

The Art and Creative Materials Institute (ACMI) sponsors a certification program for the toxicological evaluation of art materials used by children and adults. Depending upon the outcome, member companies can use the program's seals on certified (non-toxic) products, in accordance with federal law and the certification program's requirements. Some of these products contain polystyrene, and therefore might contain very small quantities of unreacted styrene monomer. ACMI is concerned that in spite of its certification program, its members may find themselves in an untenable situation where private enforcers of the Proposition 65 warning requirement may unduly expose ACMI members to law suits, but where a Proposition 65 warning label will not permit the use of ACMI's certification label.

Response:

These comments are not relevant to the criteria for listing a chemical under Proposition 65. 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. It is not clear that a warning would be required for the products AMCI refers to in its comments. In the event the industry wishes for OEHHA to assist them in determining whether a warning may be required for certain exposures, they may request a Safe Use Determination for those products.

7. Request for removal of styrene from food and drink

Comment:

Nicolette Good asks that styrene be removed from food and drink products.

¹⁵³ See Section 25705

¹⁵⁴ Section 25701 *et seq.*

Response:

OEHHA appreciates the concerns of Ms. Good. However, Proposition 65 does not give OEHHA authority to remove products or chemicals from the market. Proposition 65 requires OEHHA to publish a list of chemicals known to cause cancer or birth defects or other reproductive harm. It also requires businesses to warn Californians about significant exposures to chemicals in the products they purchase, in their homes or workplaces, or that are released into the environment. By providing this information, Proposition 65 enables Californians to make informed decisions about protecting themselves from exposure to these chemicals.

8. No human cancer risk at anticipated exposure levels

Comment:

SIRC states that styrene does not present a human cancer risk at anticipated exposure levels. The CA GA, AMA, NMMA, EPSIA, NAMI, ACC and AI support SIRC's comments.

Response:

Listing of a chemical under Proposition 65 concerns only a determination that the chemical causes cancer, as provided in Section 25306(e)(2). Dose-response assessment under Proposition 65 is carried out after a chemical is listed¹⁵⁵. The dose-response 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). If a given exposure does not pose a significant risk, the warning and discharge-prohibition provisions of Proposition 65 would not apply¹⁵⁶.

9. Reviews by other regulatory bodies

Comment:

Komatsu America Corp. comments that styrene is not hazardous based on a 2002 review by the European Union (EU) entitled "*European Union Risk Assessment Report. Styrene. Part I – Environment*"; a 2003 Environment Canada report assessing whether styrene constitutes a danger to the environment under the Canadian Environmental Protection Act (CEPA); and a 2000 US EPA Air Toxics hazard summary.

¹⁵⁵ See *ExxonMobil v OEHHA* (2009) 169 Cal.App.4th 1264, see also *Western Crop Protection Assn. v. Davis* (2000) 80 Cal.App.4th 741.

¹⁵⁶ See Section 25701 *et seq.*

Response:

Neither the EU nor Environment Canada are authoritative bodies recognized under Proposition 65 regulations. In addition, the EU (2002) and Environment Canada (2003) documents submitted by Komatsu did not evaluate the human health hazards of styrene, but rather focused on the hazard evaluation of styrene in the environment (e.g., air, water, aquatic and terrestrial wildlife and plants). While US EPA is an authoritative body under Proposition 65, the cited document is not a cancer risk assessment document. In fact, the summary states that “EPA has not given a formal carcinogen classification to styrene.” None of these documents provide additional information relevant to consideration of styrene for listing under Proposition 65 as known to cause cancer, and thus they do not provide evidence that the criteria in Section 25306(e)(2) are not met.

10. Other Comments

10.1 Comment:

ACMI commented: “In the current aggressive private enforcement climate, the most practical way to avoid an enforcement action is, as the law permits, by providing a Proposition 65 warning even if an exposure to a listed chemical is not at level requiring a warning. That is because, among other reasons, private enforcers routinely discount pre-enforcement toxicological analyses undertaken by businesses. Thus, art material manufacturers struggle with the challenges posed by the twin goals of compliance and avoiding enforcement actions. In this regard, ACMI members face an untenable situation, for ACMI’s certification program currently prohibits the use of the AP seal in connection with a Proposition 65 warning. Instead, products bearing a Proposition 65 warning must either bear a CL seal or no seal at all.”

“This has a significant consequence for art materials containing one or more Proposition 65 chemicals at levels not requiring precautionary labeling. This situation creates the absurd result that in 49 U.S. states, the product may bear the AP seal and be sold to school districts, but in California that same art material either would be prohibited from being sold to school districts (because it bears the protective Proposition 65 warning, but not the AP seal) or potentially would subject the manufacturer to a Proposition 65 enforcement action (because it bears the AP seal, but no warning).” (ACMI, p. 4)

Response:

OEHHA is sympathetic to the concerns expressed in the comments; however these issues are not relevant to the criteria for listing a chemical under Proposition 65.

OEHHA does not have enforcement authority under Proposition 65 and thus does not control the litigation aspects of the law, but as noted above, OEHHA does provide compliance assistance through the adoption of safe harbor levels for listed chemicals, guidance concerning how to calculate such levels and guidance concerning safe uses of particular products. It is not clear that the ACMI products at issue will require a Proposition 65 warning for exposures to styrene. OEHHA encourages ACMI to pursue a Safe Use Determination or other guidance concerning these exposures.

10.2 Comment:

SIRC commented: “Both of the definitional provisions [25306(e)(1) and (2)] expressly incorporate the sufficient evidence requirement, which includes the question of whether the listing of styrene in the Report of [sic] Carcinogens is consistent with accepted scientific principles.” (SIRC, p. 3-4) The CA GA, AMA, NMMA, EPSIA, NAMI, ACC and AI support SIRC’s comments.

Response:

OEHHA cannot substitute its scientific opinion for that of NTP. The law, regulations and legal cases that have interpreted the Authoritative Bodies listing process under Proposition 65 clearly delineate OEHHA’s role in the listing process. See for example, *Exxon Mobil Corp. v OEHHA*¹⁵⁷, which discusses in depth the role of OEHHA in reviewing the evidence relied on by the authoritative body when it identifies a chemical as a carcinogen or reproductive toxicant. The *Exxon* case dealt directly with the issue of what constitutes “substantial evidence” in the context of authoritative body listings. As is discussed above in response to the scientific arguments presented by APTCO and others, OEHHA’s decision to list styrene based on the NTP *Report on Carcinogens* designation is entirely consistent with the decision in the *Exxon* case. The State’s Qualified Experts¹⁵⁸ have designated the National Toxicology Program as an authoritative body for purposes of identifying carcinogens under Proposition 65¹⁵⁹. OEHHA must follow NTP’s determination that a chemical causes cancer if the NTP relied on sufficient evidence as defined under the regulation.

10.3 Comment: SIRC cited the *SIRC v OEHHA* decision as supporting the premise that there must be sufficient human or animal evidence to identify a chemical as known to

¹⁵⁷ *ExxonMobil v OEHHA* (2009 169 Cal.App.4th 1264, see also *Western Crop Protection Assn. v. Davis* (2000) 80 Cal.App.4th 741.

¹⁵⁸ The Carcinogen Identification Committee, see Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Reg., section 25

¹⁵⁹ See section 25102(c)(1) definition of “State’s Qualified Experts” includes the Carcinogen Identification Committee (CIC), 25302(b)(1) the CIC designates Authoritative Bodies”25305(a)(2), NTP is an Authoritative Body 25306(m)

cause cancer under Proposition 65. (SIRC, page 4, footnote 3, ACC and others support SIRC's comments).

Response:

The *SIRC v OEHHA* decision is not controlling here, since that case dealt with the question whether styrene could be listed via the Labor Code listing process, which is completely separate from the Authoritative Bodies listing process¹⁶⁰.

10.4 Comment: APTCO generally objects to the listing of styrene based on the Federal Constitution's First Amendment, Due Process, and Commerce Clauses and the general concept of federal preemption because the federal Food and Drug Administration and federal Occupational Safety and Health Administration have jurisdiction over some products that contain styrene or workplaces where it is used.

Response:

APTCO cites no specific case law or federal statutory provision that would be violated by the listing of styrene under Proposition 65. OEHHA notes that the federal Food and Drug Act contains a specific savings clause that applies to Proposition 65¹⁶¹. In addition, the mere fact that a federal agency has jurisdiction over a particular issue does not automatically result in preemption of all state actions related to that issue¹⁶². As explained in earlier responses to APTCO comments and others, styrene meets the legal and scientific criteria for listing under Proposition 65 and therefore must be added to the list. The listing of this chemical is fully consistent with California law, does not violate the US Constitution, and is not preempted by federal law.

10.5 Comment

APTCO said that the settlement in *Sierra Club v Brown* cannot authorize OEHHA to take an action that is beyond its statutory authority.

¹⁶⁰ See Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs., section 25904 for the statutory and regulatory criteria for Labor Code listings. The Authoritative Bodies listing criteria is contained in Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306 *et seq.*

¹⁶¹ 21 U.S.C. § 379r(d)(2) ("This section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997.").

¹⁶² See *Bond v. United States* (2014) 134 S. Ct. 2077, 2088-89 ("It has long been settled . . . that we presume federal statutes do not . . . preempt state law." (citations omitted)).

Response:

OEHHA agrees that the settlement in the *Sierra Club v Brown* case¹⁶³ cannot authorize OEHHA to take an action that exceeds its statutory authority under Proposition 65, and in fact the Consent Judgement did not do so. The judgment simply imposes specific timeframes for OEHHA to make decisions concerning whether or not to list chemicals via the authoritative bodies listing mechanism. As it relates to the consideration for listing of styrene, the judgment requires OEHHA to make a determination as to whether or not to publish a Notice of Intent to List (NOIL) for a given chemical within one year of OEHHA's receipt of the relevant documents from the authoritative body. It further requires that within one year of the close of the comment period for a NOIL, OEHHA must determine whether or not to list the chemical as known to cause cancer for purposes of Proposition 65. Neither of these requirements exceeds the scope of OEHHA's authority under the statute because these provisions simply impose timelines for action already required by Proposition 65 and its implementing regulations. The settlement does not impose any particular outcome in OEHHA's consideration of a chemical for listing. OEHHA maintains its ability to determine whether or not a chemical meets the criteria for listing.

10.6 Comment

APTCO argued that in *Baxter Healthcare Corporation v. Denton*¹⁶⁴, "The court held that substantial evidence showing that the biological mechanism through which a chemical causes cancer in rodents does not exist in humans establishes that a chemical poses no significant risk of causing cancer in humans. Likewise, OEHHA cannot proceed to list styrene as a known human carcinogen if there is new mode of action data the NTP did not consider showing that styrene does not pose a risk of cancer in humans due to metabolic or physiologic differences between laboratory mice and humans."

Response:

The scientific issues related to this comment are addressed above in response to comment 4.3. In regard to the assertion that OEHHA is prohibited by the *Baxter* decision from listing styrene as a carcinogen under Proposition 65, the commenter is incorrect. That case does not prevent the listing of a chemical that is known to cause cancer. In fact, the chemical at issue in that case, DEHP, remains on the Proposition 65 list. The issue decided in the *Baxter* case was whether or not DEHP could cause *human* cancer via a particular mode of action. While the scientific understanding of the mode of action for DEHP has progressed since the court decided that case, the court

¹⁶³ *Sierra Club v Brown et al.*, Alameda County Superior Court Case #RG07356881, Partial Consent Judgement (August 2013) available at:

http://www.oehha.ca.gov/prop65/law/pdf_zip/SierraClubProposedOrderRG07356881.pdf

¹⁶⁴ *Baxter Healthcare Corporation v. Denton* (2004)120 Cal.App.4th 333

decided based on the evidence presented in the case that DEHP did not cause cancer in humans and therefore Baxter was not required to provide a warning for exposures to DEHP from its products. The court did not address the separate question whether a chemical can be listed under Proposition 65 where the currently available information shows that the chemical likely does not cause cancer via a mechanism relevant to humans. The Baxter case is not relevant here because, as is discussed in response to comments 3.5 and 4.3 there is evidence that the mechanisms by which styrene causes cancer in animals are relevant to humans.