INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO:
SECTION 25705(b) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

STYRENE

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS OF REGULATION

This proposed regulatory amendment is to adopt a No Significant Risk Level (NSRL) for styrene under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 27 micrograms per day (µg/day) is based on carcinogenicity studies in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are insignificant. The NSRL provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

Styrene was listed as known to the state to cause cancer under Proposition 65 on April 22, 2016.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as “Proposition 65” or “The Act”.
[2] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[3] Title 27, Cal. Code of Regs., section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for styrene, OEHHA relied on the data analysis and cancer potency estimate presented in the December 2010 OEHHA Public Health Goal (PHG) for Styrene in Drinking Water document[5]. The cancer dose response assessment presented in the 2010 OEHHA PHG for styrene[6] is a reliable scientific basis for the NSRL and is consistent with Section 25703 guidance. The cancer potency estimate presented in the 2010 OEHHA PHG for styrene[7] is consistent with the evidence and standards that serve as the basis for the listing of styrene as causing cancer under Proposition 65, via the authoritative bodies listing mechanism[8]. Indeed, the same two studies selected as the basis for the PHG's cancer potency estimate[9] were identified by the 2011 National Toxicology Program (NTP) *Report on Carcinogens, Twelfth Edition*[10], which served as the basis for the listing under Proposition 65, as the most robust animal inhalation exposure studies of styrene, and were among the studies identified by NTP[11] as providing sufficient evidence of carcinogenicity in experimental animals. The 2010 OEHHA PHG for styrene[12] underwent internal and external scientific review, as well as a public comment process, before being released as a final document by OEHHA.

[5] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[6] *Ibid.*
[7] *Ibid.*
[8] Styrene is listed as causing cancer under Proposition 65 based on formal identification by the National Toxicology Program (NTP) in the 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.]
[9] Chronic inhalation exposure studies conducted in male and female CD-1 mice and reported by Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA et al. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21(3):185-98.
[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] *Ibid.*
[12] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

Selection of Studies Used to Determine Cancer Potency

The 2010 OEHHA PHG for styrene[13] identified the chronic inhalation exposure studies conducted in male and female CD-1 mice and reported by Cruzan *et al*.[14] as providing the best estimates of cancer potency. The 2010 OEHHA PHG for styrene[15] notes that these studies were conducted recently, were of lifetime duration, used several concentrations of styrene, and used adequate numbers of animals.

In these studies, CD-1 mice (70 per sex per dose) were exposed to styrene vapors at target levels of 0, 20, 40, 80, or 160 parts per million (ppm) for six hours per day, five days per week for 104 weeks (males) and 97 weeks (females). Interim necropsies (6 to 10 animals per sex per dose) were conducted at 52 and 78 weeks. In the study in male mice, a statistically significant increased incidence of bronchiolar-alveolar adenoma and combined bronchiolar-alveolar adenoma and carcinoma was observed at the 40, 80, and 160 ppm exposure levels. Significant trends for bronchiolar-alveolar adenoma and combined bronchiolar-alveolar adenoma and carcinoma were observed in male mice. In the study in female mice, a statistically significant increased incidence of bronchiolar-alveolar adenoma and combined bronchiolar-alveolar adenoma and carcinoma was observed at the 20, 40 and 160 ppm exposure levels. An increased incidence of bronchiolar-alveolar carcinoma was observed in female mice at 160 ppm; the incidence (7/50, 14 percent) was outside the historical control incidence range of 0 to 4 percent for female mice reported by Cruzan *et al*.[16]. Significant trends for bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma, and combined bronchiolar-alveolar adenoma and carcinoma were observed in female mice.

The tumor incidence data[17,18] from these studies are presented in Table 1. These data were used to estimate the cancer potency that serves as the basis for the NSRL.

[13] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[14] Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA et al. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21(3):185-98.
[15] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[16] Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA et al. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21(3):185-98.
[17] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[18] SIRC (1998). Styrene. 104-Week Repeat Dose Inhalation Combined Toxicity/Carcinogenicity Study in Mice. Vol. 1. (unpublished report). Prepared by Huntingdon Life Sciences Ltd. for the Styrene Information Research Center, Washington, DC, as cited in OEHHA (2010).

Table 1. Tumor incidences[a] in CD-1 mice exposed to styrene vapors by inhalation. Adapted from Table 18 in the 2010 OEHHA PHG for styrene[b].

Organ	Tumor	Styrene vapor target concentration (ppm)					Trend test p-value[c]
		0	20	40	80	160	
Male mice							
Lung	Bronchiolar-alveolar adenoma	19/70	28/68	40/70***	39/70***	37/69**	p < 0.01
	Bronchiolar-alveolar carcinoma	5/54	5/55	3/57	7/57	7/51	NS
	Bronchiolar-alveolar adenoma and carcinoma combined	22/70	31/68	41/70**	39/70**	40/69**	p < 0.01
Female mice							
Lung	Bronchiolar-alveolar adenoma	8/66	22/67**	21/69**	14/70	27/67***	p < 0.01
	Bronchiolar-alveolar carcinoma	0/51	0/49	3/51	0/54	7/54**	p < 0.001
	Bronchiolar-alveolar adenoma and carcinoma combined	8/66	22/67**	22/69**	14/70	30/67***	p = 0.001

[a] Data from SIRC (1998), as cited in OEHHA (2010). Effective number equals number of animals alive at week 35 for male bronchiolar-alveolar adenoma, week 79 for male bronchiolar-alveolar carcinoma, week 35 for male bronchiolar-alveolar adenoma/carcinoma combined, week 38 for female bronchiolar-alveolar adenoma, week 79 for female bronchiolar-alveolar carcinoma, and week 38 for female bronchiolar-alveolar adenoma/carcinoma combined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA);
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[b] OEHHA (2010) Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

[c] p-values for exact trend test conducted by OEHHA, NS = not significant; prior to analysis, doses were converted to mg/kg-day (male mice: 0, 17.514, 35.028, 70.056, 140.113; female mice: 0, 18.779, 37.558, 75.115, 150.230)

Estimation of Human Cancer Potency

The 2010 OEHHA PHG for styrene[19] includes an extensive review of the data on possible mechanisms of carcinogenic action for styrene, including a number of studies assessing styrene's genotoxicity. With regard to genotoxicity, the 2010 OEHHA PHG for styrene concluded, "The weight of evidence strongly suggests that styrene is genotoxic in humans, rodents, and non-mammalian species"[20]. Consistent with this conclusion, the 2010 OEHHA PHG for styrene[21] assumed linearity at low doses in estimating cancer potency from the tumor incidence data presented in Table 1 above. This approach is consistent with Section 25703 guidance.

[19] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[20] *Ibid.*
[21] *Ibid.*

This approach to cancer dose-response assessment for styrene is further supported by the discussion of genotoxicity as a mechanism of styrene carcinogenicity by the National Toxicology Program (NTP) Report on Carcinogens:

> "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."[22]

In order to derive a measure of the cancer response to styrene (per mg/kg-day) from the mouse inhalation studies described above, physiologically-based pharmacokinetic (PBPK) adjustments were made to the applied doses; details are discussed in the 2010 OEHHA PHG for styrene[23]. The dose associated with a 10% increased risk of developing a tumor was calculated for each study and the lower bound for this dose was estimated using US EPA's Benchmark Dose Software (BMDS)[24]. The ratio of the extra risk to the lower bound on dose provides the basis for the animal cancer potency.

Human cancer potency is then estimated by an interspecies scaling procedure involving the default human body weight, denoted 'bw_h' and average animal body weight, denoted 'bw_a', obtained from study data. It is assumed that sufficient pharmacokinetic adjustment has already been made with the use of PBPK adjusted dosimetry; thus pharmacodynamic factors are scaled using $(bw_h/bw_a)^{1/8}$. This approach assumes equal contributions of pharmacokinetic and pharmacodynamic factors to the overall animal to human extrapolation.

Average body weights of 0.043 kilogram (kg) and 0.035 kg for male and female mice, respectively, were used in the calculation. The default human body weight is 70 kg. As shown in Table 60 of the 2010 OEHHA PHG for styrene[25], cancer potency estimates of 0.026 milligrams per kilogram per day $(mg/kg\text{-}day)^{-1}$ and 0.027 $(mg/kg\text{-}day)^{-1}$ were derived from the Cruzan *et al*.[26] female mouse and male mouse studies, respectively,

[22] 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.]
[23] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[24] US EPA (Environmental Protection Agency, 2015). Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment. Available from: http://bmds.epa.gov
[25] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[26] Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA et al. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21(3):185-98.

and a human cancer potency estimate of 0.026 (mg/kg-day)$^{-1}$ was identified as the best potency value from these studies.

Calculation of No Significant Risk Level

The NSRL can be calculated from the human cancer potency estimate for styrene as follows. The Proposition 65 no significant risk value is one excess case of cancer per one hundred thousand people exposed, expressed as 10^{-5}. This value is divided by the human cancer potency estimate, expressed in units of one divided by milligram per kilogram bodyweight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the bodyweight for humans. When the calculation is for the general population, the bodyweight is assumed to be 70 kg in NSRL calculations (Section 25703(a)(8)). The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\,\text{kg}}{\text{human cancer potency estimate}} \times 1000\,\mu\text{g/mg}$$

As indicated previously, the human cancer potency estimate for styrene derived in the 2010 OEHHA PHG for styrene[27] is 0.026 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 27 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline and strikeout.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

[27] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

Chemical name	*Level (micrograms per day)*
Acrylonitrile	0.7
…	
Styrene	27

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, that does not require a warning or for which a discharge is not prohibited.

ECONOMIC IMPACT ASSESSMENT (see below)

NECESSITY

This proposed regulatory amendment would adopt an NSRL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about styrene. The NSRL provides assurance to the regulated community that exposures or discharges at or below this level are considered not to pose a significant risk of cancer. Exposures at or below the NSRL are exempt from the warning and discharge requirements of Proposition 65[28].

BENEFITS OF THE PROPOSED REGULATION

See “Benefits of the Proposed Regulation” under ECONOMIC IMPACT ANALYSIS below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The 2010 OEHHA PHG entitled “Public Health Goals for Chemicals in Drinking Water: Styrene”[29], was relied on by OEHHA for calculating the NSRL for styrene. It includes data used in the potency calculation and on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. OEHHA also relied on the discussion of mechanisms of styrene

[28] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[29] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

carcinogenicity by the NTP Report on Carcinogens[30]. A copy of the 2010 OEHHA PHG for styrene[31] and the NTP Report on Carcinogens[32] will be included in the regulatory record for this proposed action, as well as a copy of Cruzan *et al*.[33] which is cited in the 2010 OEHHA PHG for styrene[34]. These documents are available from OEHHA upon request.

OEHHA also relied on the attached Economic Impact Analysis in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt a NSRL for the chemical. Failure to adopt a NSRL would leave the business community without a "safe harbor" level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

[30] 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.]
[31] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
[32] 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.]
[33] Cruzan G, Cushman JR, Andrews LS, Granville GC, Johnson KA et al. (2001). Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. J Appl Toxicol 21(3):185-98.
[34] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL provides a “safe harbor” level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation given that its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation or Elimination of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. Styrene is listed under Proposition 65; therefore, effective April 22, 2017, businesses and individuals who manufacture, distribute or sell products with styrene in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California: This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California: This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The NSRL provides a “safe harbor” value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be exposed to litigation for a failure to warn of an exposure to or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.