FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: STYRENE

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL) for styrene. On April 22, 2016, the Office of Environmental Health Hazard Assessment (OEHHA) announced the listing of styrene as a chemical known to the state to cause cancer for purposes of Proposition 65[1]. At the same time, OEHHA issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 27 micrograms per day (µg/day) for styrene under Title 27, California Code of Regulations, section 25705(b)[2]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation. A public comment period was provided from April 22 to June 6, 2016. OEHHA received written public comments on the proposed rulemaking from the following organizations:

1. Styrene Information and Research Center (SIRC). The comments are comprised of SIRC's comment letter and the following attachment:
   "Derivation of an NSRL for Styrene", prepared for SIRC by CR Kirman and SM Hays of Summit Toxicology, LLP.
2. American Chemistry Council (ACC). Their comment letter also refers to the Summit Toxicology report provided as an attachment to SIRC's comments.

PEER REVIEW

On April 22, 2016, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed NSRL for styrene to the members of the Carcinogen Identification Committee for their review and comment as required by Section 25302(e). A written comment was received from committee member Dr. Jason Bush (Associate Professor, California State University, Fresno).

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq*., 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.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

In developing the NSRL for styrene, OEHHA relied on a 2010 OEHHA document entitled "Public Health Goal for Styrene in Drinking Water" (PHG)[3] which summarizes the available scientific data from human epidemiology, rodent carcinogenicity studies and other information relevant to the carcinogenic activity of styrene. The PHG used these data to derive a value for carcinogenic potency as well as other health-effect measures, which were used to calculate a health-protective level for styrene in drinking water. The NSRL is based upon the carcinogenic potency analysis in the PHG, which used the most sensitive scientific study deemed to be of sufficient quality. OEHHA also relied on the discussion in the National Toxicology Program (NTP) *Report on Carcinogens, Twelfth Edition*[4].

A summary of the relevant comments received is provided below, along with OEHHA's responses to those comments.

SIRC COMMENT 1: Introduction and Summary

SIRC requests that OEHHA calculate NSRLs for styrene based on the internal dose for the target sub-tissue, rather than using whole tissue or administered dose. "In contrast to the approach taken by OEHHA, a substantially higher NSRL results if mouse lung tumors are assessed in terms of internal dose for the target sub-tissue (AUC [area under the curve] for styrene oxide in club cells) using a physiologically based pharmacokinetic (PBPK) model. This produces NSRL values of 2,100 (inhalation) and 5,600 (oral) µg per day for styrene." Details of the analysis supporting SIRC's proposed alternative NSRL are given in the report by Summit Toxicology attached to SIRC's comment.

Response 1

OEHHA does not agree that extrapolation of the internal dose calculated for the sub-tissue in the mouse studies to that in the corresponding site in humans is an appropriate basis for assessing the carcinogenic risk to humans from styrene. In the response to Comment 3b below, OEHHA explains the substantial problems with extrapolating the internal dose calculated using this PBPK model approach from mice to humans. These include the lack of concordance in styrene tumorigenesis target sites between species

[3] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf.

[4] 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: https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.]

at the tissue level, let alone the sub-tissue target. NTP[5] noted in its review of styrene "studies of workers exposed to styrene that showed (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers." The NTP also noted: "There is also some evidence for increased risks of esophageal and pancreatic cancer among styrene-exposed workers." While NTP concluded that "the possibility that the results were due to chance or to confounding by exposure to other carcinogenic chemicals cannot be completely ruled out" it found nonetheless "a causal relationship between styrene exposure and cancer in humans is credible…" Thus the sites observed associated with cancer in human studies differ from those observed in mouse studies.

Similarly, genotoxicity is observed in humans at sites other than the lung. NTP[6] notes findings of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers, and OEHHA (2010)[7] cites evidence of genotoxicity at various sites in humans, as well as plausible evidence of carcinogenicity at various sites in humans. In aggregate, the human genotoxicity and carcinogenicity findings present a compelling case that it is inappropriate to assume site concordance between rodents and humans for the carcinogenic effects of styrene. It is a generally accepted principle that although there may be site concordance between humans and animal test species in specific cases, it is not necessarily going to occur. For risk assessment purposes site concordance is not assumed unless there is evidence to support this assumption[8].

SIRC COMMENT 2: The Proposed NSRL

SIRC Comment 2a

"OEHHA relied on the data analysis and a cancer potency estimate presented in the December 2010 OEHHA Public Health Goal (PHG) for Styrene in Drinking Water document [OEHHA, 2010]. There, OEHHA concluded that best human cancer potency estimate was 0.026 $(mg/kg\text{-}day)^{-1}$, based on cancer potency estimates derived from a female and male mouse study [Cruzan et al., 2001]. … Similarly, OEHHA concluded that the PHG cancer potency estimate is consistent with the evidence and standards

[5] 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: https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.]
[6] *Ibid.*
[7] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf.
[8] OEHHA (2009). Technical Support Document for Cancer Potency Factors. http://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009

that serve as the basis for the listing of styrene via the authoritative bodies listing mechanism, inasmuch as the same study used as the basis of the PHG's cancer potency estimate was identified in the 2011 Report on Carcinogens (RoC) as the most robust animal inhalation exposure studies of styrene."

Response 2a

SIRC correctly notes that OEHHA used the analysis presented in the PHG (OEHHA, 2010)[9] as the basis for the proposed NSRL, based on the results of the inhalation studies reported by Cruzan et al.[10]. These studies in male and female mice were identified in OEHHA (2010) as among the several reliable studies available for assessment of carcinogenic risk from exposure to styrene.

In addition to the studies serving as the basis of the PHG, OEHHA (2010)[11] considered and evaluated several others in its evaluation of carcinogenicity. The NTP *Report on Carcinogens, Twelfth Edition*[12] also identified multiple robust animal studies of styrene, including studies by the National Cancer Institute[13] as well as the Cruzan et al. studies. These were among the studies providing sufficient evidence of carcinogenicity in experimental animals. Although, in accordance with OEHHA risk assessment guidelines, the Cruzan et al. studies were chosen as the most reliable and sensitive basis for the potency estimate in the PHG[14], the other results were also considered as providing context and support. In addition to the data from animal bioassays, human cancer epidemiology and data on genotoxicity and metabolism in both animals and humans were considered as contextual and supporting evidence.

SIRC Comment 2b

[9] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf.
[10] Cruzan G., Cushman JR, Andrews LS, Granville GC, Johnson KA, Bevan CJ, Hardy CJ, Coombs DW, Mullins PA, Brown WR. 2001. Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks, J Appl Toxicol 21(3):185–98
[11] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf
[12] 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: https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.]
[13] NCI (1979). Bioassay of styrene for possible carcinogenicity. Technical Report Series No. 185. National Cancer Institute, National Institutes of Health, Bethesda, MD.
[14] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf

"OEHHA uses a linear extrapolation approach in the derivation of NSRLs under the Proposition 65 program. The method involves using the Multistage model to estimate the cancer potency factor (CPF) or cancer slope factor (CSF), also termed the q1*, which is the method outlined by US EPA [EPA, Guidelines for Carcinogen Risk Assessment, 51 Fed. Reg. 33, 992-4,003 (Sep. 24, 1986)]. Although default methods are described for NSRL calculations, use of alternative approaches is supported. The regulations provide that: 'Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk.' "

Response 2b

The methodology used by OEHHA to derive the NSRL was the Benchmark Dose (BMD) method, as described both in OEHHA's guidelines[15] and in the US Environmental Protection Agency's (US EPA's) current cancer risk assessment guidelines[16]. OEHHA applied a multistage mathematical model to describe the relationship between the risk of cancer and the dose. While the OEHHA PHG document (OEHHA 2010) presented both the linearized multistage approach and the BMD analysis, OEHHA's calculation of the NSRL for styrene follows current practice in emphasizing the benchmark dose analysis. The newer BMD method and the earlier linearized multistage method produce essentially the same results for the styrene data from the Cruzan et al. studies.

As part of the procedure OEHHA used for determining the cancer potency using the BMD method, a determination is made as to the proper type of extrapolation from the point of departure (typically the 95 % lower confidence limit of the ED_{05} or ED_{10} for tumor induction) to low doses. For genotoxic carcinogens, and by default for other carcinogens in the absence of specific evidence to the contrary, a slope factor is determined by linear extrapolation from the point of departure to zero dose. As noted by SIRC, other methods to determine cancer risk at low doses may be used, but OEHHA's and US EPA's guidelines specifically indicate that any alternatives will be considered only when supported by chemical-specific information identifying such an alternative is appropriate. OEHHA considered this issue in its derivation, as noted in the Initial Statement of Reasons:

> "With regard to genotoxicity, the 2010 OEHHA PHG for styrene concluded, 'The weight of evidence strongly suggests that styrene is genotoxic in humans,

[15] OEHHA (2009). Technical Support Document for Cancer Potency Factors. http://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009

[16] US EPA (2005). Guidelines for Carcinogen Risk Assessment. March, 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

rodents, and non-mammalian species'. Consistent with this conclusion, the 2010 OEHHA PHG for styrene assumed linearity at low doses in estimating cancer potency from the tumor incidence data..."[17]

SIRC COMMENT 3: A higher NSRL is warranted based on specific tissue-level exposure

SIRC Comment 3a

"In the six years since OEHHA developed the PHG for styrene and the five years since NTP listed styrene in the RoC, both science and the scientific literature on styrene have evolved. A number of these studies were referenced in SIRC's prior comments in response to OEHHA's notice of intention to list."

Response 3a

There have been a number of additional studies published during this time, including several sponsored by SIRC. The studies cited by SIRC addressed specifically the mechanism of causation and human relevance of the mouse lung tumors induced by styrene exposure. However, there are no new primary data on cancer dose response in bioassays. Recent data relating to mouse lung carcinogenesis caused by styrene were considered in the NTP *Report on Carcinogens, Twelfth Edition*[18]. The more recent investigations have mostly been directed to pursuing in greater depth the mechanistic hypotheses already laid out by SIRC and their sponsored investigators in publications previously considered by OEHHA in development of the PHG for styrene, and by the NTP in its *Report on Carcinogens, Twelfth Edition*. The claim that the tumor findings in mouse lung were not indicative of human cancer risk was rejected by the NTP in the *Report on Carcinogens, Twelfth Edition* and by OEHHA in both the PHG and the identification of styrene as a carcinogen for the purposes of Proposition 65[19]. The same arguments are now made in an attempt to argue for a higher NSRL. These arguments entirely miss the point made in OEHHA's response to comment 1 above, which is that site concordance is neither required nor necessarily expected when using an animal

[17] OEHHA (2016) Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Styrene. Available at https://oehha.ca.gov/proposition-65/crnr/proposed-amendment-section-25705-specific-regulatory-levels-posing-no-3

[18] 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: https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.]

[19] See OEHHA's Response to Comments Pertaining to the Notice of Intent to List Styrene as Causing Cancer under Proposition 65. OEHHA, April 2016. Available at: https://oehha.ca.gov/media/downloads/crnr/042216styrenenoilresponsecoms.pdf

carcinogenicity finding as the basis of human cancer risk assessment. This is especially important in regard to a chemical such as styrene, which shows carcinogenic and genotoxic potential at other sites in animal species and humans.

SIRC Comment 3b

"SIRC sponsored the attached derivation of an NSRL [the Summit Toxicology report] based on best available science using a PBPK model assuming, for purposes of analysis, that styrene is a carcinogen."

"Because lung toxicity is a key to styrene-induced mouse lung tumorigenesis, such data should be used to guide human health assessments for styrene, including OEHHA's development of an NSRL. Therefore, available dose-response data sets for carcinogenesis in rodents were assembled, analyzed, and pooled, consistent with U.S. EPA guidelines for benchmark dose methods. This yielded no showing of a dose-response relationship for lung tumors in rats of either sex, leaving six sets of mouse lung tumor data sets for dose-response analysis."

"In assessing the dose-response relationship, the derivation used styrene oxide in the PBPK model calculations, rather than the hydroxylated-benzene-ring derivatives identified in the mode of action. PBPK modeling was performed using acslXtreme (AEgis Technologies, Version 3.0.2.1) and used model code files. After making normalizing adjustments to extrapolate from the mouse data to humans, only one data set - the combined male mouse data set from lung tumors in male mice combined across oral and inhalation studies - could serve as a basis for extrapolating human equivalent doses of SO [styrene oxide] concentrations. Importantly, based on visual inspection and comparison of Akaike's information criteria (AIC values), sub-tissue dose measures (club cell cumulative tissue exposure (AUC) SO) provided a more consistent description (that is, dose-response concordance) than the whole tissue measure (lung AUC SO) of the dose-response relationship for this data set."

Response 3b

OEHHA notes the use of a PBPK model in the analysis presented by Summit Toxicology and cited by SIRC. This model makes assumptions that are intended to more accurately model the pharmacokinetic events in the terminal bronchioles/club cell tissue following exposure to styrene. As noted in the Summit Toxicology report, not all these assumptions are in line with the detailed mechanistic description proposed by SIRC, which they state involves the metabolism of styrene to hydroxylated-benzene-ring derivatives. Instead of these metabolites, Summit Toxicology used styrene oxide as an internal dose measure as a surrogate in their analysis. Summit Toxicology used modeled levels of styrene oxide formation in the terminal bronchioles/club cell tissue in both humans and animals in their estimation of the NSRL. Because they predicted

human levels to be roughly 100 fold less compared to the mouse, their proposed NSRL is roughly 100 fold higher than OEHHA's.

A feature of the Summit Toxicology PBPK model emphasized by SIRC is the attempt to model dose levels in sub-tissue compartments, in particular the club cell (Clara cell). The objective is to better model the toxicokinetics at the presumed site of action. However, the Summit Toxicology report notes that the metabolic pathway the report currently proposes (i.e., benzene-ring hydroxylation) as the likely source of proximate carcinogenic metabolites or reactive oxygen could not be modeled for lack of data. The relationship of the chosen dose metric (AUC for styrene oxide) to the detailed toxicokinetics and toxicodynamics for styrene carcinogenicity is unclear.

Summit Toxicology reports some success with their PBPK sub-tissue approach in fitting the data on mouse lung tumors. However, only one data set of the various single and pooled data sets examined provided an analysis satisfactory to the authors. It is unclear whether the superior fit obtained in this one case with the sub-tissue approach as opposed to the whole tissue model is the result of a more biologically relevant model or merely the result of data selection. Furthermore, the assumption that the Clara cell is the exclusive site of both metabolic activation and carcinogenic impact is not established, even in those rodent species for which it has been proposed as an important mechanism of action[20]. This degree of PBPK model specialization makes many assumptions even for the single case of lung tumors in mice. It is clearly inapplicable to other tumor sites or to other species such as humans where the lung histology, distribution of enzyme activities and tumor responses are different.

Further, OEHHA notes that the models used in Summit Toxicology's benchmark dose analysis are not the standard multistage cancer model recommended by US EPA's benchmark dose guidance. Summit Toxicology used a number of the models recommended for non-cancer endpoints: dichotomous Hill, log-logistic, Weibull. Summit Toxicology's preferred dataset was the "combined" male mouse data (i.e., combined data from oral and inhalation studies). Use of such a 'combined' dataset, generated at different laboratories and different times, is itself a departure from standard procedures for cancer dose-response assessment. Summit Toxicology fitted this non-standard dataset with the dichotomous Hill model, which shows marked low-dose nonlinearity. Although Summit Toxicology claims adherence to standard cancer risk assessment guidelines by their use of linear low-dose extrapolation from the point of departure, the choice of these non-cancer models to obtain the point of departure is a non-standard choice. Neither the Summit Toxicology report nor SIRC's comments explain or provide

[20] Van Winkle LS, 2014. Species Difference in Response and Cell of Origin. Presented in Session 2 of the US Environmental Protection Agency's 2014 Mouse Lung Tumor Workshop. Available at https://www.epa.gov/iris/mouse-lung-tumor-workshop-jan-2014

adequate justification for these model choices. Such a departure from standard procedure is inappropriate in the absence of compelling supporting evidence.

SIRC notes the existence of multiple lung tumor data sets in mice, as also reported in the analyses by OEHHA[21]. They also point out that Summit Toxicology found no dose-response for lung tumors in rats. However, the comments do not provide any dose-response analysis of the significant incidences of tumors observed at other sites. These sites are included in the consideration of cancer potency in OEHHA's styrene PHG[22]. For example, OEHHA analyzed the dose response information for human lymphoma observed by Kogevinas et al. and obtained a cancer potency value similar to the one estimated from the mouse lung tumor data[23]. The Summit Toxicology report confines itself exclusively to lung tumors and does not address tumors at any other site.

Given the evidence for carcinogenicity of styrene in humans at sites other than the lung, the attempt to extrapolate from mouse to human sub-tissue level compartments using a PBPK model is inappropriate. SIRC comments elsewhere that the site-specific metabolic processes observed in mice do not have exact counterparts in humans. Thus, OEHHA will use a deliberately less specific PBPK model, which is applicable with reasonable confidence to a range of different data sets, in its analysis of the styrene mouse lung tumor data. The dose metric selected by OEHHA (2010)[24] for the analysis, namely the AUC for styrene oxide in the mouse, makes fewer assumptions than those used in the Summit Toxicology PBPK model, and the extrapolation from animals to humans was based on measures of uptake and standard interspecies extrapolation factors, again avoiding questionable assumptions with large uncertainties.

SIRC Comment 3c

"Thus, based on the best available dose measure (SO in club cell tissue), NSRL values of 2,100 µg per day (inhalation exposure) and 5,600 µg per day (oral exposure) were calculated. The impossibility of calculating human equivalent doses for the other five [mouse] data sets supports the view that the tumor responses observed in mice are not relevant to human health, and the corollary conclusion that even these higher Summit Toxicology thresholds are both conservative and protective of human health."

Response 3c

[21] OEHHA (2010). Public Health Goals for Chemicals in Drinking Water: Styrene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA Available at: http://oehha.ca.gov/media/downloads/water/chemicals/phg/122810styrene.pdf
[22] *Ibid.*
[23] *Ibid*, see Table 60 on page 230.
[24] *Ibid.*

As previously noted, the NTP concluded in the *Report on Carcinogens, Twelfth Edition*[25] that mouse lung tumors are relevant to humans, and thus indicative of human cancer hazard. Expert scientific peer review of the PHG[26] has also confirmed OEHHA's conclusion that the animal data on styrene tumorigenicity is indicative of a potential cancer risk to humans. The Summit Toxicology PBPK model fails to provide human equivalent dose solutions for numerous elements of the available data, and makes unreasonable extrapolation of sub-tissue level doses to the human situation (as noted in response to comment 3b above). The NSRL values calculated by Summit Toxicology and proposed by SIRC (i.e., 2,100 µg per day for inhalation exposure and 5,600 µg per day for oral exposure) are unlikely to be "*conservative and protective of human health*".

SIRC Comment 4: Conclusion

"Once a chemical is listed, OEHHA is authorized to establish an NSRL based on the best available data. However, the NSRL proposed by OEHHA is not based on the best available PBPK data, which supports an inhalation NSRL of 2,100 µg/day for inhalation and 5,600 µg/day for ingestion based on the best available measure of dose/exposure, which are the internal dose concentrations of styrene oxide in club cells at the sub-tissue dose level. These levels are protective of human health and reflect several conservative assumptions."

Response 4

On the contrary, OEHHA finds that the NSRL values proposed by SIRC are not well supported by the underlying data. The PBPK model used by SIRC is speculative and fails to accurately model substantial elements of the available dataset. It inappropriately extrapolates a hypothetical sub-tissue dose measure to humans, it relies on selection of a metabolite not thought to reflect molecular events at the level of detail assumed in the model, and it fails to accommodate the demonstrated lack of tumor site concordance between species. The benchmark dose modeling performed by Summit Toxicology to generate the proposed NSRL values also relies on non-standard and unsupported model choices. Under these circumstances, SIRC's proposed NSRLs are not likely to be sufficiently protective of human health. OEHHA instead has determined that the NSRL of 27 micrograms per day (µg/day) for styrene, which was proposed in the ISOR, is the appropriate value.

[25] 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: https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.]

[26] OEHHA (2010). Responses to Major Comments on Technical Support Document. Public Health Goal for Styrene in Drinking Water. Available at: https://oehha.ca.gov/media/downloads/water/chemicals/122810respstyrene.pdf

Comments received from the American Chemistry Council's (ACC) Plastics Foodservice Packaging Group (PFPG)

ACC Comment 1: Polystyrene food packaging

"Polystyrene food packaging is critical to the food and agricultural industries in California, and appropriately warning consumers about the presence of styrene – when styrene's presence presents a carcinogenic risk– is a critical issue [sic] PFPG members."

Response 1

It should be emphasized that the chemical that is listed under Proposition 65 is styrene, not polystyrene. As noted by ACC, styrene is the monomer used for production of polystyrene. A warning for styrene would only be required in cases where residual levels of styrene in polystyrene food packaging materials result in exposures that pose a significant cancer risk, i.e., styrene exposures greater than 27 µg/day. The levels of such residual styrene in polystyrene food packaging materials are generally thought to be fairly low in most cases. OEHHA can provide compliance assistance for affected businesses via Safe Use Determinations for styrene exposures from specific products where requested[27].

ACC Comment 2: NSRL value and SIRC's comments

ACC drew OEHHA's attention to the comments submitted by SIRC:
"While PFPG does not object to the proposed NSRL for the polystyrene food packaging products referenced above, we encourage OEHHA to consider the May 7, 2016 report, *Derivation of an NSRL for Styrene*, by Summit Toxicology."

Response 2

OEHHA has responded to the points raised by SIRC and Summit Toxicology in the responses to SIRC's comments above.

Comment received from Carcinogen Identification Committee member Dr. Jason Bush (Associate Professor, California State University, Fresno)

"The one query I would raise is the use of the general population assumption for bodyweight as 70 kg (man) in NSRL calculations according to Section 25703(a)(8) for

[27] See Section 25204 and the OEHHA Safe Use Determination fact sheet available at: http://oehha.ca.gov/media/downloads/crnr/sudfacts03112016_0.pdf

Quantitative Risk Assessment. In the recent comprehensive review by Gelbke *et al.* (2015)* and references within, the authors evaluated the evidence for elevated serum levels of prolactin found in exposed GFR workers. They rigorously conclude that no plausible MoA could be attributed to styrene while several flaws/conflicting results were identified in the relevant studies. However, given the available data and the suggestion of possible neuroendocrine influence, I wonder whether the NSRL calculation might be more appropriately based on a subpopulation. Specifically, risk to woman. If the 58 kg body weight were to be used, the NSRL would then be slightly lowered to ~22 µg/day from the proposed 27 µg/day."

Response

OEHHA acknowledges that individual subpopulations can have different sensitivities to chemical carcinogens, but does not have sufficient information on the degree that men and women may differ in their carcinogenicity responses to styrene exposure to make a population specific cancer potency determination. For this and other reasons described in response to comments received by other commenters, OEHHA applied the default approaches in Section 25703.

In the particular case of styrene there is, as Dr. Bush notes, considerable uncertainty in the mode of action. Thus, it is unclear whether any subpopulation (e.g., women) is likely to have greater sensitivity to exposure to this carcinogen than the general adult population. Thus, in calculating the NSRL for styrene, OEHHA used the general population assumption for bodyweight of 70 kg, together with the standard "adult" potency calculation, which is the default value in Section 25703(a)(8).

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses “no significant risk” of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish a No Significant Risk Level for styrene. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25349.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.