INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

VINYLIDENE CHLORIDE

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT OF REGULATION

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for vinylidene chloride under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 0.88 micrograms per day (µg/day) is based on a carcinogenicity study 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. NSRLs provide guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., 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] Section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

OEHHA has proposed to list vinylidene chloride as known to the state to cause cancer under Proposition 65 via the authoritative bodies mechanism. The proposed listing is based on the National Toxicology Program (NTP) report entitled "Toxicology and Carcinogenesis Studies of Vinylidene Chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F$_1$/N Mice (Inhalation Studies)"[5]. The NTP is a body recognized as authoritative for the listing of chemicals as known to cause cancer under Proposition 65 (Section 25306(m)). In the event the chemical is not listed, this rulemaking will be withdrawn.

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for vinylidene chloride, OEHHA relied on the above-mentioned NTP report and Volume 71 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide"[6]. The NTP report summarizes the available data from rodent carcinogenicity studies of vinylidene chloride, as well as other information relevant to the carcinogenic activity of the chemical. The IARC monograph summarizes data available in 1999 from rodent carcinogenicity studies, as well as genotoxicity studies and other information relevant to the mechanism of action of vinylidene chloride that was available at that time. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[7].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of vinylidene chloride discussed by NTP[8] and IARC[9], and determined that the two-year inhalation studies conducted by NTP in male F344/N rats and male and female

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[5] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

[6] International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php

[7] Section 25703(a)(4)

[8] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

[9] International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php

B6C3F$_1$/N mice met the criterion in Section 25703 as being sensitive studies of sufficient quality.

In the NTP male rat study[10], groups of 50 male rats were exposed to vinylidene chloride by inhalation at concentrations of 0, 25, 50, or 100 parts per million (ppm), 6 hours and 10 minutes per day, 5 days per week for up to 105 weeks. The lifetime average daily doses of vinylidene chloride administered in the studies were calculated to be: 0, 11, 21, and 43 milligrams per kilogram of bodyweight per day (mg/kg-day) in male rats. Survival of male rats was not affected by treatment with vinylidene chloride at any dose.

A statistically significant increase in the incidence of malignant mesothelioma was observed in all dose groups, with a statistically significant positive trend. A statistically significant increase in the incidence of adenomas of the nasal respiratory epithelium was observed in the high dose group, with a statistically significant positive trend. Rare renal tubule carcinomas were also observed in treated male rats (none in controls, 2 in the low dose, 1 in the mid dose and 1 in the high dose groups) and considered treatment-related, though neither the incidence nor the dose-response trend was statistically significant. The tumor incidence data used to estimate cancer potency from the male rat study are presented in Table 1.

Table 1. Tumor incidences[a] of treatment-related lesions in male F344/N rats administered vinylidene chloride by inhalation (NTP, 2015)

Organ	Tumor type[b]	Vinylidene chloride administered concentrations (ppm)				Trend test p-value[c]
		0	25	50	100	
All organs	Malignant mesothelioma (first occurrence of tumor: day 449)	1/49	12/48***	28/47***	23/48***	$p < 0.001$
Nose	Adenoma of the respiratory epithelium (first occurrence of tumor: day 635)	0/40	0/34	1/33	4/32*	$p < 0.01$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor
[b] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
[c] p-values for exact trend test conducted by OEHHA

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[10] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

In the NTP mouse studies[11], groups of 50 male and female mice were exposed to vinylidene chloride by inhalation at concentrations of 0, 6.25, 12.5, or 25 ppm, 6 hours and 10 minutes per day, 5 days per week for up to 105 weeks. The lifetime average daily doses of vinylidene chloride administered in the studies were calculated to be: 0, 5.1, 10, and 20 mg/kg-day in male mice and 0, 4.9, 9.8, and 20 mg/kg-day in female mice. Survival of male mice exposed to 25 ppm was significantly less than that of the chamber control group, with a statistically significant trend[12]. Survival of female mice exposed to 6.25 and 25 ppm was significantly less than that of the chamber control group.

In male mice, statistically significant increases in incidences of renal tubule adenomas, carcinomas, and adenomas and carcinomas (combined) were observed in all dose groups, with statistically significant positive trends. In female mice, a statistically significant increase in the incidence of systemic hemangiomas and hemangiosarcomas (combined) was observed in the high dose group, with a statistically significant positive trend. A statistically significant increase in the incidence of hepatocellular adenomas and carcinomas (combined) was also observed in female mice in the mid and high dose groups, with a statistically significant positive trend. In addition, a treatment-related increase in rare hepatocholangiocarcinoma was observed in females (none in controls, 1 in the low dose, 1 in the mid dose and 2 in the high dose groups), though neither the incidence nor the dose-response trend was statistically significant. The tumor incidence data used to estimate cancer potency from each of the mouse studies are presented in Table 2.

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[11] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC
[12] *Ibid.*

Table 2. Tumor incidences of treatment-related lesions in B6C3F₁/N mice administered vinylidene chloride by inhalation (NTP, 2015)

Organ	Tumor type[a]	Vinylidene chloride administered concentrations (ppm)				Trend test p-value[b]
		0	6.25	12.5	25	
Male Mice						
Kidney	Renal tubule adenoma or carcinoma[c] (first occurrence of tumor: day 429)	0/50	11/50***	37/48***	27/49***	$p < 0.001$
Female Mice						
All organs	Systemic hemangioma or hemangiosarcoma[d] (first occurrence of tumor: day 471)	4/44	6/41	6/44	11/40*	$p < 0.05$
Liver	Hepatocellular adenoma or carcinoma[d] (first occurrence of tumor: day 415)	28/46	30/46	37/47*	38/45*	$p < 0.01$

[a] 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] p-values for exact trend test conducted by OEHHA.
[c] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
[d] The numerator represents the number of tumor-bearing animals. The denominator has been adjusted with the poly-3 method to account for intercurrent mortality during the 105-week study.

<u>Estimation of Cancer Potency Using the Multistage-in-Dose Weibull-in-Time Model and the Multistage Model</u>

In the discussion of the mechanistic data on vinylidene chloride, the 2015 NTP report[13] concluded:

> "Results from a variety of published *in vitro* genetic toxicology studies with vinylidene chloride, including approaches such as bacterial mutagenicity assays, yeast test systems, and mammalian cell lines, demonstrate that under appropriate exposure conditions that control for the volatility of vinylidene chloride, the chemical has mutagenic, clastogenic, and aneugenic properties. In *in vivo* studies, the limited available genotoxicity test data are negative, with the exception of one study that detected low levels of DNA alkylation in liver and kid-ney, tissues associated with vinylidene chloride-induced tumorigenesis (Reitz *et*

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[13] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

al., 1980). Because alkylating agents in general possess mutagenic, clastogenic, and aneugenic properties, and many are known carcinogens, DNA alkylation may be one possible mode of action for vinylidene chloride associated tumorigenesis, consistent with the results obtained in well-conducted *in vitro* assays but not captured in the micronucleus studies that rely on exposure of proerythrocytes in the bone marrow."

A multistage model was used to derive cancer potency estimates from the male rat study (tumor incidence expressed as effective number) and the female mouse study (tumor incidence adjusted with the poly-3 method). A time-to-tumor extension of this model was used to derive a cancer potency estimate from the male mouse study, following the guidance in Section 25703. Based on consideration of the available mechanistic information on vinylidene chloride summarized by IARC[14] and NTP[15], and the above conclusions reached by NTP[16], it appears that carcinogenicity of vinylidene chloride may be the result of genotoxic mechanisms of action. There are no specific mechanistic data to suggest any deviation from the standard assumptions, including low-dose linearity, usually applied in cancer dose-response analysis. The multistage model and the time-to-tumor extension of that model are therefore the most scientifically appropriate models to use, based on the available data.

In the multistage polynomial model, the lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is given as:

$$p(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where the coefficients q_i, i = 1…k, are non-negative. The q_is are parameters of the model, which are taken to be constants and are estimated with US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[17] using a maximum likelihood procedure.

The multistage polynomial model defines the probability of dying with a tumor at a single site. To derive a measure of the cancer response in studies where increases in

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[14] International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php

[15] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

[16] *Ibid.*

[17] US EPA Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds

treatment-related tumors were observed at a single site, the multistage polynomial model for cancer in BMDS can be used to estimate the lower bound on the dose associated with a 5% increased risk of developing a tumor. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, as was observed in the male rat and female mouse studies, the multisite model in BMDS[18] can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage model for each of the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. In order to derive a measure of the total cancer response to vinylidene chloride (per mg/kg-day) in each of these studies, the dose associated with a 5% increased risk of developing a tumor at one or more of the sites of interest was calculated and the lower bound for this dose was estimated using the multisite model in BMDS. The ratio of the 5% risk level to that lower bound on dose is known as the multisite "animal cancer slope factor (CSF_{animal})," or "animal cancer potency."

In order to account for the treatment-related intercurrent mortality observed in the female mouse study, the poly-3 method was used to adjust the denominator (N) of tumor incidence as shown in Table 2. The differential mortality was accounted for by assigning a reduced contribution towards N, proportional to the third power of the fraction of time on study, only to animals lacking site-specific tumors that died before 104 weeks[19]. The equation is shown below:

$$\text{Contribution to N} = \left(\frac{\text{Week on study}}{104 \text{ weeks}}\right)^3$$

When a large fraction of the animals die before the end of the study, as occurred in the male mouse study by NTP, the multistage-in-dose Weibull-in-time (multistage Weibull) model can be used to estimate the cancer potency. The multistage Weibull model is an extension of the multistage polynomial model given above, with the probability of an incidental tumor (p(t,d)) by time t and lifetime dose rate d given as:

$$p(t,d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ...+ q_k d^k)(t)^c]$$

with $q_i \geq 0$, for all i and the age exponent, c, restricted to be between 0 and 6. The dose associated with a 5% increased risk of developing an incidental tumor at the site of

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[18] US EPA Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds

[19] Bailer AJ and Portier CJ (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. Biometrics **44**(2):417-31.

interest was calculated at the assumed standard lifetime of 104 weeks for mice and the lower bound for this dose was estimated, using the multistage Weibull time-to-tumor model in US EPA's BMDS[20]. The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor (CSF_{animal})," or the "animal cancer potency."

Calculation of Average Daily Doses

The lifetime average dose in units of mg/kg-day of vinylidene chloride was calculated for each of the relevant dose groups, based on the dose level, duration, exposure regimen, and animal body weights reported by NTP[21]. The average body weight for male rats was calculated to be 0.4458 kg, and the average body weights for male and female mice were calculated to be 0.0479 kg and 0.0521 kg, respectively, from the data reported by NTP[22] for control animals.

The inhalation rate (IR), in m^3/day, for male rats, female rats, male mice, and female mice was calculated based on the equations of Anderson *et al.* (1983)[23], which were derived using experimental data on animal breathing rates (m^3/day) and corresponding body weights (kg):

$$IR_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3}$$

$$IR_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3}$$

The constants 0.105 and 0.0345 are in m^3/day and the constants 0.113 and 0.025 are in kg. The calculated inhalation rates were 0.262 m^3/day for male rats, 0.0532 m^3/day for male mice, and 0.0563 m^3/day for female mice. Lifetime average doses (D_{avg}) were determined by multiplying the chamber air concentration (C_{air}) of vinylidene chloride in units of mg/m^3 by the following factors: the inhalation rate divided by the body weight; 6.17/24 to account for the 6 hours and 10 minutes per day exposure; 5/7 to account for a five day per week dosing. The equations for lifetime average dose (mg/kg-day) calculation for each species/sex are:

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[20] US EPA (2009). MSW Time to Tumor Model and Supporting Documentation. US Environmental Protection Agency, Washington, DC. Available from:
https://cfpub.epa.gov/ncea/bmds/recordisplay.cfm?deid=217055
[21] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.
[22] *Ibid.*
[23] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983), Quantitative approaches in use to assess cancer risk. *Risk Analysis.***3**:277-295.

$$D_{avg} = C_{air}(\text{ mg}/\text{m}^3) \times \frac{IR_{rats}(\text{ m}^3/\text{day})}{bw_{rats}} \times \frac{6.17}{24} \times \frac{5}{7}$$

$$D_{avg} = C_{air}(\text{ mg}/\text{m}^3) \times \frac{IR_{mice}(\text{ m}^3/\text{day})}{bw_{mice}} \times \frac{6.17}{24} \times \frac{5}{7}$$

<u>Estimation of Human Cancer Potency</u>

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(\text{mg/kg-day})^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human} / bw_{animal})^{1/4}$$

The default human body weight is 70 kg. As noted above, the average body weights for male rats was calculated to be 0.4458 kg, and the average body weights for male and female mice were calculated to be 0.0479 kg and 0.0521 kg, respectively. The derivation of the human cancer slope factors using these body weights are summarized below in Table 3.

Table 3. Derivation of CSF$_{human}$ using mean animal body weights for the studies and data presented in Tables 1 and 2

Sex/strain/ species	Type of neoplasm	Body Weight (kg)	CSF$_{animal}$ (mg/kg-day)$^{-1}$	CSF$_{human}$ (mg/kg-day)$^{-1}$
Male F344/N rats[a]	Malignant mesothelioma[b]	0.4458	0.0373	
	Adenoma of the nasal respiratory epithelium		0.00400	
	Multisite: malignant mesothelioma; adenoma of the nasal respiratory epithelium		0.0394	0.14
Male B6C3F$_1$ mice[c]	Renal tubule adenoma or carcinoma	0.0479	0.129	**0.80**
Female B6C3F$_1$ mice[d]	Hemangioma or Hemangiosarcoma	0.0521	0.0177	
	Hepatocellular adenoma or carcinoma		0.0800	
	Multisite: hemangioma or hemangiosarcoma; hepatocellular adenoma or carcinoma		0.0906	0.55

[a] The multistage model was used for analyses of the male rat study, using tumor incidence data expressed as effective number.
[b] The top dose group had to be removed during the modeling process to achieve sufficient goodness of fit.
[c] The multistage Weibull model was used for analyses of the male mouse study.
[d] The multistage model was used for analyses of the female mouse study, using poly-3 adjusted tumor incidences.

As shown in Table 3, male mice were the most sensitive to the carcinogenic effects of vinylidene chloride, and thus the NSRL for vinylidene chloride will be based on the human cancer slope factor derived from that study, 0.80 (mg/kg-day)$^{-1}$.

Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}. This value is divided by the slope factor, 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 body weight for humans. When the calculation is for the general population, the body weight is assumed to be 70 kg[24]. The intake can be converted to a µg per day amount by

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[24] Section 25703(a)(8)

multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$NSRL = \frac{10^{-5} \times 70 \, kg}{CSF_{human}} \times 1000 \, \mu g/mg.$$

As indicated previously, the human cancer slope factor for vinylidene chloride derived from the male mouse study data presented in Table 1 is 0.80 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 0.88 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

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

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

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
Vinylidene chloride	0.88
…	

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 vinylidene chloride. 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[25].

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 NTP report entitled "Toxicology and Carcinogenesis Studies of Vinylidene Chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F$_1$/N Mice (Inhalation Studies)"[26], the IARC monograph[27] and the publications by Bailer and Portier (1988)[28] and Anderson *et al.* (1983)[29] were relied on by OEHHA for calculating the NSRL for vinylidene chloride. The NTP report and the IARC monograph include 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. Bailer and Portier (1988) describes the poly-3 method used to adjust for intercurrent mortality. Anderson *et al.* (1983) provides equations to calculate inhalation rates. Copies of these documents will be included in the regulatory record for this proposed action. 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

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[25] Health and Safety Code sections 25249.9(b) and 25249.10(c)

[26] National Toxicology Program (NTP, 2015). Toxicology and Carcinogenesis Studies of Vinylidene Chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F$_1$/N Mice (Inhalation Studies). NTP Technical Report Series No. 582. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

[27] International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php

[28] Bailer AJ and Portier CJ (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. Biometrics **44**(2): 417-431.

[29] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983), Quantitative approaches in use to assess cancer risk. *Risk Analysis.***3**:277-295.

25705(b) would be to not adopt a NSRL for the chemical. Failure to adopt an 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.

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. Vinylidene chloride has been proposed to be listed as known to the state to cause cancer under Proposition 65; therefore, businesses that manufacture, distribute or sell products with vinylidene chloride in the state will be required to provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure.

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 Californian residents.