PRE-REGULATORY DRAFT – FOR DISCUSSION PURPOSES ONLY
SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65
TITLE 27, CALIFORNIA CODE OF REGULATIONS

POSSIBLE AMENDMENTS TO: SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK AND ARTICLE 9: MISCELLANEOUS

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Since the addition of vinyl acetate[1] to the Proposition 65[2] list, the Office of Environmental Health Hazard Assessment (OEHHA) issued an information letter on exposure to vinyl acetate from consumer products, and has heard from multiple stakeholders about the absence of a safe harbor level for this chemical. *As a starting point for discussion*, OEHHA has developed a possible set of amendments to the existing regulations which are being published for public comment. This document provides a general discussion of those possible amendments.

The regulatory amendments would add a no significant risk level (NSRL) for vinyl acetate to Title 27, California Code of Regulations, section 25705(b)[3] and add a new section 25901 to clarify the analytical methods that may be used to demonstrate vinyl acetate exposures when establishing the basis of a Certificate of Merit for Proposition 65 purposes.

[1] Vinyl acetate was listed for cancer on January 3, 2025.

[2] 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, is hereafter referred to as “Proposition 65” or “The Act.”

[3] All further regulatory references are to Title 27 of the Cal. Code of Regs., unless otherwise indicated.

GENERAL BACKGROUND

Proposition 65

Proposition 65 was enacted as a ballot initiative on November 4, 1986. OEHHA is the lead state entity responsible for the implementation of Proposition 65.[4] OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act.[5] 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.[6] The Act also prohibits the discharge of listed chemicals to sources of drinking water.[7] Warnings are not required when exposures to a listed chemical do not pose a significant risk.[8]

Vinyl acetate

Vinyl acetate is used as monomer in the production of polymers and copolymers such as polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate copolymers, and polyvinyl chloride-acetate copolymers. These polymers are used in adhesives, heat sealing films, paper coatings, textile and leather finishings, plastics, resins, paints, inks, lacquers, pesticides, and cosmetics. Vinyl acetate and vinyl acetate-based polymers have been approved for use as food additives.

Proposition 65 No Significant Risk Levels

The NSRLs adopted by OEHHA provide a “safe harbor” in that any exposure that does not exceed the adopted value is deemed not to require a warning. Thus, a person knowingly and intentionally causing an exposure in the course of doing business that conforms to this limit has certainty that no warning is required. In cases where exposure to a chemical exceeds the NSRL, that protection no longer applies. In such a case, the person causing the exposure must either provide a warning or be prepared to demonstrate that the exposure poses no significant risk, defined in section 25703 as one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question.

[4] Health and Safety Code section 25249.12 and Cal. Code of Regs., Title 27, section 25102(o).

[5] Health and Safety Code section 25249.12(a).

[6] Health and Safety Code section 25249.6.

[7] Health and Safety Code section 25249.5.

[8] Health & Safety Code section 25249.10(c). Likewise, a warning is not required if a discharge or release does not cause a significant amount of the listed chemical to enter any source of drinking water, Health and Safety Code section 25249.9(b).

Under section 25705(a), OEHHA's NSRLs are safe harbor levels that are deemed to comply with the Act. However, businesses are not required to rely on an NSRL to demonstrate that their product does not require a Proposition 65 warning. As stated in existing section 25701(a), "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." Thus, an NSRL does not create a requirement or a mandatory threshold; rather, it provides guidance to businesses that choose to rely on the NSRL instead of developing their own analysis. These safe harbor levels are intended to simplify compliance.

POSSIBLE NSRL FOR VINYL ACETATE

The possible NSRL for vinyl acetate is 11 micrograms per day (µg/day). This level is based on a carcinogenicity study in rodents and was derived using the methods described in section 25703.

To develop the proposed NSRL for vinyl acetate, OEHHA relied primarily on the 2024 OEHHA document entitled "Evidence on the Carcinogenicity of Vinyl Acetate",[9] and Volume 63 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans entitled "Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals".[10] The OEHHA document and the IARC monograph summarize the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of vinyl acetate.

The NSRL for vinyl acetate is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.[11]

[9] Office of Environmental Health Hazard Assessment (OEHHA), 2024. Evidence on the Carcinogenicity of Vinyl Acetate. California Environmental Protection Agency, OEHHA. Reproductive and Cancer Hazard Assessment Branch. Available at: https://oehha.ca.gov/sites/default/files/media/downloads/crnr/vinylacetatehid100424.pdf

[10] International Agency for Research on Cancer (IARC) 1995. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 63, Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Dry-Cleaning-Some-Chlorinated-Solvents-And-Other-Industrial-Chemicals-1995.

[11] Section 25703(a)(4).

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the data from the available rodent carcinogenicity studies of vinyl acetate, which were summarized in OEHHA (2024),[12] and determined that the long-term drinking water studies conducted by the Ramazzini Institute in male and female F_1 Wistar rats[13] and male and female F_1 Swiss mice[14] and by researchers at the National Cancer Institute (NCI) in female F344 rats[15,16] met the criterion in section 25703 as being sensitive studies of sufficient quality. Other studies in which tumors were observed following vinyl acetate exposure were determined to be less sensitive than these studies. This determination was made because the selected studies had: (i) higher incidences of tumors across more tissue sites, (ii) tumors at multiple administered concentrations, and (iii) tumors at lower administered concentrations compared to less sensitive studies.

In the F344 female rat study conducted by NCI researchers and Lijinsky and Reuber (1983)[17] and Experimental Pathology Laboratories, Inc. (EPL 1982),[18] female rats (n = 20) were exposed to vinyl acetate starting at seven or eight weeks of age in drinking water at concentrations of 0, 1000, or 2500 milligrams per liter (mg/L; equivalent to parts per million [ppm]) five days per week for 100 weeks and observed for up to an additional 30 weeks. The lifetime average daily doses of vinyl acetate administered in this study were calculated by OEHHA to be 0, 57.14, and 142.86 milligram per kilogram-body weight per day (mg/kg-day). Survival in vinyl acetate treated groups was not significantly different from controls.

In this study rare uterine adenocarcinomas were observed in treated animals, with a statistically significant increasing trend with dose. Additionally, statistically significant increases in tumor incidences of endometrial stromal polyps, hepatocellular adenoma, and thyroid C-cell adenoma were observed in the high-dose group by pairwise comparison with control, each with statistically significant dose-related trends. A significant dose-related trend in the incidence of pituitary gland adenomas was also

[12] OEHHA (2024), full citation provided above.

[13] Belpoggi F, Soffritti M, Minardi F, Ciliberti A, Padovani M, Cattin E, and Maltoni C. (2002). Results of a long-term carcinogenicity bioassay on vinyl acetate monomer in Wistar rats. Eur J Oncol 7:279-293.

[14] Maltoni C, Ciliberti A, Lefemine G. Soffritti M. (1997). Results of a long-term experimental study on the carcinogenicity of vinyl acetate monomer in mice. Ann N Y Acad Sci 837:209-238.

[15] Experimental Pathology Laboratories (EPL 1982). Bioassay of Vinyl Acetate in F344 Rats Pathology Report Addendum.

[16] Lijinsky W and Reuber MD. (1983), Chronic toxicity studies of vinyl acetate in Fischer rats. Toxicol Appl Pharmacol 68:43-53.

[17] Lijinsky and Reuber 1983, full citation provided above.

[18] EPL 1982, full citation provided above.

observed (Table 1). The tumor incidence data presented in Table 1 were used to estimate cancer potency. As adenocarcinomas of the uterus and endometrial stomal polyps arise from different cell types, they will be treated as separate tumor types.[19]

Table 1. Tumor incidences[a] of treatment-related lesions in female F344 rats administered vinyl acetate in drinking water (EPL 1982; Lijinsky and Reuber 1983)

Tumor site	Tumor type	Administered Concentration (ppm)			Trend Test p-value
		0	1000	2500	
Liver	Hepatocellular adenoma	0/20	0/20	6/20**	< 0.001
Uterus	Adenocarcinoma	0/18	1/20	4/20	< 0.05
	Endometrial stromal polyp	0/18	3/20	5/20*	< 0.05
Thyroid gland	C-cell adenoma	0/17	2/19	5/20*	< 0.05
Pituitary	Adenoma	6/17	8/19	12/18	< 0.05

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined at the end of the study.
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.1$. Exact trend test conducted by OEHHA.
ppm, parts per million

In the Belpoggi et al. 2002 Wistar rat studies,[20] male (n = 64–86) and female (n = 69–95) F_1 rats were exposed to vinyl acetate in drinking water at concentrations of 0, 1000, or 5000 ppm starting *in utero* and through lactation (via exposure to F_0 rats), and post-weaning via drinking water (*ad libitum*) until 104 weeks of age. At the end of the treatment period, all animals received tap water until natural death. The lifetime average daily doses of vinyl acetate administered in the studies were calculated by OEHHA to be 0, 64.16, and 320.82 mg/kg-day for male F_1 rats, and 0, 63.82, and 319.08 mg/kg-day for female F_1 rats. Survival of male F_1 rats was slightly decreased in the low-dose group compared to controls, and survival in the high-dose group was not significantly different than controls. In female F_1 rats survival in vinyl acetate treated groups was not significantly different from controls.

In the male F_1 rat study, statistically significant increases in incidences of squamous cell carcinoma of the oral cavity and lips and of adrenal gland pheochromoblastoma were observed in the high dose group by pairwise comparison with control, each with statistically significant dose-related trends. A statistically significant increased incidence

[19] McConnell EE, Solleveid HA, Swenberg JA, Boorman GA (1986). Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies. J Natl Cancer Inst 76:283-289

[20] Belpoggi et al. (2002), full citation provided above.

of exocrine adenoma of the pancreas was observed in the low dose group by pairwise comparison with control. Additionally, significant increases by trend test were observed for squamous cell carcinoma of the esophagus and of the forestomach, and for carcinoma of the pharynx (Table 2). The tumor incidence data presented in Table 2 were used to estimate cancer potency.

In the female F_1 rat study, statistically significant increases in incidences of lymphoma and leukemia, squamous cell carcinoma of the oral cavity and lips and of the tongue, and adenocarcinoma of the uterus were observed in the high dose group by pairwise comparison with control, each with statistically significant dose-related trends. Additionally, significant increases by trend test were observed for squamous cell carcinoma of the esophagus and of the forestomach (Table 2). The tumor incidence data presented in Table 2 were used to estimate cancer potency.

Table 2. Tumor incidences[a] of treatment-related lesions in male and female F_1 Wistar rats administered vinyl acetate in drinking water (Belpoggi et al. 2002)

Sex	Tumor site	Tumor type	Administered Concentration (ppm)			Trend Test p-value
			0	1000	5000	
Male	Oral cavity and lips	Squamous cell carcinoma	3/86	1/64	12/82**	< 0.001
	Pharynx	Carcinoma	0/86	0/64	3/82	< 0.05
	Esophagus	Squamous cell carcinoma	0/86	0/64	3/82	< 0.05
	Forestomach	Squamous cell carcinoma	0/86	0/64	4/82	< 0.05
	Pancreas	Exocrine adenoma	6/86	14/64**	4/82	NS
	Adrenal gland	Pheochromoblastoma	0/86	1/64	5/82*	0.01
Female	Hemolympho-reticular tissues	Lymphomas and leukemias	3/69	5/73	14/95*	< 0.01
	Oral cavity and lips	Squamous cell carcinoma	5/69	11/73	24/95**	< 0.01
	Tongue	Squamous cell carcinoma	0/69	0/73	6/95*	< 0.01
	Esophagus	Squamous cell carcinoma	0/69	1/73	4/95	< 0.05
	Forestomach	Squamous cell carcinoma	0/69	0/73	4/95	< 0.05
	Uterus	Adenocarcinoma	4/69	5/73	19/95**	< 0.001

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined at the end of the study.
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.1$, *** $p < 0.001$, NS not significant.
Exact trend test conducted by OEHHA.
ppm, parts per million

In the Maltoni et al. 1997 F_1 Swiss mouse studies,[21] male (n = 37–49) and female (n = 44–48) mice were exposed to vinyl acetate in drinking water at concentrations of 0, 1000, or 5000 ppm starting *in utero* on gestation day 12 and through lactation (via exposure to F_0 mice), and post-weaning via drinking water *ad libitum* for 78 weeks. After the treatment period ended, mice were given tap water until natural death. The lifetime average daily doses of vinyl acetate administered in the studies were calculated by OEHHA to be 0, 114.42, and 572.08 mg/kg-day for male F_1 mice, and 0, 129.2, and

[21] Maltoni et al. (1997), full citation provided above.

645.99 mg/kg-day for female F_1 mice. Survival of male and female F_1 mice in these studies was increased in the high-dose groups compared to controls.

In the male F_1 mouse study, statistically significant increases in tumor incidences of squamous cell carcinoma of the oral cavity, and esophagus, and of forestomach acanthoma were observed in the high-dose group by pairwise comparison with control, each with statistically significant dose-related trends (Table 3). Additionally, an increase in tumor incidence of squamous cell carcinoma of the tongue was observed with a statistically significant dose-related trend. The tumor incidence data presented in Table 3 were used to estimate cancer potency.

In the female F_1 mouse study, statistically significant increases in tumor incidences of squamous cell carcinoma of the oral cavity, tongue, esophagus, and forestomach, and of forestomach acanthoma were observed in the high-dose group by pairwise comparison with control, each with statistically significant dose-related trends. Significant dose-related trends for esophagus acanthoma, uterine leiomyosarcoma, lung adenoma, mammary gland liposarcoma, and Zymbal gland carcinoma were also observed (Table 3). The tumor incidence data presented in Table 3 were used to estimate cancer potency. Due to the way the incidences of acanthoma and squamous cell carcinoma of the esophagus and forestomach were reported,[22] the combined incidences of acanthoma and squamous cell carcinoma of the esophagus and of the forestomach are not known, thus incidence data for these separate tumor types were used in the multi-site cancer potency analysis.

[22] Maltoni et al. (1997), full citation provided above.

Table 3. Tumor incidences[a] of treatment-related lesions in male and female F_1 Swiss mice administered vinyl acetate in drinking water (Maltoni et al. 1997)

Sex	Tumor site	Tumor type	Administered Concentration (ppm)			Trend Test p-value
			0	1000	5000	
Male	Oral cavity	Squamous cell carcinoma	0/38	0/37	10/49**	< 0.0001
	Tongue	Squamous cell carcinoma	1/38	0/37	7/49	< 0.01
	Esophagus	Squamous cell carcinoma	0/38	0/37	12/49***	< 0.0001
	Forestomach	Acanthoma	0/38	1/37	8/49**	< 0.01
Female	Oral cavity	Squamous cell carcinoma	0/48	0/44	9/48**	< 0.0001
	Tongue	Squamous cell carcinoma	0/48	0/44	12/48***	< 0.0001
	Esophagus	Acanthoma	0/48	0/44	3/48	< 0.05
		Squamous cell carcinoma	0/48	0/44	18/48***	< 0.0001
	Forestomach	Acanthoma	0/48	0/44	11/48***	< 0.0001
		Squamous cell carcinoma	0/48	0/44	7/48**	< 0.001
	Uterus	Leiomyosarcoma	0/48	2/44	4/48	< 0.05
	Lung	Adenoma	6/48	3/44	11/48	< 0.05
	Mammary gland	Liposarcoma	0/48	0/44	3/48	< 0.05
	Zymbal gland	Carcinoma	0/48	2/44	4/48	< 0.05

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined at the end of the study.
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Exact trend test conducted by OEHHA.
ppm, parts per million

Model Used to Estimate Cancer Potency

As summarized in OEHHA (2024)[23] mechanistic data, including mechanistic information discussed in IARC (1995), support the observations that vinyl acetate (i) can be metabolically activated to an electrophilic chemical (acetaldehyde) and form DNA adducts, (ii) causes genotoxicity including clastogenicity and DNA damage, and (iii) induces cell proliferation and pre-neoplastic lesions such as hyperplasia and dysplasia.

[23] OEHHA (2024), full citation provided above.

More specific data relevant to possible mechanisms of vinyl acetate carcinogenicity are summarized and discussed in OEHHA (2024).

Based on consideration of the available mechanistic information, a multistage model was applied to derive cancer potency estimates for the studies summarized above, following the guidance in section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial:

$$p(d) = \beta_0 + (1 - \beta_0)\left(1 - \exp\left[-\left(\beta_1 d + \beta_2 d^2 + \cdots + \beta_j d^j\right)\right]\right)$$

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

To derive a measure of the cancer response to vinyl acetate (per mg/kg-day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's Benchmark Dose Software (BMDS).[24] The multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in US EPA's 2005 cancer risk assessment guidelines.[25]

For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS[26] 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 models for 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 in a given study, 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."

[24] US EPA Benchmark Dose Software (BMDS). National Center for Environmental Assessment. Available from: BMDS Online, BMDS Desktop, and pybmds | US EPA

[25] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

[26] US EPA BMDS, full citation provided above.

Calculation of Average Daily Doses

The lifetime average daily dose in units of mg/kg-day of vinyl acetate was calculated for each dose group within each study, based on the administered concentrations, exposure regimen, animal body weights and water consumption. In making these calculations, it is assumed that 1 mg of vinyl acetate per L of water is equivalent to 1 ppm.

Use of the body weight data for male and female F_1 Wistar rats in Belpoggi et al. (2002),[27] which was reported for animals aged 24 to 104 weeks would yield an overestimate of body weight during the exposure period, which started *in utero*. Therefore, body weights for male and female Wistar rats were estimated based on NTP historical control data from drinking water studies in Wistar Han rats.[28] In the case of the female F344 rat study,[29,30] body weight was calculated based on the author's report of the lifetime intake of vinyl acetate. Body weight data for male and female F_1 Swiss mice were presented in Figures 3 and 4 of Maltoni et al. (1997)[31] and values were extracted using GetData Graph Digitizer. The average animal body weights (BW_{animal}) for controls in each of the studies are shown in Table 4 below.

None of the studies reported drinking water consumption; therefore, default values from Gold and Zeiger (1997)[32] were used and are listed in Table 4 below.

[27] Belpoggi et al. (2002), full citation provided above.

[28] National Toxicology Program (NTP) 2016. Historical Control Body Weights for Gavage/Water Studies. Historical Controls Database. National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/historical_controls/ntp2000_2016/whrats_bodywt_combined_2016.pdf

[29] EPL (1982), full citation provided above.

[30] Lijinsky and Reuber (1983), full citation provided above.

[31] Maltoni et al. (1997), full citation provided above.

[32] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

Table 4. Average body weights of experimental animals from the control groups

Publication	Sex/strain/species	Average body weight (kg)	Average water consumption (mL/day)
Belpoggi et al. (2002)	Male F_1 Wistar rats	0.5208	25
	Female F_1 Wistar rats	0.3117	20
EPL (1982), Lijinsky and Reuber (1983)	Female F344 rats	0.2500	20
Maltoni et al. (1997)	Male F_1 Swiss mice	0.0431	5
	Female F_1 Swiss mice	0.0387	5

kg, kilograms; mL/day, milliliters per day

For the studies in male and female F_1 Wistar rats[33] and male and female F_1 Swiss mice,[34] average daily doses (D_{avg}) were determined using the following equation:

$$D_{avg}\ (\text{mg/kg-day}) = \frac{\text{concentration (ppm [mg/L])}}{1000\ (\text{mL/L}) \times BW_{animal}\ (\text{kg})} \times \text{average water consumption (mL/day)}$$

For the study in female F344 rats,[35] average daily doses (D_{avg}) were determined by multiplying the administered concentration of vinyl acetate (in units of mg/kg-bw) by 5/7 to account for a five day per week dosing regimen.

$$D_{avg}\ (\text{mg/kg-day}) = \frac{\text{concentration (ppm [mg/L])}}{1000\ (\text{mL/L}) \times BW_{animal}\ (\text{kg})} \times \text{average water consumption (mL/day)} \times \frac{5}{7}$$

The lifetime average daily doses, calculated using the equations as specified above, are shown in Table 5 below.

[33] Belpoggi et al. (2002), full citation provided above.

[34] Maltoni et al. (1997), full citation provided above.

[35] EPL 1982, full citation provided above.

Table 5. Lifetime average daily doses for selected animal carcinogenicity studies of vinyl acetate (Belpoggi et al. 2002; EPL 1982, Lijinsky and Reuber 1983; Maltoni et al. 1997).

Publication	Sex/strain/species	Lifetime average daily doses (mg/kg-day)
Belpoggi et al. (2002)	Male F_1 Wistar rats	0, 48.00, 240.02
	Female F_1 Wistar rats	0, 63.82, 319.08
EPL (1982), Lijinsky and Reuber (1983)	Female F344 rats	0, 57.14, 142.86
Maltoni et al. (1997)	Male F_1 Swiss mice	0, 114.42, 572.08
	Female F_1 Swiss mice	0, 129.2, 645.99

mg/kg-day, milligram per kilogram per day

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to section 25703(a)(6), dose in units of milligrams of chemical per kilogram of bodyweight per day, scaled to the three-quarters power, is assumed to produce the same degree of effect in different species.[36] There is no "assumptio[n] scientifically more appropriate, based upon the available data" for vinyl acetate, so the default assumption was used.[37] This adjustment accounts for interspecies differences in toxicokinetics and toxicodynamics. The default toxicokinetic and toxicodynamic factors are the square root of the interspecies factor.

Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by taking the animal potency (CSF_{animal}) and multiplying 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 $(mg/kg\text{-}day)^{-1}$:

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

The default human body weight is 70 kg. The average body weights are shown above in Table 4. The derivations of the human cancer slope factors using these body weights are summarized below in Table 6.

[36] Three-quarter power scaling for bodyweight is mathematically equivalent to ¼ power scaling for cancer potency due to the unit conversion of kg to $(mg/kg\text{-}day)^{-1}$.

[37] Section 25703(a).

Table 6. Derivation of CSF_{human} using multisite CSF animal values and mean animal body weights for the studies and data presented in Tables 4 and 5

Publications	Sex/ Strain/ Species	Tumor sites used to estimate potency	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Belpoggi et al. (2002)	Male F_1 Wistar rats	Oral cavity SCC Pharynx SCC Esophagus SCC Forestomach SCC Pancreas exocrine adenoma Adrenal gland pheochromoblastoma	0.5208	0.00740	0.025
	Female F_1 Wistar rats	Lymphoma and leukemias Oral cavity SCC Tongue SCC Esophagus SCC Forestomach SCC Uterine adenocarcinoma	0.3117	0.00252	0.0098
EPL (1982), Lijinsky and Reuber (1983)	Female F344 rats	Liver adenomas Uterine adenocarcinoma Uterine endometrial stromal polyps Thyroid C-cell adenoma Pituitary adenoma	0.2500	0.0160	**0.065**
Maltoni et al. (1997)	Male F_1 Swiss mice	Oral cavity SCC Tongue SCC Esophagus SCC Forestomach Acanthoma	0.0431	0.00160	0.010
	Female F_1 Swiss mice	Oral cavity SCC Tongue SCC Esophagus Acanthoma Esophagus SCC Forestomach SCC Uterine Leiomyosarcoma Mammary gland liposarcoma Zymbal gland carcinoma	0.0387	0.00292	0.019

First degree multistage polynomial model fit to data.
SCC: squamous cell carcinoma
Bolded value represents potency used for no significant risk level calculation

As shown in Table 6, dose-response modeling of the multisite data from the female F344 rat study yielded the highest cancer slope factor. Consistent with section 25703(a)(3), the human cancer slope factor derived from the female F344 rat study was selected; it is the most sensitive study and the most health protective. Thus, the human cancer slope factor of 0.065 $(mg/kg\text{-}day)^{-1}$, derived from the study in female F344 rats, was used to calculate the vinyl acetate NSRL.

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 calculated to result in one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}.[38] This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram body weight 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/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.[39] The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{\text{CSF}_{\text{human}}} \times 1000\ \mu\text{g/mg}$$

As indicated previously, the human cancer slope factor for vinyl acetate derived from the female rat study data and exposure parameters presented in Table 1 is 0.065 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 11 µg/day.

POSSIBLE NEW SECTION 25901

Proposed section 25901 would state as follows:

> To provide the Attorney General with factual information sufficient to establish the basis of a certificate of merit, as required by Health and Safety Code section 25249.7(d), a private party alleging exposure to vinyl acetate must provide facts showing exposure to the listed vinyl acetate monomer, CAS no. 108-05-4. If such factual information includes the concentration of vinyl acetate monomer in a product, that concentration must not include the amount of vinyl acetate monomer resulting from the breakdown of vinyl acetate-containing polymers in a manner which would not otherwise occur during a consumer product exposure, as defined in Cal. Code Regs., tit. 27, section 25600.1.

[38] Section 25703(b).

[39] Section 25703(a)(8).

The cited section defines a “consumer product exposure” as “an exposure that results from a person's acquisition, purchase, storage, consumption, or any reasonably foreseeable use of a consumer product, including consumption of a food.”

Under Health and Safety Code section 25249.7(d), a person bringing a Proposition 65 action in the public interest may do so only if the person has first provided notice to the alleged violator, along with the Attorney General and the district attorney, city attorney, or prosecutor in whose jurisdiction the violation occurred. For warning violations, the notice must be accompanied by a “certificate of merit” that the person executing the certificate “has consulted with one or more persons with relevant and appropriate experience or expertise who has reviewed facts, studies, or other data regarding the exposure to the listed chemical that is the subject of the action, and that, based on that information, the person executing the certificate believes there is a reasonable and meritorious case for the private action.”[40] Factual information sufficient to establish the basis of the certificate must be served on the Attorney General. (*Id.*).

This proposal clarifies the methods that can provide sufficient factual information for this purpose. This is necessary because vinyl acetate is mainly used in the production of polymers and copolymers, for instance polyvinyl acetate (PVA), polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate (EVA) copolymers, polyvinyl chloride-acetate copolymers, and vinyl acetate-vinyl laurate copolymers. However, these polymers and copolymers are not listed under Proposition 65; only the vinyl acetate monomer, CAS no. 108-05-4, is listed. This monomer is uncommon in consumer products, although residual unreacted monomer *may* be present in some products made with vinyl acetate polymers and copolymers.

The fact that a consumer product contains a vinyl acetate-based polymer or copolymer is not, by itself, factual information sufficient to establish a potential exposure to vinyl acetate. A test which broke down the bonds of a vinyl acetate-containing polymer or copolymer could therefore give misleading results, if those bonds would otherwise remain intact during a consumer product exposure. By making that fact explicit, this proposed regulation ensures accuracy when conducting product testing.

Of course, whenever a chemical monomer is listed under Proposition 65, only an exposure to that specific monomer, with its individual CAS number, requires a warning for that specific listed chemical. This is true under existing law and would not be changed by proposed section 25901, which is only intended to provide information and does not alter existing Proposition 65 requirements for other listed monomers. It is thus possible that additional listed monomers, other than vinyl acetate, may be components of unlisted polymers, thus posing testing issues similar to vinyl acetate. The proposed

[40] Health & Safety Code section 25249.7(d)(1).

regulation addresses only vinyl acetate because of that monomer's relative rarity in consumer goods and its frequent use in polymers, as discussed above, and because it provides clarity to both the regulated community and to persons enforcing Proposition 65 to provide this guidance simultaneously with a proposed NSRL for vinyl acetate.

INPUT ON THE SET OF POSSIBLE AMENDMENTS

OEHHA is seeking public input concerning these possible regulatory amendments to adopt an NSRL for vinyl acetate in section 25705(b) and add a new section 25901 to clarify the analytical methods that may be used to demonstrate vinyl acetate exposures when establishing the basis of a Certificate of Merit for Proposition 65 purposes.