INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

TRICHLOROACETIC ACID

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for trichloroacetic acid (CAS No. 76-03-9) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 9.9 micrograms per day (µg/day) for trichloroacetic acid 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. The NSRL provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

Trichloroacetic acid was listed as known to the state to cause cancer under Proposition 65 on September 13, 2013.

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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).

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for trichloroacetic acid, OEHHA relied on two studies by DeAngelo *et al*. (2008)[5,6], a study by Bull *et al*. (2002)[7], Volume 106 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents"[8], the National Toxicology Program (NTP) report entitled "Toxicology Studies of Bromodichloroacetic Acid (CAS No. 71133-14-7) in F344/N Rats and B6C3F$_1$/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F$_1$/N Mice (Drinking Water

[5] DeAngelo AB, Daniel FB, Wong DM, George MH (2008). The induction of hepatocellular neoplasia by trichloroacetic acid administered in the drinking water of the male B6C3F1 mouse. J Toxicol Environ Health A 71(16):1056-68.

[6] Individual animal survival and tumor data provided by the study authors were obtained from the US EPA in August 2016 (104-week study) and January 2017 (60-week study).

[7] Bull RJ, Orner GA, Cheng RS, Stillwell L, Stauber AJ, Sasser LB, Lingohr MK, Thrall BD (2002). Contribution of dichloroacetate and trichloroacetate to liver tumor induction in mice by trichloroethylene. Toxicol Appl Pharmacol 182(1):55-65.

[8] International Agency for Research on Cancer (IARC 2014). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 106, Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol106/index.php

Studies)"[9], 11 additional genotoxicity studies[10,11,12,13,14,15,16,17,18,19,20], and two reviews[21,22]. The 2014 IARC Monograph summarizes the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of trichloroacetic acid. The 2015 NTP report primarily discusses toxicological effects of bromodichloroacetic acid, but also summarizes genotoxic information on dichloroacetic acid, a metabolite of trichloroacetic acid. Anderson et al. (1972), Zhang et al. (2016), Hu et al. (2017), Varshney et al. (2013; 2014), Hassoun et al. (2014), Stalter et al. (2016), Kurinnyi (1984), Zuo et al. (2017), Ono et al. (1991), Hassoun and Dey (2008), NRC (1987), and Daniel et al. (1993) provide additional information on genotoxicity.

[9] National Toxicology Program (NTP 2015). Toxicology Studies of Bromodichloroacetic Acid (CAS No. 71133-14-7) in F344/N Rats and B6C3F$_1$/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F$_1$/N Mice (Drinking Water Studies). NTP Technical Report Series No. 583. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

[10] Anderson KJ, Leighty EG, Takahashi MT (1972). Evaluation of Herbicides for Possible Mutagenic Properties. J. Agric. Food Chem. 20(3), pp 649–656.

[11] Zhang SH, Miao DY, Tan L, Liu AL, Lu WQ (2016). Comparative cytotoxic and genotoxic potential of 13 drinking water disinfection by-products using a microplate-based cytotoxicity assay and a developed SOS/umu assay. Mutagenesis. 31(1):35-41.

[12] Hu Y, Tan L, Zhang SH, Zuo YT, Han X, Liu N, et al. (2017). Detection of genotoxic effects of drinking water disinfection by-products using Vicia faba bioassay. Environ Sci Pollut Res Int. 24(2):1509-1517.

[13] Varshney M, Chandra A, Chauhan LK, Goel SK (2013). Micronucleus induction by oxidative metabolites of trichloroethylene in cultured human peripheral blood lymphocytes: a comparative genotoxicity study. Environ Sci Pollut Res Int. 20:8709-8716.

[14] Varshney M, Chandra A, Chauhan LK, Goel SK (2014). In vitro cytogenetic assessment of trichloroacetic acid in human peripheral blood lymphocytes. Environ Sci Pollut Res Int. 21(2):843-50.

[15] Hassoun E, Cearfoss J, Mamada S, Al-Hassan N, Brown M, Heimberger K, Liu MC (2014). The effects of mixtures of dichloroacetate and trichloroacetate on induction of oxidative stress in livers of mice after subchronic exposure. J Toxicol Environ Health A. 77(6):313-23.

[16] Stalter D, O'Malley E, von Gunten U, Escher BI. (2016). Fingerprinting the reactive toxicity pathways of 50 drinking water disinfection by-products. Water Res 91: 19-30.

[17] Kurinnyĭ A. (1984). Cytogenetic activity of the herbicide sodium trichloroacetate. TSitologiia i genetika 18(4): 318-319.

[18] Zuo YT, Hu Y, Lu WW, et al. (2017). Toxicity of 2,6-dichloro-1,4-benzoquinone and five regulated drinking water disinfection by-products for the Caenorhabditis elegans nematode. J Hazard Mater 321: 456-463.

[19] Ono Y, Somiya I, Kawamura M (1991). The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorination and ozonation processes. Water Science and technology 23(1-3): 329-338.

[20] Hassoun EA, Dey S (2008). Dichloroacetate- and trichloroacetate-induced phagocytic activation and production of oxidative stress in the hepatic tissues of mice after acute exposure. J Biochem Mol Toxicol 22(1): 27-34.

[21] National Research Council (NRC 1987). Chemistry and toxicity of selected disinfectants and by-products. Drinking water and health: disinfectants and disinfectant by-products 7: 133-143,182-133.

[22] Daniel F, Meier J, Deangelo A. (1993). Advances in research on carcinogenic and genotoxic by-products of chlorine disinfection: chlorinated hydroxyfuranones and chlorinated acetic acids. Annali dell'Istituto superiore di sanita 29(2): 279-291.

The NSRL for trichloroacetic acid is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[23].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of trichloroacetic acid and determined that two studies in male mice by DeAngelo *et al*. (2008) and another study in male mice by Bull *et al*. (2002) met the criterion in Section 25703 as being sensitive studies of sufficient quality.

A 60-week study by DeAngelo *et al*. (2008)[24] exposed groups of 35 male B6C3F1 mice to trichloroacetic acid in drinking water at concentrations of 0, 0.05, 0.5, and 5 g/L for 60 weeks. Individual animal survival and liver tumor data were provided by the study authors, and obtained from the US EPA by OEHHA. The lifetime average daily doses of trichloroacetic acid administered in this study were calculated by OEHHA to be 0, 7.7, 68.2, and 602.1 mg/kg-day, based on measured concentrations of trichloroacetic acid and reported average daily water intakes. Survival was not reported to be affected by treatment with trichloroacetic acid at any dose in this study. Statistically significant increases in hepatocellular adenomas, hepatocellular carcinomas, and combined hepatocellular adenomas and carcinomas were observed in the 0.5 and 5 g/L dose groups in male mice compared to controls, with a statistically significant positive trend.

A 104-week study by DeAngelo *et al*. (2008)[25] exposed groups of 65 male B6C3F1 mice to trichloroacetic acid in drinking water at concentrations of 0, 0.05, and 0.5 g/L for 104 weeks. Individual animal survival and liver tumor data were provided by the study authors, and obtained from the US EPA by OEHHA. The lifetime average daily doses of trichloroacetic acid administered in this study were calculated by OEHHA to be 0, 6.7, and 81.2 mg/kg-day, based on measured concentrations of trichloroacetic acid and reported average daily water intakes. Survival was not reported to be affected by treatment with trichloroacetic acid at any dose in this study. A statistically significant increase in hepatocellular adenomas was observed in the 0.5 g/L dose group in male mice compared to controls, with statistically significant positive trends for hepatocellular adenomas, hepatocellular carcinomas, and combined hepatocellular adenomas and carcinomas.

Bull *et al*. (2002)[26] exposed groups of 20 male B6C3F1 mice to trichloroacetic acid in drinking water at concentrations of 0, 0.5, and 2 g/L for 52 weeks. The lifetime average daily doses of trichloroacetic acid administered in this study were calculated by OEHHA

[23] Section 25703(a)(4).
[24] DeAngelo et al. (2008). Full citation provided in footnote 5.
[25] *Ibid*.
[26] Bull et al. (2002). Full citation provided in footnote 7.

to be 0, 54.6, and 237.5 mg/kg-day. Survival was not affected by treatment with trichloroacetic acid at any dose in this study. Statistically significant increases in hepatocellular adenomas and combined hepatocellular adenomas and carcinomas were observed in the 0.5 and 2 g/L dose groups in male mice compared to controls, with statistically significant positive trends for hepatocellular adenomas and combined hepatocellular adenomas and carcinomas.

The tumor incidence data used to estimate cancer potency from each of these studies are presented in Table 1.

Table 1. Liver tumor incidences of treatment-related lesions in male B6C3F$_1$ mice administered trichloroacetic acid via drinking water (DeAngelo *et al*. 2008[a]; Bull *et al.* 2002)

Study	Study duration	Tumor type	Administered concentrations (g/L)					Trend test p-value[b]
			0	0.05	0.5	2	5	
DeAngelo *et al*. (2008)[a,c]	60 weeks	Hepatocellular adenoma or carcinoma[d] (first occurrence of tumor: week 45)	4/35	5/32	12/34*		19/34***	$p < 0.001$
DeAngelo *et al*. (2008)[a,c]	104 weeks	Hepatocellular adenoma or carcinoma[d] (first occurrence of tumor: week 52)	31/56	21/48	36/51			$p < 0.05$
Bull *et al*. (2002)[e]	52 weeks	Hepatocellular adenoma or carcinoma[d]	0/20		6/20*	8/20**		$p < 0.01$

[a] Individual animal survival and tumor data obtained from US EPA

[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] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[e] The first occurrence of tumor was not given by Bull *et al.* (2002). The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined.

The range of concentrations of trichloroacetic acid administered in drinking water and tested for carcinogenicity was comparable across the three studies. However, the

60-week study of DeAngelo *et al*. (2008) and the Bull *et al*. (2002) study were of shorter duration and had fewer animals in each treatment group than the 104-week study of DeAngelo *et al*. (2008). In addition, the 104-week DeAngelo *et al*. (2008) study is preferable to both the 60-week study of DeAngelo *et al*. (2008) and the 52-week study of Bull *et al.* (2002), as the lifetime study duration does not require application of a correction factor to extrapolate to two years (104 weeks) in estimating lifetime[27] animal cancer incidence. Given these considerations, the 104-week DeAngelo *et al*. (2008) study was judged to be more robust and to provide a better overall estimate of the cancer dose-response. Data from the 60-week DeAngelo *et al*. (2008) study and the 52-week Bull *et al*. (2002) study were also analyzed for comparison.

Estimation of Cancer Potency Using the Multistage Model

In the 2014 monograph, IARC[28] reviewed the mechanistic data for trichloroacetic acid, and concluded there is "moderate evidence suggesting that trichloroacetic acid may act through multiple nongenotoxic mechanisms, leading to liver carcinogenesis". With regard to genotoxicity, IARC stated "the available evidence suggests that trichloroacetic acid is not a genotoxic agent". In mammalian systems, the evidence that IARC reviewed includes positive studies in chromosomal aberrations (CA) *in vivo,* a mixture of positive and negative genotoxicity studies in the induction of DNA strand breaks and micronucleus (MN) formation *in vivo*, three positive and numerous negative bacterial mutation studies, and negative *in vitro* studies for other genotoxicity endpoints.

Besides the mechanistic studies reviewed by IARC (2014), OEHHA identified several additional genotoxicity studies and two earlier reviews[29,30] on trichloroacetic acid. The additional studies include two negative studies[31,32] and one weakly positive) study[33] (SOS/umu mutation assay) in *Salmonella*, one positive study[34] of CA and MN formation in *Vicia faba*, two positive *in vitro* studies of CA[35] and MN formation[36,37] in human peripheral blood lymphocytes, negative *in vitro* studies of CA formation in human

[27] The natural life span of the mouse is assumed to be two years (Gold LS and Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton; and US EPA (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Health and Environmental Assessment, Washington D.C. EPA/600/6-87/008.)
[28] IARC 2014. Full citation provided in footnote 8.
[29] NRC (1987). Full citation provided in footnote 21.
[30] Daniel et al. (1993). Full citation provided in footnote 22.
[31] Anderson et al. (1972). Full citation provided in footnote 10.
[32] Stalter et al. (2016). Full citation provided in footnote 16.
[33] Zhang et al. (2016). Full citation provided in footnote 11.
[34] Hu et al. (2017). Full citation provided in footnote 12.
[35] Varshney et al. (2014). Full citation provided in footnote 14.
[36] *Ibid.*
[37] Varshney et al. (2013). Full citation provided in footnote 13.

peripheral blood lymphocytes and in *C. tectorum* and *A. cepa* seedlings[38], one positive *in vivo* study[39] of liver DNA single strand breaks in mice, one negative *in vivo* study[40] of CA formation in bone marrow in mice, and one negative *in vivo* study[41] of nuclear DNA damage in *C. elegans*.

The 2015 NTP report[42] summarizes the genotoxicity information on dichloroacetic acid, a metabolite of trichloroacetic acid, as follows:

> "Dichloroacetic acid, is consistently positive in bacterial mutagenicity assays in the absence of metabolic activation, gives mixed results in DNA damage (comet) assays, and shows signs of *in vivo* mutagenicity and effects on chromosomal stability in rodents after long-term exposures at high doses".

In addition to the genotoxicity studies of dichloroacetic acid reviewed by NTP (2015), OEHHA identified other genotoxicity studies of this trichloroacetic acid metabolite. These include two positive[43,44] and one negative[45] mutation assays in *Salmonella*, one positive study[46] of chromosomal aberration (CA) and micronucleus (MN) formation in *Vicia faba*, one positive *in vitro* study[47] of MN formation in human peripheral blood lymphocytes, and two positive *in vivo* studies[48,49] of liver DNA single strand breaks in mice.

Based on consideration of the available mechanistic information, a multistage model is applied to derive cancer potency estimates from the two DeAngelo *et al*. (2008) studies and the Bull *et al.* (2002) study, 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 model:

[38] Kurinnyĭ (1984). Full citation provided in footnote 17.
[39] Hassoun et al. (2014). Full citation provided in footnote 15.
[40] Kurinnyĭ (1984). Full citation provided in footnote 17.
[41] Zuo et al. (2017). Full citation provided in footnote 18.
[42] NTP 2015. Full citation provided in footnote 9.
[43] Zhang et al. (2016). Full citation provided in footnote 11.
[44] Ono et al. (1991). Full citation provided in footnote 19.
[45] Stalter et al. (2016). Full citation provided in footnote 16.
[46] Hu et al. (2017). Full citation provided in footnote 12.
[47] Varshney et al. (2013). Full citation provided in footnote 13.
[48] Hassoun et al. (2014). Full citation provided in footnote 15.
[49] Hassoun and Dey (2008). Full citation provided in footnote 20.

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

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 trichloroacetic acid (per mg/kg/day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor at the site of interest was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in the US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[50]. 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". Animal cancer potencies were estimated for each of the three male mouse studies described above.

The natural lifespan of mice is assumed to be two years (104 weeks)[51,52]. To estimate the animal cancer potency from experiments of duration T_e, rather than the natural life span of the animals T, it is assumed that the lifetime incidence of cancer increases with the third power of age. Following Gold and Zeiger[53] and US EPA[54], a correction factor to extrapolate to two years (104 weeks) was required for the cancer slope factors derived from the 52-week study of Bull *et al.* (2002) and the 60-week study of DeAngelo *et al*. (2008). The adjustment was calculated as follows:

$$CSF_{animal,\ adj.} = CSF_{animal} \times (104/\text{length of study in weeks})^3$$

No adjustment was required for the cancer slope factor derived from the 104-week study of DeAngelo *et al*. (2008).

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 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

[50] US EPA Benchmark Dose Software (BMDS) Version 2.7. National Center for Environmental Assessment, US EPA. Available from: http://bmds.epa.gov
[51] Gold and Zeiger (1997). Full citation provided in footnote 27.
[52] US EPA (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Health and Environmental Assessment, Washington D.C. EPA/600/6-87/008.
[53] Gold and Zeiger (1997). Full citation provided in footnote 27.
[54] US EPA (1988). Full citation provided in footnote 27.

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 $(mg/kg\text{-}day)^{-1}$:

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

The default human body weight is 70 kg. As noted above, the average body weights for male mice were calculated to be 0.0400 kg and 0.0447 kg for the 60-week and 104-week studies by DeAngelo *et al*. (2008), respectively, based on the data reported by the study authors for control animals. In the study by Bull *et al*. (2002), the average body weight for the male mice in the control group at 52 weeks was reported to be 0.0462 kg. The derivations of the human cancer slope factors using these body weights are summarized below in Table 2.

Table 2. Derivation of CSF_{human} using mean animal body weights for the studies and data presented in Table 1

Study	Sex/ strain/ species	Type of neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{animal} $(mg/kg\text{-}day)^{-1}$ adjusted for less-than-lifetime study duration	CSF_{human} $(mg/kg\text{-}day)^{-1}$
DeAngelo *et al*. (2008)[a] 60 weeks	Male B6C3F1 mice	Hepatocellular adenoma or carcinoma	0.0400	0.00181	0.00944	0.061
DeAngelo *et al*. (2008)[a] 104 weeks	Male B6C3F1 mice	Hepatocellular adenoma or carcinoma	0.0447	0.0113	Not applicable	**0.071**
Bull *et al*. (2002) 52 weeks	Male B6C3F1 mice	Hepatocellular adenoma or carcinoma	0.0462	0.00449	0.0359	0.22

[a] Individual animal survival and tumor data obtained from US EPA.

OEHHA compared the three studies and determined that the 104-week DeAngelo *et al*. (2008) study was the most appropriate study for cancer dose-response analysis. This study was conducted for 104 weeks, while the two other studies were of shorter duration and had fewer animals in each treatment group. For studies in which the final sacrifice occurs before the assumed natural rodent lifespan (104 weeks), the CSF_{animal} must be adjusted by assuming cancer risk increases with the third power of age. This extrapolation introduces additional uncertainty in the analysis, thus the 104-week DeAngelo *et al*. (2008) study, which also had more animals in each treatment group, is preferred.

The 104-week DeAngelo *et al*. (2008) study was chosen for assessing the carcinogenic effects of trichloroacetic acid, and thus the NSRL for trichloroacetic acid will be based on the human cancer slope factor derived from that study, 0.071 $(mg/kg\text{-}day)^{-1}$.

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[55]. 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 trichloroacetic acid derived from the 104-week male mouse study data of DeAngelo *et al*. (2008)[56] and exposure parameters presented in Table 1 is 0.071 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 9.9 µg/day (rounded to two significant figures).

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
…	
Trichloroacetic acid	9.9

[55] Section 25703(a)(8)
[56] Individual animal survival and tumor data provided by the study authors were obtained from the US EPA.

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 trichloroacetic acid. 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[57].

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 60-week and 104-week studies by DeAngelo *et al*. entitled "The induction of hepatocellular neoplasia by trichloroacetic acid administered in the drinking water of the male B6C3F1 mouse"[58], along with additional data from these studies provided by the study authors and obtained from US EPA[59], were relied on by OEHHA for calculating the NSRL for trichloroacetic acid. OEHHA also relied on a 2002 study by Bull *et al*. entitled "Contribution of Dichloroacetate and Trichloroacetate to Liver Tumor Induction in Mice by Trichloroethylene"[60], on a 2014 IARC monograph[61] summarizing the available data from rodent carcinogenicity studies of trichloroacetic acid and other information relevant to its carcinogenic activity, on a 2015 NTP report[62] summarizing genotoxicity information on the trichloroacetic acid metabolite dichloroacetic acid, and

[57] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[58] DeAngelo et al. (2008). Full citation provided in footnote 5.
[59] Individual animal survival and tumor data provided by the study authors were obtained from the US EPA, in August 2016 and January 2017.
[60] Bull et al. (2002). Full citation provided in footnote 7.
[61] IARC 2014. Full citation provided in footnote 8.
[62] NTP 2015. Full citation provided in footnote 9.

on several other genotoxicity studies[63,64,65,66,67,68,69,70,71,72,73,74,75]. In addition, OEHHA relied on information presented in two additional documents[76,77] in making adjustments for less than lifetime study duration. 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 following Economic Impact Analysis, included in this document, in developing this proposed regulation.

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

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt an 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.

[63] Anderson et al. (1972). Full citation provided in footnote 10.
[64] Zhang et al. (2016). Full citation provided in footnote 11.
[65] Hu et al. (2017). Full citation provided in footnote 12.
[66] Varshney et al. (2014). Full citation provided in footnote 14.
[67] Varshney et al. (2013). Full citation provided in footnote 13.
[68] Hassoun et al. (2014). Full citation provided in footnote 15.
[69] Stalter et al. (2016). Full citation provided in footnote 16.
[70] Kurinnyĭ (1984). Full citation provided in footnote 17.
[71] Zuo et al. (2017). Full citation provided in footnote 18.
[72] Ono et al. (1991). Full citation provided in footnote 19.
[73] Hassoun and Dey (2008). Full citation provided in footnote 20.
[74] NRC (1987). Full citation provided in footnote 21.
[75] Daniel et al. (1993). Full citation provided in footnote 22.
[76] Gold and Zeiger (1997). Full citation provided in footnote 27.
[77] US EPA (1988). Full citation provided in footnote 27.

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 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. Trichloroacetic acid is listed under Proposition 65; therefore, businesses that manufacture, distribute, sell or use products with trichloroacetic acid in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of the 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 Currently Doing Business within the State of California: This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

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