INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

DICHLOROACETIC 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 dichloroacetic acid (CAS No. 79-43-6) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 17 micrograms per day (µg/day) for dichloroacetic 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.

Dichloroacetic acid was listed as known to the state to cause cancer under Proposition 65 on May 1, 1996.

[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 dichloroacetic acid, OEHHA relied on a study by DeAngelo *et al*. (1999)[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 Studies)"[9], and additional genotoxicity studies[10,11,12,13,14,15,16]. The 2014 IARC Monograph summarizes the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of dichloroacetic acid. The 2015 NTP report primarily discusses toxicological effects of bromodichloroacetic acid,

[5] DeAngelo AB, George MH, House DE (1999). Hepatocarcinogenicity in the male B6C3F$_1$ mouse following a lifetime exposure to dichloroacetic acid in the drinking water: Dose-response determination and modes of action. J Toxicol Environ Health A 58(8):485-507.
[6] Individual animal survival and tumor data provided by Dr. DeAngelo, December 2007.
[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
[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] 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.
[11] Hu Y, Tan L, Zhang SH, Zuo YT, Han X, Liu N, Lu WQ, Liu AL (2017). Detection of genotoxic effects of drinking water disinfection by-products using Vicia faba bioassay. Environ Sci Pollut Res Int. 2016 Oct 26. [Epub ahead of print]
[12] 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 (12): 8709-16.
[13] 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.
[14] 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.
[15] 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.
[16] 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.

but also summarizes genotoxic information on dichloroacetic acid, a metabolite of bromodichloroacetic acid. Zhang et al. (2016), Hu et al. (2017), Varshney et al. (2013), Hassoun et al. (2014), Ono et al. (1991), Stalter et al. (2016), and Hassoun and Dey (2008) provide additional information on genotoxicity. The NSRL for dichloroacetic acid is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[17].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of dichloroacetic acid, and determined that the studies in male mice by DeAngelo *et al*. (1999) and Bull *et al*. (2002) met the criterion in Section 25703 as being sensitive studies of sufficient quality.

DeAngelo *et al*. (1999)[18] exposed groups of 83, 35, 55, 71, 55 and 46 male B6C3F$_1$ mice to dichloroacetic acid in drinking water at concentrations of 0, 0.05, 0.5, 1, 2, and 3.5 g/L, respectively, for 26-100 weeks. Individual animal survival and liver tumor data was obtained from Dr. DeAngelo[19]. Interim sacrifices of 10 animals per treatment group were made at 26, 52, and 78 weeks for the 0, 0.5, 1, 2, and 3.5 g/L dose groups; an additional 10 animals in the control group were sacrificed at week 2. There were no interim sacrifices of the animals in the 0.05 g/L dose group. Animals from the 2- and 26-week interim sacrifices were not included in this dose-response analysis. The lifetime average daily doses of dichloroacetic acid administered in this study were calculated and reported by DeAngelo *et al*. (1999) to be 0, 8, 84, 168, 315, and 429 mg/kg-day[20]. Survival was significantly decreased in the two highest dose groups compared to controls, with a significant trend[21]. The majority of early deaths were due to liver tumors. Statistically significant increases in combined hepatocellular adenomas and carcinomas were observed in the 1, 2, and 3.5 g/L dose groups in male mice, with a statistically significant positive trend.

Bull *et al*. (2002)[22] exposed groups of 20 male B6C3F$_1$ mice to dichloroacetic acid in drinking water at concentrations of 0, 0.1, 0.5, and 2 g/L for 52 weeks. The lifetime average daily doses of dichloroacetic acid administered in this study were calculated by OEHHA to be 0, 10.8, 54.1, and 216.5 mg/kg-day. Survival was not affected by treatment with dichloroacetic acid at any dose in this study. Statistically significant

[17] Section 25703(a)(4)
[18] DeAngelo et al. (1999). Full citation provided in footnote 5.
[19] Individual animal survival and tumor data provided by Dr. DeAngelo, December 2007.
[20] DeAngelo et al. (1999). Full citation provided in footnote 5.
[21] *Ibid*.
[22] Bull et al. (2002). Full citation provided in footnote 7.

increases in combined hepatocellular adenomas and carcinomas were observed in the 0.5 and 2 g/L dose groups in male mice, with a statistically significant positive trend.

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 dichloroacetic acid via drinking water (DeAngelo *et al*., 1999 and DeAngelo personal communication, 2007; Bull *et al*., 2002)

Study	Study duration	Tumor type	Administered Concentrations (g/L)							Trend test p-value[a]
			0	0.05	0.1	0.5	1	2	3.5	
DeAngelo *et al*. (1999); DeAngelo, personal communication (2007)[b]	52 – 100 weeks[c]	Hepato-cellular adenoma or carcinoma[d]	20/70	11/33		16/45	35/55***	31/41***	27/31***	$p <$ 0.001
Bull *et al*. (2002)[e]	52 weeks	Hepato-cellular adenoma or carcinoma[d]	0/20		1/20	5/20*		10/19***		$p <$ 0.001

[a] p-values for exact trend test conducted by OEHHA
[b] 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
[c] Tumor incidences are reported for animals exposed to dichloroacetic acid for 52 to 100 weeks (the 26-week interim sacrifice group is excluded)
[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 numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined.

The range of concentrations of dichloroacetic acid administered in drinking water and tested for carcinogenicity was comparable across the two studies. However, the study of Bull *et al*. (2002) was of shorter duration and had fewer animals in each treatment group than the study of DeAngelo *et al*. (1999). In addition, the longer study duration of DeAngelo *et al*. (1999), up to 100 weeks, is preferable to the 52-week study duration of Bull *et al.* (2002), as it requires less extrapolation in estimating lifetime[23] animal cancer incidence. Given these considerations, the DeAngelo *et al*. (1999) study was judged to

[23] The natural life span of the mouse is assumed to be two years (Gold LS, 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.)

be more robust and to provide a better overall estimate of the cancer dose-response. Data from Bull *et al*. (2002) was also analyzed for comparison.

Estimation of Cancer Potency Using the Multistage-in-Dose Weibull-in-Time Model and the Multistage Model

In the 2014 review of the mechanistic data for dichloroacetic acid, IARC[24] states:

> "Weak to moderate experimental evidence was available to suggest that dichloroacetic acid is a genotoxic agent… Available data suggested that dichloroacetic acid may also act through multiple non-genotoxic mechanisms in liver carcinogenesis".

Regarding the toxicokinetics of dichloroacetic acid, IARC[25] described metabolism of dichloroacetic acid by multiple routes, including reaction with glutathione to form glyoxylic acid. This reaction may result in covalent inactivation of the glutathione transferase enzyme catalyzing it. IARC also states:

> "Major similarities exist between humans and laboratory animals with regard to the absorption, distribution, metabolism and excretion of dichloroacetic acid. Dichloroacetic acid has a very similar plasma half-life in humans and laboratory animals."

The 2015 NTP report[26] summarizes the genotoxicity information on dichloroacetic acid, a metabolite of bromodichloroacetic 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".

Besides the mechanistic studies reviewed by IARC (2014) and the genotoxicity studies of dichloroacetic acid reviewed by NTP (2015), OEHHA identified several additional genotoxicity studies. These include two positive[27,28] and one negative[29] mutation assays in *Salmonella*, one positive study[30] of chromosomal aberration (CA) and micronucleus (MN) formation in *Vicia faba*, one positive *in vitro* study[31] of MN formation

[24] IARC (2014). Full citation provided in footnote 8.
[25] *Ibid.*
[26] NTP (2015). Full citation provided in footnote 9.
[27] Zhang et al. (2016). Full citation provided in footnote 10.
[28] Ono et al. (1991). Full citation provided in footnote 14.
[29] Stalter et al. (2016). Full citation provided in footnote 15.
[30] Hu et al. (2017). Full citation provided in footnote 11.
[31] Varshney et al. (2013). Full citation provided in footnote 12.

in human peripheral blood lymphocytes, and two positive *in vivo* studies[32,33] of liver DNA single strand breaks in mice.

A multistage model[34] was used to derive a cancer potency estimate from the Bull *et al.* study and a time-to-tumor extension of this model was used to derive a cancer potency estimate from the DeAngelo *et al*. study. These are the default models listed in Section 25703. The available mechanistic information and the data on toxicokinetics and metabolism of dichloroacetic acid were reviewed by NTP[35] and IARC[36]. As noted above, it appears that carcinogenicity of dichloroacetic acid may be the result of multiple mechanisms of action, including several types of both genotoxic and non-genotoxic processes. There are no specific mechanistic or toxicokinetic data to suggest any deviation from the standard assumptions, including low-dose linearity, usually applied in cancer dose-response analysis. These default models are therefore the most scientifically appropriate, 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:

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

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 dichloroacetic acid (per mg/kg/day) in the study by Bull *et al.*, 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 US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[37]. 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."

When a large fraction of the animals die before the end of the study, as occurred in the study by DeAngelo *et al*., the multistage-in-dose Weibull-in-time (multistage Weibull) model can be used to estimate the cancer potency. The treatment-related tumors

[32] Hassoun et al. (2014). Full citation provided in footnote 13.
[33] Hassoun and Dey (2008). Full citation provided in footnote 16.
[34] Section 25703
[35] NTP (2015). Full citation provided in footnote 9.
[36] IARC (2014). Full citation provided in footnote 8.
[37] US EPA Benchmark Dose Software (BMDS) Version 2.7. National Center for Environmental Assessment. Available from: https://www.epa.gov/bmds.

observed in this study were judged to be non-fatal (incidental) tumors. 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 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 model in US EPA's BMDS. 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." The BMDS multistage Weibull time-to-tumor technical documentation[38] contains more details about this model, including how censoring, incidental tumors and fatal tumors are incorporated into the model.

The natural lifespan of mice is assumed to be two years (104 weeks)[39,40]. 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[41] and US EPA[42], a correction factor to extrapolate to two years (104 weeks) was required for the cancer slope factor derived using the multistage polynomial model for cancer in US EPA's BMDS from the data in the study of Bull *et al.*[43], as that study was concluded after 52 weeks. The adjustment was calculated as follows:

$$CSF_{animal,\ adj.} = CSF_{animal} \times (104/52)^3$$

No such adjustment for less-than-lifetime study duration was required for the cancer slope factor derived from the data in the study of DeAngelo *et al.*[44] using the multistage Weibull model.

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

[38] BMDS multistage Weibull time-to-tumor technical documentation. Available at available at http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=522999
[39] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.
[40] 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.
[41] Gold and Zeiger (1997). Full citation provided in footnote 39.
[42] US EPA (1988). Full citation provided in footnote 40.
[43] Bull et al. (2002). Full citation provided in footnote 7.
[44] DeAngelo et al. (1999). Full citation provided in footnote 5.

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

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

The default human body weight is 70 kg. The average body weight for male mice was calculated to be 0.0414 kg in DeAngelo *et al*. (1999), 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 male mice 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[a]	Sex/ strain/ species	Type of neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
DeAngelo *et al*. (1999); DeAngelo, personal communica-tion (2007)	Male B6C3F1 mice	Hepatocellular adenoma or carcinoma	0.0414	0.00636	**0.041**
Bull *et al*. (2002)	Male B6C3F1 mice	Hepatocellular adenoma or carcinoma	0.0462	(0.00574)[b] 0.0459[c]	(0.036)[b] 0.29[c]

[a] The linearized multistage model was used for analyses of male mice in the Bull *et al*. (2002) study; the multistage Weibull model was used for analyses of male mice in the DeAngelo *et al*. (1999) study.
[b] Not adjusted for shorter study duration.
[c] Adjusted for less than lifetime study duration.

OEHHA compared the two studies and determined that the DeAngelo *et al*. (1999) study was the most appropriate study for cancer dose-response analysis. DeAngelo *et al*. (1999) conducted the study for 100 weeks, while Bull *et al*. (2002) terminated the study after 52 weeks. 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 DeAngelo *et al*. (1999), which also had more animals in each treatment group, is preferred.

The DeAngelo *et al*. (1999) study was chosen for assessing the carcinogenic effects of dichloroacetic acid, and thus the NSRL for dichloroacetic acid will be based on the human cancer slope factor derived from that study, 0.041 $(mg/kg\text{-}day)^{-1}$.

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[45]. 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 dichloroacetic acid derived from the male mouse study data[46] of DeAngelo *et al*. (1999) and exposure parameters presented in Table 1 is 0.041 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 17 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
…	
Dichloroacetic acid	17

[45] Section 25703(a)(8)
[46] Individual animal survival and tumor data provided by Dr. DeAngelo, December 2007.

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 dichloroacetic 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[47].

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 1999 study by DeAngelo *et al*. entitled “Hepatocarcinogenicity in the male B6C3F$_1$ mouse following a lifetime exposure to dichloroacetic acid in the drinking water: Dose-response determination and modes of action”[48], along with additional data from this study provided by DeAngelo[49] were relied on by OEHHA for calculating the NSRL for dichloroacetic 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”[50], on a 2014 IARC monograph[51] summarizing the available data from rodent carcinogenicity studies of dichloroacetic acid, as well as other information relevant to the carcinogenic activity of the chemical, and on a 2015 NTP report[52] summarizing the genotoxicity information on dichloroacetic acid, along with additional

[47] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[48] DeAngelo et al. (1999). Full citation provided in footnote 5.
[49] Individual animal survival and tumor data provided by Dr. DeAngelo, December 2007
[50] Bull et al. (2002). Full citation provided in footnote 7.
[51] IARC (2014). Full citation provided in footnote 8
[52] NTP (2015). Full citation provided in footnote 9.

genotoxicity studies[53,54,55,56,57,58,59]. In addition, OEHHA relied on information presented in two additional documents[60,61] 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.

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

[53] Zhang et al. (2016). Full citation provided in footnote 10.
[54] Hu et al. (2017). Full citation provided in footnote 11
[55] Varshney et al. (2013). Full citation provided in footnote 12.
[56] Hassoun et al. (2014). Full citation provided in footnote 13.
[57] Ono et al. (1991). Full citation provided in footnote 14.
[58] Stalter et al. (2016). Full citation provided in footnote 15.
[59] Hassoun and Dey (2008). Full citation provided in footnote 16.
[60] Gold and Zeiger (1997). Full citation provided in footnote 39.
[61] US EPA (1988). Full citation provided in footnote 40.

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. Dichloroacetic acid is listed under Proposition 65; therefore, businesses that manufacture, distribute, sell or use products with dichloroacetic 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.