INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

DIBROMOACETIC 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 dibromoacetic acid (CAS No. 631-64-1) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 2.8 micrograms per day (µg/day) for dibromoacetic 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.

Dibromoacetic acid was listed as known to the state to cause cancer under Proposition 65 on June 17, 2008.

[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 dibromoacetic acid, OEHHA relied on the National Toxicology Program (NTP) report entitled "Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies)"[5], Volume 101 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water"[6], and additional publications on genotoxicity[7,8,9,10,11,12]. The 2007 NTP report and the IARC monograph summarize the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of dibromoacetic acid. Hu et al. (2017), Nelson et al. (2001), Stalter et al. (2016), Zhang et al. (2012; 2016), and Zuo et al. (2017) provide additional information on genotoxicity. The NSRL for dibromoacetic acid is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[13].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of dibromoacetic acid discussed by NTP (2007)[14] and IARC (2013)[15] and determined that

[5] National Toxicology Program (NTP 2007). Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Technical Report Series No. 537. NIH Publication No. 07-4475. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr537.pdf

[6] International Agency for Research on Cancer (IARC 2013). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 101, Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water. IARC, World Health Organisation, Lyon France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol101/index.php

[7] Hu Y, Tan L, Zhang SH, 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.

[8] Nelson GM, Swank AE, Brooks LR, Bailey KC, George SE. (2001). Metabolism, microflora effects, and genotoxicity in haloacetic acid-treated cultures of rat cecal microbiota. Toxicol Sci 60(2): 232-241.

[9] Zhang L, Xu L, Zeng Q, Zhang S, Xie H, Liu A, et al. (2012). Comparison of DNA damage in human-derived hepatoma line (HepG2) exposed to the fifteen drinking water disinfection byproducts using the single cell gel electrophoresis assay. Mutat Res 741(1-2): 89-94.

[10] Zhang S-h, Miao D-y, Tan L, Liu A-l, Lu W-q. (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] 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.

[12] 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.

[13] Section 25703(a)(4)

[14] NTP (2007). Full citation provided in footnote 5.

[15] IARC (2013). Full citation provided in footnote 6.

the two-year drinking water studies conducted by NTP in male and female $B6C3F_1$ mice met the criterion in Section 25703 as being sensitive studies of sufficient quality.

In the NTP mouse studies[16], groups of 50 male and female mice were exposed to dibromoacetic acid in drinking water at concentrations of 0, 50, 500 or 1000 mg/L for 105 or 106 weeks. The lifetime average daily doses of dibromoacetic acid administered in these studies were calculated and reported by NTP (2007) to be: 0, 4, 45, 87 mg/kg-day in male mice and 0, 4, 35, and 65 mg/kg-day in female mice. Survival was not affected by treatment with dibromoacetic acid at any dose in either of the studies.

In male mice, statistically significant increases in incidences of hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas were observed. Statistically significant increases in combined hepatocellular adenomas, carcinomas and hepatoblastomas were observed in all dose groups, with a statistically significant positive trend.

Treatment-related increases in alveolar/bronchiolar adenomas were also observed, with a statistically significant positive trend. The increase in alveolar/bronchiolar adenomas in the 500 mg/L dose group was statistically significant by pairwise comparison with controls. The tumor incidence data used to estimate cancer potency are presented in Table 1.

Table 1. Tumor incidences[a] of treatment-related lesions in male $B6C3F_1$ mice administered dibromoacetic acid via drinking water (NTP 2007)[17]

Organ	Tumor type	Administered Concentrations (mg/L)				Trend test p-value[b]
		0	50	500	1000	
Liver	Hepatocellular adenoma, carcinoma or hepatoblastoma[c] (first occurrence of tumor: day 451)	28/48	41/49**	43/48***	48/50***	$p < 0.001$
Lung	Alveolar/bronchiolar adenoma[c] (first occurrence of tumor: day 482)	7/46	5/49	17/48*	12/48	$p < 0.05$

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

[16] NTP (2007). Full citation provided in footnote 5.
[17] *Ibid.*

In female mice, statistically significant increases in incidences of hepatocellular adenomas and hepatocellular carcinomas were observed. Statistically significant increases in combined hepatocellular adenomas and carcinomas were observed in the 500 and 1000 mg/L dose groups, with a statistically significant positive trend.

Treatment-related increases in alveolar/bronchiolar adenomas were also observed, with a statistically significant positive trend. The tumor incidence data used to estimate cancer potency are presented in Table 2.

Table 2. Tumor incidences[a] of treatment-related lesions in female B6C3F$_1$ mice administered dibromoacetic acid via drinking water (NTP 2007)[18]

Organ	Tumor type	Administered Concentrations (mg/L)				Trend test p-value[b]
		0	50	500	1000	
Liver	Hepatocellular adenoma or carcinoma [c] (first occurrence of tumor: day 573)	22/46	28/47	37/47**	37/48**	$p < 0.001$
Lung	Alveolar/bronchiolar adenoma[c] (first occurrence of tumor: day 490)	1/49	3/48	3/49	6/48	$p < 0.05$

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

Estimation of Cancer Potency Using the Multistage Model and Multisite Analysis

In the 2013 review of the mechanistic data on dibromoacetic acid, IARC[19] concluded:

> "The mechanism of tumour induction by dibromoacetic acid has not been clearly identified. The reduction of glutathione *S*-transferase-zeta activity may be involved. DNA hypomethylation and increased expression of a proto-oncogene and a growth factor gene were also suggested as possible early events. There is moderate evidence that the carcinogenicity of dibromoacetic acid involves a genotoxic mechanism. Moreover, glyoxylate, a metabolite of dibromoacetic acid, is mutagenic in bacteria."

Besides the mechanistic data reviewed by IARC (2013), OEHHA identified additional genotoxicity studies. In these studies dibromoacetic acid was positive in assays testing

[18] NTP (2007). Full citation provided in footnote 5.
[19] IARC (2013). Full citation provided in footnote 6.

for bacterial mutagenicity[20,21,22], induced DNA strand breaks in *Vicio faba* root cells[23] and human cells[24] *in vitro* in the comet assay, and induced micronuclei in *Vicio faba* root cells[25]. It did not cause nuclear DNA damage in *C. elegans in vivo*[26].

Based on consideration of the available mechanistic information, a multistage model is applied to derive a cancer potency estimate, 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:

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

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.

The multistage polynomial model defines the probability of dying with a tumor at a single site. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, the US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[27] 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, using BMDS (MS_Combo). This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. To derive a measure of the total cancer response to dibromoacetic acid (per mg/kg/day) 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 MS_Combo 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". Animal cancer potencies were estimated using this approach for the male and female mouse studies described in Tables 1 and 2.

[20] Zhang et al. (2012). Full citation provided in footnote 9.
[21] Stalter et al. (2016). Full citation provided in footnote 11.
[22] Nelson et al. (2001). Full citation provided in footnote 8.
[23] Hu et al. (2017). Full citation provided in footnote 7.
[24] Zhang et al. (2016). Full citation provided in footnote 10.
[25] Hu et al. (2017). Full citation provided in footnote 7.
[26] Zuo et al. (2017). Full citation provided in footnote 12.
[27] US EPA Benchmark Dose Software (BMDS) Version 2.7. National Center for Environmental Assessment, US EPA. Available from: http://bmds.epa.gov

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 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 and female mice were calculated to be 0.0476 kg and 0.0522 kg, respectively, based on the data reported by NTP (2007) for control animals. The derivations of the human cancer slope factors using these body weights are summarized below in Table 3.

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

Sex/Strain/ Species	Type of neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Male $B6C3F_1$ mice	Hepatocellular adenoma, carcinoma or hepatoblastoma	0.0476	0.0372	
	Alveolar/ bronchiolar adenoma	0.0476	0.0048	
	Multisite: Hepatocellular adenoma, carcinoma or hepatoblastoma and alveolar/ bronchiolar adenoma	0.0476	0.0400	**0.25**
Female $B6C3F_1$ mice	Hepatocellular adenoma or carcinoma	0.0522	0.0217	
	Alveolar/bronchiolar adenoma	0.0522	0.00273	
	Multisite: Hepatocellular adenoma or carcinoma and alveolar/bronchiolar adenoma	0.0522	0.0231	0.14

As shown in Table 3, male mice were the most sensitive to the carcinogenic effects of dibromoacetic acid and thus the NSRL for dibromoacetic acid will be based on the human cancer slope factor of 0.25 $(mg/kg\text{-}day)^{-1}$, derived from the study in male mice.

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[28]. The intake can be converted to a µg per day amount by

[28] Section 25703(a)(8)

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

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

As indicated previously, the human cancer slope factor for dibromoacetic acid derived from the male mouse study data and exposure parameters presented in Table 1 is 0.25 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 2.8 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
…	
<u>Dibromoacetic acid</u>	<u>2.8</u>

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 dibromoacetic 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[29].

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 2007 NTP report entitled "Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)"[30], and Volume 101 in the series of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water"[31], were relied on by OEHHA for calculating the NSRL for dibromoacetic acid. OEHHA also relied on studies containing findings from genotoxicity tests of dibromoacetic acid[32,33,34,35,36,37]. These documents include data used in the potency calculation and on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. 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

[29] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[30] NTP (2007). Full citation provided in footnote 5.
[31] IARC (2013). Full citation provided in footnote 6.
[32] Hu et al. (2017). Full citation provided in footnote 7.
[33] Nelson et al. (2001). Full citation provided in footnote 8.
[34] Zhang et al. (2012). Full citation provided in footnote 9.
[35] Zhang et al. (2016). Full citation provided in footnote 10.
[36] Stalter et al. (2016). Full citation provided in footnote 11.
[37] Zuo et al. (2017). Full citation provided in footnote 12.

effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL provides a “safe harbor” level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation given that its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation or Elimination of Jobs 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. Dibromoacetic acid is listed under Proposition 65 therefore, businesses that manufacture, distribute, sell or use products with dibromoacetic 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.