INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

BROMODICHLOROACETIC ACID

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT OF REGULATION

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for bromodichloroacetic acid under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 0.95 micrograms per day (µg/day) is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are insignificant. NSRLs provide guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

[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).

Bromodichloroacetic acid was listed as known to the state to cause cancer under Proposition 65 on July 29, 2016.

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for bromodichloroacetic acid, OEHHA relied on 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)"[5]. This document summarizes the available data from rodent carcinogenicity studies of bromodichloroacetic acid, as well as other information relevant to the carcinogenic activity of the chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[6].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of bromodichloroacetic acid discussed by NTP[7], and determined that the two-year drinking water studies conducted by NTP in male and female F344/NTac rats and B6C3F$_1$ mice met the criterion in Section 25703 as being sensitive studies of sufficient quality.

In the NTP rat studies[8], groups of 50 male and female rats were exposed to bromodichloroacetic acid in drinking water at concentrations of 0, 250, 500 or 1000 mg/L for up to 104 weeks. The lifetime average daily doses of bromodichloroacetic acid administered in these studies were calculated and reported by NTP (2015) to be: 0, 11, 21, and 43 mg/kg-day in male rats and 0, 13, 28, and 57 mg/kg-day in female rats.

Survival was not affected by treatment with bromodichloroacetic acid at any dose in male rats. Survival of female rats was significantly decreased in the mid and high dose groups compared to controls, with a significant trend[9]. Female rats in the 500 and 1000 mg/L dose groups had a 14% and 4% probability of survival at the end of the study, respectively. Most of the female rats died with mammary tumors. In the 500 and 1000

[5] 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.
[6] Section 25703(a)(4)
[7] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.
[8] *Ibid*.
[9] *Ibid*.

mg/L dose groups, 96% and 84%, respectively, of the female rats died with mammary gland tumors. Since 16% of the animals in the high dose group died without tumor, there likely were competing causes of death in this group.

Statistically significant increases in incidences of malignant mesothelioma, subcutaneous fibroma, and combined incidences of epithelial tumors of the skin were observed in male rats. Significant increases in the incidences of mammary gland fibroadenoma and carcinoma occurred in female rats. The tumor incidence data used to estimate cancer potency from each of the rat studies are presented in Table 1.

Table 1. Tumor incidences[a] of treatment-related lesions in F344/NTac rats administered bromodichloroacetic acid via drinking water (NTP, 2015)

Organ	Tumor type	Bromodichloroacetic acid administered concentration (mg/L)				Trend test p-value[b]
		0	250	500	1000	
Male rats						
Multiple organs	Malignant mesothelioma[c] (first occurrence of tumor: day 309)	1/50	12/49***	18/50***	37/50***	$p < 0.001$
Skin	Combined epithelial tumors[c] (first occurrence of tumor: day 436)	9/49	7/48	15/50	21/49**	$p < 0.001$
	Subcutaneous fibromas[c] (first occurrence of tumor: day 442)	4/49	6/48	10/50	15/48**	$p < 0.01$
Female rats						
Mammary gland	Fibroadenoma or carcinoma[c] (first occurrence of tumor: day 414)	28/49	47/50***	47/48***	41/48**	$p < 0.01$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor

[b] 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): ** $p < 0.01$, *** $p < 0.001$

In the NTP mouse studies[10], groups of 50 male and female mice were exposed to bromodichloroacetic acid in drinking water at concentrations of 0, 250, 500 or 1000 mg/L for up to 104 weeks. The lifetime average daily doses of bromodichloroacetic acid administered in these studies were calculated and reported by NTP (2015) to be: 0, 23, 52, and 108 mg/kg-day in male mice and 0, 17, 34, and 68 mg/kg-day in female mice.

[10] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.

Survival was significantly decreased in male mice in the mid and high dose groups compared to controls, with a significant trend[11]. Male mice in the 500 and 1000 mg/L dose groups had a 25% and 20% probability of survival at the end of the study, respectively. The majority of male mice died with hepatocellular carcinomas or hepatoblastomas. In the 500 and 1000 mg/L groups, 96% and 88%, respectively, of the male mice died with liver tumors. Since 12% of the animals in the high dose group died without tumors, there likely were competing causes of death in this group. Survival of female mice was not affected by treatment with bromodichloroacetic acid at any dose.

In male mice, statistically significant increases in hepatocellular carcinoma and hepatoblastoma and increased incidences of Harderian gland adenoma or carcinoma (combined) were observed. Statistically significant increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma were observed in female mice. The tumor incidence data used to estimate cancer potency from each of the mouse studies are presented in Table 2.

[11] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.

Table 2. Tumor incidences[a] of treatment-related lesions in B6C3F$_1$ mice administered bromodichloroacetic acid via drinking water (NTP, 2015)

Organ	Tumor type	Bromodichloroacetic acid administered concentration (mg/L)				Trend test p-value[b]
		0	250	500	1000	
Male mice						
Liver	Hepatocellular carcinoma or hepatoblastoma[c] (first occurrence of tumor: day 260)	15/50	34/50***	48/49***	44/50***	$p < 0.001$
Harderian gland	Adenoma or carcinoma[c] (first occurrence of tumor: day 458)	6/48	11/48	14/49*	20/47***	$p < 0.001$
Female mice						
Liver	Hepatocellular adenoma, carcinoma, or hepatoblastoma[c] (first occurrence of tumor: day 386)	36/48	44/49*	43/47*	46/49**	$p < 0.01$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor

[b] 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

In the discussion of the mechanistic data on bromodichloroacetic acid, NTP[12] concluded, the "data supports the role of a genotoxic mechanism for the mouse liver neoplasms due to bromodichloroacetic acid." The mechanism for induction of rat mammary gland tumors is unknown, but the "data suggest that mammary gland carcinogenesis in bromodichloroacetic acid-exposed animals may be influenced in part by *Tgfβ*-dependent mechanisms"[13]. One of bromodichloroacetic acid's metabolites, "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"[14].

Based on consideration of the available mechanistic information on bromodichloroacetic acid and the above conclusions reached by NTP[15], a multistage model is applied to

[12] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.
[13] *Ibid*.
[14] *Ibid*.
[15] *Ibid*.

derive a cancer potency estimate for each of the studies, 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:

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

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. To derive a measure of the cancer response to bromodichloroacetic acid (per mg/kg-day) in studies where increases in treatment-related tumors were observed at a single site, 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 the US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[16]. The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor (CSF_{animal})", or "animal cancer potency". Animal cancer potencies were estimated using this approach for the female rat and mouse studies described in Tables 1 and 2, respectively.

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[17] 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 to bromodichloroacetic 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 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

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

potency". Animal cancer potencies were estimated using this approach for the male rat and mouse studies described in Tables 1 and 2, respectively.

Due to the high tumor incidences of mammary tumors in treated female rats and liver tumors in treated male mice, the top dose group had to be removed during the modeling process from each of these sets of data in order to achieve sufficient goodness of fit. As discussed above, 96% of the mid-dose female rats died with mammary tumors and 96% of the mid-dose male mice died with liver tumors. Thus the cancer potency estimates based on the female rat and male mouse studies are unlikely to be overestimates.

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. The average body weights for male and female rats were calculated to be 0.451 kg and 0.272 kg, respectively, and the average body weights for male and female mice were calculated to be 0.0506 kg and 0.0529 kg, respectively, based on the data reported by NTP (2015)[18] for control animals. The derivation of the human cancer slope factors using these body weights are summarized below in Table 3.

[18] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.

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 F344/NTac rats	Malignant mesothelioma	0.451	0.0311	
	Combined epithelial tumors of the skin	0.451	0.0126	
	Subcutaneous fibroma	0.451	0.0101	
	Multisite: malignant mesothelioma, combined epithelial tumors of the skin and subcutaneous fibroma	0.451	0.0478	0.17
Female F344/NTac rats	Mammary gland fibroadenoma or carcinoma	0.272	0.184	**0.74**
Male $B6C3F_1$ mice	Hepatocellular carcinoma or hepatoblastoma	0.0506	0.0434	
	Harderian gland adenoma or carcinoma	0.0506	0.00578	
	Multisite: hepatocellular adenoma or hepatoblastoma and Harderian gland adenoma or carcinoma	0.0506	0.0472	0.29
Female $B6C3F_1$ mice	Hepatocellular adenoma, carcinoma, or hepatoblastoma	0.0529	0.0395	0.24

As shown in Table 3, female rats were the most sensitive to the carcinogenic effects of bromodichloroacetic acid and thus the NSRL for bromodichloroacetic acid will be based on the human cancer slope factor, 0.74 $(mg/kg\text{-}day)^{-1}$, derived from the study in female rats.

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

[19] Section 25703(a)(8)

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

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

As indicated previously, the human cancer slope factor for bromodichloroacetic acid derived from the female rat study data and exposure parameters presented in Table 1 is 0.74 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 0.95 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

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

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

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
<u>Bromodichloroacetic acid</u>	<u>0.95</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 bromodichloroacetic 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[20].

BENEFITS OF THE PROPOSED REGULATION

See "Benefits of the Proposed Regulation" under Economic Impact Analysis below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The NTP report entitled "Toxicology 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)"[21] was relied on by OEHHA for calculating the NSRL for bromodichloroacetic acid. This document includes 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 this document will be included in the regulatory record for this proposed action. This document is available from OEHHA upon request.

OEHHA also relied on the Economic Impact Analysis below 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 a NSRL for the chemical. Failure to adopt an NSRL would leave the business community without a "safe harbor" level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

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

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses.

[20] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[21] National Toxicology Program (NTP, 2015), full citation provided in footnote 5.

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. Bromodichloroacetic acid is listed under Proposition 65 and effective July 29, 2017, businesses that manufacture, distribute or sell products with bromodichloroacetic acid in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California: This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses Currently Doing Business within the State of California: This regulatory action will not impact the expansion of businesses currently doing business 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.