INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

BROMOCHLOROACETIC 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 bromochloroacetic acid under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 0.70 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.

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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).

Bromochloroacetic acid was listed as known to the state to cause cancer under Proposition 65 on April 6, 2010.

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for bromochloroacetic acid, OEHHA relied on the National Toxicology Program (NTP) report, entitled "Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies)"[5], and 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]. These two documents summarize the available data from rodent carcinogenicity studies of bromochloroacetic 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[7].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of bromochloroacetic acid discussed by NTP[8] and IARC[9], and determined that 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[10], groups of 50 male and female mice were exposed to bromochloroacetic acid in drinking water at concentrations of 0, 50, 500 or 1000 mg/L for 105 weeks. The lifetime average daily doses of bromochloroacetic acid administered in the studies were calculated and reported by NTP (2009) to be: 0, 25, 50, 90 mg/kg-day in male mice and 0, 15, 30, and 60 mg/kg-day in female mice[11]. Survival was not affected by treatment with bromochloroacetic acid at any dose in the study in female mice[12]. Survival of male mice in the 90 mg/kg-day dose group was

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[5] National Toxicology Program (NTP, 2009). Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Technical Report Series No. 549. NIH Publication No. 09-5890. US Department of Health and Human Services, NTP, Research Triangle Park, NC.
[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 Organization, Lyon France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol101/index.php
[7] Section 25703(a)(4).
[8] National Toxicology Program (NTP, 2009), full citation provided in footnote 5.
[9] International Agency for Research on Cancer (IARC, 2013), full citation provided in footnote 6.
[10] National Toxicology Program (NTP, 2009), full citation provided in footnote 5.
[11] *Ibid.*
[12] *Ibid.*

significantly lower than that of the control, mainly due to an increase of malignant liver neoplasms.

Statistically significant increases in incidences of hepatocellular adenomas and hepatocellular carcinomas were observed in both male and female mice. A significant increase in the incidence of hepatoblastomas also occurred in male mice. Statistically significant increases in combined hepatocellular adenomas, carcinomas and hepatoblastomas were observed in all dose groups in male mice, with a statistically significant positive trend. Statistically significant increases in combined hepatocellular adenomas and carcinomas were observed in all dose groups in female 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. Tumor incidences[a] of treatment-related lesions in B6C3F$_1$ mice administered bromochloroacetic acid in the drinking water (NTP, 2009)

Organ	Tumor type	Bromochloroacetic acid administered concentrations (mg/L)				Trend test p-value[b]
		0	250	500	1000	
Male Mice						
Liver	Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma[c] (first occurrence of tumor: day 328)	35/50	45/50*	49/49***	50/50***	$p < 0.001$
Female Mice						
Liver	Hepatocellular adenoma or hepatocellular carcinoma[c] (first occurrence of tumor: day 551)	31/45	49/50***	46/49**	46/48***	$p < 0.001$

[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 2013 review of the mechanistic data for bromochloroacetic acid, IARC[13] concluded:

"The mechanism by which bromochloroacetic acid induces tumours is not known, but a reduction in glutathione *S*-transferase-zeta activity may be involved. There is

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[13] International Agency for Research on Cancer (IARC, 2013), full citation provided in footnote 6.

moderate evidence that the carcinogenicity of bromochloroacetic acid may involve a genotoxic mechanism because this chemical is a bacterial mutagen, produces 8-hydroxydeoxyguanosine in mouse liver (after acute oral administration or administration for three weeks in the drinking-water) and induces DNA damage in Chinese hamster ovary cells. Glyoxylate, a metabolite of bromochloroacetic acid, is also mutagenic in bacteria."

Based on consideration of the available mechanistic information on bromochloroacetic acid and the above conclusions reached by IARC[14], 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:

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

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 bromochloroacetic acid (per mg/kg-day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in the US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[15]. 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 two $B6C3F_1$ mouse studies described above.

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

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[14] International Agency for Research on Cancer (IARC, 2013), full citation provided in footnote 6.
[15] 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

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 mice were calculated to be 0.0483 kg and 0.0526 kg, respectively, based on the data reported by NTP (2009) for control animals. The derivation 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

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, hepatocellular carcinoma, or hepatoblastoma	0.0483	0.0893	0.55
Female B6C3F$_1$ mice	Hepatocellular adenoma or hepatocellular carcinoma[a]	0.0526	0.325	2.0

[a] Due to the high tumor incidences in the female mouse study in all three dose groups, the top two dose groups had to be removed during the modeling process in order to achieve sufficient goodness of fit.

As indicated in Table 2, in order to achieve sufficient goodness of fit in modeling the female mouse liver tumor data, the top two dose groups were removed from the analysis. Considering this, together with the observation that high liver tumor incidences ($\geq$90%) occurred in all three dose groups in both the male and female mouse studies, a geometric mean of the human cancer potency estimates derived from the two studies was taken as the basis of the overall cancer potency estimate. This yields a mean human cancer potency estimate of 1.0 $(mg/kg\text{-}day)^{-1}$.

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 body weight per day. The result of the calculation is a

dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg 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[16]. The intake can be converted to a µg per day amount by 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 bromochloroacetic acid derived from the data and exposure parameters presented in Table 1 is 1.0 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 0.70 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
…	
Bromochloroacetic acid	0.70
…	

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)

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[16] Section 25703(a)(8)

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 bromochloroacetic 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[17].

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 2009 NTP technical report entitled "Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies)"[18], 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"[19], were relied on by OEHHA for calculating the NSRL for bromochloroacetic acid. 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 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 a NSRL for the chemical. Failure to adopt a 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

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[17] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[18] National Toxicology Program (NTP, 2009), full citation provided in footnote 5.
[19] International Agency for Research on Cancer (IARC, 2013), full citation provided in footnote 6.

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. Bromochloroacetic acid is listed under Proposition 65; therefore, businesses that manufacture, distribute or sell products with bromochloroacetic 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 benefit to the health and safety of Californians.