



February 12, 2018

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
P.O. Box 4010, MS-23B
Sacramento, California 95812-4010
Email: monet.vela@oehha.ca.gov

Submitted via the Comments Submission Portal: <https://oehha.ca.gov/comments>

**Re: Notice of Proposed Rulemaking Title 27, California Code of Regulations
Amendment to Section 12705 Specific Regulatory Levels Posing No Significant
Risk: Bromodichloroacetic Acid**

Dear Ms. Vela:

The American Chemistry Council¹ (ACC) Chlorine Chemistry Division² appreciates this opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHHA) on the proposed rulemaking to adopt a Proposition 65 No Significant Risk Level (NSRL) for bromodichloroacetic acid of 0.95 micrograms/day³ and “Initial Statement of Reasons” (ISOR) document⁴ for the proposed amendment.

Millions of lives have been saved and countless illnesses avoided since the inception of continuous chlorine use in conjunction with filtration in water treatment over 100 years ago,⁵ and the majority of U.S. community water systems still rely on chlorine or a chlorine-

¹ ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people’s lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a \$768 billion enterprise and a key element of the nation’s economy. It is among the largest exports in the nation, accounting for 14 percent of all U.S. goods exports. Chemistry companies are among the largest investors in research and development, investing \$91 billion in 2016.

² The Chlorine Chemistry Division represents the major producers and users of chlorine in North America and works to promote and protect the sustainability of chlorine chemistry processes, products and applications.

³ <https://oehha.ca.gov/proposition-65/crn/notice-proposed-rulemaking-title-27-california-code-regulations-amendment-10>.

⁴ <https://oehha.ca.gov/media/downloads/crn/isorbromodichloroaceticacid122917.pdf>.

⁵ See review by McGuire, M.J. 2013. The Chlorine Revolution: Water Disinfection and the Fight to Save Lives. AWWA: Denver, Colorado.



based disinfection process to protect their consumers.⁶ A wide variety of organic and inorganic disinfection byproducts (DBPs), including bromodichloroacetic acid, can be formed unintentionally at low levels when chlorine and other disinfectants react with naturally occurring organic matter in raw (natural) sources of drinking water. As the World Health Organization strongly cautions: “In attempting to control DBP concentrations, it is of paramount importance that the efficiency of disinfection is not compromised and that a suitable residual level of disinfectant is maintained throughout the distribution system.”⁷

Given the clear public health importance of chlorine and chlorine-based disinfection, it is of critical importance that the proposed NSRL for bromodichloroacetic reflect the use of best available science and apply a transparent approach for its derivation.

The attached comments, prepared by Jay Murray, PhD, DABT, detail ACC’s technical concerns with the proposed NSRL—including that OEHHA should explicitly state that the NSRL for bromodichloroacetic acid does not specifically consider the role of chlorine-based disinfection, and that an alternative risk level would be appropriate when bromodichloroacetic acid results from chlorine disinfection.

Should you have questions or would like to discuss these comments, please contact me at judith_nordgren@americanchemistry.com or Mark Gibson at mark_gibson@americanchemistry.com.

Respectfully,



Judith Nordgren
Managing Director, Chlorine Chemistry Division

Attachment:

Comments on the Proposed Proposition 65 No Significant Risk Level (NSRL) for Bromodichloroacetic Acid (February 7, 2018)

⁶ See American Chemistry Council. 2016. Drinking Water Chlorination: A Review of U.S. Disinfection Practices and Issues, <https://chlorine.americanchemistry.com/Chlorine-Benefits/Safe-Water/Disinfection-Practices.pdf>.

⁷ WHO (2011), Guidelines for Drinking-water Quality, 4th Edition. WHO Press: Geneva, Switzerland, p. 173, http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/.



**Comments on the Proposed Proposition 65 No
Significant Risk Level (NSRL) for Bromodichloroacetic
Acid**

February 7, 2018

Prepared for:

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Prepared by:

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I was asked by the American Chemistry Council (ACC) to review the Office of Environmental Health Hazard Assessment's (OEHHA) "Notice of Proposed Rulemaking Title 27, California Code of Regulations Amendment to Section 12705 Specific Regulatory Levels Posing No Significant Risk: Bromodichloroacetic Acid"¹, and the associated Initial Statement of Reasons (ISOR) for the proposed No Significant Risk Level (NSRL) for bromodichloroacetic acid.² The following comments are provided in response to OEHHA's request for public comments in response to these documents.

- 1. OEHHA should specifically state that the NSRL for bromodichloroacetic acid does not consider the role of chlorine-based disinfection, and that an alternative risk level would be appropriate when bromodichloroacetic acid results from chlorine disinfection.**

The NSRL proposed for bromodichloroacetic acid does not evaluate the propriety of an alternative risk level, as supported by Section 25703(b) of the Proposition 65 regulations. Section 25703(b) states:

"b) For chemicals assessed in accordance with this section, the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question, *except where sound considerations of public health support an alternative level*, as, for example:

- (1) where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination; or
- (2) *where chlorine disinfection in compliance with all applicable state and federal safety standards is necessary to comply with sanitation requirements*; or

¹ <https://oehha.ca.gov/proposition-65/cnr/notice-proposed-rulemaking-title-27-california-code-regulations-amendment-10>

² <https://oehha.ca.gov/media/downloads/cnr/isorbromodichloroaceticacid122917.pdf>

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(3) where a clean-up and resulting discharge is ordered and supervised by an appropriate governmental agency or court of competent jurisdiction.” [emphases added]

Bromodichloroacetic acid is recognized as a disinfection by-product of chlorine disinfection of drinking water. The NTP cancer bioassay of bromodichloroacetic acid (the pivotal study used for the proposed NSRL) states: “Bromodichloroacetic acid is a haloacetic acid that forms when drinking water supplies containing natural organic matter are disinfected with chlorine-containing oxidizing compounds and when bromide is present in the source water.”³ In fact, bromodichloroacetic acid was nominated for testing by the NTP by the American Water Works Association Research Foundation and the United States Environmental Protection Agency because of the widespread human exposure to this water disinfection by-product.

Bromodichloroacetic acid is a compelling example of a chemical that merits an alternative risk level. Chlorine disinfection is critical to providing safe drinking water. Using an alternative risk level (e.g., 10^{-4} or 10^{-3}) would result in a significant increase in the NSRL (e.g., a 10-fold increase in the NSRL at an alternative risk level of 10^{-4}). The ISOR and the regulation should mention the possibility and propriety of an alternative risk level for this chlorine disinfectant by-product.

Furthermore, this is not a theoretical concern. At the proposed NSRL of 0.95 micrograms/day, consumption of 2 L of water (i.e., the default consumption of drinking water under Proposition 65) containing more than 0.475 micrograms/L (approximately 0.5 ppb) of bromodichloroacetic acid would provide an exposure in excess of the NSRL. Based on limited data, it does not appear that drinking water levels of bromodichloroacetic acid are comfortably below 0.475 micrograms/L. Of note, the Introduction section of the NTP cancer bioassay report (TR 583) states:

³ National Toxicology Program (NTP, 2015). Toxicology Studies of Bromodichloroacetic Acid (CAS No. 71133-14-7) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F1/N Mice (Drinking Water Studies). NTP Technical Report Series No. 583. US Department of Health and Human Services, NTP, Research Triangle Park, NC, p. 7

“A nationwide study of disinfection by-product occurrence in diverse geographic regions of the United States was conducted between October 2000 and April 2002 (Weinberg et al., 2002). In this study, 12 water treatment plants that had different source water quality and bromide levels and that employed the major disinfectants chlorine, chloramines, ozone, and chlorine dioxide were sampled quarterly. Concentrations of bromodichloroacetic acid in finished water samples and in the distribution systems ranged from less than 2 to 15 µg/L. Bromodichloroacetic acid’s portion of the total HAAs can range from 1% to 20% (Weinberg et al., 2002). The Environmental Working Group (2009) has developed a database of chemical analyses from 47,576 water suppliers, of which 938 have tested for bromodichloroacetic acid from 2004 to 2009. Similar to the study by Weinberg et al. (2002), most facilities were below the detection limit of 2 µg/L; the highest yearly average level of bromodichloroacetic acid reported in drinking water from a single facility was 11.12 µg/L with a seasonal range of 7.22 to 16.85 µg/L.”⁴

These data illustrate why it is important for OEHHA to explicitly state that an alternative risk level for developing a NSRL for bromodichloroacetic acid would be appropriate in those circumstances where section 25703(b) applies.

- 2. The combination of mammary tumors in female rats used to derive the NSRL is scientifically inappropriate. Mammary fibroadenomas are benign and do not progress to malignant tumors; these benign tumors were incorrectly combined with adenomas and carcinomas to estimate the mammary tumor cancer slope factor.**

The combination of mammary tumor types in female rats used to derive the NSRL is scientifically inappropriate. Three different types of mammary tumors were observed in all groups (including the control group): adenoma, carcinoma and fibroadenoma. In cancer risk assessment, it is common to combine malignant tumors (e.g., carcinoma) with benign tumors that are known to progress to malignant tumors. For example, mammary adenomas, which are

⁴ NTP (2015), p. 26.

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derived from glandular tissue, in rats are known to have the potential to progress to mammary carcinomas, and mammary adenomas and carcinomas are commonly combined in cancer risk assessment. In contrast, fibroadenomas do not progress to carcinomas or to malignant tumors of any type, and mammary fibroadenomas in rats are not considered predictive of cancer in women.⁵ In humans, fibroadenomas, which are derived from connective tissue, are the most common type of breast tumor, most often occurring in women in their 20s and 30s. They are solid (not fluid-filled) masses, have clearly defined edges, and are typically round or oval in shape. In humans, fibroadenomas are benign, and they do not progress to malignant tumors (i.e., cancer). Unless there is clear evidence that fibroadenomas progress to the same malignant tumors as do adenomas, the cancer slope factor calculations for mammary tumors should exclude fibroadenomas; I am not aware of any such evidence.

What difference would it make if fibroadenomas were not combined with adenomas and carcinomas? The incidences of combined adenomas and carcinomas were 1/50, 3/50, 6/50 and 9/50 at 0, 13, 28, and 57 mg/kg bw/day, respectively.⁶ As shown in Appendix A (attached), the cancer slope factor using these data is 0.00496, compared to the animal cancer slope factor of 0.184 derived when fibroadenomas were combined with adenomas and carcinomas.⁷ It is also noteworthy that removing the fibroadenomas provides a dose-response curve that fits the model much better than the dose-response curve used by OEHHA, even after the high dose group was excluded. Using the same allometric scaling factors used by OEHHA, the NSRL for bromodichloroacetic acid (using a 10^{-5} target risk level) would be 35 micrograms per day compared to the proposed NSRL of 0.95 micrograms per day. ***This 37-fold difference is significant, and if an alternative risk level had been used, the difference would have been even greater.*** As a practical matter, female rat mammary tumors would no longer be used as the basis

⁵ Rudmann D, Cardiff R, Chouinard L (2012) Proliferative and Nonproliferative Lesions of the Rat and Mouse Mammary, Zymbal's, Preputial, and Clitoral Glands. *Toxicologic Pathology* 40(6):7S-39S. <http://journals.sagepub.com/doi/full/10.1177/0192623312454242>

⁶ The number of animals in the denominators vary slightly from those used by OEHHA for mammary tumors because OEHHA used the number of animals alive at the first day of tumor occurrence. This practice is concerning and should be the subject of further discussion. However, the slight difference in the number of animals in the denominator is not expected to have a significant impact on the cancer slope factor in this particular case and so these comments do not contain a further discussion of this issue.

⁷ ISOR (2017), p. 8.

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for establishing a NSRL for bromodichloroacetic acid because other tumors (e.g., liver tumors) would have a cancer slope factor greater than 0.00496.

3. The ISOR should acknowledge the significant uncertainty in estimating a cancer slope factor based on a set of mammary tumor data where every dose level had a tumor response in the range of 85% to 98%.

The ISOR should acknowledge there is an inherent problem with predicting a 5% tumor response dose from a set of data where every dose level of the test material had a tumor response in the range of 85% to 98% and where the *lowest* tumor response (85%) was observed at the high dose. The ISOR should state that this is a poor set of data for purposes of modeling a BMDL05 since the only way the data could be made to fit the model is to exclude the high dose level. The data give no indication of the shape of the dose-level at a tumor response rate below 85% to 98%. As a result, there is considerable uncertainty in the estimated BMDL05 for mammary tumors. It is important to note this uncertainty in the ISOR, particularly since the highest estimate of the cancer slope factor (and the resulting NSRL) is based on the mammary tumor data.

4. The NSRL should be based on a BMDL10 rather than a BMDL05.

The US EPA software employed by OEHHA to calculate the BMDL uses a default BMDL10. OEHHA did not explain its decision to depart from this default approach. Ideally, the tumor response data is within or close to the BMDL value. Since the tumor rate was so high at all three dose levels, it would be more appropriate to use a BMDL10, rather than a BMDL05. Using the BMDL10 would have resulted in a slightly higher NSRL of 0.98 micrograms/day.

5. The liver tumor data suffered from many of the same problems as noted for the mammary tumor data.

The increased incidence of liver tumors in male and female mice were responsible for the highest cancer slope factors calculated by OEHHA next to the cancer slope factor for mammary tumors in female rats. Like the mammary tumors in female rats, the liver tumors in mice occurred at a

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very high incidence in all dose groups. The same comments that were made above about the dose-response curve for mammary tumors would also apply to the mouse liver tumors. As in the case with mammary tumors, OEHHA had to exclude the high dose in male and female mice in order to estimate a cancer slope factor.

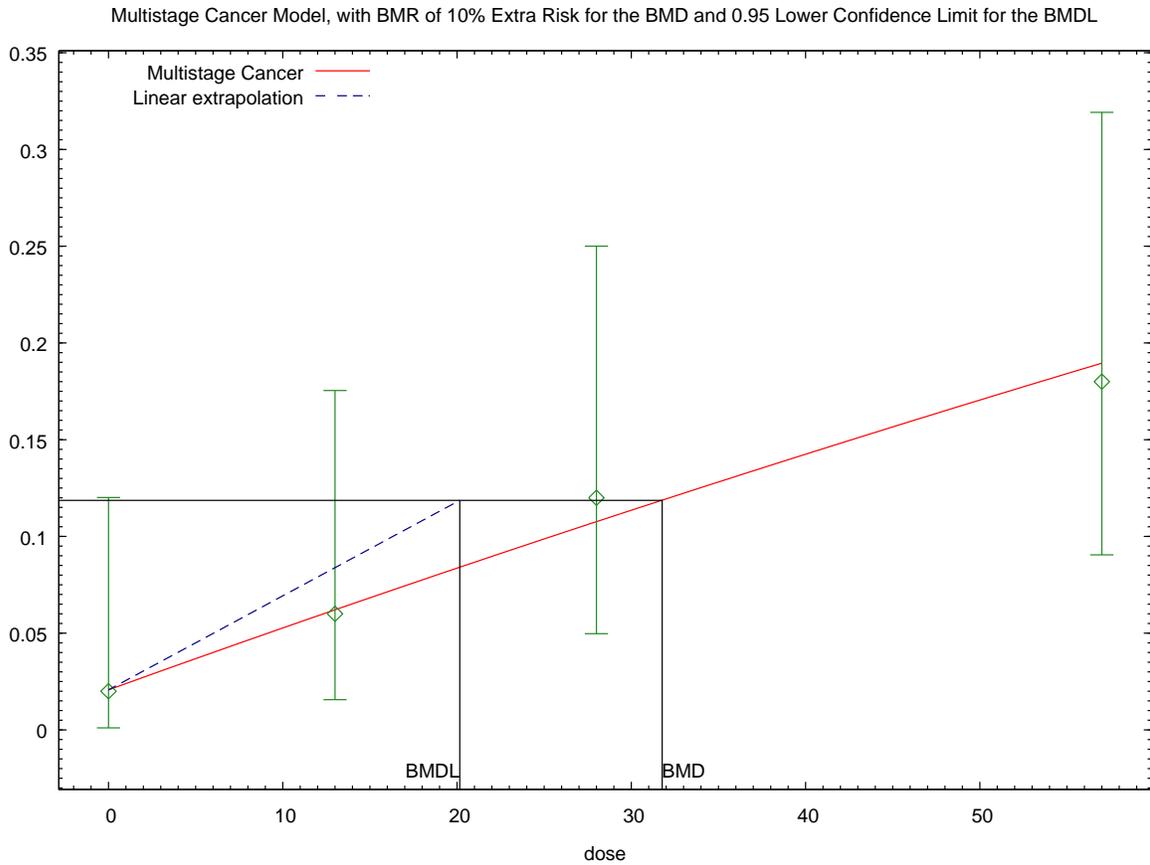
6. OEHHA should delete the sentence in ISOR that states: “There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.”

It is scientifically more appropriate to exclude mammary fibroadenomas from the mammary adenomas and mammary carcinomas in developing a NSRL. In contrast, the ISOR states: “Based on consideration of the available mechanistic information on bromodichloroacetic acid and the above conclusions reached by NTP, a multistage model is applied to 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.”⁸ This last sentence is not correct, is not supported by an analysis of all of the scientific assumptions and principles that were utilized in calculating the NSRL, and the sentence is not necessary. OEHHA should delete this sentence.

⁸ ISOR (2017), p. 5-6.

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Appendix A. BMDL and Cancer Slope Factor Calculations for Mammary Gland Tumors (Adenomas and Carcinomas Combined Excluding Fibroadenomas) among Female Rats Exposed to Bromodichloroacetic Acid



10:23 01/27 2018

```
=====  
Multistage Model. (Version: 3.4; Date: 05/02/2014)  
Input Data File:  
C:/Users/Jay/Documents/BMDS/BMDS2704/Data/msc_Dax_Setting.(d)  
Gnuplot Plotting File:  
C:/Users/Jay/Documents/BMDS/BMDS2704/Data/msc_Dax_Setting.plt  
Sat Jan 27 10:22:53 2018  
=====
```

```
BMDS_Model_Run  
~~~~~
```

The form of the probability function is:
$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = Effect

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Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.024377
Beta(1) = 0.00315966
Beta(2) = 0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2)
have been estimated at a boundary point, or have been specified by the
user,
and do not appear in the correlation matrix)

	Background	Beta(1)
Background	1	-0.52
Beta(1)	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.0206995	0.0189448	-0.0164317	0.0578306
Beta(1)	0.00331629	0.001096	0.00116816	0.00546441
Beta(2)	0	NA		

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-58.1663	4			
Fitted model	-58.2223	2	0.11204	2	0.9455
Reduced model	-62.7912	1	9.24983	3	0.02615

AIC: 120.445

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled	
				Size	Residual

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0.0000	0.0207	1.035	1.000	50.000	-0.035
13.0000	0.0620	3.101	3.000	50.000	-0.059
28.0000	0.1075	5.377	6.000	50.000	0.284
57.0000	0.1894	9.469	9.000	50.000	-0.169

Chi² = 0.11 d.f. = 2 P-value = 0.9445

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

 BMD = 31.7706

 BMDL = 20.1565

 BMDU = 68.8609

Taken together, (20.1565, 68.8609) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.00496117

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