FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: BROMODICHLOROACETIC ACID

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL) for bromodichloroacetic acid. Bromodichloroacetic acid was listed as a chemical known to the state to cause cancer for purposes of Proposition 65[1] on July 29, 2016. On December 29, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 0.95 micrograms per day (µg/day) for bromodichloracetic acid under Title 27, California Code of Regulations, section 25705(b)[2]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation. A public comment period was provided from December 29, 2017 to February 12, 2018. OEHHA received written public comments on the proposed rulemaking from the following organizations:

1. Environmental Working Group (EWG). The comments are comprised of EWG's comment letter.
2. American Chemistry Council (ACC). The comments are comprised of ACC's comment letter, and an attachment:
   "Comments on the Proposed Proposition 65 No Significant Risk Level (NSRL) for Bromodichloroacetic Acid", prepared for Mark Gibson, Director, Chlorine Issues, ACC, by F. Jay Murray of Murray & Associates.

PEER REVIEW

OEHHA also provided the Notice of Proposed Rulemaking and the Initial Statement of Reasons for the proposed NSRL for bromodichloroacetic acid to the members of the Carcinogen Identification Committee for their review and comment, as required by Section 25701(e). OEHHA received peer-review comments from committee member Jason Bush, Ph.D.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq*., 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.

SUMMARY AND RESPONSE TO PEER REVIEW COMMENTS RECEIVED

Comment: Dr. Bush reviewed the materials, and indicated that he supports the rationale for the proposed NSRL value for bromodichloroacetic acid, and concurs with the NSRL calculations.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

SUMMARY AND RESPONSE TO PUBLIC COMMENTS RECEIVED

In developing the 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 B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F1/N Mice (Drinking Water Studies)"[3]. 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[4].

OEHHA's responses to the comments received from the commenters listed above are incorporated within this Final Statement of Reasons (FSOR). Some of the comments submitted included observations or opinions regarding the benefits of chlorine-based disinfection processes and other assessments OEHHA might perform on bromodichloroacetic acid and other disinfection by-products. Such remarks do not constitute an objection to or recommendation specifically directed at the proposed action or the procedures followed in this rulemaking action. Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[5], OEHHA does not provide responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA in any way agrees with them.

A summary of the public comments received that are relevant to this rulemaking is provided below, along with OEHHA's responses to those comments. As explained in

[3] 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 B6C3F1/N Mice (Drinking Water Studies). NTP Technical Report Series No. 583. US Department of Health and Human Services, NTP, Research Triangle Park, NC.
[4] Section 25703(a)(4).
[5] California Government Code section 11346.9(a)(3)

detail in the responses to comments, OEHHA declines to change the proposed NSRL based on the comments.

Comment 1 (EWG): EWG supports OEHHA's NSRL for bromodichloroacetic acid and the scientific rationale behind it.

Response 1: OEHHA acknowledges the comment.

Comment 2 (ACC): Bromodichloroacetic acid is a disinfection by-product of chlorine disinfection of water. 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. The commenter cites Section 25703(b), and states that the regulation should mention the possibility and propriety of an alternative risk level for this chlorine disinfection by-product.

Response 2: Section 25703(b) states that "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 alternate risk level", and gives as one such example "where chlorine disinfection in compliance with all applicable state and federal safety standards is necessary to comply with sanitation requirements".

OEHHA recognizes the public health benefits of the use of chlorination to disinfect drinking water, and at the same time notes that nothing in Proposition 65 prohibits or places limits on drinking water disinfection using chlorination. In fact, the statute expressly exempts all agencies of the federal, state, or local government, as well as entities operating public water systems, from the requirements of Proposition 65[6], including the warning requirement.

In developing a NSRL for this carcinogen OEHHA only conducted the evaluation necessary to identify a level that would meet the 1 excess cancer in 100,000 standard. OEHHA did not consider whether sound considerations of public health would support an alternative risk level and nothing in the analysis would prohibit a business from proposing an alternative risk level for this chemical, should the business determine that one is warranted.

No changes to the proposed regulation were made based on this comment.

[6] Health and Safety Code section 25249.11(b)

Comment 3 (ACC): 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.

Removing the fibroadenomas results in incidences of 0/48, 1/50, 3/44, and 8/45 in control, 250, 500, and 1000 mg/L dose groups, respectively, and a lower cancer potency. Thus, the female rat study would no longer be used as the basis for the NSRL, as it would no longer be the most sensitive study.

Response 3: It is incorrect that mammary fibroadenomas cannot progress to malignant tumors. As explained in *Boorman's Pathology of the Rat*, "Adenocarcinomas can arise within fibroadenomas or adenomas, occurring as a focal adenocarcinomatous change within a benign neoplasm"[7]. In reporting the mammary tumor pathology findings in the NTP female rat study of bromodichloroacetic acid, NTP specifically stated that "Mammary gland carcinomas occasionally arose within fibroadenomas"[8].

NTP determined that "Bromodichloroacetic acid exposure caused clear exposure concentration-dependent increases in incidences of mammary gland fibroadenoma (including multiples) and carcinoma in female F344/NTac rats…The determination of clear evidence is supported by the exposure concentration-dependent increase in the incidences of fibroadenomas that are associated with possible progression to mammary gland carcinomas"[9]. In summary, mammary gland fibroadenomas were observed to progress to malignant carcinomas in female rats treated with bromodichloroacetic acid, thus it is appropriate to use tumor incidence data on the combined incidence of mammary gland fibroadenoma and adenocarcinoma in estimating a cancer slope factor (CSF_{animal}) from this study.

The comment also suggests that mammary gland adenomas were combined with mammary gland fibroadenomas and carcinomas to estimate cancer potency, but this is not correct. Only increased incidences of fibroadenoma and carcinoma of the mammary gland were considered treatment-related, and thus mammary gland adenoma data were not included in the dose-response analysis.

No change to the proposed regulation was made based on this comment.

[7] Eighmy JJ, Sharma AK, Blackshear PE (2018). Chapter 21 – Mammary Gland. In: Boorman's Pathology of the Rat. Reference and Atlas (Second Edition), eds. Suttie AW, Leininger JR, Bradley AE. Academic Press. pp. 376-379, 380-382.
[8] NTP (2015), full citation provided in footnote 3.
[9] NTP (2015), full citation provided in footnote 3.

Comment 4 (ACC): 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.

Response 4: OEHHA expressed tumor incidence as the number of tumor-bearing animals (numerator) over the number of animals alive at the time of first occurrence of the tumor (denominator), i.e., effective number. This method of tallying tumor incidence removes animals from the assessment that died before they are considered at risk for tumor development. The use of the effective number is standard practice by the US Environmental Protection Agency (US EPA) and OEHHA. US EPA reports tumor incidences as the number of tumor-bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor or before a particular week of the study. For example, US EPA's evaluation of iprodione reported tumor incidences as the "# of tumor-bearing rats/# of rats examined, excluding those that died or were sacrificed before observation of the first tumor"[10], and the evaluation of CMNP reported tumor incidences as "Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53"[11]. OEHHA uses effective numbers for cancer hazard identification (for example, C.I. Disperse Yellow 3[12]), as well as for cancer dose-response assessment (for example, vinylidene chloride[13], hexavalent chromium[14], and *tertiary*-butyl acetate[15]). Additionally, there are other ways to account for early deaths of animals. For example, NTP uses the Poly-3 method for cancer hazard identification. The Poly-3 method calculates a survival-adjusted rate that "accounts for differential mortality by assigning a reduced risk

[10] US Environmental Protection Agency (US EPA, 1994). Carcinogenicity Peer Review of Iprodione. Health Effects Division, Office of Prevention, Pesticides, and Toxic Substances. See p. 5.
[11] US Environmental Protection Agency (US EPA, 2011). Cancer Assessment Document. Evaluation of the carcinogenic potential of CMNP (Pyrazachlor) PC Code 207100. Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, September 20. See p. 10.
[12] OEHHA (2012). Evidence on the carcinogenicity of C.I. Disperse Yellow 3. Reproductive and Cancer Hazard Assessment Branch, OEHHA, California Environmental Protection Agency, August. See pp. 10, 12. Available at https://oehha.ca.gov/media/downloads/proposition-65/chemicals/081012ciyhid.pdf.
[13] OEHHA (2017a). Initial Statement of Reasons. Title 27, California Code of Regulations, Proposed Amendment to Section 25705(b) Specific Regulatory Levels Posing No Significant Risk: Vinylidene Chloride. See p. 3. Available at https://oehha.ca.gov/media/downloads/crnr/isorvinylidenechloride092217.pdf.
[14] OEHHA (2011). Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Pesticide and Environmental Toxicology Branch, OEHHA, California Environmental Protection Agency, July. See p. 51. Available at https://oehha.ca.gov/media/downloads/water/chemicals/phg/cr6phg072911.pdf.
[15] OEHHA (2018). Air Toxics Hot Spots Program *Tertiary*-Butyl Acetate Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors. Appendix B. Air and Site Assessment and Climate Indicator Branch, OEHHA, California Environmental Protection Agency, August. See p. 50. Available at https://oehha.ca.gov/media/downloads/crnr/tbaccanceriur081018.pdf.

of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice"[16].

Thus, OEHHA's use of effective number in reporting tumor incidence is well justified, and consistent with the practices of other authoritative bodies, including US EPA and NTP, that also take into account early deaths in assessing tumor data from animal studies.

No changes to the proposed regulation were made based on this comment.

Comment 5 (ACC): OEHHA 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%, and 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.

Response 5: OEHHA acknowledges that in general there exists some uncertainty in mathematical modeling of biological processes such as carcinogen dose-response relationships. Given the high level of response at all doses treated with the carcinogen in the female rat study, it would be desirable if additional female rat tumor incidence data corresponding to doses lower than those used in that study were available to help characterize the shape of the dose-response curve in the low dose region. As described below, the data from the female rat study were adequate for purposes of cancer dose response modeling.

As stated in the ISOR[17], OEHHA determined that the most sensitive study was the female rat study in which treatment-related increases in mammary gland tumors were observed. Use of the multistage cancer model is generally accepted as the default approach to modeling lifetime cancer data as it is considered sufficiently flexible to fit most cancer bioassay data[18]. When using US EPA's Benchmark Dose Software (BMDS) to fit the multistage cancer model, in cases where the fitted model fails to meet the goodness-of-fit criteria[19], US EPA recommends recursive removal of the high dose

[16] NTP (2015). Full citation provided in footnote 3.
[17] OEHHA (2017b). 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. Available at https://oehha.ca.gov/media/downloads/crnr/isorbromodichloroaceticacid122917.pdf
[18] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In Benchmark Dose Software (BMDS) Training Webinars. Available from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800
[19] A p-value greater than 0.05 (the standard significance level used for models selected *a priori*), scaled residuals less than two in absolute value, and a plot in which the curve appears to fit the data appropriately are the markers of sufficient goodness-of-fit.

in an attempt to improve model fit[20]. This guidance is consistent with longstanding US EPA cancer dose-response practice[21]. OEHHA followed the US EPA guidance and removed the top dose in the female rat study to achieve sufficient goodness-of-fit, and the human potency estimate derived from this study in female rats was taken as the basis for the overall cancer potency estimate.

No changes to the proposed regulation were made based on this comment.

Comment 6 (ACC): The NSRL should be based on BMDL10 instead of BMDL05. The default in the US EPA software is BMDL10, and OEHHA does not explain its decision to depart from the default approach.

Response 6: OEHHA notes that a $BMDL_{10}$, which is obtained by setting the benchmark response (BMR) to 10% when modeling dose-response data using US EPA's BMDS[22], is not in fact a default. US EPA states:

> "For quantal data, an extra risk of 10% is the BMR for standard reporting (to serve as a basis for comparisons across chemicals and endpoints), and often for hazard ranking, since the 10% response is near the limit of sensitivity in most cancer bioassays and in some noncancer bioassays as well. **Note that this is not a default BMR**. For determination of a POD, a lower (or sometimes higher) BMR is often used based on statistical and biological considerations."[23] (emphasis added)

OEHHA determined that it was appropriate to set the BMR to correspond to an extra risk of 5% when fitting the multistage cancer model to the data for bromodichloroacetic acid. In doing so, OEHHA followed a common scientific practice that is consistent with use of a BMR of 5% in other cancer dose-response assessments developed for

[20] US EPA (2012). Benchmark Dose Technical Guidance. Risk Assessment Forum, US EPA, June. p. 35. Available from: https://www.epa.gov/sites/production/files/201501/documents/benchmark_dose_guidance.pdf
[21] Anderson EL and the U.S. Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. Risk Analysis 3:277-295.
[22] Available from: https://www.epa.gov/bmds/what-benchmark-dose-software-bmds
[23] US EPA (2012). Full citation provided in footnote 20.

Proposition 65[24] and other OEHHA programs[25], as well as the guidance in the resources provided by US EPA regarding use of BMDS[26].

No changes to the proposed regulation were made based on this comment.

Comment 7 (ACC): The liver tumor data suffered from many of the same problems as noted for the mammary tumor data. The liver tumors in mice occurred at a very high incidence in all dose groups, and OEHHA had to drop the high dose groups in male and female mice in order to estimate cancer slope factors.

Response 7: OEHHA disagrees with the comment's characterization of the liver tumor incidence in male mice as being very high in all dose groups. A dose-dependent increase in liver tumors (e.g., combined hepatocellular carcinoma or hepatoblastoma) was apparent in male mice: 30% (15/50) in controls, 68% (34/50) in the low-dose group, 98% (48/49) in the mid-dose group, and 88% (44/50) in the high-dose group. When using US EPA's BMDS to fit the data to the multistage cancer model it was necessary to drop the high-dose group to achieve sufficient goodness-of-fit.

While it is correct that the liver tumor incidence in female mice was high in all dose groups (36/48, 44/49, 43/47, and 46/49 in the control, low-, mid-, and high-dose groups, respectively), it was not necessary to drop any doses in order to achieve sufficient goodness-of-fit of the multistage cancer model.

Since neither male nor female mice were the most sensitive to the carcinogenic effects of bromodichloroacetic acid, neither study was used as the basis for the NSRL.

No changes to the proposed regulation were made based on this comment.

Comment 8 (ACC): OEHHA should delete the sentence in the ISOR that states: "There are no principles or assumptions scientifically more appropriate, based on the available

[24] *E.g.*, OEHHA (2017a). Initial Statement of Reasons Title 27, California Code of Regulations, Proposed Amendment to Section 25705(b) Specific Regulatory Levels Posing No Significant Risk: Vinylidene Chloride. Available at https://oehha.ca.gov/media/downloads/crnr/isorvinylidenechloride092217.pdf.; and OEHHA (2017c). Initial Statement of Reasons Title 27, California Code of Regulations, Proposed Amendment to Section 25705(b) Specific Regulatory Levels Posing No Significant Risk: Malathion. Available at https://oehha.ca.gov/media/downloads/crnr/malathionnsrlisor012017.pdf

[25] *E.g.,* OEHHA (2018). Air Toxics Hot Spots Program *Tertiary*-Butyl Acetate Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors. Appendix B. Air and Site Assessment and Climate Indicator Branch, OEHHA, California Environmental Protection Agency, August. Available at https://oehha.ca.gov/media/downloads/crnr/tbaccanceriur081018.pdf.; and OEHHA (2016). Air Toxics Hot Spots Program Perchloroethylene Inhalation Cancer Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Air, Community, and Environmental Research Branch, OEHHA, California Environmental Protection Agency, September. Available at https://oehha.ca.gov/media/downloads/crnr/pceurf090816.pdf.

[26] US EPA (2012). Full citation provided in footnote 20.

data, than this approach"; it is not correct. It is scientifically more appropriate to exclude mammary fibroadenomas from the mammary adenomas and mammary carcinomas in developing a NSRL.

Response 8: As explained above in Response 3, OEHHA disagrees that mammary gland fibroadenomas should be excluded from the dose-response analysis of the treatment-related tumors observed in the NTP female rat study[27]. No data have been provided that demonstrate a more appropriate approach to the analysis. OEHHA maintains that the sentence quoted in the comment from the ISOR is correct. Additionally, the incidence of mammary gland adenomas was not combined with the incidences of mammary gland fibroadenomas and carcinomas. Only increased incidences of fibroadenoma and carcinoma of the mammary gland were considered treatment-related.

No changes were made to the proposed regulation based on this comment.

Alternatives Determination

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. No alternatives have been suggested. OEHHA has determined that no reasonable alternative would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses "no significant risk" of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish a No Significant Risk Level for bromodichloroacetic acid. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow businesses subject to the Act to determine whether a given discharge to

[27] NTP (2015). Full citation provided in footnote 3.

sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25249.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

Local Mandate Determination

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.

Nonsubstantive Changes Made to the Final Text During OAL Review

Several changes were made to the final regulatory text to conform with existing text in the California Code of Regulations.