FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

NO SIGNIFICANT RISK LEVEL: BROMOCHLOROACETIC ACID

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL) for bromochloroacetic acid. Bromochloroacetic acid was listed as a chemical known to the state to cause cancer for purposes of Proposition 65[1] on April 6, 2010. 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 0.7 micrograms per day (µg/day) for bromochloroacetic 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 Bromochloroacetic 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 bromochloroacetic 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 bromochloroacetic 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 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)"[3], 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"[4]. 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[5].

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 bromochloroacetic 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

[3] 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.
[4] 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 at: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-15/
[5] Section 25703(a)(4)

FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[6], 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 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 bromochloroacetic acid and the scientific rationale behind it.

Response 1: OEHHA acknowledges the comment.

Comment 2 (ACC): Bromochloroacetic acid is a disinfection by-product of chlorine disinfection of water. OEHHA should explicitly state that the NSRL for bromochloroacetic acid does not specifically consider the role of chlorine-based disinfection, and that an alternative risk level would be appropriate when bromochloroacetic 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".

In developing NSRLs for these carcinogens OEHHA only conducted the evaluation necessary to identify a level that would meet the 1 in 100,000 standard. 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[7], including the warning requirement.

[6] California Government Code section 11346.9(a)(3)
[7] Health and Safety Code section 25249.11(b)

In developing NSRL for this carcinogen OEHHA only conducted the evaluation necessary to identify a level that would meet the 1 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 calculating an alternative risk level for this chemical, should the business determine that one is needed.

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

Comment 3 (ACC): OEHHA should acknowledge the significant uncertainty in estimating a cancer slope factor based on liver tumor data in male and female mice where every dose group of bromochloroacetic acid had a tumor response in the range of 90% to 100%. The commenter states that this is a weak set of data for purposes of modeling a cancer slope factor and that the data give no indication of the shape of the dose-level at a tumor response rate below 90%. As a result, there is considerable uncertainty in the estimated BMDL05 for liver tumors.

Response 3: OEHHA acknowledges that in general there exists some uncertainty in mathematical modeling of biological processes such as carcinogen dose-response relationships. Given the high response at all doses of carcinogen tested in these studies, it would be desirable if additional tumor incidence data corresponding to doses lower than those used in these studies were available to help characterize the shape of the dose-response curve in the low dose region. It is notable, however, that the doses used in the NTP study in female mice were in fact lower than those used in the NTP study in male mice; for example, the low dose in the study in female mice was 15 milligrams per kilogram of bodyweight per day (mg/kg-day) compared to a low dose of 25 mg/kg-day in the study in male mice. Thus, the females in the low dose group received only 60% of the dose received by the males in the low dose group, and yet the tumor response in females was greater than that of males in the low-dose groups (98% compared to 90%).

As stated in the ISOR[8], OEHHA determined that the most sensitive study was the female mouse study in which treatment-related increases in liver tumors were observed. The next most sensitive study was the male mouse study. 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[9]. When using the

[8] 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. Bromochloroacetic acid. Available at: https://oehha.ca.gov/media/downloads/crnr/isorbromochloroaceticacid122917.pdf

[9] US Environmental Protection Agency (US EPA, 2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In Benchmark Dose Software (BMDS) Training Webinars. Available at: https://clu-

US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS) to fit the multistage cancer model, in cases where the fitted model fails to meet the goodness-of-fit criteria[10], US EPA recommends recursive removal of the high dose in an attempt to improve model fit[11]. This guidance is consistent with longstanding US EPA cancer dose-response practice[12]. OEHHA followed the US EPA guidance and removed the top two doses in the female mouse study to achieve sufficient goodness-of-fit. As explained in the ISOR[13], in consideration of this, together with the observation that high liver tumor incidences (≥90%) occurred in all three dose groups in both the female mouse study and the second most sensitive study, the study in male mice, a geometric mean of the human potency estimates derived from the studies in male and female mice was taken as the basis of the overall cancer potency estimate.

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

Comment 4 (ACC): The NSRL should be based on BMDL10 instead of BMDL 05. The default in the US EPA software is BMDL10, and OEHHA does not explain its decision to depart from the default approach.

Response 4: 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 Benchmark Dose Software (BMDS)[14], 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."[15] (emphasis added)

in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[10] 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.

[11] US EPA (2012). Benchmark Dose Technical Guidance. Risk Assessment Forum, US EPA, June. See p. 35. Available at: https://www.epa.gov/sites/production/files/201501/documents/benchmark_dose_guidance.pdf.

[12] 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.

[13] OEHHA (2017a). Full citation provided in footnote 8.

[14] Available at: https://www.epa.gov/bmds/what-benchmark-dose-software-bmds

[15] US EPA (2012). Full citation provided in footnote 11.

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 bromochloroacetic 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 Proposition 65[16] and other OEHHA programs[17], as well as the guidance in the resources provided by US EPA regarding use of BMDS[18].

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

Comment 5 (ACC): OEHHA departs from the traditional method of expressing the tumor incidence (i.e., using the total number of animals in the group in the denominator). Instead, OEHHA uses in the denominator the number of animals alive at the time of the occurrence of the first tumor. Because of this difference, the tumor incidences used by OEHHA to calculate the NSRL differ from those presented by the NTP in its cancer bioassay. This practice is concerning, is not adequately justified, and should be the subject of further discussion.

Response 5: The effective tumor incidence is the number of tumor-bearing animals (numerator) over the number of animals alive at the time of first occurrence of the tumor (denominator). 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 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"[19], and the evaluation of CMNP reported tumor incidences as "Number of

[16] *E.g.*, 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: 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

[17] *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

[18] US EPA (2012). Full citation provided in footnote 11.

[19] US EPA (1994). Carcinogenicity Peer Review of Iprodione. Health Effects Division, Office of Prevention, Pesticides, and Toxic Substances. See p. 5.

tumor bearing animals/Number of animals examined, excluding those that died before week 53"[20]. OEHHA uses effective numbers for cancer hazard identification (for example, C.I. Disperse Yellow 3[21]), as well as for cancer dose-response assessment (for example, vinylidene chloride[22], hexavalent chromium[23], and *tertiary*-butyl acetate[24]). 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 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"[25].

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 6 (ACC): OEHHA should acknowledge that the dose-response analysis assumes mouse liver tumors are relevant to humans. The human relevance of the mouse liver tumors is debatable. OEHHA should delete the sentence in the ISOR that states: "There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach." There is a substantial body of scientific evidence that certain types of liver tumors observed in mice are not relevant to humans.

Response 6: Animal models are routinely used to study the toxicity of chemicals, and the results of those studies are extrapolated to humans. IARC and NTP consider liver tumors induced in mice by bromochloroacetic acid to be relevant to humans. NTP explained, "Biotransformation of dihaloacetates to glyoxylate occurs primarily in liver

[20] 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.
[21] 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.
[22] 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: Vinylidene Chloride. See p. 3. Available at: https://oehha.ca.gov/media/downloads/crnr/isorvinylidenechloride092217.pdf.
[23] 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.
[24] 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.
[25] NTP (2009). Full citation provided in footnote 3.

cytosol of rats and humans by a glutathione-dependent process (James *et al.*, 1997) catalyzed by glutathione-*S*-transferase zeta (GST-ζ) (Tong *et al.*, 1998a)[26]". And, as stated in the ISOR[27], IARC's 2013 review of the mechanistic data 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 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."[28]

These metabolic pathways and proposed genotoxic mechanisms are not specific to mice, and there is no basis to conclude that mouse liver tumors induced by bromochloroacetic acide are not relevant to humans. The sentence from the Initial Statement of Reasons that is quoted in the comment is correct.

No changes were made based on this comment.

Comment 7 (ACC): OEHHA should mention the underlying uncertainty of estimating the human cancer slope factor by using the default allometric scaling factor. The default interspecies scaling procedure assumes that larger animals with greater body surface area are more susceptible to carcinogens than smaller animals with lesser body surface area. Based on the same allometric scaling approach, rats are assumed to be 2 times more sensitive than mice to the potential carcinogenicity of bromochloroacetic acid, but the data show the opposite (i.e., the cancer slope factor based on the mouse data is greater than the cancer slope factor based on rat data). The default allometric scaling factor approach in the regulations is conservative, and it is worth mentioning that in the case of rats, the mouse data over-predicted the carcinogenicity of bromochloroacetic acid.

Response 7: OEHHA disagrees. The commenter's statement, "The default interspecies scaling procedure assumes that larger animals with greater body surface area are more susceptible to carcinogens than smaller animals with lesser body surface area," is not correct. Allometric scaling is used to calculate a human cancer potency estimate equivalent to the data-derived animal cancer potency estimate in consideration of body size differences between species. It is an adjustment made to establish

[26] NTP (2009). Full citation provided in footnote 3.
[27] OEHHA (2017a). Full citation provided in footnote 8.
[28] IARC (2013). Full citation provided in footnote 4.

analogous values in species of different mass, and is based on the assumption that dose administered to different species produces the same level of effect when it is expressed as an amount per bodyweight to the ¾ power. In this particular case, the mouse was the more sensitive species, and following the Proposition 65 regulations for dose response analysis[29], the potency was based on the mouse, the more sensitive species. Interindividual variability in the human population is far more extensive than in the rodent strains studied in carcinogenicity bioassays and this can lead to underestimation of potency in humans[30]. Thus there are more dimensions to consider in characterizing potency estimates as conservative or not conservative.

US EPA uses the same default interspecies scaling factor as OEHHA[31], and, as explained in the US EPA's Guidelines for Carcinogen Risk Assessment:

> "For oral exposures, administered doses should be scaled from animals to humans on the basis of equivalence of mg/kg^{¾}-d (milligrams of the agent normalized by the ¾ power of body weight per day) (U.S. EPA, 1992b). The ¾ power is consistent with current science, including empirical data that allow comparison of potencies in humans and animals, and it is also supported by analysis of the allometric variation of key physiological parameters across mammalian species…This scaling is intended as an unbiased estimate rather than a conservative one"[32].

Thus, the default scaling approach is not conservative and the mouse data did not "over-predict the carcinogenicity."

No changes to the proposed regulation were made 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

[29] Section 25703
[30] National Research Council/National Academy of Sciences (2009). Chapters 4 and 5. In: Science and Decisions, Advancing Risk Assessment, National Academy Press, Washington, DC. Available at https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment.
[31] Section 25703(a)(6)
[32] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

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 bromochloroacetic 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 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 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.