# FINAL STATEMENT OF REASONS
# TITLE 27, CALIFORNIA CODE OF REGULATIONS

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

## NO SIGNIFICANT RISK LEVEL: DIBROMOACETIC ACID

This is the Final Statement of Reasons (FSOR) for the adoption of a No Significant Risk Level (NSRL) for dibromoacetic acid. On June 17, 2008, dibromoacetic acid was listed for purposes of Proposition 65[1] as a chemical known to the state to cause cancer. On May 22, 2020, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Title 27, California Code of Regulations, section 25705(b)[2], Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 2.8 micrograms per day (µg/day) for dibromoacetic acid. The Initial Statement of Reasons (ISOR) sets forth the grounds for the amendment to the regulation.

### SUMMARY

In developing the NSRL for dibromoacetic acid, OEHHA relied on the National Toxicology Program (NTP) report entitled "Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies)"[3], 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

[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.
[3] National Toxicology Program (NTP 2007). Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Technical Report Series No. 537. NIH Publication No. 07-4475. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr537.pdf

Drinking-water"[4], and additional publications on genotoxicity[5,6,7,8,9,10]. The NSRL for dibromoacetic acid is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[11].

## PEER REVIEW

OEHHA provided the Notice of Proposed Rulemaking and the Initial Statement of Reasons for the proposed NSRL for dibromoacetic 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 members Jason Bush, PhD, Dana Loomis, PhD, MPH, Thomas Mack, MD, MPH, and Luoping Zhang, PhD.

## RESPONSE TO PEER REVIEW COMMENTS

**Comment 1:** Drs. Loomis, Mack, and Zhang peer reviewed the materials, and indicated that they did not have any comments.

**Response 1:** OEHHA acknowledges the responses.

**Comment 2:** Dr. Bush indicated that he supports the rationale for the proposed NSRL for dibromoacetic acid, and concurs with the calculations and the proposed NSRL.

**Response 2:** OEHHA acknowledges the comments in support of the proposed NSRL.

[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 Organisation, Lyon France. Available from: https://publications.iarc.fr/125

[5] Hu Y, Tan L, Zhang SH, et al. (2017). Detection of genotoxic effects of drinking water disinfection by-products using Vicia faba bioassay. Environ Sci Pollut Res Int 24(2): 1509-1517.

[6] Nelson GM, Swank AE, Brooks LR, Bailey KC, George SE. (2001). Metabolism, microflora effects, and genotoxicity in haloacetic acid-treated cultures of rat cecal microbiota. Toxicol Sci 60(2): 232-241.

[7] Zhang L, Xu L, Zeng Q, Zhang S, Xie H, Liu A, et al. (2012). Comparison of DNA damage in human-derived hepatoma line (HepG2) exposed to the fifteen drinking water disinfection byproducts using the single cell gel electrophoresis assay. Mutat Res 741(1-2): 89-94.

[8] Zhang SH, Miao DY, Tan L, Liu AL, Lu WQ. (2016). Comparative cytotoxic and genotoxic potential of 13 drinking water disinfection by-products using a microplate-based cytotoxicity assay and a developed SOS/umu assay. Mutagenesis 31(1): 35-41.

[9] Stalter D, O'Malley E, von Gunten U, Escher BI. (2016). Fingerprinting the reactive toxicity pathways of 50 drinking water disinfection by-products. Water Res 91: 19-30.

[10] Zuo YT, Hu Y, Lu WW, et al. (2017). Toxicity of 2,6-dichloro-1,4-benzoquinone and five regulated drinking water disinfection by-products for the Caenorhabditis elegans nematode. J Hazard Mater 321: 456-463.

[11] Section 25703(a)(4).

PUBLIC COMMENTS

A public comment period was provided from May 22, 2020 to July 7, 2020. OEHHA received written public comments on the proposed rulemaking from the following organizations:

1. Southern California Water Coalition (SCWC)
2. American Chemistry Council's (ACC) Chlorine Chemistry Division (CCD)

RESPONSE TO PUBLIC COMMENTS

A summary of the relevant comments received and OEHHA's responses are provided in this 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 dibromoacetic 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[12], 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.

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

**Comment 1 (SCWC, ACC):** NSRLs should not be based on draft risk assessments still under development in other programs. CCD [ACC's Chlorine Chemistry Division] is "troubled by OEHHA's decision to move ahead with NSRLs before the Office has considered the information submitted in response to the PHG [Public Health Goal] proposal and before the science that is the basis for both the PHGs and NSRLs has been subject to peer review". The NSRL should not be released until the process for the PHG for haloacetic acids has been completed. It is premature and inappropriate for OEHHA to use draft PHG risk assessments to support Proposition 65 NSRLs or any other regulatory decisions until those draft risk assessments are completed. SCWC is concerned that using the draft PHG risk assessments as the basis for enforceable NSRLs would undermine the PHG development process because the proposed NSRLs would create an institutional bias against meaningful changes to the draft PHG risk assessments.

**Response 1:** The NSRL does not rely on the draft Public Health Goal (PHG), which was developed in parallel with the NSRL. This process allows for adequate time for the

[12] California Government Code section 11346.9(a)(3)

NSRL and the PHG to undergo external peer review and encourages consistency between the two programs within OEHHA. The process for the dose-response assessment and development of the NSRL for dibromoacetic acid was conducted in collaboration with the OEHHA program that produces PHGs. Both programs critically evaluated the same key rodent carcinogenicity studies of dibromoacetic acid (NTP 2007[13]) and used the same data analysis principles, methods, and software to calculate the cancer potencies. After careful consideration by both programs, the male mouse study by NTP (2007) was chosen for assessing the carcinogenic effects of dibromoacetic acid, and thus, the human cancer slope factor derived from that study was used as the basis for both the NSRL and the PHG. An assessment by one OEHHA program does not preclude another OEHHA program from making changes to a draft document. The proposed levels for both programs are based on the best available science and have undergone rigorous scientific review.

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

**Comment 2 (SCWC, ACC):** There is no justification for proposing the NSRLs at this time. These chemicals were listed several years ago, yet OEHHA saw no need to develop the NSRL until now. Dibromoacetic acid appears to be limited only to narrow laboratory applications. However, there is nothing in the ISOR indicating an increase in consumer product uses or other applications that would justify the development of an NSRL at this time.

**Response 2:** OEHHA develops NSRLs for chemicals listed as carcinogens under Proposition 65 as time and resources allow. There are no limits on the time between the date of listing and the development of an NSRL. In recent years, multiple haloacetic acids (HAAs) have been added to the Proposition 65 list and OEHHA has developed NSRLs for each of the five HAAs listed (trichloroacetic acid, dibromoacetic acid, dichloroacetic acid, bromochloroacetic acid, and bromodichloroacetic acid) in order to provide compliance assistance for businesses and guidance for Proposition 65 enforcers.

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

**Comment 3 (SCWC):** These NSRLs present a potential public health threat because they prioritize reduction of exposure to disinfection by-products (DBPs) over drinking water disinfection. OEHHA should establish alternative Safe Harbor Levels pursuant to Section 25703(b) that allows for such exceptions to the default NSRL.

[13] NTP (2007). Full citation provided in footnote 3.

**Response 3:** OEHHA followed the guidance in Section 25703(b), which 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 the NSRL for this carcinogen, OEHHA 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 chlorine disinfection, and at the same time notes that nothing in Proposition 65 prohibits or places limits on drinking water disinfection. In fact, the statute[14] 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, including the warning requirement.

Nothing in the analysis for the NSRL prohibits 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 4 (ACC):** The NSRL does not consider the long history of low-level exposure to these substances (i.e., HAAs) and several other DBPs considered to be liver carcinogens by OEHHA (chloroform, bromodichloromethane, and dibromochloromethane). This history reveals a lack of consistent evidence of an increased incidence of liver cancer resulting from exposure to DBPs in the multiple epidemiology studies that have been conducted.

**Response 4:** The NSRL for dibromoacetic acid was based on a study conducted in mice because it was deemed to be a sensitive study of sufficient quality, consistent with the requirements described in Section 25703. To our knowledge, no human epidemiological studies of sufficient quality and sensitivity have been published in the scientific literature that would be adequate for conducting a cancer dose-response assessment for dibromoacetic acid. Thus, the NTP (2007) study in male mice in which liver and lung tumors were observed was chosen as the most sensitive study of sufficient quality. Regarding the lack of consistent evidence of an increased incidence of liver cancer in humans, tumor site concordance across species is neither required, nor predicted, for chemical carcinogens. It is a generally accepted principle that although there may be site concordance between humans and animal test species in specific cases, it is not necessarily going to occur. For risk assessment purposes, site

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

concordance is not assumed unless there is evidence to support this assumption[15]. In the absence of data to the contrary, the ability of an agent to induce tumors in animals is considered predictive of the potential for the agent to induce tumors in humans.

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

**Comment 5 (SCWC):** Although there is evidence of the genotoxicity of dibromoacetic acid, the mechanism for tumor induction has not been clearly identified and may involve precursor events that are non-genotoxic.

**Response 5:** As explained in the ISOR, the mechanism for tumor induction by dibromoacetic acid has not been clearly identified, but may involve genotoxicity, oxidative stress, epigenetic alterations, and other possible mechanisms. It is common for multiple mechanisms to contribute to tumor development. In light of this, a multistage model is an appropriate model to derive a cancer potency estimate. The commenter did not provide data to support the use of an alternative model.

No changes to the proposed regulation were made based on these comments.

**Comment 6 (ACC):** ACC states that "[t]he NSRL for DBA [dibromoacetic acid] should not be based on carcinogenicity", and provided the following in support of this claim.

> "The cancer evidence for DBA is limited to a National Toxicology Program (NTP) drinking water study reporting liver tumors in male and female mice and an increase in lung tumors in male mice.[12] Liver and lung tumors were not observed in rats in the NTP study.[13] The control groups for both the male and female mice exhibited a high rate of spontaneous liver tumors, however, and the incidence of lung tumors was increased in the control group of the male mice. In addition, the lung tumors did not show a clear dose-response in the male mice – tumors were significantly increased at a mid-dose of 500 mg/L, but not at the highest dose of 1000 mg/L.
>
> Given the limited cancer data available for DBA, and the conflicting results reported in mice and rats, the mouse cancer data should not be used as the basis for the NSRL. Moreover, any estimate of cancer risk should not include the lung tumors in male mice as a result of the high spontaneous incidence in the control animals and the lack of a clear dose-response in the male mice."

**Response 6:** No Significant Risk Levels are specific to chemicals that are listed as carcinogens under Proposition 65 and are always based on carcinogenicity. As explained in Section 25701(a), "The determination of whether a level of exposure to a chemical known to the state to cause cancer poses no significant risk for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of

[15] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Available from http://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009

comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer". The regulations go on to state that "Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality"[16].

Dibromoacetic acid was listed under Proposition 65 via the "Authoritative Bodies" listing mechanism, based on NTP's conclusion that there was clear evidence of carcinogenic activity of dibromoacetic acid in male and female mice[17].

The commenter is correct in that liver tumors were observed in the NTP studies of male and female mice and lung tumors were observed in male mice. However, lung tumors were also observed in female mice in the NTP study: treatment-related increases in alveolar/bronchiolar adenomas were observed with a statistically significant positive trend[18], as shown in Table 2 in the ISOR. As noted by IARC in its evaluation of the NTP mouse studies, "[I]n mice, dibromoacetic acid increased the incidence of hepatocellular adenoma and hepatocellular carcinoma in males and females, of hepatoblastoma in males, and of alveolar/bronchiolar adenoma in males and females."[19]

Regarding the comment that liver and lung tumors were not observed in rats, tumor site concordance across species is neither required, nor predicted, for chemical carcinogens. It is a generally accepted principle that although there may be site concordance between different animal test species in specific cases, this is not true in general. It is common for a chemical to induce tumors at a particular site in one species of rodent (e.g., mice), but induce tumors in an entirely different organ in another species of rodent (e.g., hamsters). The observation of differences in tumor sites between species is not considered evidence of "conflicting results." Treatment-related increases in tumors were observed at other sites in rats in the NTP studies of dibromoacetic acid, i.e., malignant mesothelioma in males and mononuclear-cell leukemia in females[20].

The incidences of liver tumors in the control groups of the male and female mouse studies conducted by NTP (2007) do not diminish the significance of the liver tumor findings in these studies. Hepatocellular adenomas and carcinomas are commonly observed in untreated male and female $B6C3F_1$ mice. NTP (2007) reports historical control incidences in 2-year drinking water studies of 124/197 (62.9%; range: 52%–85%) for combined hepatocellular adenomas, carcinomas, and hepatoblastomas in

[16] Section 25703(a)(3).
[17] NTP (2007). See pp. 9 and 79. Full citation provided in footnote 3.
[18] NTP (2007). Full citation provided in footnote 3.
[19] IARC (2013). Full citation provided in footnote 4.
[20] NTP (2007). Full citation provided in footnote 3.

male mice[21,22,23], and 110/248 (44.4%; range: 20%–63%) for combined hepatocellular adenomas and carcinomas in female mice[24]. Thus the control incidences of these liver tumors observed in the dibromoacetic acid studies of 28/48 (58%) in males and 22/46 (47.8%) in females fall within the range of historical control incidences. Similarly, the 15.2% (7/46) incidence of lung tumors (i.e., alveolar/ bronchiolar adenoma) in the control group of the male mouse study conducted by NTP (2007) does not diminish the significance of the lung tumor findings in this study, as it falls within the range of alveolar/bronchiolar adenoma historical control incidence in male mice reported by NTP (26/199; 13.1%; mean: 10.5%; range: 6–20%)[25].

Regarding the assertion that lung tumors did not show a clear dose-response in male mice, OEHHA notes that while a higher lung tumor incidence was observed in the mid-dose group relative to the high-dose group, there is in fact a statistically significant dose-related positive trend in lung tumor incidence ($p < 0.05$ for exact trend test) in male mice treated with dibromoacetic acid. In evaluating the dose-response data for the purpose of calculating the NSRL, the mathematical model applied takes into account the entirety of the dose-response data, including that of the mid-dose group.

In summary, OEHHA does not agree with the commenter that the cancer data for dibromoacetic acid are limited.

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 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-

[21] *Ibid*.
[22] NTP. Sodium chlorate (7775-09-9). Chemical Effects in Biological Systems (CEBS). Research Triangle Park, NC (USA): National Toxicology Program (NTP). Accessed 2021-05-10. https://manticore.niehs.nih.gov/cebssearch/test_article/7775-09-9.
[23] NTP. Sodium nitrite (7632-00-0). Chemical Effects in Biological Systems (CEBS). Research Triangle Park, NC (USA): National Toxicology Program (NTP). Accessed 2021-05-10. https://manticore.niehs.nih.gov/cebssearch/test_article/7632-00-0.
[24] NTP (2007). Full citation provided in footnote 3.
[25] *Ibid.*

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 dibromoacetic 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.