CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986

NOTICE OF MODIFICATION TO PROPOSED REGULATION AND ADDITION OF DOCUMENTS TO RULEMAKING FILE

TITLE 27, CALIFORNIA CODE OF REGULATIONS
ARTICLE 7 NO SIGNIFICANT RISK LEVELS

1-BROMOPROPANE AND DIETHANOLAMINE (DERMAL)

June 10, 2026

Public Availability and Public Comment through June 25, 2026

The Office of Environmental Health Hazard Assessment (OEHHA) is providing notice of modifications made to a previously proposed regulation, namely the Proposition 65 dermal No Significant Risk Level (NSRL) for diethanolamine in Title 27, California Code of Regulations (CCR), section 25705(b)(1),[1] and the addition of eight documents to the rulemaking file. OEHHA is providing this notice pursuant to Government Code sections 11346.8(c) and 11347.1(b), and Title 1, CCR, section 44. OEHHA first proposed the regulation to adopt a dermal NSRL for diethanolamine by publishing a Notice of Proposed Rulemaking in the California Regulatory Notice Register (CRNR) on August 22, 2025. In parallel, OEHHA issued an Initial Statement of Reasons (ISOR) for the proposal. The aforementioned Notice and ISOR also included a proposal to adopt a NSRL for 1-bromopropane. There are no modifications to the proposed NSRL for 1-bromopropane.

OEHHA provided a 45-day comment period on the original proposal, from August[2] 22 to October 6, 2025, which was subsequently extended to November 7, 2025.

After reviewing the comments received on this proposed regulation, OEHHA has determined that modifications to the original regulatory text for the diethanolamine dermal NSRL are needed. In addition, OEHHA is relying upon several additional documents in this rulemaking and is adding these documents to the rulemaking file.

[1] All further section references are to Title 27 of the CCR, unless otherwise indicated.

[2] The original notice of modification issued on June 10, 2026, stated that the 45-day comment period on the NSRL for diethanolamine and 1-bromopropane began on September 22, 2025. It has been corrected to August 22, 2025, which is noted elsewhere in the original notice of modification.

OEHHA has complied with Title 1, CCR section 44 and has sent this notice, together with a copy of the full text of the regulation as originally proposed, with the proposed change clearly indicated, to the persons specified in subsection (a) on the date listed above, June 10, 2026. The purpose of this notice is: (1) to provide the public with notice of the modified proposed regulatory text and the additional documents included in the rulemaking file, and (2) to open a public comment period and a public availability period, running from June 10, 2026, through June 25, 2026.

Consistent with the Administrative Procedure Act, OEHHA will only address comments received during this comment period that address the modifications to the text of the proposed regulation or the documents added to the record. Details on how to submit comments are provided below.

Summary of Proposed Modifications

OEHHA is modifying proposed Section 25705(b)(1) as shown below. The originally proposed change is shown in single underline (example), and the proposed modification is shown in bold double-underline (**example**) and strikeout (~~example~~).

…

Chemical name	*Level (micrograms per day)*
Acrylonitrile	0.7
…	
1-Bromopropane	54
…	
Dieldrin	0.04
Diethanolamine	~~6.4~~**5.8** (dermal)

…

A copy of the full updated proposed regulatory text (amendments to Section 25705(b)(1)), reflecting the modifications, is provided as Attachment 1.

Rationale for the Proposed Modifications

During the comment period on the original proposal, OEHHA received a number of comments, including comments on design aspects of the two-year dermal carcinogenicity studies conducted in mice by the National Toxicology Program (NTP) that were used to determine the cancer potency of diethanolamine, mechanisms by which diethanolamine induces liver tumors and the dose-response model used to estimate cancer potency, and the studies used to account for differences in dermal absorption between mice and humans.

During careful consideration of comments on these issues, OEHHA reevaluated its analysis and has modified its derivation of the factor used to account for species differences in dermal absorption. OEHHA used the same study referenced in the Initial Statement of Reasons and subtracted the background DEA levels present in the subjects' blood before treatment began. OEHHA also used data from the most sensitive human subject, in accordance with OEHHA's usual practices, rather than averaging the data.

As a result, a modified factor of 1.96 is now used (instead of the previous 2.19 discussed in the Initial Statement of Reasons) to account for differences in dermal absorption between mice and humans. This results in modified human cancer slope factors (CSF_{human}) of 0.12 per milligram per kilogram per day [$(mg/kg\text{-}day)^{-1}$] based on the male mouse study, and 0.027 $(mg/kg\text{-}day)^{-1}$ based on the female mouse study. These modifications result in the proposed modification of the dermal NSRL for diethanolamine of 5.8 micrograms per day (µg/day).

i. Pharmacokinetics and Metabolism of Diethanolamine and Differences in Dermal Absorption between Rodents and Humans

Diethanolamine has been shown to penetrate skin and enter the blood stream via dermal exposure with differences observed in absorption across species.[3] *In vitro* studies showed that diethanolamine penetrates human skin less compared to skin of other species: mice > rabbits > rats > humans (Sun et al., 1996).[4] Therefore, it is appropriate to adjust for these pharmacokinetic differences when data are available.

[3] International Agency for Research on Cancer (IARC 2012). 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://publications.iarc.fr/125.

[4] Sun JD, Beskitt JL, Tallant MJ, Frantz SW. (1996). In vitro skin penetration of monoethanolamine and diethanolamine using excised skin from rats, mice, rabbits, and humans. Journal of Toxicology: Cutaneous and Ocular Toxicology, 15(2):131-146.

OEHHA determined that using data from the study by Craciunescu et al. (2009),[5] the only available study comparing plasma concentrations following dermal application of diethanolamine in human volunteers and mice, allows for interspecies adjustment of pharmacokinetic differences. Craciunescu et al. 2009 provides diethanolamine plasma concentration data from five nonpregnant female mice exposed dermally to 80 mg/kg-day diethanolamine for 11 days and three nonpregnant female human volunteers exposed dermally to 0.6 mg/kg-day diethanolamine for 3–4 weeks. In separate experiments these authors also investigated the accumulation of diethanolamine and its metabolites in the liver and plasma of pregnant mice and diethanolamine's effects on fetal mouse brain progenitor cell proliferation and apoptosis.[6] Authors stated that "rough calculations suggest that occupational exposure to DEA [diethanolamine] will not approach the 80 mg/kg/day dose needed to alter neurogenesis in mice," and suggest that these "conclusions should be used cautiously as it is possible that human embryonic hippocampus is more sensitive" than the mouse hippocampus.[7] Authors additionally suggest that while the human data can be considered pilot data due to variability and small sample size (N=3), the data "provide an estimate of the order or magnitude of response to exposure in humans relative to the mouse."[8] No other studies in exposed humans were identified. The variability in diethanolamine plasma levels observed between the human participants in Craciunescu et al. (2009)[9] captures some of the variability that exists within the human population.

Although *in vitro* studies by Sun et al. (1996)[10] quantified differences in skin absorption of a single application of diethanolamine between human and mouse skin, the single application, shorter exposure duration, and *in vitro* study design of Sun et al. (1996) is more limited compared to the *in vivo* study design of Craciunescu et al. (2009). In addition, the repeated (daily) applications of diethanolamine to the mice and the human volunteers over the study durations employed by Craciunescu et al. (2009) more closely resemble the exposure patterns in the NTP diethanolamine carcinogenicity studies and those expected to occur in humans.

In Craciunescu et al. (2009)[11] the human volunteers applied a leave-on lotion containing 1.8 µg/g diethanolamine for up to 4 weeks. The mice received daily dermal applications

[5] Craciunescu CN, Niculesu MD, Guo Z, Johnson AR, Fischer L, Zeisel SH. (2009). Dose response effects of dermally applied diethanolamine on neurogenesis in fetal mouse hippocampus and potential exposure of humans. Toxicol Sci 107(1): 220–226.

[6] *Id.*

[7] *Id.*

[8] *Id.*

[9] *Id.*

[10] Sun JD et al (1996), full citation provided above.

[11] Craciunescu et al. (2009), full citation provided above.

of diethanolamine dissolved in acetone (1.78 microliters per gram body weight [µL/g bw]) to a depilated intrascapular area, which was non-occluded during the 11-day dosing period. These dosing regimens resulted in a 133.33-fold lower administered dose to the human volunteers compared to the mice. The mouse plasma concentration of diethanolamine was reported to be 1,253 nanomole per milliliter (nmol/mL) on day 11; in OEHHA's original analysis, this concentration was used. However, by subtracting the concentration reported in the plasma prior to dosing on day 0 (58 nmol/mL), the results show an 11-day treatment-attributable diethanolamine plasma concentration of 1,195 nmol/mL. OEHHA has revised its calculations accordingly.

OEHHA used GetData software and data from Figure 1 in Craciunescu *et al.* 2009[12] to estimate the plasma concentrations of diethanolamine in the three human volunteers on day 11 for comparison with the mouse plasma concentrations on day 11. Estimated 11-day treatment-attributable diethanolamine plasma concentrations were determined for each volunteer. For these results, OEHHA has revised its analysis as described in the Initial Statement of Reasons by subtracting plasma concentrations measured prior to dosing on day 0, just as it did for the concentrations in mice.

Additionally, in OEHHA's original calculations, an average of the three volunteers' plasma levels was used. However, OEHHA has determined that it should rely on the results of the most sensitive human subject. This practice ensures that even sensitive individuals will be adequately protected. Volunteer 2 had the largest 11-day treatment-attributable diethanolamine plasma concentration, 4.58 nmol/mL, and given the pharmacokinetic variability observed among the three human volunteers, this value was selected for use in deriving a factor to account for differences in dermal absorption between mice and humans. The number of human volunteers in this study does not pose any statistical issues in the context of how OEHHA is utilizing the findings. The aim is to identify how much diethanolamine humans can absorb through the skin. If the sample size was increased, either volunteer 2 would remain the individual exhibiting the greatest dermal absorption or a new volunteer would exhibit higher dermal absorption. Therefore, the 11-day treatment-attributable plasma concentration of diethanolamine in humans is likely to be similar or possibly increased with a larger sample size.

By multiplying the 11-day treatment-attributable plasma concentration in humans by the fold difference of the administered dose between humans and mice (4.58 nmol/mL*133.33), a plasma concentration of 610.65 nmol/mL would be expected in humans for the same dose that was administered to mice. This results in a difference of 1.96-fold (1,195 nmol/mL divided by 610.65 nmol/mL) in the plasma concentration of diethanolamine following dermal application in mice compared to humans.

[12] Craciunescu et al. (2009), full citation provided above.

OEHHA therefore used a factor of 1.96 to account for differences in dermal absorption between mice and humans.

ii. Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight per day scaled to the three-quarters power is assumed to produce the same degree of effect in different species, in the absence of information indicating otherwise. This adjustment accounts for interspecies differences in toxicokinetics and toxicodynamics. The default toxicokinetic and toxicodynamic factors are the square root of the interspecies factor.

As detailed above, to adjust for the known species difference in dermal absorption of diethanolamine between mice and humans, a factor of 1.96 was applied instead of 2.19 as used in OEHHA's initial calculations. Upon absorption, diethanolamine is efficiently incorporated into phospholipids by the same biosynthetic pathway as endogenous ethanolamine. Diethanolamine is subsequently eliminated in the urine primarily as its unmetabolized form.[13] Given this, it is assumed that interspecies toxicokinetic differences have been accounted for by adjusting for differences in dermal absorption between mice and humans. In order to account for toxicodynamic differences between mice and humans, the toxicodynamic portion of the interspecies scaling factor (i.e., ratio of bw_{human} to $bw_{animal,}$ raised to the one-eighth power) was applied. Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by dividing the animal potency (CSF_{animal}) by 1.96, and multiplying by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-eighth power[14] when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = \frac{CSF_{animal}}{1.96} \times \left(\frac{bw_{human}}{bw_{animal}}\right)^{1/8}$$

The default human body weight is 70 kg. The average body weights for male and female mice were calculated to be 0.0448 kg and 0.0441 kg, respectively, based on the

[13] National Toxicology Program (NTP 1999). Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies). NTP Technical Report Series No. 478. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available from https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr478.pdf.

[14] OEHHA (2009). Technical support document for cancer potency factors. Appendix B: Chemical specific summaries of the information used to derive unit risk and cancer potency values. Ethylbenzene pp. B-275-B315. Long-term Health Effects of Exposure to Ethylbenzene. May 2009, Office of Environmental Health Hazard Assessment, California. Available at: https://oehha.ca.gov/sites/default/files/media/downloads/air/report/ethylbenzenefinal110607.pdf

data reported for control animals by NTP (1999).[15] The derivations of the human cancer slope factors using these body weights are summarized below in Table A.

Table A. Derivation of dermal CSF_{human} using mean animal body weights for the studies and data presented in Tables 1 and 2 of the Initial Statement of Reasons

Sex/ Strain/ Species	Type of neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Male B6C3F1 mice	Liver hepatocellular adenoma, carcinoma or hepatoblastoma	0.0448	0.0957	Not calculated
	Kidney renal tubule adenoma		0.00284	
	Multisite: liver hepatocellular adenoma, carcinoma or hepatoblastoma, and kidney renal tubule adenoma		0.0973	**0.12**
Female B6C3F1 mice	Liver hepatocellular carcinoma	0.0441	0.0214	0.027

Due to the limitations associated with modeling the combined incidence of hepatocellular adenoma and carcinoma in the female mouse study, discussed in the Initial Statement of Reasons, the cancer slope factor derived solely from female mouse hepatocellular carcinoma incidence is an underestimate of potency. As shown in Table A, dose-response modeling of the hepatocellular carcinoma data from the female mouse study yielded a lower cancer slope factor than did multisite modeling of the liver and kidney tumor data from the male mouse study. Consistent with Section 25703(a)(3), the human cancer slope factor derived from the male mouse study was selected, as it is the most health protective. Thus, the human cancer slope factor of 0.12 $(mg/kg\text{-}day)^{-1}$, derived from the study in male mice, was used to calculate the diethanolamine (dermal) NSRL.

[15] NTP (1999), full citation provided above.

iii. Calculation of No Significant Risk Levels

The NSRL can be calculated from the cancer slope factor, as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}.[16] This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram body weight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg/day by multiplying by the body weight for humans. When the calculation is for the general population, the body weight is assumed to be 70 kg.[17] The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{\text{CSF}_{\text{human}}} \times 1000\ \mu\text{g/mg}$$

As indicated previously, the human cancer slope factor for diethanolamine by the dermal route derived from the male mouse study data and exposure parameters presented in Table 3 is 0.12 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 5.8 µg/day for diethanolamine by the dermal route.

Documents Added to the Record

OEHHA has added to the rulemaking record the following documents to those it relies on in this rulemaking:

Beskitt JL and Sun JD. (1997). In vitro skin penetration characteristics of ethanol in the rabbit, mouse, rat, and human. J Toxicol: Cutaneous and Ocular Toxicology 16(1):61-75. https://doi.org/10.3109/15569529709048888

Hayashi SM, Ton TV, Hong HH, Irwin RD, Haseman JK, Devereux TR, Sills RC. (2003). Genetic alterations in the Catnb gene but not the H-ras gene in hepatocellular neoplasms and hepatoblastomas of B6C3F(1) mice following exposure to diethanolamine for 2 years. Chem Biol Interact 146(3):251-261. https://doi.org/10.1016/j.cbi.2003.07.001

Krealing MEK, Yourick JJ, Bronaugh RL. (2004). In vitro human skin penetration of diethanolamine. Food Chem Toxicol 42:1553-1561.

Lehman-McKeeman L, Gamsky E, Hicks S, Vassallo J, Mar M-H, Zeisel S. (2002). Diethanolamine induces hepatic choline deficiency in mice. Toxicol Sci 67(1):38-45.

[16] 27 CCR § 25703(b).

[17] 27 CCR § 25703(a)(8).

Mathews JM, Garner, CE, Black SL, Matthews HB. (1997). Diethanolamine absorption, metabolism and disposition in rat and mouse following oral, intravenous and dermal administration. Xenobiotica 27(7):733-746, DOI:10.1080/004982597240316

Muñoz ER and Barnett BM. (2003). Chromosome malsegregation induced by the rodent carcinogens acetamide, pyridine and diethanolamine in Drosophila melanogaster females. Mutat Res 539(1-2):137-144. https://doi.org/10.1016/s1383-5718(03)00158-x

OEHHA (2009). Technical support document for cancer potency factors. Appendix B: Chemical specific summaries of the information used to derive unit risk and cancer potency values. Ethylbenzene pp. B-275-B315. Long-term Health Effects of Exposure to Ethylbenzene. May 2009, Office of Environmental Health Hazard Assessment, California. Available at: https://oehha.ca.gov/sites/default/files/media/downloads/air/report/ethylbenzenefinal110607.pdf

OEHHA (2024) Model run using US EPA BMDS version 3.3.2. Oct. 10, 2024.

Copies of these documents are available upon request.

Submission of Public Comments

OEHHA is requesting comments on the modifications to the regulatory text, shown above and in Attachment 1. To be considered, **OEHHA must receive comments by 11:59 p.m. on June 25, 2026, which is the designated close of the comment period.** OEHHA strongly recommends that comments be submitted electronically through our website at https://oehha.ca.gov/comments, rather than in paper form. Alternatively, the submission can be in paper form, either by mail or delivered in person.

Electronic Submission (preferred):

Through OEHHA website at: https://oehha.ca.gov/comments

Mailed Submission:

Attention: Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P. O. Box 4010 Sacramento, California 95812-4010

In-person delivery submission:

Attention: Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
1001 I Street, 12th[18] Floor
Sacramento, California 95814

OEHHA encourages all submissions to be in a format compliant with Section 508 of the federal Rehabilitation Act, Web Content Accessibility Guidelines (WCAG) 2.1 (see the World Wide Web Consortium [W3C] WCAG 2 Overview), and California Government Code sections 7405 and 11135, so that they can be read using screen reader technology.

OEHHA is subject to the California Public Records Act and other laws that require the release of certain information upon request. If you provide a submission, please be aware that your name, address and e-mail may be available to third parties.

If you have any questions, please contact Esther Barajas-Ochoa at Esther.Barajas-Ochoa@oehha.ca.gov or at (916) 445-6900.

[18] The original notice of modification issued on June 10, 2026, stated that the in-person delivery address was the 23rd floor. It has been corrected to the 12th floor.