INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENTS TO:
SECTION 25705(b) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

1-BROMOPROPANE AND DIETHANOLAMINE (DERMAL)

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

I. Introduction and Overall Problem to be Addressed

These proposed regulatory amendments would adopt a No Significant Risk Level (NSRL) for 1-bromopropane, as well as an NSRL for dermal exposure to diethanolamine, under Proposition 65. [1] The proposal amends Title 27, California Code of Regulations, section 25705(b).[2]

Proposition 65 was enacted as a ballot initiative on November 4, 1986. OEHHA is the lead state entity responsible for the implementation of Proposition 65.[3] OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act.[4] The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity.[5] The Act also prohibits the discharge of listed chemicals to sources of drinking water.[6]

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, is hereafter referred to as "Proposition 65" or "The Act."

[2] All further section references are to Title 27 of the Cal. Code of Regs. unless otherwise indicated.

[3] Section 25102(o).

[4] Health and Safety Code section 25249.12(a).

[5] Health and Safety Code section 25249.6.

[6] Health and Safety Code section 25249.5.

Proposition 65 warnings are not required when exposures to a listed chemical do not pose a significant risk.[7]

Under section 25705(a), OEHHA's NSRLs are safe harbor levels that are deemed to comply with the Act. However, businesses are not required to rely on an NSRL to demonstrate that their product does not require a Proposition 65 warning. As stated in existing section 25701(a), "Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk." Thus, an NSRL does not create a requirement or a mandatory threshold; rather, it allows businesses to rely on the NSRL, if they choose to do so, instead of developing their own analysis. These safe harbor levels are intended to simplify compliance.

The proposed NSRL for 1-bromopropane is 54 micrograms per day (µg/day). This proposed NSRL is based on the cancer potency value developed by the Office of Environmental Health Hazard Assessment (OEHHA) in "1-Bromopropane Cancer Inhalation Unit Risk Factor. Technical Support Document for Cancer Potency Factors, Appendix B" (OEHHA 2022).[8] The cancer potency value was derived based on a carcinogenicity study in rodents using methods consistent with those described in Section 25703.

The proposed NSRL for dermal exposures to diethanolamine is 6.4 µg/day. This proposed NSRL is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703. This NSRL does not apply to non-dermal routes of exposure.

[7] Health & Safety Code section 25249.10(c). Likewise, a warning is not required if a discharge or release does not cause a significant amount of the listed chemical to enter any source of drinking water, Health and Safety Code section 25249.9(b).

[8] OEHHA (2022). 1-Bromopropane Cancer Inhalation Unit Risk. Technical Support Document for Cancer Potency Factors Appendix B. December 2022, Office of Environmental Health Hazard Assessment, California. Available at: https://oehha.ca.gov/media/downloads/crnr/1-bpcanceriur120622.pdf

II. Specific Amendments

Section 25705(b)

The proposed changes to Section 25705(b) are provided below, in underline.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
<u>1-Bromopropane</u>	<u>54</u>
…	
<u>Diethanolamine</u>	<u>6.4 (dermal)</u>
…	

a. Addition of the NSRL for 1-Bromopropane

The purpose of this amendment is to adopt an NSRL for 1-bromopropane (also known as 1-BP) which conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about the chemical. This is necessary to assist businesses who would prefer to rely on OEHHA's analysis rather than calculating their own NSRLs for 1-bromopropane. This rulemaking provides assurance to the regulated community that exposures at or below the proposed NSRLs are not considered to pose a significant risk of cancer. This amendment is needed to convey that information to the public and the regulated population. This amendment also eases compliance for business, furthering the right-to-know and public health purposes of Proposition 65.

1-Bromopropane is used as a solvent cleaner in degreasing operations and is also used in dry cleaning, asphalt production, and in solvent and adhesive sprays. It can be used as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary

ammonium compounds, flavors, and fragrances. On August 5, 2016, 1-bromopropane was listed as a carcinogen under Proposition 65.[9]

On December 9, 2022, OEHHA adopted cancer inhalation unit risk and slope factors for 1-bromopropane for use in the Air Toxics Hot Spots Program;[10] these have also been used to develop the proposed NSRL. The 1-bromopropane cancer risk assessment for the Air Toxics Hot Spots Program underwent internal scientific review and peer review by the state's Scientific Review Panel (SRP) on Toxic Air Contaminants, as well as a public comment process, before being released as a final document.

The human cancer slope factor (CSF) for 1-bromopropane was based on the dose-response analysis for pulmonary alveolar/bronchiolar adenomas or carcinomas combined in the two-year carcinogenicity study conducted by the National Toxicology Program (NTP) in female mice (NTP 2011).[11]

In the 2022 1-bromopropane risk assessment, OEHHA described its derivation of the CSF as follows:

> "Two-year 1-BP [1-bromopropane] inhalation studies conducted by the NTP established evidence of carcinogenicity in male and female rats, and female mice. Supporting evidence for the carcinogenicity of 1-BP include some positive genotoxic results from *in vitro* studies, a positive *in vivo* study for DNA adduct formation, development of similar tumors in long-term rodent exposure studies by structurally related brominated compounds, and CYP-mediated oxidation of 1-BP to known mutagenic compounds. Rodent CSFs were calculated from the NTP tumor incidence data for each tumor type in each affected species and sex. This was performed by calculating the lower 95% confidence limit on the inhalation concentration associated with a 5% tumor response (BMDL) using the multistage or Weibull cancer models in Benchmark Dose Software (BMDS) version 3.1 (US EPA, 2020b). Linear extrapolation from the BMDL to the origin was used to determine the

[9] The chemical is also listed under Proposition 65 for reproductive toxicity. It was listed for developmental toxicity, male reproductive toxicity, and female reproductive toxicity on December 7, 2004.

[10] Notice of Adoption of Cancer Inhalation Unit Risk and Slope Factors for 1-Bromopropane (Dec. 9, 2022), available at https://oehha.ca.gov/air/crnr/notice-adoption-cancer-inhalation-unit-risk-and-slope-factors-1-bromopropane.

[11] National Toxicology Program (NTP 2011). Toxicology and Carcinogenesis Studies of 1-Bromopropane (CAS No. 106-94-5) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP Technical Report Series No. 564. NIH Publication No. 11-5906. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr564.pdf

> slope of the dose-response curve for low level exposure, the inhalation CSF." (OEHHA, 2022, page 35.)[12]

OEHHA then converted the rodent CSFs to human equivalent CSFs. This was done using body weight scaling, raised to the one-fourth power when animal potency is expressed in units of (milligram per kilogram body weight per day)$^{-1}$, i.e., (mg/kg-day)$^{-1}$. The human CSF for 1-bromopropane, based on the most sensitive species and sex, was 0.013 (mg/kg-day)$^{-1}$ for pulmonary alveolar/bronchiolar adenomas or carcinomas combined in female mice.

The CSF of 0.013 (mg/kg-day)$^{-1}$ derived in OEHHA (2022) is thus used as the basis for calculating the proposed NSRL for 1-bromopropane, as described below.

Under Proposition 65, the NSRL is calculated as one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}.[13] 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 per 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.[14] The intake can be converted to µg/day by multiplying by 1,000. This sequence of calculations can be expressed mathematically as:

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

Inserting the human cancer slope factor ($\text{CSF}_{\text{human}}$) for 1-bromopropane of 0.013 (mg/kg-day)$^{-1}$ into the equation above results in an NSRL of 54 µg/day for 1-bromopropane.

b. Addition of the NSRL for Dermal Exposures to Diethanolamine

This proposed regulatory amendment would also adopt an NSRL for diethanolamine (also known as DEA), that conforms with the Proposition 65 implementing regulations

[12] OEHHA (2022), full citation provided above.

[13] Section 25703(b).

[14] Section 25703(a)(8).

and reflects the currently available scientific knowledge about that chemical. As with 1-bromopropane, the proposed NSRL for diethanolamine is necessary to assist businesses who would prefer to rely on OEHHA's analysis rather than calculating their own NSRL. The NSRL is a safe harbor which provides assurance to the regulated community that exposures at or below this level are not considered to pose a significant risk of cancer. This amendment is needed to convey that information to the public and the regulated population. This NSRL will also ease compliance for business, furthering the right-to-know and public health purposes of Proposition 65.

Because this proposed NSRL only applies to dermal exposures, businesses with products that expose Californians to diethanolamine by other routes will still have to determine the level at which the exposure does not cause a significant risk of cancer. However, dermal exposure is a common route of exposure for this chemical, and OEHHA expects this NSRL to be valuable for the majority of businesses with products containing this chemical.

Diethanolamine is used as a corrosion inhibitor in metalworking fluids, as an emulsifier and dispersing agent in formulations of agricultural chemicals, in industrial gas purification, to produce lubricants for use in the textile industry, and to produce diethanolamides and diethanolamine salts of fatty acids for use in consumer products such as cosmetics, shampoos, hair conditioners, and liquid laundry and dishwashing detergents. Diethanolamine was listed as a carcinogen under Proposition 65 on June 22, 2012.

To develop the proposed NSRL for diethanolamine by the dermal route, OEHHA relied on the 1999 National Toxicology Program (NTP) technical report entitled "Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)," 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."[15] The NTP technical report and the IARC monograph summarize

[15] 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. 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.

the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of diethanolamine.

The NSRL for diethanolamine by the dermal route is based upon the results of the most sensitive scientific studies deemed to be of sufficient quality.[16]

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the data from the available rodent carcinogenicity studies of diethanolamine and determined that the two-year dermal studies conducted by NTP in male and female B6C3F1 mice met the criterion in Section 25703 as being sensitive studies of sufficient quality.

In the NTP mouse studies,[17] groups of 50 mice of each sex were exposed to diethanolamine by dermal application at doses of 0, 40, 80, or 160 mg/kg of body weight (mg/kg-bw), 5 days per week for 103 weeks. The lifetime average daily doses of diethanolamine administered in the studies were calculated by OEHHA to be 0, 28.57, 57.14, and 114.29 mg/kg-bw per day (mg/kg-day). Survival of male mice in diethanolamine treated groups was not significantly different from the vehicle control group.[18] Survival of female mice in diethanolamine treated groups at 103 weeks was lower compared to the vehicle control group, however, the animals that died before 103 weeks had hepatocellular adenomas.

In the male mouse study, by both pairwise comparison and trend test, statistically significant increases in tumor incidences were observed for renal tubule adenomas, hepatocellular adenomas, hepatocellular carcinomas, hepatoblastomas, and for the combined incidence of hepatocellular adenomas, hepatocellular carcinomas and hepatoblastomas (Table 1). The tumor incidence data for renal tubule adenomas and for the combined incidence of hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas were used to estimate cancer potency.

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

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

[18] *Id*.

Table 1. Tumor incidences[a] of treatment-related lesions in male B6C3F$_1$ mice administered diethanolamine via dermal application (NTP 1999)

Organ	Tumor type	Administered Dose (mg/kg-bw)				Trend test p-value
		0	40	80	160	
Liver	Hepatocellular adenoma (first occurrence of tumor: day 386)	31/50	42/50*	49/50***	45/49***	< 0.001
	Hepatocellular carcinoma (first occurrence of tumor: day 445)	12/49	17/50	33/50***	34/48***	< 0.001
	Hepatoblastoma (first occurrence of tumor: day 633)	0/44	2/48	8/44*	5/43*	< 0.05
	Hepatocellular adenoma, carcinoma or hepatoblastoma combined (first occurrence of tumor: day 386)	39/50	47/50*	50/50***	49/49***	< 0.001
Kidney	Renal tubule adenoma (first occurrence of tumor: day 540)	1/47	6/49	8/49*	7/47*	< 0.05

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, *** $p < 0.001$. Exact trend test conducted by OEHHA.

In the female mouse study, statistically significant increases in the incidences of hepatocellular adenomas and hepatocellular carcinomas were observed, with all animals in the low dose group developing hepatocellular adenomas (Table 2). Given the 100 percent incidences of hepatocellular adenomas and hepatocellular adenomas and carcinomas combined in the low dose females, and the issues associated with modeling

those data (US EPA's Benchmark Dose Software [BMDS][19] generates the following messages: "BMD computation failed; lower limit includes zero" and "BMDL not estimated", i.e., the upper bound estimate on cancer potency is infinity), cancer potency was estimated for this female mouse study based solely on the hepatocellular carcinoma incidence data.

Table 2. Tumor incidences[a] of treatment-related lesions in female B6C3F$_1$ mice administered diethanolamine via dermal application (NTP 1999)

Organ	Tumor type	Administered Doses (mg/kg-bw)				Trend test p-value
		0	40	80	160	
Liver	Hepatocellular adenoma (first occurrence of tumor: day 418)	32/50	50/50***	48/50***	48/50***	< 0.001
	Hepatocellular carcinoma (first occurrence of tumor: day 423)	5/50	19/48***	38/50***	42/50***	< 0.001
	Hepatocellular adenoma or carcinoma (first occurrence of tumor: day 418)	33/50	50/50***	50/50***	50/50***	< 0.001

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
Treatment group tumor incidences with asterisk indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): *** $p < 0.001$. Exact trend test conducted by OEHHA.

Model Used to Estimate Cancer Potency

The IARC Monograph[20] discussed possible mechanisms by which diethanolamine induces liver tumors as follows:

> "The induction of liver tumours in mice by diethanolamine was suggested to be a consequence of choline deficiency. This mechanism is applicable to human health, especially for subgroups that are highly susceptible to dietary choline deficiency. Other possible mechanisms include diacylglycerol accumulation and activation of protein kinase C (Leung *et al*., 2005), incorporation of

[19] US EPA Benchmark Dose Software (BMDS) Version 3.3. National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds.

[20] IARC (2012), full citation provided above.

> diethanolamine into membrane phospholipids and generation of lipid second messengers, e.g. aberrant ceramides (Mathews *et al.*, 1995; NTP, 1999b), and induction of aneuploidy (Muñoz & Barnett, 2003)." [21]

Regarding genotoxicity of diethanolamine, IARC stated:

> "A genotoxic mechanism is supported by the induction of aneuploidy in Drosophilia [*sic*] and the elevated frequency of mutations in β-catenin *Catnb* genes in liver tumours induced by diethanolamine. However, diethanolamine was not genotoxic in most *in-vitro* systems and did not increase the frequency of micronuclei in exposed mice." [22]

In summarizing the mechanistic evidence for diethanolamine, IARC concluded:

> "There is weak evidence that a genotoxic mechanism is involved in the induction of liver tumours by diethanolamine. There is moderate experimental support for choline deficiency as a mechanism for diethanolamine-induced liver cancer in rodents. The human relevance of this mechanism to humans cannot be excluded, especially for subgroups that are highly susceptible to dietary choline deficiency. No mechanistic data are available on the induction of kidney tumours by diethanolamine." [23]

Based on consideration of the available mechanistic information, a multistage model was applied to derive cancer potency estimates from the male and female mouse NTP studies, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial:

$$p(d) = \beta_0 + (1 - \beta_0)\left(1 - \exp\left[-\left(\beta_1 d + \beta_2 d^2 + \cdots + \beta_j d^j\right)\right]\right)$$

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

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[21] IARC (2012), full citation provided above, p. 135.

[22] IARC (2012), full citation provided above, p. 136.

[23] *Id.*

To derive a measure of the cancer response to diethanolamine (per mg/kg-day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's BMDS.[24] The multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in US EPA's 2005 cancer risk assessment guidelines.[25]

For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS[26] can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models for the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. In order to derive a measure of the total cancer response in a given study, the dose associated with a 5% increased risk of developing a tumor at one or more of the sites of interest was calculated and the lower bound for this dose was estimated using the multisite model in BMDS. The ratio of the 5% risk level to that lower bound on dose is known as the multisite "animal cancer slope factor (CSF_{animal})," or "animal cancer potency."

The natural lifespan of mice and rats is assumed to be two years (104 weeks).[27, 28] To estimate the animal cancer potency from experiments of duration T_e, rather than the natural life span of the animals T, it is assumed that the lifetime incidence of cancer increases with the third power of age. Following Gold and Zeiger[29] and US EPA[30], a correction factor to extrapolate to two years (104 weeks) was required for the cancer slope factors derived from the data in male and female mice,[31] as those studies were concluded after 103 weeks. The adjustment was calculated as follows:

$$CSF_{animal,\ adj.} = CSF_{animal} \times (104/103)^3$$

[24] US EPA BMDS, full citation provided above.

[25] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

[26] US EPA BMDS, full citation provided above.

[27] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

[28] US EPA (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Health and Environmental Assessment, Washington D.C. EPA/600/6-87/008.

[29] Gold LS, Zeiger E (1997), full citation provided above.

[30] US EPA (1988), full citation provided above.

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

Calculation of Average Daily Doses

The lifetime average daily dose in units of mg/kg-day of diethanolamine was calculated for each dose group, based on the administered dermal doses reported by NTP[32] and the exposure regimen. Average doses (D_{avg}) were determined by multiplying the administered dose of diethanolamine (in units of mg/kg-bw) by 5/7 to account for a five day per week dosing regimen. The lifetime average daily doses were calculated to be 28.57, 57.14, and 114.29 mg/kg-day for the low-, mid-, and high-dose groups in male and female mice.

Differences in Dermal Absorption between Mice and Humans

In vitro, diethanolamine has been shown to be poorly absorbed by human skin compared to other species: mice > rabbits > rats > humans.[33] Therefore, it is appropriate to adjust for the difference in dermal absorption between mice and humans.

In the only available study comparing plasma concentrations following dermal application of diethanolamine in human volunteers and mice[34], mice were exposed to 80 mg/kg-day for 11 days while human volunteers were exposed to 0.6 mg/kg-day for 3–4 weeks. The dosing regimen represents a 133.33-fold lower administered dose in humans compared to the mice. The mouse plasma concentration of diethanolamine was reported to be 1253 nmol/mL on day 11. Meanwhile, the estimated diethanolamine concentration in human plasma at 11 days was 4.30 nmol/mL (based on Figure 1 in Craciunescu *et al.* 2009[35] using GetData software). By multiplying the plasma concentration by the fold change of the administered dose (4.30 nmol/mL*133.33), a plasma concentration of 573.32 nmol/mL would be expected in humans for the same dose; resulting in a difference of 2.19-fold (1253 nmol/mL / 573.32 nmol/mL) in the plasma concentration of diethanolamine following dermal application in mice compared to humans.

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

[33] 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.

[34]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.

[35] *Id.*

OEHHA therefore used a factor of 2.19 to account for differences in dermal absorption between mice and humans.

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 2.19 was applied. 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.[36] 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 2.19, and multiplying by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-eighth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = \frac{CSF_{animal}}{2.19} \times \left(\frac{bw_{human}}{bw_{animal}}\right)^{1/8}$$

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 data reported for control animals by NTP (1999).[37] The derivations of the human cancer slope factors using these body weights are summarized below in Table 3.

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

[37] *Id.*

Table 3. Derivation of CSF_{human} using mean animal body weights for the studies and data presented in Tables 1 and 2

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	**0.11**
Female B6C3F1 mice	Liver hepatocellular carcinoma	0.0441	0.0214	0.025

Due to the limitations associated with modeling the combined incidence of hepatocellular adenoma and carcinoma in the female mouse study, discussed above, the cancer slope factor derived solely from female mouse hepatocellular carcinoma incidence is an underestimate of potency. As shown in Table 3, 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 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 0.11 $(mg/kg\text{-}day)^{-1}$, derived from the study in male mice, was used to calculate the diethanolamine (dermal) NSRL.

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}. [38] 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.[39] The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

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

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 0.11 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 6.4 µg/day.

III. Economic Impact Assessment Required by Gov. Code Section 11346.3(b)

In compliance with Government Code section 11346.3, OEHHA has assessed all the elements pursuant to sections 11346.3(b)(1)(A) through (D). No costs are estimated for this proposed regulatory action because products that expose people to 1-bromopropane or diethanolamine at levels that posed a significant risk of cancer are already required to provide a Proposition 65 warning, under existing law. Although it is common for businesses to use NSRLs in the process of evaluating exposures, they are not required to do so.

An NSRL is not a mandatory limit and does not create a threshold above which warnings are always mandated. Regardless of this rulemaking package, the standard for when a warning is required for 1-bromopropane and diethanolamine remains the same: no warning is needed if “the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer…” (Health & Safety Code, §25249.10(c).) Businesses are not required to rely on an NSRL to demonstrate this and are still free to conduct their own analysis.

[38] Section 25703(b).

[39] Section 25703(a)(8).

a. Creation or Elimination of Jobs within the State of California

This regulatory action will not impact the creation or elimination of jobs within the State of California. The proposed regulation will help businesses already subject to the requirements of Proposition 65 by providing the No Significant Risk Level for titanium dioxide (airborne, unbound particles of respirable size).

b. Creation of New Businesses or Elimination of Existing Businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. Businesses are not required to take any action in response to this rulemaking, as described above.

c. Expansion of Businesses Currently Doing Business within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. Businesses are not required to take any action in response to this rulemaking, as described above.

d. Benefits of the Proposed Regulation

Regulated businesses that choose to rely on the proposed NSRLs will have an easier time calculating whether their products expose Californians to levels of 1-bromopropane or diethanolamine that pose no significant risk of cancer. Easing compliance furthers the right-to-know purposes of the Act, to protect the health and welfare of California residents. In addition, although the adoption of NSRLs do not require businesses to alter their products, the proposal may nonetheless encourage businesses to reduce exposures to the listed chemicals to levels that do not pose a significant risk, thereby providing public health and environmental health benefits to Californians. Adopting these NSRLs using the best available science also provides more accurate and current information about risk to Californians, which is also a scientific and public health benefit.

IV. Technical, Theoretical, and/or Empirical Studies, Reports, or Documents Relied Upon

These documents are included in the regulatory file for this action and are available from OEHHA upon request.

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Mathews JM, Garner CE, Matthews HB. (1995). Metabolism, bioaccumulation, and incorporation of diethanolamine into phospholipids. Chem Res Toxicol 8:625-633.

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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.

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US EPA (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Health and Environmental Assessment, Washington D.C. EPA/600/6-87/008.

US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

V. Reasonable Alternatives to the Regulation and the Agency's Reasons for Rejecting Those Alternatives

OEHHA has determined that there is no reasonable alternative to the proposed regulation. No alternative is less burdensome and equally effective in achieving the purposes of the regulation in a manner that achieves the purposes of the Act. Failure to adopt these NSRLs would leave the business community without this compliance assistance for 1-bomoproane and dermal exposures to diethanolamine.

VI. Reasonable Alternatives to the Proposed Regulatory Action That Would Lessen Any Adverse Impact on Small Businesses and the Agency's Reasons for Rejecting Those Alternatives

As described above, there are no significant costs that impact small businesses in compliance with the proposed action. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees, so it has no effect on very small businesses. [40]

OEHHA has initially determined that no reasonable alternative considered by OEHHA, or that has otherwise been identified and brought to its attention, would be more effective in carrying out the proposed action, or would be as effective and less burdensome to small business, or would be more cost-effective and equally effective in implementing the statutory policy or other provision of law to small business.

Small businesses that are covered by Proposition 65 (i.e. those with 10 or more employees) benefit from the development of NSRLs, which requires scientific resources that smaller businesses may lack.

VII. Use of Specific Technologies or Equipment

This proposal does not mandate the use of any specific technology or equipment.

[40] Health and Safety Code, section 25249.11(b)

VIII. Evidence Supporting Finding of No Significant Adverse Economic Impact on Business

OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. Products that cause a significant exposure to 1-bromopropane or diethanolamine already required Proposition 65 warnings, prior to this rulemaking. The proposed NSRLs provides a “safe harbor” level for businesses to use when determining compliance with Proposition 65.

IX. Efforts to Avoid Unnecessary Duplication or Conflicts with Federal Regulations Contained in the Code of Federal Regulations

Proposition 65 is a California law that has no federal counterpart. OEHHA has determined that the regulations do not duplicate and will not conflict with federal regulations.