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 ONE DOCUMENT TO RULEMAKING FILE

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

ETHYLENE OXIDE

DECEMBER 19, 2023

Public Availability Date: December 19, 2023
Deadline for Public Comment: January 10, 2024

The Office of Environmental Health Hazard Assessment (OEHHA) is providing notice of modifications made to a previously proposed regulation, namely the updated Proposition 65 No Significant Risk Level (NSRL) for ethylene oxide in Title 27, California Code of Regulations, section 25705(b)(1), and the addition of one document to the rulemaking file. OEHHA is providing this notice pursuant to Government Code sections 11346.8(c) and 11347.1(b), and Title 1, California Code of Regulations, section 44.

OEHHA first proposed the regulation by publishing a Notice of Proposed Rulemaking in the California Regulatory Notice Register (CRNR) on April 7, 2023. In parallel, OEHHA issued an Initial Statement of Reasons (ISOR) for the proposal.

OEHHA provided a 45-day comment period on the original proposal, from April 7 to May 23, 2023, which was subsequently extended to June 14, 2023.

After reviewing the comments received on this proposed regulation, OEHHA has determined that modifications to the original regulatory text are needed. In addition, OEHHA is relying upon one additional document in this rulemaking and is adding this document to the rulemaking file. The purpose of this notice is: (1) to provide the public with notice of the modified proposed regulatory text and the additional document included in the rulemaking file, and (2) to open a public comment period, running from December 19, 2023, through January 10, 2024. This public comment period is longer than 15 days to accommodate the holidays. 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 document 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 strikeout (~~example~~), and the proposed modification is shown in bold double-underline (**example**).

…

Chemical name	*Level (micrograms per day)*
Acrylonitrile	0.7
Aldrin	0.04
Ethylene oxide	~~2~~0.058 **(inhalation)**
	1.5 (oral)
Lead acetate	23 (oral)

…

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

Limitation of the Proposed NSRL Value to the Inhalation Route

During the comment period on the original proposal, OEHHA received comments regarding the applicability of the proposed updated NSRL (0.058 µg/day) to the oral route of exposure. The proposed NSRL was derived from an occupational epidemiological study with inhalation as the route of exposure to ethylene oxide. OEHHA has determined that the NSRL proposed in April 2023 should be limited to the inhalation route and that another NSRL should be proposed for the oral route, derived from a suitable oral carcinogenicity study for ethylene oxide.

Development of Proposed NSRL for the oral route

Selection of Study and Cancer Findings

The NSRL for ethylene oxide (oral) is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.[1] OEHHA reviewed the available data

[1] Section 25703(a)(3).

from the rodent carcinogenicity studies of ethylene oxide by the oral route, and determined that the study by Dunkelberg (1982) in female Sprague-Dawley rats met the criterion in Section 25703(a)(3) of the California Code of Regulations as being the most sensitive study of sufficient quality for the oral route of exposure.

In the Dunkelberg (1982)[2] study, groups of 50 female Sprague-Dawley rats were administered either 0, 7.5, or 30 milligram per kilogram bodyweight (mg/kg-bw) ethylene oxide dissolved in salad oil via gavage twice weekly for a total of 214 exposures. The study duration was 150 weeks. The lifetime average daily doses of ethylene oxide administered in the study were calculated to be 0, 2.08, and 8.34 mg/kg-day[3] for female rats. The study authors noted that animals exposed in the 8.34 mg/kg-day dose group died earlier from tumors compared to controls. No additional issues in survival were noted.

A statistically significant increase in the incidence of squamous cell carcinomas of the forestomach were observed in both treatment groups, as well as a statistically significant increase by trend. In addition, two forestomach fibrosarcomas were observed in the high dose group, with none observed in the low dose group or in controls. The tumor incidence data used to estimate cancer potency for the oral route from this study are presented in Table 1.

[2] Dunkelberg H (1982), Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Br J Cancer 46:924-933.
[3] Updated from values presented in the ISOR (See footnote 1 to Table 1 in this Notice for calculation details).

Table 1. Tumor incidences of treatment-related lesions in female Sprague-Dawley rats administered ethylene oxide by gavage (Dunkelberg 1982).

Experiment	Tumor site and type	Ethylene oxide dose (mg/kg-day)[1]			Exact trend test *p*-value
		0	2.08	8.34	
Female rats	Squamous cell carcinomas of the forestomach	0/50	8/50**	29/50***	$p < 0.001$

Tumor incidences are expressed as the number of tumor-bearing animals over the number of animals in each group at the start of the study. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): ** $p < 0.01$, *** $p < 0.001$. Exact trend test conducted by OEHHA.

[1] Lifetime average daily doses were calculated by multiplying the dose (in mg/kg-bw) administered by gavage on each day of administration by the total number of gavage administrations (214), and dividing by the length of the study's dosing period, 770 days. The dosing period of 110 weeks (i.e., 770 days) was calculated as follows: 107 weeks (with twice weekly dosing) plus 3 weeks (when dosing was paused due to the presence of infection, i.e., pneumonia).

Application of the multistage model

Based on the consideration that there is strong evidence for the genotoxicity of ethylene oxide, a multistage model is applied to derive a cancer potency estimate using data from animal cancer bioassays. There are no specific mechanistic data to suggest any deviation from the standard assumptions, including low-dose linearity, usually applied in cancer dose-response analysis. For purposes of this NSRL and 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 model:

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

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.

To derive a measure of the cancer response to ethylene oxide (per mg/kg-day) in the Dunkelberg[4] study in female rats, 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 Benchmark Dose

[4] Dunkelberg (1982), full citation provided in footnote 2.

Software (BMDS).[5] The multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in US EPA's 2005 cancer risk assessment guidelines.[6] The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor (CSF_{animal})," or "animal cancer potency."

Dunkelberg (1982) reported higher mortality in the highest dose group compared to the control group. The survival curves show that the difference in survival rates occurred late in the study (after 100 weeks), and further, the authors attributed the early deaths to tumors. Thus, time to tumor modeling is not performed.

Typically, it would be appropriate to use effective number of animals to represent tumor incidence for this study, with tumor incidence being the number of animals with specified tumor divided by the effective number of animals in the dose group. Effective number is the number of animals in a dose group that survive to the time of the first occurrence of the specified tumor type in the study. However, the effective number is not provided in the Dunkelberg publication and this number cannot be determined without access to the individual animal data. Therefore, the number of animals the total initial number of animals in each group is used in modeling the cancer potency in lieu of effective number (see Table 1).

Estimation of Oral Human Cancer Potency from the Animal 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 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. Thus, for the Dunkelberg study described above, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human} / bw_{animal})^{1/4}$$

The default human body weight is 70 kg. The average body weight for female rats used was 0.35 kg following standard values given by Gold and Zeiger (1997),[7] since the average bodyweight value was not reported for the rats in the Dunkelberg study. The

[5] US EPA Benchmark Dose Software (BMDS) Version 3.3.2. National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds.
[6] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.
[7] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

derivation of the human cancer slope factor using this body weight is summarized below in Table 2.

Table 2. Derivation of CSF_{human} using CSF_{animal} values

Sex/strain/species	Body weight (kg)	Tumor sites used in estimating potency	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Female Sprague-Dawley rats	0.35	Squamous cell carcinoma of the forestomach[1]	0.125	0.47

[1] First degree multistage polynomial model fit to data.

Calculation of the Oral No Significant Risk Level

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

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

As indicated previously, the human cancer slope factor for ethylene oxide derived from the Dunkelberg study is 0.47 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 1.5 µg/day for the oral route.

Document Added to the Record

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

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

Copies of this document are available upon request.

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

Submission of Public Comments

OEHHA is requesting comments on the modifications to the regulatory text, shown below. To be considered, **OEHHA must receive comments by 11:59 p.m. on January 10, 2024, 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, 23rd 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.