June 14, 2023

Comments on the Ethylene Oxide Cancer Inhalation Unit Risk Factor and No Significant Risk Levels under consideration by OEHHA

Comments submitted via oehha.ca.gov

These comments are submitted on behalf of the undersigned scientists. We declare collectively that we have no direct or indirect financial or fiduciary interest in the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support unless indicated otherwise.

We appreciate the opportunity to provide comments on the Office of Environmental Health Hazard Assessment's (OEHHA) drafts on both the cancer inhalation unit risk factor and the no significant risk level for ethylene oxide.[1,2] It is crucial that OEHHA regulate ethylene oxide to protect public health, particularly for the workers exposed to the chemical in facilities and the communities living adjacent to them, who are most impacted by the adverse health outcomes from both acute and long-term exposures.

We are aware that the American Chemistry Council (ACC), an industry trade group whose members have a financial interest in the outcome of OEHHA activities and regulations, has criticized OEHHA's consideration of the US Environmental Protection Agency's (EPA) quantitative cancer risk analyses, and we note that the alleged "flaws" in EPA's approach touted by the ACC have been raised before and have been rejected by EPA and its independent scientific review board.[3] In fact, it is the TCEQ approach supported by ACC that is seriously flawed.[4,5,6]

We support OEHHA's hazard conclusion, the quantitative risk estimation approach, and the rejection of TCEQ's analysis in the IUR draft. However, there are scientific improvements needed to the cancer inhalation unit risk factor as we describe below.

Inhalation Unit Risk Factor

[1] OEHHA. 2023. Draft Cancer Inhalation Unit Risk Factor For Ethylene Oxide. Available: https://oehha.ca.gov/air/crnr/notice-extension-public-comment-period-draft-cancer-inhalation-unit-risk-factor-ethylene

[2] OEHHA. 2023. Updated No Significant Risk Level for Ethylene Oxide. Available: https://oehha.ca.gov/proposition-65/crnr/updated-no-significant-risk-level-ethylene-oxide

[3] 87 FR 77985

[4] US EPA. 2022. Review of National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing. Comment submitted by University of California, San Francisco (UCSF), Program on Reproductive Health and the Environment (PRHE) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OAR-2018-0746-0308

[5] US EPA. 2021. Pesticide Registration Review: Draft Human Health and/or Ecological Risk Assessments for Ethylene Oxide. Comment submitted by Veena Singla, Associate Director, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPP-2013-0244-0039

[6] UCSF Program on Reproductive Health and the Environment Blog: TCEQ. Available: https://prheucsf.blog/?s=TCEQ

1. **The OEHHA IUR draft fails to consider the impact ethylene oxide has during susceptible life stages, which is inconsistent with US EPA and its own practices.**

On page 42 of the draft, OEHHA characterizes its chosen IUR as an "adult-exposure-only IUR" from EPA (2016a), however this characterization is incorrect on multiple fronts. [7] First, EPA's value is a full lifetime IUR, i.e., for full lifetime exposure, but calculated under the assumption that RR is independent of age. Second, the presumption in the draft is that OEHHA's IUR of 6.1 per ppb is the same as US EPA (2016a), which is untrue as US EPA ultimately selected an IUR of 9.1 per ppb on an assumption of increased early-life susceptibility stemming from the finding that ethylene oxide has a mutagenic mode of action.[8,9]

OEHHA's approach to unit risk derivation is similar to EPA's approach, but without the assumption of increased early-life susceptibility. For those familiar with US EPA's approach or looking to compare OEHHA's approach with that of EPA, OEHHA must explicitly note that its derivation was under the assumption that RR is independent of age across all life-stages; in particular, in Section VII. Additionally, in the conclusions, where the draft states that OEHHA's updated IUR is "consistent with US EPA's analysis of the EtO exposure-response relationship and the combined IUR for breast cancer and lymphoid cancer" [10], OEHHA should clarify that the draft is consistent **with the exception of EPA's use of an assumption of increased early-life susceptibility**, and in contrast, OEHHA used an assumption of similar susceptibility across ages.

It is unclear why OEHHA chose to forego the use of an age-dependent adjustment factor in this draft, particularly as the OEHHA recognizes that "early life stages are generally more sensitive to carcinogen exposure than adults, and that cancer risk assessment practices should take increased sensitivity of the young into account" and has an established protocol for using adjustment factors to characterize increased early-life susceptibility to carcinogens.[11] (Table below)

[7] OEHHA. 2023. Draft Cancer Inhalation Unit Risk Factor For Ethylene Oxide. pp42. Available: https://oehha.ca.gov/air/crnr/notice-extension-public-comment-period-draft-cancer-inhalation-unit-risk-factor-ethylene

[8] U.S. EPA. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-16/350F, 2016.

[9] If OEHHA has any questions about US EPA's different IUR derivations, please contact Jennifer Jinot (jjinot@hotmail.com), who was a co-author of US EPA's assessment.

[10] OEHHA. 2023. Draft Cancer Inhalation Unit Risk Factor For Ethylene Oxide. pp49. Available: https://oehha.ca.gov/air/crnr/notice-extension-public-comment-period-draft-cancer-inhalation-unit-risk-factor-ethylene

[11] OEHHA. 2009. In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures. Available: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

Table 13. Comparison of cancer risk estimates[1] for lifetime exposure to 0.0001 mg/kg-d of a carcinogen with potency 1 (mg/kg-d)$^{-1}$ based on different parameters of ASF distributions, or U.S. EPA values.

Lifestage	Years of life exposed	No adjustment		50th percentile		70th percentile		Mean		95th percentile		U.S. EPA (2005)	
		ASF	Risk	ASF	Risk	ASF	Risk	ASF	Risk	ASF	Risk	Factor	Risk
In utero	0.75	0	0.0	3	3.2×10^{-6}	10	1.1×10^{-5}	21	2.2×10^{-5}	115	1.2×10^{-4}	0	0.0
Birth to <2 yr	2	1	2.9×10^{-6}	13	3.7×10^{-5}	28	7.9×10^{-5}	79	2.3×10^{-4}	350	1.0×10^{-3}	10	2.9×10^{-5}
2 to <16 yr	14	1	2×10^{-5}	5	1.0×10^{-4}	7	1.4×10^{-4}	7	1.4×10^{-4}	20	4.0×10^{-4}	3	6.0×10^{-5}
16 to 70 yr	55	1	7.9×10^{-5}	1	7.9×10^{-5}	1	7.9×10^{-5}	1	7.9×10^{-5}	1	7.9×10^{-5}	1	7.9×10^{-5}
Total lifetime risk			1.0×10^{-4}		2.2×10^{-4}		3.1×10^{-4}		4.7×10^{-4}		16×10^{-4}		1.7×10^{-4}

[1] Risk accrued in age window = potency x ASF x exposure rate x (years exposed/70 years).

We recommend that OEHHA modify the IUR in the draft to either be consistent with the EPA IUR or to be consistent with its own practices around increased early-life susceptibility to carcinogens and utilize an adjustment factor either at the median (50th percentile) or, ideally, the 70th percentile to be more protective as outlined in the Table above.

While there are no specific data on early-life susceptibility for ethylene oxide, EPA applies age-dependent adjustment factors, acknowledging the potential for increased early-life susceptibility for carcinogens with a mutagenic action, such as ethylene oxide, and OEHHA has historically applied more protective age-dependent adjustment factors than EPA, identifying that EPA's adjustment factors "may result in underestimates of risk for a reasonable fraction of chemicals".[12]

There is one limitation of EPA's adjustment factors, which is that they are general factors that primarily convey increased susceptibility to the earliest life stages and are not specific to a particular chemical, a limitation which OEHHA has also identified. This means, for example, that they may imperfectly characterize breast carcinogens such as ethylene oxide, as there is evidence suggesting that puberty and early adulthood may be particularly susceptible life stages, rather than early-life. [13,14] OEHHA itself acknowledges this, saying:

"…there are few data available on which to base an estimate for the juvenile life stage. A factor of three accounts for the long available time for cancer to manifest when exposure occurs in this period but ***would not fully account for inherent differences in susceptibility to cancer, as is observed in breast tissue of pubescent girls exposed to radiation.****"* [15]

This same consideration holds as well for breast carcinogens such as ethylene oxide.

[12] OEHHA. 2009. In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures. Available: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

[13] U.S. EPA. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-16/350F, 2016.

[14] US EPA (2005) Supplemental Guidance for assessing susceptibility from early-life exposure to carcinogens (EPA/630/R-03/003F); Russo JFC and Russo IH (1999) Cellular basis of breast cancer susceptibility [Review] Oncol Res 11:169-178.

[15] OEHHA. 2009. In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures. Available: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

Therefore, the lack of ethylene oxide data on early-life susceptibility is not indicative of a lack of hazard or risk from carcinogens with mutagenic modes of action and does not justify OEHHA failing to apply a protective adjustment factor for early-life susceptibility or throwing out the adjusted IUR from EPA while simultaneously mischaracterizing its own IUR as consistent with EPA.

2. **OEHHA's approach to analyzing rodent data is overly restrictive**

OEHHA's approach to determining the animals at risk for their analyses of rodent carcinogenicity studies is overly restrictive. If this is the general approach used by OEHHA and not just the approach used in this draft, then this is a general comment on OEHHA's methodology.

In determining the animals at risk for the tumor of interest (i.e., the denominators of the tumor incidences), OEHHA appears to have used the time of first tumor for the tumor of interest and discounted all animals dying before that time (across all exposure groups), without providing any scientific justification for choosing this approach. Relying on the time of first tumor from the small numbers of tumors in a particular study is an overly restrictive way to define animals at risk in that study and can result in discounting, from what are already small sample sizes, an excessive number of animals that are actually at risk.

For example, for the National Toxicology Program (NTP) ethylene oxide study data of alveolar/bronchiolar adenoma or carcinoma in female mice, OEHHA appears to have used a cut-point of week 87 for determining animals at risk based on the time of the first observed tumor of interest in this study, an adenoma in a high-dose mouse. This cut-point resulted in OEHHA discounting (i.e. removing from the incidence denominators) an additional 13 animals from the control group, 17 animals from the low-dose group, and 4 animals from the high-dose group; that's a **significant** number of animals to discount from dose group sizes of 50 animals.

Moreover, in NTP's study of tetrabromobisphenol A, the same tumor was observed at day 563, or week 81, in control female mice, indicating that animals before week 87 should be considered at risk. Had OEHHA used week 81 as a cut-point instead, 5 fewer animals would have been eliminated from the low-dose group and 4 from the high-dose group. In the absence of good historical control data on times of first tumors, EPA's approach is to discount animals dying before the time of the first tumor or 1 year, whichever comes first. Had OEHHA used EPA's approach for defining at-risk animals in the NTP EtO bioassay, 5 animals (vs. 13) would have been discounted from the control group, 4 animals (vs.17) in the low-dose group, and 0 animals (vs. 4) in the high-dose group. This illustrates how OEHHA's approach, which is based on an overly restrictive assumption of when animals are at risk, can result in an arbitrary and undue loss of data. OEHHA should immediately modify this approach as it inappropriately decreases the sample sizes in already small studies.

3. **Other minor comments on the IUR Draft**

On page 15 of the draft, in the 2nd paragraph in the "key results" column, the phrase "(lagged out)" after the OR of 1.00 should be removed. It is the exposures that are "lagged out", yielding the 0 exposure (referent) group. The OR for the referent group is 1.00 by definition. Instead, it should be clarified on page 21, in the sentence beginning "The reference exposure category…" that the reference group is not a "group with no EtO exposure" but rather that the exposures are "lagged out".

On page 30 of the draft, the year for the Rietjens et al. citation should be 2022 not 2021. It is correct in the reference list.

On page 37, OEHHA presents a modified Figure 4-9 from US EPA (2016a) and notes that data points are missing. In the EPA report, however, this figure was intended to depict models being compared for deriving risks for selected *occupational* exposure scenarios, not for deriving a IUR. The relevant figure for OEHHA's document is Figure 4-3, which compares models considered for the derivation of the IUR, and which OEHHA could modify by removing some of the models, if desired.

On page 47, the 1st sentence should be revised to say "These studies lend support to the breast cancer findings in the NIOSH cohort *and other studies reviewed by US EPA (2016a)*, …". It's not just the NIOSH studies that provide evidence for a breast cancer association.

No Significant Risk Level - Initial Statement of Reasons

Many of the comments we provided on the IUR draft also apply to this draft; we recommend OEHHA consider our comments across both documents.

Additionally, in the middle of page 29, OEHHA states:

However, since the two-piece linear spline model is a linear model, and linear extrapolation was used to estimate risks below the POD, using either an EC01 or an EC10 (or their respective lower 95% CIs) would give the same cancer unit risk. [16]

The assertion OEHHA makes is not strictly true. The model is comprised of two linear splines, but the overall exposure-response relationship is **not linear across the two splines**. Thus, the claim that linear extrapolation from either the EC_{01} or EC_{10} would give the same result is only true **if the selected point of departure is below the knot of 1,600 ppm x days**, which appears to be the case here. However, it's not as absolute as stated in the draft text.

Regarding Table 12, the entry in column 1 with the text "unit risk based on adult exposure" is misleading; see our comments above. [17] The unit risk estimate is based on adult exposure, since the data used for

[16] OEHHA. 2023. Updated No Significant Risk Level for Ethylene Oxide. pp29. Available: https://oehha.ca.gov/proposition-65/crnr/updated-no-significant-risk-level-ethylene-oxide

[17] OEHHA. 2023. Updated No Significant Risk Level for Ethylene Oxide. pp50. Available: https://oehha.ca.gov/proposition-65/crnr/updated-no-significant-risk-level-ethylene-oxide

modeling were from an occupational study, but the estimate represents an estimate of extra cancer risk from *full lifetime exposure*, under an assumption of similar susceptibility across age groups. Similarly, the text in the 1st paragraph of page 51 referring to "the cancer unit risk based on adult exposure" and "the unit risk value of 6.1 … based on adult exposure" is also misleading. See also comment #2 above.

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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