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VIA E-MAIL

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Re: Comments on California Office of Environmental Health Hazard Assessment's (OEHHA's) Draft Inhalation Unit Risk Factor (IUR) for Ethylene Oxide (EtO)

Dear Ms. Gottlieb,

The California Office of Environmental Health Hazard Assessment (OEHHA) released a public review Technical Support Document for an updated Ethylene Oxide (EtO) Cancer Inhalation Unit Risk Factor (IUR) under the Air Toxics Hot Spots Program in May 2026.[1] This letter responds to the Advanced Medical Technology Association's (AdvaMed's) request for analysis of this document.

Although OEHHA did perform its own literature review to identify more recent studies published since release of the 2016 US Environmental Protection Agency (EPA) IUR, OEHHA ultimately adopted the EPA's adult IUR of 5.5×10^{-3} per parts per billion (ppb) or 3.0×10^{-3} per $\mu g/m^3$ for lymphohematopoietic cancer (LHC) and breast cancer combined.[2]

OEHHA's IUR is an overly conservative value that is well below the background levels of EtO that occur naturally in the human body and found in ambient air across the entire US. The *practical* issues with OEHHA's IUR are illustrated in **Figure 1** and discussed below.

[1] OEHHA. 2026. California Office of Environmental Health Hazard Assessment. Ethylene Oxide Cancer Inhalation Unit Risk Factor. Technical Support Document for Cancer Potency Factors. Appendix B. Public Review Draft, May 11, 2026.

[2] EPA Integrated Risk Information System website. https://iris.epa.gov/ChemicalLanding/&substance_nmbr=1025. Visited on June 11, 2026.

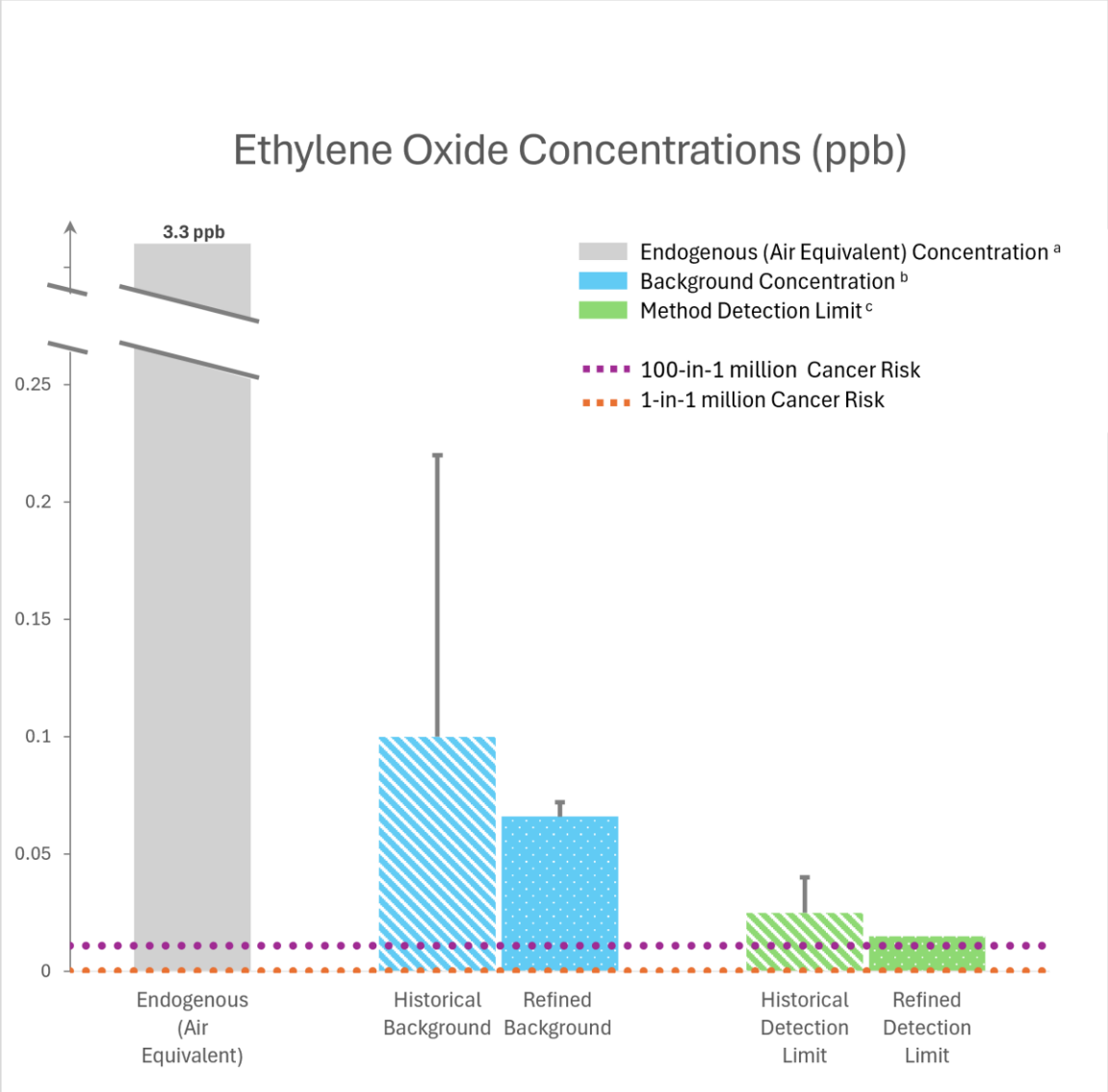

FIGURE NOTES

a. Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. International Journal of Environmental Research and Public Health, 22(4), 597.

b. Historical Method TO-15 (diagonal stripes): National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf; Refined Method TO-15A (dotted): Kirman et al. (2025). Blue bars represent mean concentrations and error bars represent the upper limit of the measurement range.

c. Historical Method TO-15 (diagonal stripes): Willowbrook, IL Ethylene Oxide Concentrations in Outdoor Air - 24 Hour Samples. https://www.epa.gov/il/outdoor-air-monitoring-willowbrook-community; Refined Method TO-15A (dotted): Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. ACS Es&t Air, 1(8), 747-754. Green bars represent mean concentrations and error bars represent the upper limit of the measurement range.

First, internal EtO levels reflect a stressor to which humans are expected to have evolved and adapted over millions of years. This likely means that there is an EtO level (in the range of endogenous EtO production) below which deoxyribonucleic acid (DNA) damage, a precursor to

cancer, does not occur because biological defenses prevent it.[3] The gray bar in **Figure 1** represents the endogenous EtO air equivalent estimated by Kirman et al. (2025).[4] Analyses of the National Institute of Occupational Safety and Health (NIOSH) cancer data have suggested increases in male LHC and breast cancer in the highest cumulative exposure groups *only*, which is consistent with exceeding biological repair mechanisms only at high exposures. Smoking has not been associated with any of the various LHC, despite the fact that EtO is a component of tobacco smoke and DNA adducts attributable to EtO are more than an order of magnitude higher in smokers (i.e., smokers are exposed to much higher EtO levels).[5] This also supports the notion that there is an exposure level below which EtO-induced cancer does not occur. Regardless of whether EtO can be demonstrated to have a true threshold dose-response, **Figure 1** demonstrates that EtO concentrations in air are much lower than endogenous EtO levels, as reflected by endogenous air equivalents, implying no detectable increase in risk due to EtO exposures from ambient air,[6] as described below.

The blue bars in **Figure 1** represent background EtO concentrations in ambient air (the diagonal striped bar represents historical measurements via EPA Method TO-15[7] and the dotted bar represents refined measurements via EPA Method TO-15A[8]). Based on OEHHA's IUR, the EtO air concentration corresponding to a 100-in-1 million target cancer risk is represented by the purple dotted line and the 1-in-1 million target cancer risk is represented by the red dotted line. As **Figure 1** illustrates, the background EtO air concentrations to which everybody across the US is exposed, are considerably higher than air concentrations corresponding to OEHHA's IUR.

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[3] Tates, A. D., P. J. Boogaard, F. Darroudi, A. T. Natarajan, M. E. Caubo, and N. J. van Sittert (1995). Biological effect monitoring in industrial workers following incidental exposure to high concentrations of ethylene oxide. *Mutation Research,* 329:63–77; Tompkins, E. M., K. I. McLuckie, D. J. Jones, P. B. Farmer, and K. Brown (2009). Mutagenicity of DNA adducts derived from ethylene oxide exposure in the pSP189 shuttle vector replicated in human Ad293 cells. *Mutation Research,* 678:129–37.

[4] .Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. International Journal of Environmental Research and Public Health, 22(4), 597.

[5] CR Kirman, AA Li, PJ Sheehan, JS Bus, RC Lewis & SM Hays (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, *Journal of Toxicology and Environmental Health*, Part B, 24:1, 1-29.

[6] Kirman, C.R.; Hays, S.M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165–172; Kirman, C. R., Li, A. A., Sheehan, P. J., Bus, J. S., Lewis, R. C., & Hays, S. M. (2021). Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *Journal of Toxicology and Environmental Health, Part B*, *24*(1), 1-29; Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, *22*(4), 597.

[7] National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf

[8] Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. International Journal of Environmental Research and Public Health, 22(4), 597.

Specifically, background concentrations range from 10 (~ 0.1 ppb ÷ 0.011 ppb) to 600 (~ 0.066 ppb ÷ 0.00011 ppb) times the concentrations corresponding to target cancer risks (100-in 1 million to 1-in-1 million) based on the OEHHA IUR. This implies that further restricting EtO emissions is unlikely to materially affect ambient background concentrations, regardless of how stringent EtO regulations become.

Analytical detection limits *potentially* achievable for EtO in air samples are represented by the green bars in **Figure 1**. The detection limits range from *approximately* 0.015 ppb (refined EPA Method TO-15A) to 0.040 ppb (historical EPA Method TO-15) in specialized/optimized systems designed to detect trace concentrations.[9] **Figure 1** illustrates that detection limits for EtO air samples have consistently been higher than the air concentrations corresponding to OEHHA's IUR (~ two times [0.25 ppb ÷ 0.011 ppb] to more than 100 times (0.015 ppb ÷ 0.00011 ppb) the OEHHA IUR, depending on the target cancer risk level). Therefore, reductions in air concentrations potentially resulting from use of the OEHHA IUR to regulate EtO emissions are unlikely to be confirmable because the analytical methods for EtO are incapable of detecting small changes against the backdrop of high background levels.

OEHHA IUR is highly impractical as a basis for regulation because compliance with a level below widespread background levels cannot be demonstrated. The scientific debate surrounding the 2016 EPA IUR on which the OEHHA IUR is based is not merely academic; it has enormous regulatory and economic consequences.

1. RECENTLY MEASURED BACKGROUND ETO CONCENTRATIONS APPEAR LOWER THAN PREVIOUSLY REPORTED, BUT ARE STILL WELL ABOVE OEHHA'S TARGETED CANCER RISK LEVELS

OEHHA discusses ambient background EtO concentrations in California and nationwide,[10] alluding to the fact that more recent measurements of EtO, in which updated EPA Methods[11] were used, appear to be lower than those historically reported (i.e., 2018 – 2019). The revised

[9] EPA (2021a). US Environmental Protection Agency. Effect of Canister Type on Background Ethylene Oxide Concentrations. May 7, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/ord-eto-canister-background-memo-05072021.pdf; EPA (2021b). U.S. Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, *1*(8), 747-754.

[10] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 4 – 6. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[11] EPA (2021a). US Environmental Protection Agency. Effect of Canister Type on Background Ethylene Oxide Concentrations. May 7, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/ord-eto-canister-background-memo-05072021.pdf; EPA (2021b). U.S. Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, *1*(8), 747-754.

EPA methods were spawned by concerns about the quality and reliability of ambient monitoring data for characterizing ambient background EtO concentrations. Concerns about the data revolved around: 1) high method detection limits (relative to monitored ambient concentrations);[12] and 2) the potential for monitored concentrations to be biased high as a result of (a) possible EtO growth inside cannisters with certain inner surface lining characteristics used to sample ambient air; and (b) inadequately cleaned cannisters.[13] More recently collected ambient EtO data are, therefore, considered more representative for characterizing ambient background EtO levels. The background EtO concentrations cited by OEHHA[14] are similar to those presented in **Figure 1** of this letter,[15] despite the fact that they are from different studies. It is important to note however, that despite data suggesting that recently collected ambient background are lower than previously reported,[16] measured ambient concentrations are still well above EPA's and OEHHA's targeted cancer risk levels, as illustrated in **Figure 1**.

Robinson and Dhammapala (2025)[17] reported that only about 50% of the air monitoring sites recently sampled showed an overall decrease in measured EtO concentrations, with varying results at individual monitors. The study also concluded that EtO concentrations were higher in summer than winter (as does Kirman et al., 2025[18]) and that they correlated with ozone concentrations. These findings suggest substantial spatial and temporal variability in ambient EtO concentrations, and potential links between ambient EtO concentrations and secondary

[12] EPA (2020). US Environmental Protection Agency. EPA's Work to Understand Background Levels of Ethylene Oxide. https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/epas-work-understand-background-levels-ethylene-oxide; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, *1*(8), 747-754.

[13] EPA (2021a). US Environmental Protection Agency. Effect of Canister Type on Background Ethylene Oxide Concentrations. May 7, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/ord-eto-canister-background-memo-05072021.pdf; EPA (2021b). U.S. Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, *1*(8), 747-754.

[14] Robinson, E. S., & Dhammapala, R. (2025). Analysis of Ambient Ethylene Oxide Mixing Ratios in the United States. *ACS ES&T Air*, *2*(11), 2467-2480.

[15] Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, *22*(4), 597. Table 5; National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf.

[16] Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, *22*(4), 597; Robinson, E. S., & Dhammapala, R. (2025). Analysis of Ambient Ethylene Oxide Mixing Ratios in the United States. *ACS ES&T Air*, *2*(11), 2467-2480.

[17] Robinson, E. S., & Dhammapala, R. (2025). Analysis of Ambient Ethylene Oxide Mixing Ratios in the United States. *ACS ES&T Air*, *2*(11), 2467-2480.

[18] Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. International Journal of Environmental Research and Public Health, 22(4), 597.

production pathways (e.g., photochemical formation) and biomass-burning factors. Sources of EtO in ambient air are not well understood.

2. THE CONCLUSION THAT TRAFFIC IS NOT A MAJOR SOURCE OF ETO IS UNSUBSTANTIATED

In reference to Robinson and Dhammapala (2025), OEHHA states that "The study authors suggested that traffic is not a major source of EtO because no significant difference in EtO levels was observed between weekdays and weekends."[19] Because weekday comparisons represent the combined effect of changes in emissions from multiple sectors, not just motor vehicles, Robinson and Dhammapala's (2025) conclusion that traffic is not a major source of EtO is, at a minimum, premature. EtO is consistently detected in ambient air and most of it cannot be traced to any particular industrial source. Contributions of EtO to the atmosphere by potential non-industrial sources are not well understood and have not been actively studied.[20] However, it is generally accepted that EtO is emitted as a by-product of burning hydrocarbon fuels.[21] Consistent with EtO's generally accepted association with combustion, Robinson and Dhammapala (2025) reported that EtO concentrations were higher on wildfire days.

It cannot be concluded that traffic is not a major source of ambient pollution, simply because significant differences were not observed on weekdays versus weekends. For such a finding to be persuasive: 1) information on the variation (or lack thereof) in industrial EtO emissions near the monitors on weekdays and weekends are needed; 2) contemporaneous traffic count data must be collected; and 3) rush hour and non-rush hour EtO concentrations should be monitored. The possibility that EtO is subject to secondary formation through photochemical processes similar to ozone, as suggested by Robinson and Dhammapala (2025), further complicates the potential "weekday" effect. Although weekday concentrations of pollutants associated with gasoline and diesel fuel combustion engines are often reported to be higher on weekdays than weekends, pollutants that are subject to secondary formation (e.g., ozone) do not necessarily follow this trend. Analyses of weekday/weekend ozone differences demonstrate significant variation across the country. Moreover, some sites have higher ozone on weekends, even though traffic and ozone precursor levels are substantially lower on weekends.[22] If the

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[19] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 6, line 165 - 166. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[20] Interstate Technology Regulatory Council, *Ethylene Oxide Emissions Guidance*. https://eto-1.itrcweb.org. December 2023. Accessed June 18, 2026.

[21] Interstate Technology Regulatory Council, *Ethylene Oxide Emissions Guidance*. https://eto-1.itrcweb.org. December 2023. Accessed June 18, 2026; ATSDR (2022). Agency for Toxic Substances Disease Registry. Toxicological Profile for Ethylene Oxide. Pg. 106. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=734&tid=133.

[22] Harley, R. A., Marr, L. C., Lehner, J. K., & Giddings, S. N. (2005). Changes in motor vehicle emissions on diurnal to decadal time scales and effects on atmospheric composition. *Environmental Science & Technology*, *39*(14), 5356-5362; Heuss, J. M., Kahlbaum, D. F., & Wolff, G. T. (2003). Weekday/weekend ozone differences: what can we

reference to Robinson and Dhammapala's (2025) conclusion that "traffic is not a major source of EtO" is retained, OEHHA should provide additional context for a more objective perspective.

3. OEHHA IDENTIFIED TWO NEW POTENTIALLY USEFUL PUBLICATIONS FOR EVALUATING THE EtO EXPOSURE-RESPONSE RELATIONSHIP BUT USED NEITHER TO INFORM THE IUR

OEHHA identified two new publications in its literature search and initial screening evaluations that it concluded provided potentially useful information for exposure-response assessment (Kelly-Reif et al., 2025;[23] Valdez-Flores et al., 2025[24]) but ultimately did not use either to inform EtO IUR development. OEHHA used the previous (Steenland et al., 2003[25]) NIOSH results on breast cancer incidence for breast cancer IUR calculations rather than the more recent (Kelly-Reif et al., 2025) or previous breast cancer mortality results (Steenland et al., 2004[26]) because the focus of the lifetable analyses and IUR calculations was on cancer incidence.[27] With regard to LHC, OEHHA merely stated that it concurred with EPA's conclusion that the NIOSH cohort is the best available study for conducting exposure-response analyses for IUR development.[28] However, OEHHA's review appears to emphasize evidence supporting OEHHA's and EPA's conclusions, while providing comparatively less discussion of evidence that may suggest alternative interpretations. A more complete discussion of the methods used and findings from these two studies is provided below for OEHHA's consideration in strengthening the discussion.

learn from them?. *Journal of the Air & Waste Management Association*, *53*(7), 772-788; Chinkin, L. R., Coe, D. L., Funk, T. H., Hafner, H. R., Roberts, P. T., Ryan, P. A., & Lawson, D. R. (2003). Weekday versus weekend activity patterns for ozone precursor emissions in California's South Coast Air Basin. *Journal of the Air & Waste Management Association*, *53*(7), 829-843.

[23] Kelly-Reif, K., Bertke, S. J., Stayner, L., & Steenland, K. (2025). Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort. *Environmental Health Perspectives*, *133*(5), 057013;

[24] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[25] Steenland, K., Whelan, E., Deddens, J., Stayner, L., & Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes & Control*, *14*, 531-539.

[26] Steenland, K., Stayner, L., & Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, *61*(1), 2-7.

[27] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 30, line 673 - 675. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[28] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 55, line 1284 - 1286. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

A. The Kelly-Reiff et al. (2025) Breast Cancer Mortality Update's Inadequate Adjustment for Healthy Worker Survivor Effect (HWSE) and Failure to Sufficiently Describe Composition of the Internal Control Group May Result in Biased Estimates

OEHHA concluded that the recent reanalysis of breast cancer mortality in the NIOSH cohort by Kelly-Reif et al., 2025)[29] was important because, in OEHHA's opinion, it provided strong supportive evidence that EtO is causally related to breast cancer.[30] However, the basis for this interpretation is not readily apparent from the limited discussion. Importantly, unless OEHHA has more detailed information on how the internal reference group in the Kelly-Reiff et al. (2025) breast cancer mortality update was selected (and is prepared to provide it), this statement should be removed. The strength of the inferences that can be made from the internal analyses in this study are severely limited by the authors' failure to adequately describe the composition of the internal control group. Note that the number of breast cancer deaths reported by Kelly-Reiff et al. (2025) in the unexposed internal reference group is smaller than the number of breast cancer deaths noted in the internal control group by Steenland et al. (2004).

Like previous studies (Steenland et. al., 2004; Steenland et al., 2003[31]), this update of the NIOSH breast cancer cohort failed to observe an overall increase in breast cancer mortality in external analyses in which breast cancer mortality was compared to rates in US female population and failed to show a statistically significant increase in breast cancer deaths for any exposure category. However, statistically significant increases in breast cancer mortality were observed in internal analyses (when breast cancer mortality rates were compared to rates in unexposed women in the cohort) for most exposure categories, including in a sub-cohort with data on risk factors for breast cancer (20-year lag).[32] The authors concluded that greater weight should be given to findings from internal analyses because Standard Mortality Rates (SMRs) by exposure level are not directly comparable and are subject to biases from the *Healthy Worker Effect* (HWE). One component of the HWE, the *Healthy Worker Hire Effect* (HWHE) can occur because less healthy individuals are less likely to seek, gain, or retain employment.[33,34] Bias introduced by the

[29] Kelly-Reif, K., Bertke, S. J., Stayner, L., & Steenland, K. (2025). Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort. *Environmental Health Perspectives*, *133*(5), 057013.

[30] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 30, line 670 – 672, Pg. 37, line 873 – 874, Pg. 38, line 878 - 879. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[31] Steenland, K., Whelan, E., Deddens, J., Stayner, L., & Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes & Control*, *14*, 531-539.

[32] Sub-cohort of 5,132 women employed for at least one year, for whom investigators collected information on risk factors for breast cancer (via interview) in the late 1990s (the same cohort used in internal analyses in the Steenland et al. (2003) incidence study.

[33] Kirkeleit, J., Riise, T., Bjørge, T., & Christiani, D. C. (2013). The healthy worker effect in cancer incidence studies. *American Journal of Epidemiology*, *177*(11), 1218-1224.

[34] The general population also includes persons with chronic diseases and disabilities and persons otherwise out of the active worker population; therefore worker populations may have a lower risk of disease than the general population.

HWHE can be avoided by using comparison groups within the cohort (internal analyses). The other component of the HWE, the *Healthy Worker Survivor Effect* (HWSE), is more difficult to deal with and may introduce bias in exposure-response relationships because short-term workers are often less healthy than long-term workers and may leave the workforce for reasons related to the disease under study.[35]

Even with the increase in the follow-up period (23 additional years and an average follow time of 44 years), an attenuation in risk (by comparison to the earlier breast cancer mortality study of Steenland et al., 2004) was not observed by Kelly-Reiff et al. (2025), arguing against a HWSE for breast cancer.[36] However, Picciotto et al. (2026),[37] which was co-authored by one member of the group that conducted the NIOSH EtO breast cancer mortality update by Kelly-Reiff et al. (2025), concluded that previously published estimates of LHC and female breast cancer mortality in the NIOSH cohort are underestimated because of the failure to adjust for the HWSE.

Kelly-Reif et al. (2025) attempted to account for the possibility of a HWSE[38] (previously hypothesized by Park [2020][39])[40] by matching cases and internal referents on duration of employment. Similar to Park's findings, matching on duration of employment substantially increased SMRs across all exposure categories, most of which were statistically significant. Breast cancer mortality did not increase consistently with dose, however. Although the Kelly-Reiff et al. (2025) study reports stronger associations between workplace EtO exposure and breast cancer mortality, the study's conclusions should be evaluated in light of the strengths and limitations of its methodology. The study does not clearly indicate dose-dependency and failed to adequately describe how the internal referent group was chosen. Moreover, several researchers[41] have

[35] Stayner, L., Steenland, K., Dosemeci, M., & Hertz-Picciotto, I. (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scandinavian Journal of Work, Environment & Health*, 317-324.

[36] Kirkeleit, J., Riise, T., Bjørge, T., & Christiani, D. C. (2013). The healthy worker effect in cancer incidence studies. *American Journal of Epidemiology*, *177*(11), 1218-1224; Gridley, G., Nyren, O., Dosemeci, M., Moradi, T., Adami, H. O., Carroll, L., & Zahm, S. H. (1999). Is there a healthy worker effect for cancer incidence among women in Sweden?. *American Journal of Industrial Medicine*, *36*(1), 193-199.

[37] Picciotto, S., Kelly-Reif, K., Eisen, E. A., Stayner, L. T., & Costello, S. (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *American Journal of Epidemiology*, kwag052.

[38] Healthy worker survivor bias can occur in occupational studies because of the tendency for unhealthy individuals to leave the workforce earlier, accruing less exposure than their healthier counterparts. This bias can result in attenuation of the estimated effects of exposures on health outcomes (i.e., can bias results towards the null).

[39] Park, R. M. (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *American Journal of Industrial Medicine*, 63(7), 577-588.

[40] Park (2020) observed a statistically significant negative effect of EtO exposure on employment duration.

[41] Robins, J. (1987). A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *Journal of Chronic Diseases*, 40, 139S-161S; Chevrier, J., Picciotto, S., & Eisen, E. A. (2012). A comparison of standard methods with g-estimation of accelerated failure-time models to address the healthy-worker survivor effect: application in a cohort of autoworkers exposed to metalworking fluids. *Epidemiology*, 23(2), 212-219; Naimi, A. I., Cole, S. R., Hudgens, M. G., Brookhart, M. A., & Richardson, D. B. (2013). Assessing the component associations of the healthy worker survivor bias: occupational asbestos exposure and lung cancer mortality. *Annals of Epidemiology*, 23(6), 334-341; Buckley, J. P., Keil, A. P., McGrath, L.

suggested that if work status is both a mediator and a confounder of the exposure-outcome relationship, as appears to be the case with EtO exposure and breast cancer mortality,[42] adjustment by employment duration may result in a biased estimate of the dose-response and more sophisticated methods (i.e., g-methods) may be needed to adequately control for the HWSE.

OEHHA raises concerns about the completeness of the HWSE assessment and the potential for bias in the Park (2020) study.[43] However, Kelly-Reif et al. (2025) appears to employ similar methodological approaches, yet OEHHA's review does not discuss whether these same limitations apply.[44] To ensure a consistent and transparent weight-of-evidence evaluation, OEHHA should clarify how these methodological concerns were considered across both studies

B. Valdez-Flores et al.'s (2025) Union Carbide Corporation (UCC) LHC Mortality Update and Re-Evaluation of NIOSH Results Does Not Support OEHHA's Supra-Linear Dose-Response for EtO

One of the most interesting aspects of the most recent evaluation of the Union Carbide Corporation (UCC) worker cohort was that Valdez-Flores et al (2025)[45] used the updated UCC cohort data as an external dataset to examine the plausibility of the different dose-response models that have been applied by EPA and other regulatory agencies to the NIOSH cancer data to derive IURs for EtO.

Steenland et al.'s (2004)[46] evaluation of the NIOSH cohort found no statistically significant excesses in males and females combined for all LHC. However, a statistically significant exposure–response relationship was observed in males for all LHC combined, but *only at the highest cumulative dose*. Steenland et al.(2004) did not, however, find a statistically significant exposure-

J., & Edwards, J. K. (2015). Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology*, 26(2), 204-212; Picciotto, S., Kelly-Reif, K., Eisen, E. A., Stayner, L. T., & Costello, S. (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *American Journal of Epidemiology*, kwag052.

[42] Park, R. M. (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *American Journal Of Industrial Medicine*, 63(7), 577-588; Picciotto, S., Kelly-Reif, K., Eisen, E. A., Stayner, L. T., & Costello, S. (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *American Journal of Epidemiology*, kwag052.

[43] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 25, line 604 – 609. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[44] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 30, line 670 – 672, Pg. 37, line 873 – 874, Pg. 38, line 878 - 879. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[45] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[46] Steenland, K., Stayner, L., & Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, *61*(1), 2-7.

response relationship in females (the slope was negative). Hence, Steenland et al. (2004) analyzed male and female LHC separately. Valdez-Flores et al.'s (2025) analyses of the NIOSH study data were generally consistent with those of Steenland et al. (i.e., increased LHC mortality in males only at the highest exposure category). However, analyses of the updated UCC cohort by Valdez-Flores et al. (2025) did not indicate any statistically significant excess LHC mortality.

OEHHA's and EPA's conclusion that the NIOSH study supports a steep risk at low exposures is based primarily on the fact that, of the large number of curve-fitting models and lag times assessed, the only one that produced a statistically significant positive slope for LHC mortality in males was the supra-linear log cumulative exposure model with a 15 year lag. Another rationale given by OEHHA[47] and EPA for using the supra-linear model was "visual fit" of a few non-parametric categorical rate ratios (to surmise the shape of continuous models), even though visual fit models are subjective and depend on how data are presented (i.e., different analysts can look at the same plot and draw different conclusions about the shape of the exposure-response curve).

EPA and OEHHA combined male and female LHC to estimate the potency of EtO in their final risk assessments, despite evidence of differences in exposure-response patterns in men and women in the NIOSH cohort, as acknowledged by Steenland et al. (2004). OEHHA justified combining males and females by stating that the EtO-associated RRs (relative risks) were elevated in both sexes and that the difference in these RRs between sexes was not statistically significant.[48] However, when combined with male data, the female data in the low exposure region alters the appearance of the slope as a steep exposure response as shown in Figure 2 of Valdez-Flores et al. (2025). OEHHA's and EPA's internal categorical results with a 15-year lag show a dip in the low exposure region for males with a significant increase at the highest exposure category (see Figure 2A of Valdez-Flores et al. [2025]). On the other hand, female LHC mortality appears to increase in the low region and then decline overall (see Figure 2B of Valdez-Flores et al. [2025]). Moreover, in Figure 3, Valdez-Flores et al. (2025) showed that neither model had a superior visual fit to the data when the data were normalized along the y-axis and different implicitly estimated baseline risks were accounted for.[49]

Based on their combined analyses of the NIOSH and UCC cohort studies, Valdez-Flores et al. (2025) concluded that there is no evidence that EtO is a highly potent carcinogen consistent

[47] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 60, line 1368 – 1372. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[48] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 34, line 756 – 758. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[49] This issue was identified by EPA as a footnote in the figure legend (Pg. 4-21, Figures 3 and 4) that states that, with the exception of the categorical results…the different models have different implicitly estimated baseline risks and are, therefore, not strictly comparable.

with a steep increase in risk at low exposures and concluded that the standard Cox Proportional Hazard model more plausibly describes the relationship between EtO exposures and LHC mortality in both the NIOSH and UCC cohorts.

4. THE GOLLAPUDI ET AL. (2026) GENOTOXICITY DOSE-RESPONSE INVESTIGATION DOES NOT SUPPORT OEHHA'S SUPRA-LINEAR DOSE-RESPONSE MODEL AND SHOULD BE INCLUDED AS POTENTIALLY RELEVANT MATERIAL IN OEHHA'S REVISED IUR DOCUMENT

OEHHA's supra-linear dose-response model on which the proposed IUR depends, does not consider all reasonably available information, in particular, the most recent mode of action study. Although not identified as potentially relevant for consideration by OEHHA, even though mechanistic studies reporting genotoxicity were targeted,[50] the Gollapudi et al. (2026)[51] study should be considered in the next version of the Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document.

The initiating event for EtO-induced mutagenicity and carcinogenicity is its reaction with the nucleophilic centers of DNA.[52] Therefore, the dose-response associated with EtO-induced genetic damage is relevant to determining which dose-response models are biologically plausible for deriving EtO cancer risks. To this end, Gollapudi et al. (2026)[53] investigated EtO-induced genetic damage to inform the biological plausibility of the various dose-response models (the log-linear CPH and 2-piece linear spline) that have been applied to the NIOSH cohort for EtO cancer risk assessment. EtO is an alkylating agent that is capable of reacting with cellular macromolecules, including hemoglobin and DNA to produce several adducts including the major DNA adduct N7-2-hydroxyethylguanine (N7-HEG), which although not mutagenic, is a useful biomarker of exposure, and *O*^{6}-2-hydroxyethylguanine (O^6-HEG), which is a minor but mutagenic DNA adduct.[54] The scientific literature on EtO-induced DNA damage indicates that relatively high

[50] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. A-3. Table A-2. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[51] Gollapudi, B. B., Bus, J. E., Cassidy, P., Weinberg, J. T., Bemis, J. C., Torous, D. K., ... & Li, A. A. (2026). Investigation of Ethylene Oxide Genotoxicity Dose-Response to Inform Cancer Risk Assessment. *bioRxiv*, 2026-03.

[52] Walker VE, Fennell TR, Upton PB, et al. Molecular dosimetry of ethylene oxide: formation and persistence of 7-(2-hydroxyethyl)guanine in DNA following repeated exposure of rats and mice. *Cancer Research,* 1992;52: 4328–34; Li F, Segal A, Solomon JJ. In vitro reaction of ethylene oxide with DNA and characterization of DNA adducts. *Chemico-Biological Interactions,* 1992;83:35–54.

[53] Gollapudi, B. B., Bus, J. E., Cassidy, P., Weinberg, J. T., Bemis, J. C., Torous, D. K., ... & Li, A. A. (2026). Investigation of Ethylene Oxide Genotoxicity Dose-Response to Inform Cancer Risk Assessment. *bioRxiv*, 2026-03.

[54] van Sittert, N. J., Boogaard, P. J., Natarajan, A. T., Tates, A. D., Ehrenberg, L. G., & Törnqvist, M. A. (2000). Formation of DNA adducts and induction of mutagenic effects in rats following 4 weeks inhalation exposure to ethylene oxide as a basis for cancer risk assessment. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *447*(1), 27-48; Kirman, C. R., & Hays, S. M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, *91*, 165-172.

exposure concentrations and longer exposure durations are required to elicit genotoxic responses in experimental *in vivo* systems.[55]

Gollapudi et al. (2026) investigated the shape of the dose-response for the induction of *Pig-a* mutations and micronuclei (a reporter for cytogenetic damage) in erythrocytes, as well as other endpoints specific to a mutagenic mode of action, in mice. An exposure-dependent increase in the formation of both hemoglobin and N7-HEG DNA adducts was observed at all concentrations of EtO evaluated, although mutagenic O^6-HEG adducts were only detected in mice exposed to ≥ 50 ppm EtO. The dose-response slopes for both adducts increased disproportionately *only* at higher EtO concentrations (i.e., ≥ 50 ppm), presumably after all detoxification and repair capacities were saturated. The shape of the observed dose-response (i.e., hockey stick, with no effects at lower exposures) for genetic damage was linear throughout the range of exposure, supporting a single-sloped dose-response model as biologically plausible. Importantly, the most abundant N7-HEG adduct, a biomarker of the critical target (i.e., DNA) showed no indication of a dose response pattern with an initial steeper linear slope that plateaus at higher concentrations, thus providing no evidence for OEHHA's and EPA's hypothesized 2-piece supra-linear spline dose-response for these endpoints across concentrations from 0.05 to 200 ppm.

DNA repair capacity in humans is similar, if not better, than that of mice,[56] including *O*^{6}-methylguanine-DNA methyltransferase, which is a highly conserved repair protein involved in the direct repair pathway of the pro-mutagenic O^6-HEG and other *O*^{6}-guanine alkyl adducts.[57] Moreover, EtO Physiologically-Based Pharmacokinetic (PBPK) modeling indicates that concentrations of EtO in blood are similar in mice and humans at EtO exposures ≤ 100 ppm, which suggests that EtO absorption, distribution, metabolism and excretion are similar across the species.[58] Therefore, the mouse is considered a valid model for predicting the genotoxicity of EtO in humans, especially at exposure levels that do not overwhelm detoxification pathways.

These results provide a biologically plausible basis for selection of a statistical dose-response model for EtO human cancer risk assessment that is rooted in the widely accepted mode

[55] Gollapudi, B. B., Su, S., Li, A. A., Johnson, G. E., Reiss, R., & Albertini, R. J. (2020). Genotoxicity as a toxicologically relevant endpoint to inform risk assessment: A case study with ethylene oxide. *Environmental and Molecular Mutagenesis*, *61*(9), 852-871; Donner, E. M., Wong, B. A., James, R. A., & Preston, R. J. (2010). Reciprocal translocations in somatic and germ cells of mice chronically exposed by inhalation to ethylene oxide: implications for risk assessment. *Mutagenesis*, *25*(1), 49-55.

[56] MacRae, S. L., Croken, M. M., Calder, R. B., Aliper, A., Milholland, B., White, R. R., ... & Vijg, J. (2015). DNA repair in species with extreme lifespan differences. *Aging (Albany NY)*, *7*(12), 1171.

[57] Klapacz, J., Pottenger, L. H., Engelward, B. P., Heinen, C. D., Johnson, G. E., Clewell, R. A., ... & Andersen, M. E. (2016). Contributions of DNA repair and damage response pathways to the non-linear genotoxic responses of alkylating agents. *Mutation Research/Reviews in Mutation Research*, *767*, 77-91; Roy, R., Shiota, S., Kennel, S. J., Raha, R., Wronski, M. V., Brent, T. P., & Mitra, S. (1995). A comparative study of the biochemical properties of human and mouse recombinant O 6-methylguanine-DNA methyltransferases. *Carcinogenesis*, 16(2), 405-411.

[58] Fennell, T. R., & Brown, C. D. (2001). A physiologically based pharmacokinetic model for ethylene oxide in mouse, rat, and human. *Toxicology and applied pharmacology*, *173*(3), 161-175.

of action key events (i.e., mutation and cytogenetic damage) for EtO mutagenicity. The mode of action data derived from mice in this study and others collectively support selection of a single-sloped linear (CPH) dose response model for risk assessment of EtO carcinogenicity. Evidence against the biological plausibility of the 2-piece linear spline dose-response model includes: 1) EtO does not require metabolic activation for mutagenicity, which could lead to saturation at higher concentrations (and a plateau in the dose-response curve); 2) the highest exposure level in this study (i.e., 200 ppm) is twice the tumorigenic level in the carcinogenicity study using the same strain of mice;[59] and 3) no genotoxicity was detected at lower exposure levels, possibly as a result of efficient detoxification/DNA repair.

The dose response pattern for genetic damage, which is the first key event of the mutagenic mode of action for the carcinogenicity of EtO, supports the biological plausibility of a single-slope linear CPH, rather than the 2-piece spline supra-linear model for the derivation of inhalation unit cancer risk for EtO.

5. MOST ASPECTS OF THE UCC COHORT ARE EQUALLY, IF NOT MORE RELIABLE THAN THE NIOSH COHORT AND SHOULD BE CONSIDERED IN DEVELOPING THE EtO IUR, EVEN IF ONLY QUALITATIVELY

In Table 8 of the OEHHA IUR document[60] OEHHA comments on the quality of UCC cohort studies. OEHHA concluded that the UCC cohort was generally of lower quality than the NIOSH cohort studies.[61] However, OEHHA's review of the UCC cohort studies would benefit from a more balanced assessment of both the strengths and limitations of the cohort.

Two characteristics of the UCC cohort studies that diminish it by comparison to the NIOSH cohort are: 1) the UCC cohort's lack of women and breast cancer as an endpoint; and 2) its small size. However, the UCC cohort studies are downgraded by OEHHA for a variety of additional reasons that suggest asymmetrical treatment of evidence from the NIOSH and UCC cohort studies. For example, the UCC cohort studies are ranked lower than the NIOSH cohort studies due to: 1) possible lack of statistical power (rated as adequate); 2) exposure assessment (low); 3) exposure validation (critical); 4) other confounder control (low); 5) reservations about lengthy follow-up time (adequate); 6) failure to evaluate the possibility of a HWSE (low); and 8) conflict of interest (critical). One strength of systematic evidence evaluation is the consistent application of study-quality criteria across the entire body of evidence. In this instance, it is not clear that

[59] NTP (1987). National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser. 1987 Nov.

[60] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 28. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[61] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. 30, line 678 – 680. https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

studies supporting and contradicting OEHHA's and EPA's conclusions were subjected to the same level of scrutiny, as discussed below.

A. UCC Cohort Studies Have Equal Power to Detect Increase in LHC from Cumulative EtO Exposure as NIOSH Cohort Studies

Although a smaller occupational cohort than the NIOSH cohort (1,896 vs 18,235 workers), the most recent UCC cohort study (Valdez-Flores et al., 2025)[62] was of high quality with a lengthy follow-up period that involved larger cumulative exposure to EtO than the NIOSH cohort (67 ppm-years vs 27 ppm-years). With the extended follow-up of the UCC cohort, the sample sizes for LHC are similar to the male numbers in the NIOSH mortality study, despite the larger overall cohort size of the NIOSH study (the number of UCC males with LHC exceeds the number of males available for analysis from the NIOSH study). The number of LHC deaths in the highest NIOSH quintile was five among 247 exposed workers, versus five among 534 UCC workers in the highest exposure category. The number of cancers are key determinants of study power.[63]

B. The UCC Exposure Assessment Is of Comparable Reliability to the NIOSH Exposure Assessment

OEHHA[64] and EPA[65] both suggest that the quality of the UCC cohort exposure assessment is lower than the NIOSH exposure assessment. While 2,700 exposure values may have been available for the NIOSH cohort, they were all collected between 1976 and 1985,[66] when workplace EtO levels were likely much lower than they had been in the distant past (i.e., the 1940's, 1950's, and 1960's).[67] As a result, all historical NIOSH worker exposure estimates were based on a statistical regression model[68] that produced exposure trends that defy both logic and

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[62] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837; TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May 15, 2020. p. 33

[63] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[64] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-8, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[65] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix K, p. K-6.

[66] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-4, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[67] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[68] Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738.

experience (see **Section C** below). On the other hand, measured EtO exposure data from companies using comparable methods to produce EtO were relied upon for UCC exposure estimates for the 1940 – 1956 time period and exposure data were available for 75% of the UCC cohort from routine monitoring, personal sampling, and a plant-wide survey in another UCC plant using the same process from 1957 to 1988. OEHHA also criticizes the modeled exposures for the UCC cohort because they were based on broad job categorizations. However, the measures of exposure used in NIOSH model development similarly consisted of samples taken for a given job and/or location within each plant for a given year.[69] In its discussion, OEHHA omits the fact that EtO exposure estimates for workers in the various EtO cohorts are all highly uncertain because of lack of individual exposure monitoring, particularly prior to the mid-1970's, and methodological problems with the way in which early exposures were modeled (see **Section C**). For these reasons, the UCC cohort is concluded to have comparable, if not superior historical exposure data to the NIOSH cohort.

C. Exposure Misclassification Is No More Likely in the UCC Cohort than In the NIOSH Cohort

The NIOSH exposure model was validated against average EtO air measurements using data from the same facilities, but that were not employed in the original model[70] and validation of the model was rated by OEHHA as "adequate".[71] Per OEHHA's Study Quality Ratings Instructions and Guidance (Attachment E),[72] a rating of adequate for exposure validation indicates that "Exposure misclassification is likely to be relatively minor". OEHHA states that there were no comparisons of model estimates to known exposure values[73] and model validation for the UCC cohort was rated as "critical". Per OEHHA's Study Quality Ratings Instructions and Guidance (Attachment E),[74] a rating of critical indicates that "Exposure misclassification is likely to lead to important bias."

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[69] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[70] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. P. 3-8, 3-15 (Table 3-1), 3-68, 4-60, 4-75, Appendix K, p. K-2, etc.

[71] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-4, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[72] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. E-17, Table E-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[73] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-5, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[74] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors,

The entire "validation" dataset for the NIOSH exposure model was collected between 1976 and 1985 (i.e., no measurements were available to validate the estimates made for the early years). The purpose of developing the exposure model in the first place was to reconstruct historical exposures over previous decades, when no exposure data were available. As a result, the NIOSH model's ability to accurately reconstruct historical exposures in previous decades has not been validated.

Despite long running experience that occupational exposures tend to decrease as workplace standards are lowered and industrial hygiene procedures and workplace practices improve,[75]the NIOSH exposure assessment model predicted the lowest EtO exposures in 1938 with levels peaking in 1978.[76] The use of increasing sterilizer volume over the years as a surrogate for exposure was the factor responsible for the increasing exposure trend over time.[77] Although sterilizer volumes did increase from 1938 – 1978,[78] EtO exposures in the sterilizer industry depended not only on the amount of EtO used, but also on the volumes and air turnover rates of rooms in which sterilization and storage of sterilized materials took place.[79] Assuming that smaller scale EtO sterilization was less hazardous than larger commercial scale processing did not take into account the better worker Personal Protective Equipment (PPE) and monitoring protections at the commercial scale, or the increase in cycle gas washes and better vacuum phases that remove the majority of EtO before any workers access products in the chamber. It also ignored the role that device type plays in the amount of EtO that is released from the sterilized device and exposure.

Given the failure to validate the NIOSH exposure model's performance during the earlier part of the exposure period and the fact that the NIOSH model predicted lower EtO exposures in

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Appendix B. Public Review Draft. May 28, 2026. Pg. E-17, Table E-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[75] OSHA (2005). Occupational Safety & Health Administration. Regulatory Review of the Occupational Safety and Health Administration's Ethylene Oxide Standard; Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738; LaMontagne, A. D., Oakes, J. M., & Lopez Turley, R. N. (2004). Long-term ethylene oxide exposure trends in US hospitals: Relationship with OSHA regulatory and enforcement actions. Amal J Public Health, 94(9), 1614-1619; Gardner MJ, Coggon D, Pannett B, Harris EC (1989) Workers exposed to ethylene oxide: a follow up study. Br J Ind Med 46:860–865.

[76] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[77] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[78] Pre-1960, most medical device sterilization (EO and steam) was done by hospitals or local 3rd party contract services at smaller scales for those hospitals since most devices were stainless steel reusables and would be sterilized near or at the point of use. As more single use disposable plastic devices became available, there was more volume of such devices and a need for larger scale sterilization and less use of local sterilization.

[79] Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738.

the early years than in later years, OEHHA's conclusion that exposure misclassification is likely to be relatively minor for the NIOSH cohort should be further supported.

D. Co-Exposures to Other Chemicals Is Not an Issue in Updated UCC Cohort Studies

OEHHA and others[80] have noted that workers from the UCC cohort had the potential for exposure to other chemicals in addition to EtO, raising the issue of potential confounding. OEHHA cited a 1990 paper by Greenberg[81] as the evidence for potential co-exposures. However, updated (1993) UCC cohort studies evaluated workers from the ethylene chlorohydrin and EtO units separately,[82] and subsequent studies excluded workers from the ethylene chlorohydrin unit.[83] Possible co-exposure to chemicals other than EtO is no longer a problem in the updated UCC cohort studies. OEHHA's reference to the outdated 1990 Greenberg study should be removed.

E. Concerns Raised about the Ability to Distinguish Exposure-Related Disease from Background Disease as a Result of the Lengthy UCC Cohort Follow-Up Should Similarly Be Considered for the Most Recent NIOSH Cohort Update

OEHHA notes that average follow-up for the UCC cohort is 41 years and that the authors acknowledge that "longer postexposure follow-up could potentially make it more difficult to distinguish background disease from exposure-related disease.[84] However, the UCC cohort has been examined at various lengths of follow-up, and EtO-related effects have not been observed at either shorter or longer observation periods.[85]

While the NIOSH cohort studies used by EPA and OEHHA in developing the IUR for EtO had 25 years of follow-up, the recent Kelly-Reif et al. (2025) study extended the NIOSH breast cancer mortality follow-up to 44 years (median). Given the similarity in follow-up periods for the

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[80] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-7, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide; Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[81] Greenberg, H. L., Ott, M. G., & Shore, R. E. (1990). Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study. *Occupational and Environmental Medicine*, *47*(4), 221-230.

[82] Teta, M. J., Benson, L. O., & Vitale, J. N. (1993). Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update. Occupational and Environmental Medicine, 50(8), 704-709.

[83] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, *45*(9), 2822-2837.

[84] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-3, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[85] Teta, M. J., Benson, L. O., & Vitale, J. N. (1993). Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update. Occupational and Environmental Medicine, 50(8), 704-709; Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, *45*(9), 2822-2837.

latest updates of the UCC and NIOSH cohort studies, distinguishing exposure-related disease from background disease could be a potential issue in the most recent updates for both cohorts, and yet this concern was not raised by OEHHA with regard to the Kelly Reif et al. (2025) study. Even though the Kelly Reif et al. (2025) study was not used in calculating the IUR, if the study quality of the UCC cohort studies are ranked lower than the NIOSH cohort studies on the basis of this concern, then it seems that this same issue should be raised in NIOSH cohort studies (e.g., Kelly-Reif et al, 2025) as well.

F. The Potential Existence of a HWSE Was Not Evaluated In the UCC Cohort Because There Is No Evidence that this Bias Is Operating in the Cohort

The absence of significant SMRs in the UCC study has raised concern that HWE (healthy worker effect) bias could be masking an increased risk. However, the HWE is of most concern for chronic systemic diseases (e.g., diseases of the respiratory and circulatory systems) and less pronounced for cancer deaths and incidence.[86] In other words, it is more serious for diseases with the potential for symptoms at the date of hire than for diseases without pre-diagnosis symptomatology (e.g., cancer) and in occupational cohort studies with long follow-up periods (like the NIOSH and UCC cohorts).[87] In addition, Steenland et al. (2004) concluded that the HWE was an unlikely explanation for the lack of LHC excesses in the exposed versus non-exposed comparisons. Finally, no decrease in risks with additional follow-up of the UCC cohort were seen in the most recent UCC cohort study, [88] as would be expected with a HWSE (healthy worker survivor effect) bias. Therefore, there is no evidence that the HWE is operating in the UCC cohort.

G. Evaluating Potential Conflict of Interest Solely on the Basis of Funding Is Too Narrow Because Scientific Judgment May Also Be Influenced By Non-Financial Interests

OEHHA rated the NIOSH cohort studies as "high" for conflict of interest (COI) because they were primarily government funded, while it rated the UCC cohort studies as "critical", stating that multiple potential conflicts of interest were cited.[89] Per OEHHA's Study Quality Ratings Instructions and Guidance (Attachment E),[90] a rating of high for COI indicates that "Study funding and conflict of interest information is clear and no study author, funder, or other important entity

[86] Kirkeleit, J., Riise, T., Bjørge, T., & Christiani, D. C. (2013). The healthy worker effect in cancer incidence studies. *American journal of epidemiology*, *177*(11), 1218-1224.

[87] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[88] Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

[89] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. D-8, Table D-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

[90] OEHHA (2026). California Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Ethylene Oxide Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft. May 28, 2026. Pg. E-30, Table E-1, https://oehha.ca.gov/air/crnr/inhalation-unit-risk-factor-iur-ethylene-oxide.

had an obvious financial or other related interest in the exposure or outcome", while a rating of critical means that "A study funder, author or other related entity had a strong financial interest in the study results."

COI is a situation in which an individual's judgment concerning a primary interest tends to be unduly influenced (or biased) by a secondary interest.[91] Although it is clearly acknowledged that COIs can have a negative effect on science, study funding or author employment source neither demonstrates that study results have been improperly influenced, nor guarantees unbiased results.

While government scientists generally have fewer direct financial conflicts, other non-financial influences are possible (even likely) and none of these other potential conflicts appear to have been considered by OEHHA. Government agencies generally have statutory missions and these missions can create incentives for: 1) preferences for precautionary interpretations; 2) emphasizing evidence of harm; or 3) focusing on avoiding false negatives (missing a real hazard). Moreover, once an agency has publicly adopted a scientific position, there may be significant institutional pressure to defend that position and government scientists may benefit professionally from supporting high-profile regulatory initiatives. Regulatory agencies are not passive consumers of science. They are organizations with missions, legal obligations, and established policy positions that can influence scientific interpretation.[92] Legitimate disagreements about the scientific implications of a study can arise out of honest differences linked to disciplinary training or institutional affiliation, but this is different from a COI.[93]

Evaluating potential bias solely through the lens of funding is too narrow because scientific judgment may also be influenced by non-financial interests, including institutional missions, professional advancement, ideological commitments, advocacy activities, and other organizational incentives.[94] Applying a rating system that assumes that source of funding or employment proves bias or misconduct is not an objective science-based method for judging study quality.

6. USE OF THE IUR AS BASIS FOR REGULATION WITHOUT CONSIDERING THE IMPLICATIONS OF BACKGROUND EXPOSURE IS IMPRACTICABLE

People are continuously exposed to EtO in ambient air. Taking background levels of EtO in ambient air into account need not involve changing the policy on deriving IURs. Instead,

[91] Resnik, D. (2023). Disclosing and managing non-financial conflicts of interest in scientific publications. *Research Ethics*, *19*(2), 121-138.

[92] Sunstein, C. R. (2003). Beyond the precautionary principle. *University of Pennsylvania Law Review*, *151*(3), 1003-1058; Jasanoff, S. (1993). Procedural choices in regulatory science. *RISK: Health, Safety & Environment (1990-2002)*, *4*(2), 7; Wilson, J. Q. (2019). *Bureaucracy: What government agencies do and why they do it*. Basic Books.

[93] Jasanoff, S. (1993). Procedural choices in regulatory science. *RISK: Health, Safety & Environment (1990-2002)*, *4*(2), 7.

[94] Resnik, D. (2023). Disclosing and managing non-financial conflicts of interest in scientific publications. *Research Ethics*, *19*(2), 121-138.

background EtO in the environment could be used in making risk management decisions without specifically incorporating it into the IUR. For example, an approach could be taken similar to EPA's method for characterizing risks from soil contaminants attributable to background sources under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and by many state-based Resource Conservation and Recovery Act (RCRA) clean-up programs[95]. According to EPA's CERCLA guidance:

> "In general, the presence of high background concentrations of hazardous substances, pollutants, and contaminants found at a site is a factor that should be considered in risk assessment and risk management. Contamination at a CERCLA site may originate from releases attributable to the CERCLA site in question, as well as contamination that originated from other sources, including natural and/or anthropogenic sources not attributable to the specific site releases under investigation. In some cases, the same hazardous substance, pollutant, and contaminant associated with a release is also a background constituent. These constituents should be included in the risk assessment, particularly when their concentrations exceed risk-based concentrations. In cases where background levels are high or present health risks, this information may be important to the public. Background information is important to risk managers because the CERCLA program, generally, does not clean up to concentrations below natural or anthropogenic background levels."[96]

At a minimum, background concentrations should be discussed qualitatively when communicating risk. However, if the EtO levels emitted from a particular entity do not cause a statistically significant increase above season-specific local background concentrations (or some other excursion allowance [e.g., 2 or 3 times local seasonal background]) at locations where the general public could reasonably be exposed, then no further emission reductions should be required since they are unlikely to materially affect the community's risk. This approach would be much more practical given that the OEHHA IUR corresponds to air concentrations that are much lower than ambient background concentrations (~ 0.066 to 0.1 ppb) and current detection limits for EtO in air are approximately 0.025 to 0.015 ppb, which is 2.3 to more than 200 times targeted risk-specific (100-in-1 million and 1-in-1 million) concentrations in air based on OEHHA's IUR.

7. CONCLUSIONS

- The OEHHA IUR is highly impractical as a basis for regulation because compliance with a level below widespread background levels cannot be demonstrated;
- OEHHA's conclusion that the NIOSH study supports a steep risk at low exposures is based primarily on:

[95] EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. EPA 540-R-01-003 OSWER 9285.7-41 September 2002.

[96] EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. Appendix B: Policy Considerations for the Application of Background Data in Risk Assessment and Remedy Selection. EPA 540-R-01-003 OSWER 9285.7-41 September 2002.

- the fact that, of the large number of curve-fitting models and lag times assessed, the only one that produced a statistically significant positive slope was the supra-linear model; and
- the "visual fit" of a few non-parametric categorical rate ratios was better with the supra-linear model than other models evaluated;
- however, visual fit models are subjective and depend on how data are presented (i.e., different analysts can look at the same plot and draw different conclusions about the shape of the exposure-response curve).

- New studies do not support the idea that EtO is a highly potent carcinogen with a steep risk at low concentrations.
  - Valdez-Flores et al. (2025) identified two major problems with EPA's, and by extension OEHHA's, IUR for EtO:
    - EPA and OEHHA combined male and female LHC to estimate the potency of EtO in their final risk assessments, despite evidence of differences in exposure-response patterns in men and women in the NIOSH cohort, as acknowledged by Steenland et al. (2004);
    - Ehen combined with male data, the female data in the low exposure region alters the appearance of the slope as a steep exposure response;
    - Neither model had a superior visual fit to the data when the data were normalized along the y-axis and different implicitly estimated baseline risks were accounted for;
    - Based on their combined analyses of the NIOSH and UCC cohort studies, Valdez-Flores et al. (2025) concluded that there is no evidence that EtO is a highly potent carcinogen consistent with a steep increase in risk at low exposures and that the standard CPH model more plausibly describes the relationship between EtO exposures and LHC mortality in both the NIOSH and UCC cohorts.
  - Gollapudi et al. (2026) evaluated the biological plausibility of the various dose-response models that have been applied to the NIOSH data by investigating genetic damage, which is the first key event of the mutagenic mode of action of EtO carcinogenicity, as well as other endpoints specific to a mutagenic mode of action;
    - The dose-response slopes increased disproportionately *only* at higher EtO concentrations;
    - The shape of the observed dose-response for genetic damage was linear throughout the range of exposure, supporting a single-sloped dose-response model as biologically plausible.

- OEHHA concluded that the UCC cohort was generally of lower quality than the NIOSH cohort.
    - OEHHA's review would benefit from a more balanced assessment of both the strengths and limitations of the cohort.
        - the UCC cohort studies have equal power to detect increases in LHC from cumulative EtO exposure to the NIOSH cohort studies;
        - the UCC exposure assessment is of comparable reliability to the NIOSH assessment;
        - exposure misclassification is not more likely in the UCC cohort than in the NIOSH cohort;
        - co-exposures to other chemicals is not an issue in updated UCC cohort studies.
    - Most aspects of the UCC cohort are equally, if not more reliable than the NIOSH cohort and the UCC cohort studies should be considered in the development of OEHHA's EtO IUR, even if only qualitatively.
- The scientific debate surrounding the 2016 EPA IUR on which the OEHHA IUR is based is not merely academic; it has enormous regulatory and economic consequences.

Sincerely

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