INITIAL STATEMENT OF REASONS

TITLE 27, CALIFORNIA CODE OF REGULATIONS
PROPOSED AMENDMENT TO:

SECTION 25705(b) SPECIFIC REGULATORY LEVELS

POSING NO SIGNIFICANT RISK

ETHYLENE OXIDE

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

APRIL 2023

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Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is the lead agency that implements Proposition 65[1] and has the authority to promulgate and amend regulations to implement and further the purposes of the Act. OEHHA proposes to adopt an updated No Significant Risk Level (NSRL) for ethylene oxide under Proposition 65 in Title 27, California Code of Regulations, section 25705(b)[2].

The proposed NSRL of 0.058 micrograms per day (µg/day) incorporates significant new data relevant to the estimation of the NSRL that have become available since the existing NSRL for ethylene oxide was adopted in 1988. This includes new data from cancer epidemiology studies and studies of genotoxicity and pharmacokinetics. The proposed level is based on the cancer potency value developed in a 2016 US Environmental Protection Agency (US EPA) risk assessment.[3] OEHHA reviewed the 2016 US EPA ethylene oxide risk assessment and determined that the derivation of the cancer potency value was consistent with the guidelines set forth in Section 25703.

Background and Problem to Be Addressed by the Proposed Amendment

Proposition 65 was enacted as a ballot initiative on November 4, 1986. OEHHA is the lead state entity responsible for the implementation of Proposition 65[4]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[5].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals into sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as “Proposition 65” or “the Act”.
[2] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[3] US Environmental Protection Agency (US EPA 2016a). Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) in Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC, EPA/635/R-16/350Fa. Available from: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=529970.
[4] Section 25102(o).
[5] Health and Safety Code, section 25249.12(a).

insignificant. NSRLs provide guidance for determining when a warning is required for exposures to chemicals listed as causing cancer.

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, under which a warning is not required and under which a discharge is not prohibited.

Ethylene oxide was listed as known to the state to cause cancer under Proposition 65 on July 1, 1987. An NSRL of 2 µg/day for ethylene oxide was adopted in Section 25705(b) on July 1, 1988 based on the Proposition 65 regulatory guidance and best available science at the time. Since this level was adopted, significant new scientific information has become available from epidemiologic, pharmacokinetic, and mechanistic studies relevant to the estimation of an NSRL for ethylene oxide.

US EPA's 2016 extensive review and analysis incorporates the available scientific information on the carcinogenicity of ethylene oxide and derives a cancer potency value (i.e., unit risk), based on a human epidemiology study conducted by the National Institute for Occupational Safety and Health (NIOSH). OEHHA's review of the currently available scientific information finds the cancer unit risk estimate of 6.1 per ppm (3.3×10^{-3} per µg/m^3) in the US EPA assessment to be an accurate and reliable scientific basis for updating the NSRL that is consistent with Section 25703 guidance. US EPA's risk assessment of ethylene oxide underwent extensive internal and external scientific review, as well as a public comment process, before being released as a final document by US EPA.

In the 2016 ethylene oxide risk assessment[6], US EPA described its findings as follows:

> "Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, EtO [ethylene oxide] is characterized as "carcinogenic to humans" by the inhalation route of exposure based on the total weight of evidence, in accordance with the U.S. Environmental Protection Agency's (EPA's) 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA 2005a). The lines of evidence supporting this characterization include: (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers, (2) extensive evidence of

[6] US EPA (2016a), full citation provided in footnote 3.

> carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO. Overall, confidence in the hazard characterization of EtO as 'carcinogenic to humans' is high."

The process US EPA used to calculate the cancer potency (i.e., unit risk) was described as follows[7]:

> "The unit risk estimates for cancer mortality and incidence were based on the human data from the NIOSH study (Steenland et al. 2004; Steenland et al. 2003). This study was selected for the derivation of risk estimates because it is a high-quality study, it is the largest of the available studies, and it has exposure estimates for the individual workers from a high-quality exposure assessment. Multiple modeling approaches were evaluated for the exposure-response data, including modeling the cancer response as a function of either categorical exposures or continuous individual exposure levels. Model selection for each cancer data set was primarily based on a preference for models of the individual-level continuous exposure data, prioritization of models that are more tuned to local behavior in the low-exposure data, and a weighing of statistical and biological considerations."

> "…an LEC_{01} (lower 95% confidence limit on the EC_{01}, the estimated effective concentration associated with 1% extra risk) for excess lymphoid cancer mortality (Steenland et al., 2004) was calculated using a life-table analysis and the lower spline segment from a two-piece linear spline model. Linear low-dose extrapolation below the range of observations is supported by the conclusion that a mutagenic mode of action is operative in EtO carcinogenicity. Linear low-dose extrapolation from the LEC_{01} for lymphoid cancer mortality yielded a lifetime (70 year) extra cancer unit risk estimate of 1.1×10^{-3} per $\mu g/m^3$ (2.0×10^{-3} per ppb) of continuous EtO exposure. Applying the same lower-spline regression coefficient and life-table analysis to background lymphoid cancer incidence rates and applying linear low-dose extrapolation resulted in a preferred lifetime extra

[7] US EPA (2016a), full citation provided in footnote 3.

lymphoid cancer unit risk estimate of 2.9×10^{-3} per μg/m^3 (5.3×10^{-3} per ppb), as cancer incidence estimates are generally preferred over mortality estimates." [Footnotes in quoted text not shown]

"Breast cancer incidence risk estimates were calculated directly from the data from a breast cancer incidence study of the same occupational cohort (Steenland et al. 2003). Using the same life-table approach, the lower spline segment from a two-piece linear spline model, and linear low-dose extrapolation, a unit risk estimate of 8.1×10^{-4} per μg/m^3 (1.5×10^{-3} per ppb) was obtained for breast cancer incidence. A unit risk estimate for breast cancer mortality was also calculated from the cohort mortality data; however, the incidence estimate is preferred over the mortality estimate.

"Combining the incidence risk estimates for the two cancer types resulted in a total cancer unit risk estimate of 3.3×10^{-3} per μg/m^3 (6.1×10^{-3} per ppb) [12 per mg/kg-day]."

Development of the Proposed NSRL

To develop the proposed updated NSRL for ethylene oxide, OEHHA relied on the US EPA 2016 report entitled "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) in Support of Summary Information on the Integrated Risk Information System (IRIS)", and its analyses of epidemiologic data from a cohort of more than 18000 workers with quantitative estimates of exposure to ethylene oxide, assembled by NIOSH[8,9,10,11].

[8] US EPA (2016a), full citation provided in footnote 3.
[9] US Environmental Protection Agency (US EPA 2016b). Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. Appendices. (CASRN 75-21-8). In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC, EPA/635/R-16/350Fb. Available from: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=529971.
[10] 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. Occup Environ Med 61(1):2-7.
[11] 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(6):531-9.

Several publications provide information on rodent carcinogenicity studies of ethylene oxide[12,13,14,15,16,17]. These studies are also discussed in publications by the International Agency for Research on Cancer (IARC)[18], US EPA[19], and Agency for Toxic Substances and Disease Registry (ATSDR)[20]. IARC (1994, 2008, 2012)[21,22,23], US EPA[24], and ATSDR[25] provide information on genotoxicity and pharmacokinetics (toxicokinetics). Additional information was identified from four epidemiologic studies[26,27,28,29] and three

[12] National Toxicology Program (NTP 1987). Toxicology and carcinogenesis studies of ethylene oxide (CAS No. 75-21-8) in B6C3F1 mice (inhalation studies). Natl Toxicol Program Tech Rep Ser 326: 1-114. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr326.pdf
[13] Snellings WM, Weil CS, Maronpot RR (1981). Final report ethylene oxide two-year inhalation study on rats. Bushy Run Research Center, Pittsburgh, PA.
[14] Snellings WM, Weil CS, Maronpot RR (1984). A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. Toxicol Appl Pharmacol 75: 105-117.
[15] Garman RH, Snellings WM, Maronpot RR (1985). Brain tumors in F344 rats associated with chronic inhalation exposure to ethylene oxide. Neurotoxicology 6: 117-137.
[16] Lynch DW, Lewis TR, Moorman WJ, et al. (1984). Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol Appl Pharmacol 76: 69-84.
[17] Dunkelberg H (1982). Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Br J Cancer 46: 924-933.
[18] International Agency for Research on Cancer (IARC 2012). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100F, Chemical Agents and Related Occupations. Ethylene Oxide. IARC, World Health Organization, Lyon, France. Available from: https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-28.pdf
[19] US EPA (2016a), full citation provided in footnote 3.
[20] Agency for Toxic Substances and Disease Registry (ATSDR 2022). Toxicological Profile for Ethylene Oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. August 2022. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf
[21] International Agency for Research on Cancer (IARC 1994). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 60, Some Industrial Chemicals. IARC, World Health Organization, Lyon, France. Available from: https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono60.pdf
[22] International Agency for Research on Cancer (IARC 2008). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 97, 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). IARC, World Health Organization, Lyon, France. Available from: https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono97.pdf
[23] IARC (2012), full citation provided in footnote 18.
[24] US EPA (2016a), full citation provided in footnote 3.
[25] ATSDR (2022), full citation provided in footnote 20.
[26] Jones RR, Fisher JA, Medgyesi DN, et al. (2023). Ethylene oxide emissions and incident breast cancer and non-Hodgkin lymphoma in a U.S. cohort. J Natl Cancer Inst. djad004.
[27] Bulka C, Nastoupil LJ, Koff JL, et al. (2016). Relations between residential proximity to EPA-designated toxic release sites and diffuse large B-cell lymphoma incidence. South Med J. 109(10):606-614.
[28] Hart JE, Bertrand KA, DuPre N, et al. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environ Health 17(1):28.
[29] Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health 14:14.

publications on genotoxicity[30,31,32]. The following 12 publications that provide additional information on pharmacokinetics (toxicokinetics) and endogenous production were identified[33,34,35,36,37,38,39,40,41,42,43,44].

The NSRL for ethylene oxide is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[45].

[30] Zeljezic D, Mladinic M, Kopjar N, Radulovic AH (2016). Evaluation of genome damage in subjects occupationally exposed to possible carcinogens. Toxicol Ind Health 32(9):1570-1580.
[31] Carlsson H, Aasa J, Kotova N, et al. (2017). Adductomic screening of hemoglobin adducts and monitoring of micronuclei in school-age children. Chem. Res. Toxicol. 30:1157-1167.
[32] Manjanatha MG, Shelton SD, Chen Y, et al. (2017). Dose and temporal evaluation of ethylene oxide-induced mutagenicity in the lungs of male Big Blue mice following inhalation exposure to carcinogenic concentrations. Environ Mol. Mutagen. 58:122-134.
[33] Brown CD, Wong BA, Fennell TR (1996). In vivo and in vitro kinetics of ethylene oxide metabolism in rats and mice. Toxicol Appl Pharm 136:8-19.
[34] Brown CD, Asgharian B, Turner MJ, Fennell TR (1998). Ethylene oxide dosimetry in the mouse. Toxicol Appl Pharm 148:215-221.
[35] Brugnone F, Perbellini L, Faccini G, Pasini F (1985). Concentration of ethylene oxide in the alveolar air of occupationally exposed workers. Am J Ind Med 8:67–72.
[36] Brugnone F, Perbellini L, Faccini GB, Pasini F, Bartolucci GB, DeRose E (1986). Ethylene oxide exposure. Biological monitoring by analysis of alveolar air and blood. Int Arch Occup Environ Health 58:105–112.
[37] Csanady GA, Denk B, Putz C, et al. (2000). A physiological toxicokinetic model for exogenous and endogenous ethylene and ethylene oxide in rat, mouse, and human: formation of 2-hydroxyethyl adducts with hemoglobin and DNA. Toxicol Appl Pharm 165:1-26.
[38] Fennell TR, Brown CD (2001). A physiologically based pharmacokinetic model for ethylene oxide in mouse, rat, and human. Toxicol Appl Pharm 173:161-175.
[39] Filser JG, Klein D (2018). A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. Toxicol Lett 286:54-79.
[40] Hattis D (1987). A pharmacokinetic/mechanism-based analysis of the carcinogenic risk of ethylene oxide. Available from: https://www.osti.gov/biblio/7067804.
[41] Filser JG, Denk B, Tornqvist M, Kessler W, Ehreberg L (1992). Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene. Arch Toxicol 66:157-163.
[42] Ehrenberg L, Hiesche KD, Osterman-Golkar S, Wennberg I (1974). Evaluation of genetic risks of alkylating agents: tissue doses in the mouse from air contaminated with ethylene oxide. Mutat Res 24:83-103.
[43] Filser JG, Kessler W, Artati A, et al. (2013). Ethylene oxide in blood of ethylene-exposed B6C3F1 mice, Fischer 344 rats, and humans. Toxicol Sci 136(2):344-358.
[44] Kirman CR, Li AA, Sheehan PJ, Bus JS, Lewis RC, Hays SM (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.
[45] Section 25703(a)(4).

Selection of Studies Used to Determine Cancer Potency

OEHHA identified three human epidemiological studies of ethylene oxide and cancer with quantitative exposure estimates in persons who were occupationally exposed (Table 1), and six rodent carcinogenicity studies of sufficient duration (Table 2). These studies were identified through a review of all the studies cited by US EPA (2016a)[46], and a systematic search of the published scientific literature and technical reports since January 2016.

In addition to the three human epidemiological studies in Table 1, OEHHA identified four epidemiological studies that investigated associations between residential proximity to ethylene oxide emitting facilities and increased cancer risk[47,48,49,50]. Emissions data were obtained at the community level from US EPA databases: the Toxics Release Inventory (TRI)[51,52,53] and the National Air Toxics Assessment (NATA)[54,55,56]. While these community-based air pollutant studies can be useful for hazard identification, OEHHA judged them to be less useful for dose-response assessment of ethylene oxide compared to the occupational studies[57,58,59,60] due to greater uncertainty in estimating individual exposures. This can result in non-differential exposure misclassification and bias risk estimates towards the null[61]. Furthermore, there were fewer exposed cases, and there may be less exposure contrast in these community-based studies of ethylene oxide, decreasing the sensitivity of the studies to detect an effect.

[46] The literature search for US EPA (2016a) includes scientific literature published up to August 2016.
[47] Bulka et al. (2016), full citation provided in footnote 27.
[48] Hart et al. (2018), full citation provided in footnote 28.
[49] Jones et al. (2023), full citation provided in footnote 26.
[50] Garcia et al. (2015), full citation provided in footnote 29.
[51] The Toxic Release Inventory (TRI) Program. https://www.epa.gov/toxics-release-inventory-tri-program
[52] Bulka et al. (2016), full citation provided in footnote 27.
[53] Jones et al. (2023), full citation provided in footnote 26.
[54] National Air Toxics Assessment. https://www.epa.gov/national-air-toxics-assessment
[55] Garcia et al. (2015), full citation provided in footnote 29.
[56] Hart et al. (2018), full citation provided in footnote 28.
[57] Steenland et al. (2003), full citation provided in footnote 11.
[58] Steenland et al. (2004), full citation provided in footnote 10.
[59] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM (2009). Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med. 51(6):714-23.
[60] Mikoczy Z, Tinnerberg H, Björk J, Albin M (2011). Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972-2006. Int J Environ Res Public Health. 8(6):2009-19.
[61] Shy CM, Kleinbaum DG, Morgenstern H (1978). The effect of misclassification of exposure status in epidemiological studies of air pollution health effects. Bull N Y Acad Med. 54(11):1155-65.

Table 1. Overview of human epidemiological studies of ethylene oxide and cancer with quantitative exposure estimates

Reference; Population description	Exposure assessment method and levels	Key results	Comments
US EPA (2016a)[62]; Steenland et al. 2004[63] (analyses of mortality data); Steenland et al. 2003[64] (analyses of breast cancer incidence) Population: NIOSH cohort; >18000 workers from 14 plants in 11 states exposed at least three months to ethylene oxide from 1940s–1980s, with 461000 person-years of follow-up until 1998.	Method: Quantitative cumulative exposure estimated from a large number of measurements coupled with data of historical process changes and work history. Levels: Cumulative exposure (ppm-years) for the cohort: mean 26.9, SD 65.7, median 5.6. For men: mean 37.8, SD 87.6, median 7.6. For women: mean 18.2, SD 38.2, median 4.6.	No overall excess for most cancers (including hematopoietic cancers, non-Hodgkin's lymphoma, or breast cancer) when compared to the general US population. Odds ratios (95% CI) for **lymphoid cancer mortality** in men by category of cumulative exposure (ppm-days) lagged 15 years (categories: 0, >0–1199, 1200–3679, 3680–13499, ≥13500 ppm-days): 1.00, 0.90 (0.16–5.24), 2.89 (0.65–12.86), 2.74 (0.65–11.55), 3.76 (1.03–13.64) (*p*-value for trend = 0.13). Odds ratios (95% CI) for **breast cancer mortality** by category of cumulative exposure (ppm-days) lagged 20 years (categories: 0, >0–646, 647–2779, 2780–12321, ≥12322 ppm-days): 1.00, 1.76 (0.91–3.43), 1.77 (0.88–3.56), 1.97 (0.94–4.06), 3.13 (1.42–6.92) (*p*-value for trend = 0.07).	This is the largest existing cohort of ethylene oxide exposed workers. Thorough exploration of different exposure metrics (peak exposure, average exposure, and duration of exposure) and lag times. Most suitable epidemiologic study for dose-response risk quantification due to 1) high quality of the exposure assessment, 2) the absence of confounding co-exposures, 3) large cohort size and adequate statistical power, 4) information on ethylene oxide exposure was collected prior to cancer diagnosis, 5) the diversity of data and subgroups (sex and race/ethnicity) allowed for exploratory sub-analyses of potentially susceptible populations, and 6) the very high exposures incurred in the cohort increased the sensitivity of the study to detect an effect.

[62] US EPA (2016a), full citation provided in footnote 3.
[63] Steenland et al. (2004), full citation provided in footnote 10.
[64] Steenland et al. (2003), full citation provided in footnote 11.

Reference; Population description	Exposure assessment method and levels	Key results	Comments
		Odds ratios (95% CI) for **breast cancer incidence** by category of cumulative exposure (ppm-days) lagged 15 years (categories: 0, >0–646, 647–2026, 2026–4919, 4919–14620, >14620 ppm-days): 1.00 (lagged out), 1.06 (0.66–1.71), 0.99 (0.61–1.60), 1.24 (0.76–2.00), 1.42 (0.88–2.29), 1.87 (1.12–3.10); (*p*-value for trend = 0.0005).	
Swaen et al. (2009)[65] [follow-up of Greenberg et al. (1990)[66] and Teta et al. (1993)[67]] Population: Union Carbide cohort; 2063 male ethylene oxide workers exposed 1940–1988 with 75316.2 person-years of observation. Follow-up until 2003	Method: A matrix was developed to estimate cumulative ethylene oxide exposure for each study subject combining work history (including time period and duration) and measured department-specific exposure concentrations. Levels: 67.16 ppm-years average estimated cumulative exposure	No excess of cancers when compared to the general population. For the internal analysis, hazard ratio per 1 ppm-year increment in cumulative exposure (95% CI): 0.998 (0.991–1.004) for leukemia mortality (N = 11) and 0.994 (0.985–1.003) for lymphoid malignancies mortality (N = 17)	No exploration of different exposure metrics or lag times.

[65] Swaen et al. (2009), full citation provided in footnote 59.
[66] Greenberg HL, Ott MG, Shore RE (1990). Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study. Br J Ind Med. 47:221-230.
[67] Teta MJ, Benson LO, Vitale JN (1993). Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update. Br J Ind Med. 50:704-709.

Reference; Population description	Exposure assessment method and levels	Key results	Comments
Mikoczy et al. (2011) [follow-up of Hagmar et al. (1995) and Hagmar et al. (1991)][68,69,70] Population: Swedish sterilizers; 2171 male and female workers employed for at least one year in two plants in Sweden producing medical equipment sterilized with ethylene oxide (exposed 1925–1988). Follow-up until 2003	Method: Cumulative exposure to ethylene oxide was estimated from plant specific job-exposure matrices combined with yearly statutory hygienic measurements. Levels: Cumulative exposure (ppm-years): 2.92 (mean), 0.13 (median)	No statistically significant excesses in cancers when compared to general population. Internal analyses found significantly increased rate ratios for breast cancer for the two upper quartiles of cumulative exposure as compared to the lowest quartiles of the cohort. Incidence rate ratios (95% CI) for **breast cancer** incidence by category of cumulative exposure (ppm-years) (categories: 0–0.13, 0.14–0.21, ≥0.22 ppm-years): 1.00, 2.76 (1.20–6.33), 3.55 (1.58–7.93) Incidence rate ratios (95% CI) for **lymphohematopoietic cancer** incidence by category of cumulative exposure (ppm-years) (categories: 0–0.13, 0.14–0.21, ≥0.22 ppm-years): 1.00, 1.17 (0.36–3.78), 0.92 (0.28–3.05)	Exposures were much lower than in the NIOSH and Union Carbide cohorts, which decreases the ability to detect an effect.

Abbreviations: ppm, parts per million; SD, standard deviation; 95% CI, 95% confidence interval

[68] Mikoczy et al. (2011), full citation provided in footnote 60.
[69] Hagmar L, Mikoczy Z, Welinder H (1995). Cancer incidence in Swedish sterilant workers exposed to ethylene oxide. Occup Environ Med. 52(3):154-6.
[70] Hagmar L, Welinder H, Lindén K, Attewell R, Osterman-Golkar S, Törnqvist M (1991). An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. Int Arch Occup Environ Health. 63(4):271-7.

Table 2. Overview of long-term rodent carcinogenicity studies of ethylene oxide

Sex, strain, and species	Route of administration	Duration	Doses (mg/kg-day)	Purity of test material	Treatment-related tumor findings	Reference
Male Fischer 344 rats	Inhalation	25 months	0, 3.13, 10.32, 31.27	99.9%	Mononuclear cell leukemia, testicular peritoneal mesothelioma, brain glioma	Snellings et al. (1981, 1984)[71,72]; Garman et al. (1985)[73]
Female Fischer 344 rats	Inhalation	25 months	0, 3.75, 12.38, 37.50	99.9%	Mononuclear cell leukemia, brain glioma	Snellings et al. (1981, 1984)[74,75]; Garman et al. (1985)[76]
Male Fischer 344 rats	Inhalation	104 weeks	0, 18.59, 37.18	99.7%	Mononuclear cell leukemia, peritoneal mesothelioma, brain glioma	Lynch et al. (1984)[77]
Female Sprague-Dawley rats	Gavage	150 weeks	0, 2.20, 8.82	99.7%	Forestomach squamous cell carcinoma, forestomach fibrosarcoma	Dunkelberg (1982)[78]
Male B6C3F$_1$ mice	Inhalation	102 weeks	0, 18.32, 36.64	>99%	Alveolar/bronchiolar adenoma or carcinoma, harderian gland papillary cystadenoma	NTP (1987)[79]

[71] Snellings et al. (1981), full citation provided in footnote 13.
[72] Snellings et al. (1984), full citation provided in footnote 14.
[73] Garman et al. (1985), full citation provided in footnote 15.
[74] Snellings et al. (1981), full citation provided in footnote 13.
[75] Snellings et al. (1984), full citation provided in footnote 14.
[76] Garman et al. (1985), full citation provided in footnote 15.
[77] Lynch et al. (1984), full citation provided in footnote 16.
[78] Dunkelberg (1982), full citation provided in footnote 17.
[79] NTP (1987), full citation provided in footnote 12.

Sex, strain, and species	Route of administration	Duration	Doses (mg/kg-day)	Purity of test material	Treatment-related tumor findings	Reference
Female $B6C3F_1$ mice	Inhalation	102 weeks	0, 19.21, 38.42	>99%	Alveolar/bronchiolar adenoma or carcinoma, harderian gland papillary cystadenoma, malignant lymphoma, uterine adenoma or carcinoma, mammary adenocarcinoma or adenosquamous carcinoma	NTP (1987)[80]

[80] NTP (1987), full citation provided in footnote 12.

OEHHA reviewed the available data from the epidemiological studies shown in Table 1 and the discussion of these studies in US EPA (2016a), and determined that the NIOSH study met the criterion in Section 25703 as being the most sensitive epidemiologic study of sufficient quality. OEHHA's selection of the NIOSH study for dose-response analysis and estimation of the cancer potency is consistent with the US EPA (2016a) analysis.

For completeness, OEHHA also reviewed the available data from the rodent carcinogenicity studies shown in Table 2. Each of the studies, except the study by Dunkelberg et al. (1982), was selected for dose-response modeling as sensitive studies of sufficient quality. Although Dunkelberg et al. (1982) reported increases in the incidences of forestomach squamous cell carcinoma (incidence: 0/50, 8/50, 29/50 at 0, 7.5, 30 mg/kg body weight (mg/kg bw), respectively; significant by pairwise comparison with control at both doses, and by trend test) and forestomach fibrosarcoma (incidence: 0/50, 0/50, 2/50), this female rat study was not selected for dose-response modeling because of significant uncertainties regarding animal body weights, the inability to adjust for intercurrent mortality[81], and the twice-weekly bolus dosing regime[82].

Toxicokinetic and Mechanistic Considerations

Toxicokinetics

The toxicokinetics (absorption, distribution, metabolism, and excretion) of ethylene oxide has been reviewed in recent reports by US EPA (2016a)[83] and ATSDR (2022)[84]. Much of the current understanding regarding the toxicokinetics of ethylene oxide has been gained from studies of rodents exposed to ethylene oxide via inhalation, e.g., by Brown et al. (1996; 1998)[85,86]. However, occupational studies of inhalation-exposed workers (Brugnone et al. 1985; 1986)[87,88] and *in vitro* examinations into inter-species

[81] Dunkelberg et al. (1982) reported increased mortality in the high-dose group, but did not provide sufficient information to adjust for the intercurrent mortality observed in the study. Tumor incidence data are presented here as the number of animals with the specified tumor over the number of animals per group at the beginning of the study.
[82] Animals were dosed via gavage twice per week over a 150-week period, with the exception of weeks 79-82, when dosing was interrupted due to the occurrence of pneumonia in several of the animals in the study.
[83] US EPA (2016a), full citation provided in footnote 3.
[84] ATSDR (2022), full citation provided in footnote 20.
[85] Brown et al. (1996), full citation provided in footnote 33.
[86] Brown et al. (1998), full citation provided in footnote 34.
[87] Brugnone et al. (1985), full citation provided in footnote 35.
[88] Brugnone et al. (1986), full citation provided in footnote 36.

differences (Csanady et al. 2000; Fennell and Brown 2001)[89,90] have provided additional insights into ethylene oxide toxicokinetics.

The overall literature indicates that ethylene oxide is distributed to all tissues rapidly after absorption and it readily binds to proteins (e.g., hemoglobin) and deoxyribonucleic acid (DNA) in tissues throughout the body (US EPA 2016a)[91]. Ethylene oxide metabolism occurs via two pathways (hydrolysis and glutathione conjugation), and both are considered to be detoxifying. The hydrolysis pathway, mediated by enzymatic (epoxide hydrolase; EH) and non-enzymatic means (Figure 1; IARC, 2008; ATSDR 2022)[92,93], is proposed to contribute to approximately 80%, 40%, and 20% of the ethylene oxide metabolism in humans, rats, and mice, respectively. This metabolic pathway leads to the step-wise formation of ethylene glycol, glycol aldehyde, glycolic acid, glyoxylic acid, and finally, oxalic acid, or formic acid and carbon dioxide.

The second pathway begins with glutathione conjugation of ethylene oxide via the glutathione-S-transferase (GST) enzyme. This conjugation is followed by metabolism to S-2-(hydroxyethylglutathione), and then S-2-(hydroxyethyl)cysteine, which can interconvert to S-(2-hydroxyethyl)-mercapturic acid (HEMA). S-2-(hydroxyethyl)cysteine is then metabolized to S-carboxymethylcysteine and thiodoacetic acid (Figure 1; IARC 2008; ATSDR 2022)[94,95]. GST-mediated metabolism rates are faster than EH-mediated ones by nearly two orders of magnitude in the rodent liver and approximately 2-fold in the human liver (Filser and Klein, 2018)[96]. Thus, rats and mice may be more likely to experience glutathione depletion, decreased capacity to rapidly detoxify ethylene oxide, and increased ethylene oxide concentrations in blood relative to humans at exposure concentrations > 100 ppm (182 mg/m^3; Filser and Klein 2018)[97].

[89] Csanady et al. (2000), full citation provided in footnote 37.
[90] Fennell and Brown (2001), full citation provided in footnote 38.
[91] US EPA (2016a), full citation provided in footnote 3.
[92] IARC (2008), full citation provided in footnote 22.
[93] ATSDR (2022), full citation provided in footnote 20.
[94] IARC (2008), full citation provided in footnote 22.
[95] ATSDR (2022), full citation provided in footnote 20.
[96] Filser and Klein (2018), full citation provided in footnote 39.
[97] *Ibid*.

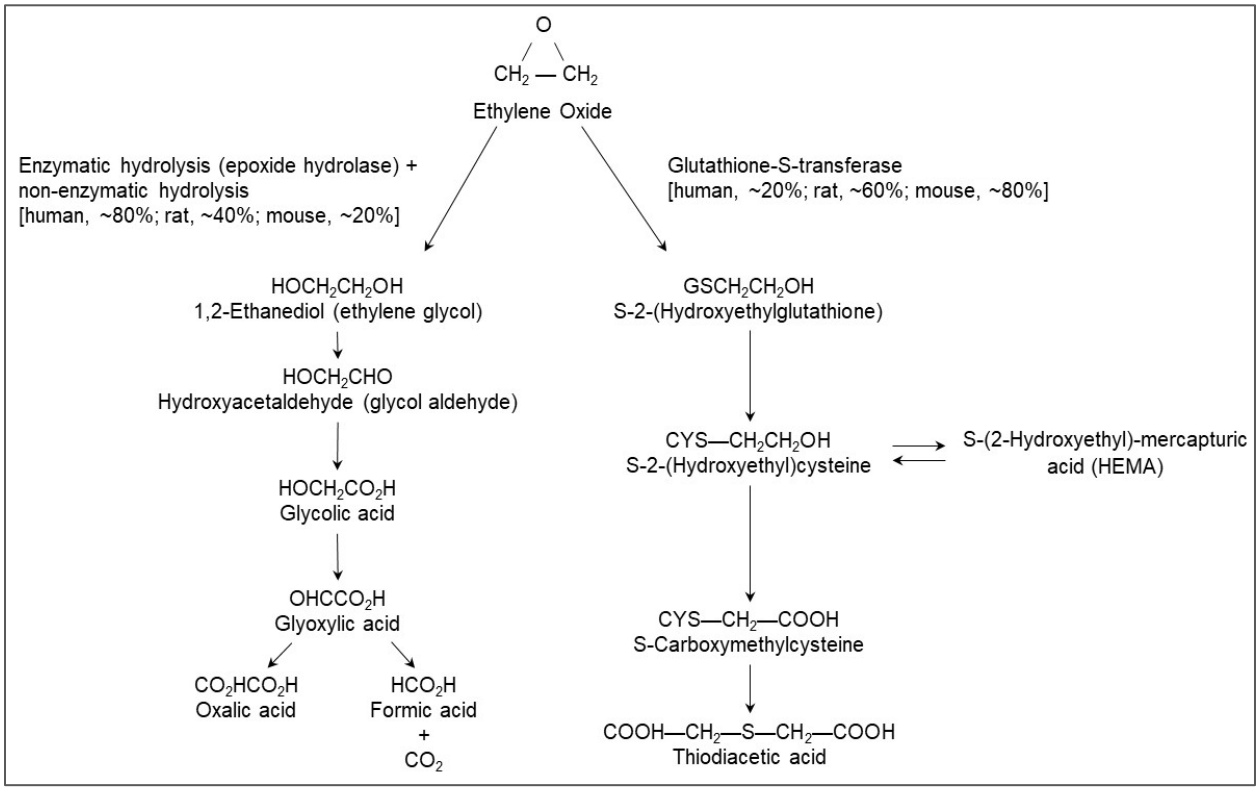

Figure 1. Proposed metabolic scheme for ethylene oxide. Adapted from IARC (2008)[98] and ATSDR (2022)[99].

Elimination of ethylene oxide is thought to follow first-order kinetics for exposures up to 200 ppm (365 mg/m^3). Thus, at ≤ 200 ppm (≤ 365 mg/m^3), the elimination of ethylene oxide depends upon its concentration in the body, and a constant fraction of ethylene oxide is eliminated per unit of time. Ethylene oxide elimination half-lives ($t_{1/2}$) in blood of approximately 40 minutes, 10–19 minutes, and 9 minutes were determined for humans exposed occupationally at 1 ppm (1.8 mg/m^3; Hattis 1987; Filser et al. 1992)[100,101], rats exposed at 100 ppm (182 mg/m^3) for 4 hours (Brown et al. 1996; Csanady et al. 2000)[102,103], and mice exposed at 1 ppm (1.8 mg/m^3) for 1 hour (Ehrenberg et al.

[98] IARC (2008), full citation provided in footnote 22.
[99] ATSDR (2022), full citation provided in footnote 20.
[100] Hattis (1987), full citation provided in footnote 40.
[101] Filser et al. (1992), full citation provided in footnote 41.
[102] Brown et al. (1996), full citation provided in footnote 33.
[103] Csanady et al. (2000), full citation provided in footnote 37.

1974)[104] or 100 ppm (182 mg/m^3) for 4 hours (Csanady et al., 2000)[105], respectively. Cumulatively, these studies suggest that ethylene oxide is eliminated faster in rats and mice than humans at exposure concentrations ≤ 100 ppm (182 mg/m^3).

Physiologically-based pharmacokinetic (PBPK) models[106] of ethylene oxide have shown comparable blood concentrations across humans, rats, and mice over a limited exposure range (Fennell and Brown 2001; Csanady et al. 2000)[107,108]. The model simulations of peak blood ethylene oxide concentrations and areas under the curves (AUCs, i.e., the total internal dose over time) in humans, rats, and mice exposed at ≤ 100 ppm (182 mg/m^3) are approximately equal and linearly related to the inhaled ethylene oxide concentrations (US EPA 2016a)[109]. Because the animal cancer potency is based on intake in mg/kg-day, the default interspecies scaling factor, which accounts for both the toxicokinetic and toxicodynamic components, has been applied.

Endogenous Production of Ethylene Oxide

Endogenous production of ethylene oxide is known to result from ethylene metabolism in humans and other mammals (Filser et al., 2013)[110]. The production of ethylene within living organisms has been shown to occur via lipid peroxidation; enzyme-, copper-, or iron-catalyzed oxidative destruction of methionine or oxidation of hemoglobin; and metabolism of intestinal bacteria (Csanady et al., 2000)[111]. Thus, all species and individuals are likely to be exposed to ethylene oxide endogenously irrespective of their exogenous exposures to ethylene oxide in the air (Kirman et al., 2021)[112].

Measurements of specific hemoglobin adduct levels, such as N-2-hydroxyethylvaline (HEV), in humans or other species reflect the integrated exposure to ethylene (endogenous + exogenous) and ethylene oxide (endogenous + exogenous). Kirman et al. (2021)[113] showed background exposures to ethylene oxide and ethylene in ambient air alone are insufficient to account for HEV levels seen in non-smokers, and endogenous ethylene oxide production contributes more to non-smoker HEV levels than

[104] Ehrenberg et al. (1974), full citation provided in footnote 42.
[105] Csanady et al. (2000), full citation provided in footnote 37.
[106] Alternatively, these models are called physiologically based toxicokinetic (PBTK) models.
[107] Fennell and Brown (2001), full citation provided in footnote 38.
[108] Csanady et al. (2000), full citation provided in footnote 37.
[109] US EPA (2016a), full citation provided in footnote 3.
[110] Filser et al. (2013), full citation provided in footnote 43.
[111] Csanady et al. (2000), full citation provided in footnote 37.
[112] Kirman et al. (2021), full citation provided in footnote 44.
[113] *Ibid*.

ambient ethylene oxide and ethylene exposures do. The ethylene oxide exposures from ambient and endogenous sources contribute to HEV levels, other adduct levels, and cumulative cancer risks (i.e., including from other chemicals and conditions). Thus, ethylene oxide and ethylene exposures are part of the risk factors accounting for the background cancer risk in the general population, including lymphoid and breast cancers (US EPA, 2016a; 2016b)[114,115].

Kirman et al. (2021)[116] cite data on hemoglobin adducts in smokers and nonsmokers to argue that the cancer potency of ethylene oxide is low at low levels of exposure. Their argument rests on a supposed lack of association between tobacco smoking and either lymphoid cancer or breast cancer, which they state would be inconsistent with mean adduct levels that are 7.5-fold higher in smokers than in nonsmokers. IARC (2012)[117], however, did find a positive association between tobacco smoking and breast cancer, though not for lymphoid cancer. Since the IARC review, new results from two large prospective cohort studies have found significant associations with lymphoid cancer. The American Cancer Society Cancer Prevention Study II identified 1926 non-Hodgkin lymphoma cases in a cohort of 152,958 men and women (Diver et al. 2012)[118]. The study found an association between current smoking and non-Hodgkin lymphoma in women (RR = 1.37, 95% confidence interval (CI) = 1.04–1.81), with a positive trend for years smoked ($p < 0.01$). The UK Million Women Study identified 7047 lymphoid cancers in a cohort of 1.3 million women (Kroll et al. 2012)[119]. This study found associations between tobacco smoking and Hodgkin lymphoma (RR = 1.45 per 10 cigarettes/day, 95% CI = 1.22–1.72) and mature T-cell malignancies (RR = 1.38, 95% CI = 1.10–1.73). These large cohort findings support the plausibility of increased cancer risks from low concentrations of ethylene oxide.

The ethylene oxide cancer potency estimate derived from the NIOSH epidemiological study (see Section “Estimation of Cancer Potency” of this document) is based on excess risk. In other words, the human CSF expresses risk over and above the

[114] US EPA (2016a), full citation provided in footnote 3.
[115] US EPA (2016b), full citation provided in footnote 9.
[116] Kirman et al. (2021), full citation provided in footnote 44.
[117] IARC (2012), full citation provided in footnote 18.
[118] Diver WR, Patel AV, Thun MJ, Teras LR, Gapstur SM (2012). The association between cigarette smoking and non-Hodgkin lymphoid neoplasms in a large US cohort study. Cancer Causes Control 23(8):1231-40.
[119] Kroll ME, Murphy F, Pirie K, Reeves GK, Green J, Beral V; Million Women Study Collaborators (2012). Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. Br J Cancer 107(5):879-87.

background risk. The background risk includes cancer risk due to endogenous exposures to ethylene oxide. Thus, in the case of ethylene oxide, the CSF is meant for use in computing risk levels associated with non-zero exogenous exposures (i.e., ambient air concentrations > 0 ppm). The dose-response relationship for endogenous ethylene oxide exposures within the homeostatic range might be different from the dose-responses seen with ambient exposures, possibly sublinear but ultimately unknown[120].

Genotoxicity

Studies on the genotoxicity of ethylene oxide have been reviewed by US EPA[121], several IARC monographs[122,123,124] , and ATSDR[125]. These studies were conducted in a variety of *in vitro* and *in vivo* systems, with and without metabolic activation, and some were observational studies in exposed workers. US EPA[126] has summarized the numerous papers investigating the genotoxicity of ethylene oxide and concluded in its Executive Summary that there is:

> "clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity."

In summarizing the evidence for genotoxicity, US EPA[127] stated:

> "In prokaryotes and lower eukaryotes, EtO induced DNA damage and gene mutations in bacteria, yeast, and fungi and gene conversions in yeast. In mammalian cells (from *in vitro* and/or *in vivo* exposures), EtO-induced effects include unscheduled DNA synthesis, DNA adducts, gene mutations, sister chromatid exchanges (SCEs), micronuclei, and chromosomal aberrations. Genotoxicity, in particular increased levels of SCEs and chromosomal aberrations, has also been observed in blood cells of workers occupationally exposed to EtO."

[120] US EPA (2016a), full citation provided in footnote 3.
[121] *Ibid*.
[122] IARC (1994), full citation provided in footnote 21.
[123] IARC (2008), full citation provided in footnote 22.
[124] IARC (2012), full citation provided in footnote 18.
[125] ATSDR (2022), full citation provided in footnote 20.
[126] US EPA (2016a), page 1-1, full citation provided in footnote 3.
[127] US EPA (2016a), page 3-28, full citation provided in footnote 3.

In its most recent Monograph on ethylene oxide, IARC (2012) summarizes the evidence (shown in Table 3) and states the following regarding genotoxicity of ethylene oxide[128]:

> "There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, operates by a genotoxic mechanism. A dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts has been observed in exposed humans and rodents, and a dose-related increase in the frequency of ethylene oxide-derived DNA adducts has been demonstrated in exposed rodents. Ethylene oxide consistently acts as a mutagen and clastogen at all phylogenetic levels, it induces heritable translocations in the germ cells of exposed rodents, and a dose-related increase in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers."

Table 3. Comparison of the evidence for key events – cytogenetic, genetic, and related changes – induced by ethylene oxide in humans, human cells, and experimental animals (table taken directly from IARC 2012, citing IARC 2008)

Endpoint	*In vivo* exposure		*In vitro* exposure
	Animals	Humans	Human cells
Haemoglobin-adduct formation	Strong	Strong	Strong
DNA-adduct formation	Strong	Weak[a]	Strong
Mutations in reporter genes in somatic cells	Strong	Weak[a]	Strong
Mutations in cancer-related genes in tumors	Strong	NR	Not applicable
Increased levels of cancer-related proteins in tumors	Strong	NR	Not applicable
Cytogenetic alterations in somatic cells			
Sister chromatid exchange	Strong	Strong	Strong
Structural chromosomal aberrations	Strong[b]	Strong	Moderate
Micronucleus formation	Strong[b]	Strong	NR

[a] Possibly due to a lack of adequate studies

[b] Positive responses were seen only at exposure concentrations above those used in the rodent cancer-bioassays

NR, not reported

[128] IARC (2012), page 395-396, full citation provided in footnote 18.

In its most recent toxicological profile for ethylene oxide, ATSDR[129] concluded that:

> "Ethylene oxide has been demonstrated to be genotoxic in human and animal studies *in vivo* and in a wide variety of test systems *in vitro*."
>
> "Available data collectively demonstrate the mutagenicity and clastogenicity of ethylene oxide both *in vitro* and *in vivo*. Ethylene oxide induced gene mutation, chromosomal aberrations, sister chromatid exchange, micronucleus formation, deoxyribonucleic acid (DNA) strand breaks, unscheduled DNA synthesis, and cell transformation *in vitro*. Ethylene oxide induced gene mutation, specific locus mutation, chromosomal aberrations, sister chromatid exchange, micronucleus formation, dominant lethal mutation, and heritable translocation in test species and/or occupationally-exposed humans. Although some conflicting results were observed in occupational studies, results of human studies support that ethylene oxide is genotoxic in humans."
>
> "In addition to these genotoxic effects, *in vitro* studies in mammal tissues, *in vivo* studies in rats and mice, and studies in humans have demonstrated the formation of DNA adducts. Ethylene oxide is an alkylating agent that forms adducts with DNA, ribonucleic acid (RNA), and proteins."

In the updated literature search, OEHHA identified three genotoxicity studies published since 2016, with two studies in humans (one in workers[130] and one in children[131]) and a third study in Big Blue mice[132]. In one study[133], workers exposed to a mixture of chemicals including ethylene oxide showed significantly greater chromosomal damage and instability in peripheral blood lymphocytes (measured as micronuclei, nuclear buds, and nucleoplasmic bridges) than workers not exposed to these chemicals. The strict use of personal protective equipment for eight months diminished levels of micronuclei and DNA damage (measured by comet assay) in the peripheral blood lymphocytes from these workers. The second study[134] was conducted using peripheral blood samples (n = 51) collected from school-age children performed by the Swedish National Food Agency. The study found that the frequency of micronuclei formation was positively associated with levels of ethylene oxide hemoglobin adducts in erythrocytes. The third

[129] ATSDR (2022), full citation provided in footnote 20.
[130] Zeljezic et al. (2016), full citation provided in footnote 30.
[131] Carlsson et al. (2017), full citation provided in footnote 31.
[132] Manjanatha et al. (2017), full citation provided in footnote 32.
[133] Zeljezic et al. (2016), full citation provided in footnote 30.
[134] Carlsson et al. (2017), full citation provided in footnote 31.

publication[135] reported additional data from an earlier study[136] conducted in Big Blue mice and found a statistically significant increase in mutational frequency of the *cII* gene in lung tissues from mice exposed for 8 or 12 weeks to 200 parts per million (ppm) ethylene oxide via inhalation. Findings from these additional studies are consistent with the overall evidence for the genotoxicity of ethylene oxide.

Estimation of Cancer Potency

The NIOSH Epidemiological Study

OEHHA thoroughly evaluated the NIOSH study that US EPA used to calculate the unit risk value. The NIOSH study was a retrospective cohort study of more than 18,000 workers exposed to ethylene oxide at 14 US sterilization facilities[137,138]. One of the small facilities lacked exposure estimates (n=705, 4% of the cohort), and was excluded, leaving 17,530 male and female workers for the exposure-response analyses. Most exposed workers were involved with sterilizing medical supplies and treating spices, and in the manufacture and testing of medical sterilizers. Both mortality (including lymphoid cancer mortality) and breast cancer incidence were assessed. The cohort was assembled by NIOSH and included all employees who worked at least 3 months (for the mortality analyses) or 12 months (for the breast cancer incidence analyses) at one of the included facilities. Each participant's ethylene oxide exposure was estimated using a validated multiple regression exposure model that incorporated information on workplace air measurements, sterilization unit size, engineering controls, timing of sterilization, product type, calendar year, and historical process changes. The workplace air measurements included 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired between 1976 and 1985 from 18 different sterilization facilities. Further details on the exposure model can be found elsewhere[139,140,141,142]. Cancer or mortality follow-up was through December 31, 1998,

[135] Manjanatha (2017), full citation provided in footnote 32.
[136] Parsons BL, Manjanatha MG, Myers MB, et al. (2013). Temporal changes in K-*ras* mutant fraction in lung tissue of Big Blue B6C3F$_1$ mice exposed to ethylene oxide. Toxicol Sci 136(1), 26-38.
[137] Steenland et al. (2004), full citation provided in footnote 10.
[138] Steenland et al. (2003), full citation provided in footnote 11.
[139] US EPA (2016a), full citation provided in footnote 3.
[140] Hornung RW, Greife AL, Stayner LT, et al. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. Am J Ind Med 25(6):825-36.
[141] Steenland et al. (2004), full citation provided in footnote 10.
[142] Steenland et al. (2003), full citation provided in footnote 11.

the date of death or breast cancer diagnosis, or the date of loss to follow-up, whichever was earlier.

US EPA judged the NIOSH study to be of "high quality" based on the availability of quantitative exposure estimates for individual workers, high-quality exposure assessment, longitudinal study design, large sample size, inclusion of males and females, adequate follow-up, absence of known confounding exposures, multiple study locations, and the use of internal comparison groups. OEHHA reviewed the NIOSH study using the Hill guidelines for causal inference and the National Toxicology Program (NTP)'s risk of bias tool[143,144], and also concluded that this study is of high quality, and unlikely to be affected by important bias or confounding.

Lymphoid Cancer Mortality

For the mortality portion of the NIOSH study, information on causes of death was obtained from the National Death Index, the Social Security Administration, and the Internal Revenue Service. The all-cause and all-cancer standardized mortality ratios (SMRs) for the cohort as a whole (regardless of ethylene oxide exposure levels) were 0.90 (95% CI = 0.88–0.93) and 0.98 (95% CI = 0.92–1.03), respectively[145]. The study identified 53 deaths due to lymphoid cancer (International Classification of Diseases 9th revision codes 200, 202, 203, and 204). Lymphoid cancer was a particular focus of this study since it was shown to be elevated in an earlier analysis of this cohort[146].

Each lymphoid cancer death was matched to 100 randomly selected controls based on race, sex, and date of birth. No other major potential confounders were identified. Males and females were combined in the analyses used by US EPA since ethylene oxide-associated relative risks were elevated in both sexes, and the difference between sexes was not statistically significant. In initial analyses, the NIOSH researchers calculated results using different lag periods, and found that the best fitting exposure-response models were those that used a 15-year lag. A lag period is a period before death or the end of follow-up during which any workplace ethylene oxide exposure that occurred is not included in the analysis. Lag periods are used to account for the fact that many

[143] Hill AB (1965). The environment and disease: association or causation? Proc R Soc Med 58:295-300.
[144] National Toxicology Program (NTP 2019). Risk of Bias Tool. National Toxicology Program. https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/riskbias/index.html. Accessed: 10/13/21.
[145] Steenland et al. (2004), full citation provided in footnote 10.
[146] Stayner L, Steenland K, Greife A, et al. (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. Am J Epidemiol 138(10):787-98.

occupationally or environmentally caused cancers are not diagnosed until many years after exposure begins[147,148,149,150].

The results for lymphoid cancer mortality using a 15-year lag and an internal comparison group are shown in Table 4. Internal comparisons between exposure subgroups within a cohort are conducted to better control for confounding since lifestyle and health status at hire (potential confounders) may be more similar within the cohort than compared to the general population[151].

The average duration of exposure was 8.7 years, the average follow-up was 26.8 years, and the average cumulative exposure was 27 ppm-days. As seen in Table 4, odds ratios (ORs) were greater than 1.0 in all non-reference categories of exposure. The ORs increased from the lowest (>0–1,200 ppm-days; OR = 1.75) to the second lowest non-reference exposure category (1201–3680 ppm-days; OR = 3.15) and appeared to plateau in the exposure categories above this. US EPA noted that plateaus like this have been seen for other carcinogens and may be due to factors like the depletion of susceptible subpopulations, mismeasurement at higher exposures, or the healthy worker survivor effect[152]. The NIOSH researchers noted that peak and average exposure did not predict cancer risk as well as cumulative exposure although detailed results for these metrics were not provided.

[147] Archer VE, Coons T, Saccomanno G, Hong DY (2004). Latency and the lung cancer epidemic among United States uranium miners. Health Phys 87(5):480-9.
[148] Lipfert FW, Wyzga RE (2019). Longitudinal relationships between lung cancer mortality rates, smoking, and ambient air quality: a comprehensive review and analysis. Crit Rev Toxicol 49(9):790-818.
[149] Marshall G, Ferreccio C, Yuan Y, et al. (2007). Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst 99(12):920-8.
[150] Selikoff IJ, Hammond EC, Seidman H (1980). Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 46(12):2736-40.
[151] McNamee R (2003). Confounding and confounders. Occ Env Med 60:227-234.
[152] US EPA (2016b), full citation provided in footnote 9.

Table 4. Odds ratios for lymphoid cancer mortality by categories of cumulative ethylene oxide exposure, males and females combined, 15-year exposure lag[153]

Cumulative exposure (ppm-days)[a]	Odds ratio[b]	95% CI	Cases (N)
0	1.00	Reference	9
>0–1200	1.75	0.59–5.25	10
1201–3680	3.15	1.04–9.49	11
3681–13500	2.44	0.80–7.50	10
>13500	3.00	1.02–8.45	13

N, number of lymphoid cancer deaths; ppm, parts per million

[a] 15-year exposure lag

[b] Adjusted or matched on age, sex, and race

Lymphoid Cancer Exposure-Response

The 1998 follow-up NIOSH study results for lymphoid cancer mortality were first published by the study authors in a peer-reviewed scientific journal in 2004[154]. Since that time, US EPA contracted with the study authors to perform additional exposure-response modeling and other analyses on these data[155]. This work included performing linear and log-linear exposure-response models; weighted linear regressions of categorical data; linear regression spline models (analyses where the slope is allowed to change at one or more points (or "knots") along the exposure range); exposure-response models using different lag periods and different mathematical transformations of the exposure variable (e.g., the logarithm or the square root of cumulative exposure); and multiple sensitivity analyses. Spline models are particularly useful for exposure-response data like those shown in Table 4 where relative risk estimates initially increase with increasing exposure but tend to plateau at higher exposures. The ultimate goal of this work was to identify the most appropriate model for cancer unit risk calculations. US EPA's objectives for final model selection included using individual data instead of categorical data, good fit in the lower exposure ranges, parsimony, biologic plausibility, and other statistical considerations.

Overall, based on the objectives listed above, US EPA concluded that a two-piece linear regression spline model with a knot at 1600 ppm-days provided the best biologically plausible fit to the underlying NIOSH study data, especially in the lower exposure

[153] US EPA (2016a), full citation provided in footnote 3.
[154] Steenland et al. (2004), full citation provided in footnote 10.
[155] US EPA (2016a), full citation provided in footnote 3.

region. An adequate fit in these lower exposure regions was a major priority since the goal of this work was to estimate cancer risks at more common, lower, general population exposure levels. Other models, including the log-linear models (e.g., Cox regression), the models using categorical data, and the models using exposure transformations generally resulted in sublinear or supra-linear exposure-response slopes that appeared to either dramatically over- or under-predict the actual study results, especially in the lower exposure ranges. Sensitivity analyses examining different knots in the two-piece spline model resulted in either higher Akaike information criterion (AIC) scores (i.e., worse fit) or too few cancer cases below the knot. Sensitivity analyses of different lag periods found the best likelihood result, lowest AIC score, and lowest *p*-value occurred at a lag period of 15 years. The lower slope of the two-piece spline model (i.e., the exposure-response slope below the knot at 1600 ppm) was 7.58 × 10^{-4} excess relative risk per ppm-days, with a 95% one-sided upper bound of 2.98 × 10^{-3} excess relative risk per ppm-days.

OEHHA did not have access to the individual data from the NIOSH study, primarily due to privacy concerns. However, OEHHA was able to evaluate a number of exposure-response models using the publicly available categorical data provided in either the 2004 scientific publication or in the US EPA document[156,157]. These models included weighted linear regressions, weighted least squares regressions, and generalized least squares regressions[158,159]. These involved both linear and log-linear models, transformed (e.g., the logarithm of cumulative exposure) and untransformed exposure variables, and models including and excluding the highest exposure categories. Overall, OEHHA found that none of the models it evaluated fit the underlying NIOSH study data as well as the two-piece linear spline model selected by US EPA. OEHHA also considered running various exposure-response analyses using US EPA's Benchmark Dose Software (BMDS)[160]. However, the available data were presented as ORs, which were calculated by matching 100 randomly selected controls to each lymphoid cancer death. Although this methodology provides efficient and reliable estimates of relative

[156] Steenland et al. (2004), full citation provided in footnote 10.
[157] US EPA (2016a), full citation provided in footnote 3.
[158] Orsini N, Bellocco R, Greenland S (2006). Generalized least squares for trend estimation of summarized dose–response data. The Stata Journal 6(1):40-57.
[159] Haneuse S (2021). Chapter 20, Regression Analysis Part I: Model Specification and Chapter 21, Regression Analysis Part II: Model Fitting and Assessment. In TL Lash, TJ VanderWeele, S Haneuse, K Rothman (Eds.), Modern epidemiology (4th ed). Lippincott Williams & Wilkins., Philadelphia, PA.
[160] US EPA Benchmark Dose Software (BMDS) Version 3.3. National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds.

risk[161], these ORs cannot be readily used in the BMDS, which requires information on absolute risks or rates. In summary, after an extensive and thorough evaluation of a number of different models and methodologies, OEHHA concluded that the US EPA's two-piece linear spline model with a knot at 1600 ppm-days provides the most appropriate and best fitting model for assessing the lower exposure lymphoid cancer risks of ethylene oxide.

Lymphoid Cancer Unit Risk Calculations

US EPA used the results of the two-piece linear spline model discussed above in an actuarial program (life-table analysis) to estimate the exposure concentration corresponding to an extra risk of 1% (EC_{01}). The exposure-response slope below the model knot was used in these calculations since the goal was to estimate cancer risks at lower, general population exposures. The life table approach was used because it takes into account other causes of mortality and accounts for the fact that baseline rates of lymphoid cancer vary by age. The occupational exposure levels reported in the NIOSH study were converted to lifetime (70-year) environmental exposure levels by making adjustments for the amount of air breathed per day (20 versus 10 m^3/day) and the number of days exposed per year (365 versus 240 days/year). The EC_{01} and its one-sided lower 95% confidence bound (the LEC_{01}) were 1.98×10^{-2} ppm and 5.03×10^{-3}, respectively.

The LEC_{01} was used as the point of departure (POD), and linear extrapolation from the POD was used to derive the cancer unit risk estimates. US EPA evaluated a variety of evidence for non-linearity but judged that this evidence was inadequate. As noted by US EPA[162],

> "Because EtO is DNA reactive and has direct mutagenic activity (see Section 3.3.3), which is one of the cases cited by the EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) for the use of linear low-dose extrapolation, a linear low-exposure extrapolation was performed. (Linear low-exposure extrapolation is also the default approach used in the absence of sufficient evidence for a nonlinear mode of action, which is also the case for EtO [see Section 3.4])."

[161] Steenland K, Deddens JA (1997). Increased precision using countermatching in nested case-control studies. Epidemiology 8(3):238-42.
[162] US EPA (2016a), full citation provided in footnote 3.

The resulting cancer unit risk estimate was 1.99 excess risk per ppm of ethylene oxide exposure. However, this estimate is based on cancer mortality, not cancer incidence, which is more common. In order to provide cancer unit risk estimates for lymphoid cancer incidence, US EPA assumed that the exposure-response relationship for lymphoid cancer incidence is the same as that for lymphoid cancer mortality. Based on this assumption, baseline rates of lymphoid cancer incidence from the US Surveillance, Epidemiology, and End Results Program (SEER) for both sexes and all races were used in the life table analysis[163]. This resulted in an EC_{01} and LEC_{01} of 7.48×10^{-3} and 1.90×10^{-3} ppm, respectively, and a cancer unit risk for lymphoid cancer incidence of **5.26 per ppm**. OEHHA replicated these life table and unit risk calculations and obtained the same result.

A 1% extra risk level was selected for the calculations described above because it is commonly used to determine the POD for low-exposure extrapolation from epidemiological cancer data involving non-rare cancers. A 10% excess risk level (EC_{10}) is also commonly used. 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 EC_{01} or an EC_{10} (or their respective lower 95% CIs) would give the same cancer unit risk.

Breast Cancer Incidence

The breast cancer portion of the NIOSH study involved 7,576 women and 319 cases of incident breast cancer[164]. The study included females who were employed for at least one year at any one of the participating facilities. Incident cases of breast cancer were ascertained through participant interviews, medical records reviews, state cancer registries, and death certificates. One hundred controls were matched to each case based on age and race. The final results used by US EPA in its exposure-response analyses were limited to the 5,139 women and 233 cases who provided interviews or had a next of kin who could. Twenty cases were carcinoma *in situ* but analyses with and without these *in situ* cases led to very similar results. The advantages of limiting the analyses to those with interviews were the availability of interview information on other breast cancer risk factors and more complete case ascertainment. Results were adjusted for year of birth, parity, and family history of breast cancer. Information on body

[163] Howlader N, Noone AM, Krapcho M, et al. (2014). SEER cancer statistics review, 1975-2012. Bethesda, MD: National Cancer Institute https://seer.cancer.gov/archive/csr/1975_2012/. Accessed: 10/16/22.
[164] Steenland et al. (2003), full citation provided in footnote 11.

mass index, age at menopause, age at menarche, socioeconomic status, and diet was collected during the interviews but these factors were not strongly related to breast cancer in this study. As noted above, US EPA deemed the NIOSH study to be of "high quality", and OEHHA's evaluations of this study led to the same conclusion.

The NIOSH study results for breast cancer incidence are presented in Table 5. The average duration of exposure was 10.7 years and the median cumulative ethylene oxide exposure was 8.6 ppm-years. In models using a 15-year lag, there were 62 breast cancer cases in the reference exposure category. The number of cases in the other exposure categories was not provided. However, given that the standard errors for the ORs in these other categories were very similar, the numbers of cases in each of these categories are likely similar as well (e.g., approximately 34–35 cases each). As seen in Table 5, ORs for breast cancer were greater than 1.0 in all non-reference categories except the second from the lowest. The upper CI of 1.60 for the OR in this category highlights the possibility that relative risks could be elevated in this category as well. The OR in the highest exposure category was statistically significant (OR = 1.87; 95% CI = 1.12–3.10).

Table 5. Odds ratios for breast cancer incidence in females by categories of cumulative ethylene oxide exposure, 15-year exposure lag[165]

Cumulative exposure (ppm-days)[a]	Odds ratio[b]	95% CI
0	1.00	Reference
>0–647	1.06	0.66–1.71
647–2026	0.99	0.61–1.60
2026–4919	1.24	0.76–2.00
4919–14620	1.42	0.88–2.29
>14620	1.87	1.12–3.10

[a] 15-year exposure lag

[b] Adjusted for year of birth, parity, and family history of breast cancer; matched on age and race

Breast Cancer Exposure-Response and Unit Risk Calculations

The NIOSH breast cancer findings were originally published in a peer-reviewed scientific journal in 2003[166]. As with lymphoid cancer mortality, US EPA contracted with the original study authors to perform additional exposure-response models and other

[165] Steenland et al. (2003), full citation provided in footnote 11.

[166] *Ibid*.

assessments. Exposure-response models in the original publication or in the work for US EPA included a combination of linear and log-linear models, models using continuous or categorical exposure data, regression splines, models with and without exposure variable transformation, and models using different exposure metrics (e.g., cumulative exposure, exposure duration, average, and peak). Based on the same objectives cited above for lymphoid cancer, US EPA selected the two-piece linear spline regression model involving individual exposure data, cumulative exposure, a 15-year exposure lag, and a knot at 5750 ppm-days. Models using peak and average exposure did not fit the data as well. Model fit using duration of exposure were somewhat better than those using cumulative exposure. However, as noted by US EPA, "…duration is less useful for estimating unit risks and the cumulative exposure models also provided statistically significant fits to the data".

The lower slope of the two-piece linear spline model selected by US EPA was 8.98×10^{-5} excess relative risk per ppm-days, with a 95% one-sided upper bound of 1.84×10^{-4} excess relative risk per ppm-days. This slope was about 8-times lower than the corresponding slope for lymphoid cancer mortality (regression slope = 7.58×10^{-4}; 95% one-sided upper bound of 2.98×10^{-3}). This model had a low *p*-value (*p*-value = 0.01) and a good visual fit, especially in the lower exposure ranges. Another advantage of this model is that it involved the use of individual rather than categorical exposure data. In addition, the linear nature of the model avoids the complexity that some of the other models would introduce into the unit risk calculations. While a few of the other models gave somewhat lower *p*-values or somewhat lower AIC scores (e.g., analyses using a 20-year exposure lag), these differences were relatively small and other models did not provide as good of a fit in the lower exposure regions.

As with lymphoid cancer mortality, OEHHA did not have the individual data for the breast cancer portion of the NIOSH study. However, OEHHA was able to evaluate a number of exposure-response models using the published publicly available categorical data. None of the models evaluated by OEHHA resulted in a better visual fit or had lower *p*-values than the two-piece linear regression model selected by US EPA. Overall, OEHHA concluded that US EPA's two-piece linear spline model is the most appropriate exposure-response model for estimating the lower exposure breast cancer risks of ethylene oxide.

US EPA used the lower portion of the two-piece linear spline model in the same actuarial program described above for lymphoid cancer to calculate the EC_{01} and LEC_{01} for breast cancer incidence. US mortality rates for females and US incidence rates for

breast cancer from SEER were used in these calculations. The EC_{01} and LEC_{01} were 1.38×10^{-2} and 6.75×10^{-3} ppm, respectively. As with lymphoid cancer, linear extrapolation from the LEC_{01} was used to estimate risks at lower exposures. The resulting cancer unit risk estimate for breast cancer was **1.48 per ppm.**

Total Cancer Risk Estimates

US EPA combined the cancer unit risk estimates for lymphoid (both sexes) and breast cancer (females). As described by US EPA[167],

> "According to the EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), cancer risk estimates are intended to reflect total cancer risk, not site-specific cancer risk; therefore, an additional calculation was made to estimate the combined risk for (incident) lymphoid and breast cancers because females would be at risk for both cancer types. The unit risk estimates for both of the individual models for these cancers were derived from linear [Relative Risk] RR models and are based on profile likelihood upper-bound estimates of the regression coefficient (Langholz and Richardson 2010). It was not possible to derive the total cancer unit risk estimate using a profile likelihood approach; thus, a Wald approach was employed to estimate the combined risk."

This approach yielded a combined cancer unit risk estimate of **6.1 per ppm** (6.1×10^{-3} per ppb; 3.3×10^{-3} per μg/m^3), with lymphoid cancer contributing about 75–80% of the total. The corresponding cancer potency factor, also known as the cancer slope factor (CSF), is 12 per mg/kg-day, and is calculated from the total cancer unit risk using the following equation[168]:

$$CSF = \frac{UR \times 70\ kg \times CF}{20\ m^3}$$

where 70 kg is the reference human body weight, 20 m^3 is the reference human inspiration rate/day, and CF is the conversion factor from mg to μg (= 1000).

[167] US EPA (2016a), full citation provided in footnote 3.
[168] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. Available from: https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009.

The cancer unit risk describes the excess cancer risk associated with an inhalation exposure to a concentration of 1 μg/m^3 of a given chemical; the CSF describes the excess cancer risk associated with exposure to 1 mg of a given chemical per kilogram of body weight[169].

Additional Evaluations of Bias

OEHHA performed a number of quantitative and qualitative evaluations of potential biases and errors in the NIOSH study. Analyses of chance, confounding, and selection bias suggested that these issues did not introduce major errors into the NIOSH study results. Other potential biases of particular focus of OEHHA were exposure misclassification and the healthy worker effect. With regards to exposure misclassification, the NIOSH study authors used a validated exposure model that accounted for 85% of the variance in an independent set of ethylene oxide sampling data, a level that is generally considered very good for retrospective exposure models of this type[170]. In addition, because exposure was assessed using the same model in all participants, much of the misclassification of exposure was likely non-differential (i.e., at roughly similar levels in cancer cases as in controls). This type of non-differential error most commonly biases relative risk estimates towards the null and not towards the positive associations reported in the NIOSH study.

OEHHA also evaluated the possibility that the inclusion of workers with higher intensity exposures but short exposure durations may affect the generalizability of the NIOSH study findings to the general population, where these types of high intensity exposures are likely to be quite rare. Workers with this type of exposure scenario (high intensity-short duration) would most likely end up in the middle categories of cumulative exposure, and this might be the reason why relative risks were elevated in these categories but tended to plateau at higher exposures. The likely magnitude of this potential issue was evaluated by estimating case and control counts in each exposure category, then recalculating ORs and exposure-response slopes after excluding various percentages of participants (e.g., 10–30% high intensity-short duration exposed workers) in the middle exposure categories. A range of percentages was assessed since data on the true percentage was not publicly available. In an attempt to simulate the removal of workers with high intensity exposures (and therefore possibly higher risks), exclusions were done at the case:control ratio equal to or slightly lower than that

[169] OEHHA (2009), full citation provided in footnote 168.
[170] Hornung et al. (1994), full citation provided in footnote 140.

reported in the highest exposure category (where almost all workers probably had at least some high intensity exposure). Overall, these exclusions (with and without replacing the excluded participants into the highest category) had little impact on exposure-response slopes (e.g., 10% or less). This suggests that this issue did not have a major effect on the unit risk calculations or the generalizability of the NIOSH findings.

Bogen *et al.* (2019) have suggested that exposures occurring prior to 1978 (the first year that ethylene oxide sampling data were available) may have been dramatically under-predicted by the NIOSH exposure model[171]. However, as noted by these authors, a number of assumptions were used in their assessment, and the information used to support these assumptions, "were limited in scope and quantitative detail". In addition, the authors were unable to validate their pre-1978 predictions since no actual worker measurements were available from that time. Overall, because of these and other weaknesses, the accuracy of the Bogen et al. (2019) assessment is unknown.

OEHHA evaluated two aspects of the healthy worker effect: the healthy hire effect and the healthy worker survivor effect[172]. The healthy hire effect is based on the finding that people who work tend to be healthier than the general population (which includes a number of people who do not work because of illness). This effect tends to bias relative risk estimates in occupational studies like the NIOSH study downwards. Importantly, this bias is unlikely to have affected the NIOSH study results used by US EPA since these results were based on an internal reference group, that is, a reference group of other workers. The healthy worker survivor effect is based on the finding that long-term workers generally have lower mortality rates than those who leave worker earlier. This effect also tends to bias relative risk estimates downwards, and most likely affects workers in the highest categories of cumulative exposure. An evaluation of the impact of healthy worker survivor bias in this cohort was published by NIOSH in 2020[173]. Adjustment for employment duration in mortality analyses resulted in statistically significant and stronger associations between cumulative ethylene oxide exposure and female breast cancer and hematopoietic cancer[174]. Importantly though, US EPA used the lower slope of a two piece regression spline for its unit risk calculations, and this

[171] Bogen KT, Sheehan PJ, Valdez-Flores C, 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).
[172] Arrighi HM, Hertz-Picciotto I (1994). The evolving concept of the healthy worker survivor effect. Epidemiology 5(2):189-96.
[173] Park RM (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. Am J Ind Med 63(7):577-588.
[174] *Ibid*.

slope is heavily influenced by workers in the lower, not higher, categories of cumulative exposure. In addition, OEHHA performed a number of quantitative analyses exploring the likely magnitude of this potential bias (e.g., lowering the excess OR in the highest exposure category by 10–30%). Overall, OEHHA found that the potential impacts of this bias would be relatively minor (e.g., decreases in exposure-response slopes of 10% or less) and would most likely have only small impacts on cancer unit risks.

Considerations regarding the TCEQ Assessment

In 2020, the Texas Commission on Environmental Quality (TCEQ) published a risk assessment document for ethylene oxide in which they calculated an upper bound inhalation cancer unit risk factor of 2.5×10^{-3} per ppm (unadjusted for age-dependent adjustment factors) (TCEQ 2020)[175]. This unit risk is markedly lower than the corresponding value of 6.1 per ppm established by the US EPA (2016a)[176], in part because of TCEQ's choice of model and lack of consideration of breast cancer. US EPA has reviewed the TCEQ unit risk value and rejected it for a number of reasons, saying there were "flawed calculations and inappropriate assumptions"[177,178].

TCEQ exclusion of breast cancer

Both the TCEQ and the US EPA unit risk calculations were based on findings from the NIOSH cohort of US sterilization workers, and both included risks of lymphoid cancer. However, while the US EPA unit risk calculations also included breast cancer, the TCEQ did not. The TCEQ decision not to include breast cancer appears to be based

[175] Texas Commission on Environmental Quality (TCEQ 2020). Ethylene Oxide Carcinogenic Dose-Response Assessment. Development Support Document. CAS Registry Number: 75-21-8. Available at: https://www.tceq.texas.gov/downloads/toxicology/dsd/final/eto.pdf
[176] US EPA (2016a), full citation provided in footnote 3.
[177] US EPA (2022a). Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. 40 CFR Part 63. [EPA-HQ-OAR-2018-0746; FRL-6494.1-02-OAR]. U.S. Environmental Protection Agency. Available at: https://www.federalregister.gov/documents/2022/12/21/2022-27522/reconsideration-of-the-2020-national-emission-standards-for-hazardous-air-pollutants-miscellaneous. Accessed: 01/07/23.
[178] US EPA (2022b). Summary of Public Comments and Responses for the Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. In: US Environmental Protection Agency. Office of Air Quality Planning and Standards Sector Policies and Programs Division (E-143-01) (ed). Available at: https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0200

primarily on two recent meta-analyses[179,180] and a recent cross-sectional study (Jain 2020)[181], all of which reportedly did not find strong evidence of an association between ethylene oxide and breast cancer. However, in its review of these studies, US EPA[182] noted that,

> "The conclusions of these meta-analyses are flawed for two major reasons: (1) the authors did not consider findings of increased cancer incidence or mortality in highly exposed study subgroups, and (2) the authors excluded published findings using internal comparison groups within the worker populations, which goes against best practice in epidemiology."

As noted by US EPA[183], these two decisions by the meta-analyses authors[184,185] led to the exclusion of the strongest evidence linking ethylene oxide to breast cancer, including the positive findings from the high quality NIOSH cohort. OEHHA also reviewed these two meta-analyses and agrees that these two issues are major flaws, and agrees with US EPA that these two meta-analyses cannot be used to justify the exclusion of breast cancer in ethylene oxide unit risk calculations. In its review of the cross-sectional study by Jain (2020)[186], US EPA[187] identified a number of flaws, including the mischaracterization of an ethylene oxide biomarker of exposure (hemoglobin adducts) as "[ethylene oxide] levels in the blood", the failure to account for potential confounding variables in the statistical model, and the cross-sectional design, which represents "a snapshot in time of exposure and health outcome" and cannot be used to rule out an association between ethylene oxide and breast cancer. Additionally, the lack of information on historical exposures is problematic because "biomarker measurements that offer a snapshot in time of one's exposure to chemicals are not necessarily representative of continuous, lifetime exposure leading to the development

[179] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019). Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919-39.
[180] Vincent MJ, Kozal JS, Thompson WJ, et al. (2019). Ethylene Oxide: Cancer Evidence Integration and Dose-Response Implications. Dose Response 17(4):1559325819888317.
[181] Jain RB (2020). Associations between observed concentrations of ethylene oxide in whole blood and smoking, exposure to environmental tobacco smoke, and cancers including breast cancer: data for US children, adolescents, and adults. Environ Sci Pollut Res Int 27(17):20912-9.
[182] US EPA (2022a), full citation provided in footnote 177.
[183] *Ibid*.
[184] Marsh et al. (2019), full citation provided in footnote 179.
[185] Vincent et al. (2019), full citation provided in footnote 180.
[186] Jain (2020), full citation provided in footnote 181.
[187] US EPA (2022a), full citation provided in footnote 177.

of breast cancer"[188]. OEHHA reviewed this study and agrees with US EPA's conclusions that this study also cannot be used to support the assertion that ethylene oxide does not cause breast cancer.

Overall, US EPA[189] found that, "…available epidemiological evidence for a causal relationship between ethylene oxide exposure and breast cancer in women was strong" and that "TCEQ's decision to exclude breast cancer as an endpoint in the derivation of their ethylene oxide risk value to be without adequate scientific basis." OEHHA agrees with these conclusions.

Furthermore, OEHHA's literature search additionally identified two community-based studies that reported positive associations between ethylene oxide exposure and breast cancer. Residential proximity to an ethylene oxide emitting facility was significantly associated with *in situ* breast cancer in the NIH-AARP cohort[190]. There was also a weak, albeit non-significant, association with invasive breast cancer in the Nurse's Health Study II cohort, which estimated exposure using census tracts[191]. These studies lend support to the breast cancer findings in the NIOSH cohort, despite their limitations and uncertainties in characterizing individual exposure (see page 9). Overall, OEHHA agrees that breast cancer should be included in the cancer unit risk calculations.

TCEQ dose-response model

The other major reason why the US EPA rejected the TCEQ ethylene oxide cancer unit risk was the dose-response model used by TCEQ. While the US EPA used a two-piece linear regression spline model, the TCEQ used a Cox Proportional Hazards model. In its 2016 risk assessment, US EPA also evaluated the Cox Proportional Hazards model but found that it provided a very poor fit to the NIOSH cohort data, especially in the more relevant lower exposure region[192,193]. As noted by US EPA (2022a)[194]:

> "The epidemiological data indicate that cancer risk rises more rapidly with increasing exposure in the lower exposure range and more gradually in the higher exposure range. TCEQ selected a model that is unable to fit the shape of

[188] *Ibid*.
[189] US EPA (2022a), full citation provided in footnote 177.
[190] Jones et al. (2023), full citation provided in footnote 26.
[191] Hart et al. (2018), full citation provided in footnote 28.
[192] US EPA (2016a), full citation provided in footnote 3.
[193] US EPA (2016b), full citation provided in footnote 9.
[194] US EPA (2022a), full citation provided in footnote 177.

> the data throughout the exposure range. The slope of TCEQ's model is more representative of higher, occupational exposures. By using a single slope (a line) to project risks, TCEQ's model predicts risks at lower exposure ranges that are inconsistent with the underlying epidemiological dose-response data. EPA rejects TCEQ's model because it is inconsistent with the underlying epidemiological dose-response data and mischaracterizes risk at the lower exposure range (i.e., the range representing potential general population exposures)."

OEHHA agrees with US EPA that the dose-response model selected by TCEQ dramatically underestimates the ethylene oxide risks in the NIOSH cohort, especially in the lower exposure range. Overall, OEHHA agrees with US EPA's selection of the two-piece linear regression spline model and concludes that it provides a better and more appropriate fit to the underlying NIOSH data.

TCEQ's "Reality check"

TCEQ[195] provided several "reality check" calculations in an attempt to justify their model selection. However, these calculations involved a number of flaws that limited their usefulness. In its main "reality check," TCEQ estimated the numbers of cases expected in the NIOSH cohort using standard mortality ratio (SMR)-type procedures, and the relative risk estimates generated from either their Cox Proportional Hazards model or US EPA's two-piece linear spline model. Here, TCEQ reported that while the Cox Proportional Hazards model resulted in a good approximation of the actual number of cases in the NIOSH cohort, the two-piece linear spline model gave a dramatic overestimation of this number. However, as pointed out by US EPA[196], the baseline cancer rates used by the TCEQ in these calculations were those resulting from external analysis using the general US population, not those from internal analyses using a comparable group of unexposed workers. As such, TCEQ's calculations did not accurately account for any differences that might exist between the general US population and the NIOSH worker cohort. As noted by US EPA:[197,198]

> "…TCEQ incorrectly assumes that, in the absence of ethylene oxide exposure, cancer incidence rates in the worker cohort (the basis of the URE [unit risk estimate] calculation in EPA's IRIS [Integrated Risk Information System]

[195] TCEQ (2020), full citation provided in footnote 175.
[196] US EPA (2022a), full citation provided in footnote 177.
[197] *Ibid*.
[198] US EPA (2022b), full citation provided in footnote 178.

> assessment) would be the same as national cancer mortality rates for the general population. This is, at best, a rough approximation and is subject to considerable error."[199]
>
> "Differences between cancer rates in a specific cohort and national rates may result from differences in population (non-[ethylene oxide] EtO) cancer risk factors including behavioral and environmental factors, differences from population genetics, and differences related to medical diagnosis and treatment. These differences overlap with but are broader than "healthy worker effects" often seen in occupational epidemiology, that can contribute to lower rates of cancers and other diseases in a worker study."[200]
>
> "Importantly, the recognition that the national cancer rates may not be appropriate for this worker cohort is a primary reason that NIOSH investigators developed Cox model "internal" risk estimates in preference to a national mortality rate-based SMR analysis. We note that TCEQ also relied on these internal dose response models for their actual risk assessment calculations."[201]

OEHHA also reviewed this "reality check" and agrees with US EPA's conclusions that these calculations were flawed. Further details on US EPA's evaluation of the TCEQ "reality checks" and its overall ethylene oxide risk assessment can be found elsewhere.[202,203]

Rodent Carcinogenicity Studies

Study Selection and Cancer Findings

OEHHA reviewed the available data from the rodent carcinogenicity studies of ethylene oxide discussed by IARC[204], US EPA[205], California Department of Health Services

[199] US EPA (2022a), full citation provided in footnote 177.
[200] US EPA (2022b), full citation provided in footnote 178.
[201] *Ibid*.
[202] US EPA (2022a), full citation provided in footnote 177.
[203] US EPA (2022b), full citation provided in footnote 178.
[204] IARC (2012), full citation provided in footnote 18.
[205] US EPA (2016a), full citation provided in footnote 3.

(CDHS 1988)[206], and CDHS (1987)[207], and determined that the two-year inhalation studies conducted by NTP (1987)[208] in male and female $B6C3F_1$ mice, by Snellings et al. (1981[209], 1984[210]) in male and female Fischer 344 rats, and by Lynch et al. (1984)[211] in male F344 rats, and the two-year gavage study by Dunkelberg (1982)[212] in female Sprague-Dawley rats met the criterion in Section 25703 of the California Code of Regulations as being sensitive studies of sufficient quality. Other studies in which tumors were observed were determined to be less sensitive than these studies.

In the NTP studies in male and female $B6C3F_1$ mice[213], groups of 50 mice were exposed to ethylene oxide by inhalation at concentrations of 0, 50, or 100 ppm, 6 hours per day, 5 days per week for 102 weeks. NTP (1987)[214] reported that animals received a total of 487 exposures throughout the study[215]. The lifetime average daily doses of ethylene oxide administered in the studies were calculated to be 0, 18.32, and 36.64 mg/kg-day for male mice and 0, 19.21, and 38.42 mg/kg-day for female mice. Survival was not affected by treatment with ethylene oxide for male or female mice at any dose.

In male mice, a statistically significant increase in the incidence of combined alveolar/bronchiolar adenoma or carcinoma was observed in the high dose group as well as a significant trend. In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in both the low and high dose groups with a significant trend. The tumor incidence data used to estimate cancer potency from this study are presented in Table 6.

In female mice, statistically significant increases in the incidences of combined alveolar/bronchiolar adenoma or carcinoma, malignant lymphoma, and combined

[206] California Department of Health Services (CDHS 1988). Proposition 65 Risk-Specific Intake Levels, Ethylene Oxide, California Department of Health Services, Berkeley, California.
[207] California Department of Health Services (CDHS 1987). Part B, Health Effects of Ethylene Oxide. Air Toxics Unit, Office of Environmental Health Hazard Assessment, California Department of Health Services, Berkeley, California.
[208] NTP (1987), full citation provided in footnote 12.
[209] Snellings et al. (1981), full citation provided in footnote 13.
[210] Snellings et al. (1984), full citation provided in footnote 14.
[211] Lynch et al. (1984), full citation provided in footnote 16.
[212] Dunkelberg (1982), full citation provided in footnote 17.
[213] NTP (1987), full citation provided in footnote 12.
[214] *Ibid*.
[215] The Experimental Design table on page 28 of NTP (1987) states that animals were exposed “6 h/d, 5 d/w for 102 weeks (except 25 d) for 487 exposures". OEHHA notes that this description of the dosing appears to be incomplete, as 5 exposures per week for 102 weeks less 25 exposures (i.e., [5 ×102] – 25) equals 485 exposures, and that no explanation is provided in NTP (1987) as to why the animals did not receive treatment on 25 days.

uterine adenoma or carcinoma were observed in the high dose group, all with significant trends. In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in both the low and high dose groups with a significant trend. A statistically significant increase in combined mammary adenocarcinoma or adenosquamous carcinoma was also observed in low dose female mice. The tumor incidence data used to estimate cancer potency from this study are presented in Table 6.

Table 6. Tumor incidences of treatment-related lesions in male and female $B6C3F_1$ mice administered ethylene oxide by inhalation (NTP 1987).

Experiment	Tumor site and type	Ethylene oxide concentration			Exact trend test *p*-value
		0 ppm	50 ppm	100 ppm	
Male mice	Alveolar/bronchiolar adenoma or carcinoma	11/48	19/48	26/48**	$p < 0.01$
	Harderian gland papillary cystadenoma	1/41	9/42**	8/38*	$p < 0.05$
Female mice	Alveolar/bronchiolar adenoma or carcinoma	2/36	5/31	22/45***	$p < 0.001$
	Harderian gland papillary cystadenoma	1/32	6/28*	8/38*	$p < 0.05$
	Malignant lymphoma	9/44	6/44	22/49*	$p < 0.01$
	Uterine adenoma or carcinoma	0/35	2/30	5/43*	$p < 0.05$
	Mammary adenocarcinoma or adenosquamous carcinoma	1/30	8/36*	6/44	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined at that site and alive at the time of first occurrence of the tumor. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$).

In the Snellings et al. studies in male and female Fischer 344 rats[216,217,218], groups of 120 rats were exposed to ethylene oxide by inhalation at concentrations of 0 (2 groups), 10, 33, or 100 ppm, 6 hours per day, 5 days per week for 2 years. Snellings et al. (1981)

[216] Snellings et al. (1981), full citation provided in footnote 13.
[217] Snellings et al. (1984), full citation provided in footnote 14.
[218] Garman et al. (1985), full citation provided in footnote 15.

reported that animals received a total of 525 exposures throughout the studies[219]. The lifetime average daily doses of ethylene oxide administered in the studies were calculated to be 0, 3.13, 10.32, and 31.27 mg/kg-day for male rats and 0, 3.75, 12.38, and 37.50 mg/kg-day for female rats. Mortality was increased after 22 months of exposure in the high dose group compared to controls in both the male and female studies.

A statistically significant increase in the incidence of mononuclear cell leukemia was observed in the mid and high dose groups in the male rat study, with a significant trend. Additionally, statistically significant increases in the incidences of testicular peritoneal mesothelioma and brain glioma were observed in high dose male rats, with significant trends. The tumor incidence data used to estimate cancer potency from this study are presented in Table 7.

In female rats, a statistically significant increase in the incidence of mononuclear cell leukemia was observed in all treated groups, with a significant trend. A significant trend in brain glioma was also observed. The tumor incidence data used to estimate cancer potency from this study is presented in Table 7.

Table 7. Tumor incidences of treatment-related lesions in male and female Fischer 344 rats administered ethylene oxide by inhalation (Snellings et al. 1981, 1984; Garman et al. 1985).

Experiment	Tumor site and type	Ethylene oxide concentration				Exact trend test *p*-value
		0 ppm	10 ppm	33 ppm	100 ppm	
Male rats	Mononuclear cell leukemia	13/97	9/51	12/39*	9/30*	$p < 0.05$
	Testicular peritoneal mesothelioma	2/97	2/51	4/39	4/30*	$p < 0.05$
	Brain glioma	1/181	0/92	3/85	6/87**	$p < 0.001$
Female rats	Mononuclear cell leukemia	11/116	11/54*	14/48**	15/26***	$p < 0.001$
	Brain glioma	0/187	1/94	2/90	2/78	$p < 0.05$

Tumor incidences for mononuclear cell leukemia and testicular peritoneal mesothelioma are expressed as the number of tumor-bearing animals over the number of animals for which histopathological diagnosis

[219] Snellings et al. (1981), full citation provided in footnote 13.

was performed. Snellings et al. (1984) reported percentages for tumor incidence; OEHHA calculated the fractional incidences which were consistent with those reported by US EPA (2016a)[220]. Tumor incidences for brain gliomas are expressed as the number of tumor-bearing animals over the number alive at the time the first glioma in any group was observed[221]. The control group incidences represent a combination of the two identical control groups in each experiment. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Exact trend test conducted by OEHHA.

In the Lynch et al. study in male Fischer 344 rats[222], groups of 80 rats were exposed to ethylene oxide by inhalation at concentrations of 0, 50, or 100 ppm, 7 hours per day, 5 days per week for 104 weeks. The lifetime average daily doses of ethylene oxide administered in the studies were calculated to be 0, 18.59, and 37.18 mg/kg-day. Lynch et al. (1984) noted that body weights were statistically significantly decreased in the treated groups and that survival was significantly decreased in the high dose group[223]. A bacterial outbreak began eight months into the study, however animals continued planned inhalation exposures other than a two-week period during the 16th month of the study. The authors suggested that the outbreak alone and in combination with ethylene oxide exposure contributed to the decrease in survival[224].

Statistically significant increases in the incidence of peritoneal mesothelioma (of testicular origin) and brain glioma were observed in the high dose group and a statistically significant increase in mononuclear cell leukemia was observed in the mid dose group. Significant trends in peritoneal mesothelioma and brain glioma were also observed.

The tumor incidence data used to estimate cancer potency from this study are presented in Table 8.

[220] US EPA (2016a), full citation provided in footnote 3.
[221] Garman al. (1985), full citation provided in footnote 15.
[222] Lynch et al. (1984), full citation provided in footnote 16.
[223] *Ibid.*
[224] *Ibid*.

Table 8. Tumor incidences of treatment-related lesions in Fischer 344 male rats administered ethylene oxide by inhalation (Lynch et al. 1984).

Tumor site and type	Ethylene oxide concentration			Exact trend test *p*-value
	0 ppm	50 ppm	100 ppm	
Mononuclear cell leukemia	24/77	38/79*	30/76	NS
Peritoneal mesothelioma (of testicular origin)	3/78	9/79	21/79***	$p < 0.001$
Brain glioma	0/76	2/77	5/79*	$p < 0.05$

Tumor incidences are expressed as the number of tumor-bearing animals over the number of animals for which histopathological diagnosis was performed[225]. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, *** $p < 0.001$. Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$).

Application of the multistage model

Based on the consideration that there is strong evidence for the genotoxicity of ethylene oxide, a multistage model is applied to derive a cancer potency estimate using data from animal cancer bioassays. There are no specific mechanistic data to suggest any deviation from the standard assumptions, including low-dose linearity, usually applied in cancer dose-response analysis. For purposes of this NSRL and following the guidance in Section 25703, there are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

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

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

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

[225] Lynch et al. (1984), full citation provided in footnote 16.

To derive a measure of the cancer response to ethylene oxide (per mg/kg-day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's Benchmark Dose Software (BMDS)[226]. The multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in US EPA's 2005 cancer risk assessment guidelines[227]. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS[228] can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models for the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. In order to derive a measure of the total cancer response in a given study, the dose associated with a 5% increased risk of developing a tumor at one or more of the sites of interest was calculated and the lower bound for this dose was estimated using the multisite model in BMDS. The ratio of the 5% risk level to that lower bound on dose is known as the multisite "animal cancer slope factor (CSF_{animal})," or "animal cancer potency." Multisite cancer slope factors were estimated for the NTP studies in male and female mice[229], the Snellings studies in male and female rats[230,231,232], and the Lynch study in male rats[233].

There were no significant differences in survival observed in the mouse studies by NTP (1987). Regarding Snellings et al. (1984), the authors reported that late in the studies (after 22 months of exposure), significantly higher mortality was observed in the highest dose group in both sexes of rats. When there are no significant differences in survival or when significant differences occur late in a study, use of effective number for tumor incidence is appropriate in modeling the cancer potency.

In the study by Lynch et al. (1984), survival of treated male rats was reported to be significantly decreased compared to control animals. However, without access to the original animal data from this study, it is not known to OEHHA which animals survived

[226] US EPA BMDS, full citation provided in footnote 160.
[227] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.
[228] US EPA BMDS, full citation provided in footnote 160.
[229] NTP (1987), full citation provided in footnote 12.
[230] Snellings et al. (1981), full citation provided in footnote 13.
[231] Snellings et al. (1984), full citation provided in footnote 14.
[232] Garman et al. (1985), full citation provided in footnote 15.
[233] Lynch et al. (1984), full citation provided in footnote 16.

until the first occurrence of tumor at each site, which of the early deaths were treatment-related, and/or how large a fraction of the animals died before the end of the study, or the dates of first occurrence of treatment-related tumors. Thus, no adjustments could be made to account for the differences in survival, such as using effective number or the poly-3 method[234] to represent tumor incidences, or using the multistage-in-dose Weibull-in-time (multistage Weibull) model to estimate cancer potency. As a result, the animal cancer slope factor derived from the incidences reported in this study (number of tumor-bearing animals over the number of animals for which histopathological diagnosis was performed) may be an underestimate of the true potency.

Calculation of Average Daily Doses

The lifetime average dose in units of mg/kg-day of ethylene oxide was calculated for each dose group, based on the dose level, duration, exposure regimen, and animal body weights reported by NTP (1987)[235], Snellings et al. (1981)[236], and Lynch et al. (1984)[237]. The average animal body weights, calculated using data reported for control animals, are shown in Table 9 below.

Table 9. Average body weight of experimental animals from the control groups

Publication	Sex/strain/species	Average body weight (kg)
NTP (1987)	Male B6C3F$_1$ mice	0.0364
	Female B6C3F$_1$ mice	0.0315
Snellings et al. (1981)	Male F344 rats	0.386
	Female F344 rats	0.225
Lynch et al. (1984)	Male F344 rats	0.355

[234] Bailer AJ and Portier CJ (1988). Effects of treatment-induced mortality and tumor-induced mortality on test for carcinogenicity in small samples. Biometrics 44(2):417-431.
[235] NTP (1987), full citation provided in footnote 12.
[236] Snellings et al. (1981), full citation provided in footnote 13.
[237] Lynch et al. (1984), full citation provided in footnote 16.

The inhalation rates for mice (IR_{mice}), in m^3/day, were calculated using the Anderson et al. (1983) formula for mice[238], which was derived using experimental data on animal breathing rates (m^3/day) and corresponding body weights (kg):

$$IR_{mice} = 0.0345\ m^3/day \times (bw_{mice}/0.025\ kg)^{2/3}$$

For the studies by NTP, the calculated inhalation rates were 0.0443 m^3/day and 0.0402 m^3/day for male mice and female mice, respectively.

The inhalation rates for rats (IR_{rats}) were calculated using the OEHHA (2018) inhalation rate equation for rats[239], which was derived using experimental data on animal breathing rates (m^3/day) and corresponding body weights (kg):

$$IR_{rats} = 0.702 \times bw_{rats}^{2/3}\ \text{ in } m^3/day$$

For the studies by Snellings et al., the calculated inhalation rates for male and female rats were 0.372 m^3/day and 0.260 m^3/day, respectively. For the study by Lynch et al., the calculated inhalation rate for male rats was 0.352 m^3/day.

Typically, average doses (D_{avg}) from inhalation studies are determined by multiplying the chamber air concentration (C_{air}) of the test substance in units of mg/m^3 by the following factors: the inhalation rate divided by the body weight; the number of exposure hours per day divided by 24; the number of exposure days divided by 7; and the number of weeks treated divided by 104 (if the treatment duration was less than 104 weeks). Since NTP (1987) and Snellings et al. (1981) reported the exact number of days animals were exposed, this information was included to obtain a more precise estimate of average dose. Thus, in place of the last two factors described above, a factor for reported number of exposures divided the total number of days on study is included. The equations for lifetime average dose (mg/kg-day) for the inhalation studies are:

$$\text{NTP (1987): } D_{avg} = C_{air}\ \left(mg/m^3\right) \times \frac{IR_{mice}}{bw_{mice}}\ \frac{\left(m^3/day\right)}{kg} \times \frac{6}{24} \times \frac{487}{728}$$

[238] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983). Quantitative approaches in use to assess cancer risk. *Risk Analysis.*3:277-295.
[239] OEHHA (2018). Calculation of Rat Breathing Rate Based on Bodyweight. OEHHA, May 2018. Available from: https://oehha.ca.gov/media/downloads/crnr/calcuratbreathingrate092818.pdf.

$$\text{Snellings et al. (1981,1984): } D_{avg} = C_{air}\left(\frac{mg}{m^3}\right) \times \frac{IR_{rats}}{bw_{rats}}\frac{\left(\frac{m^3}{day}\right)}{kg} \times \frac{6}{24} \times \frac{525}{728}$$

$$\text{Lynch et al. (1984): } D_{avg} = C_{air}\left(\frac{mg}{m^3}\right) \times \frac{IR_{rats}}{bw_{rats}}\frac{\left(\frac{m^3}{day}\right)}{kg} \times \frac{7}{24} \times \frac{5}{7}$$

The lifetime average doses calculated using these equations are shown in the table below.

Table 10. Lifetime average doses for selected animal carcinogenicity studies of ethylene oxide (NTP 1987; Snellings et al. 1981, 1984; Lynch et al. 1984).

Study	Sex/strain/species	Lifetime average daily doses (mg/kg-day)
NTP (1987)	Male B6C3F$_1$ mice	0, 18.32, 36.64
	Female B6C3F$_1$ mice	0, 19.21, 38.42
Snellings et al. (1981, 1984)	Male F344 rats	0, 3.13, 10.32, 31.27
	Female F344 rats	0, 3.75, 12.38, 37.50
Lynch et al. (1984)	Male F344 rats	0, 18.59, 37.18

Estimation of Human Cancer Potency from the Rodent Carcinogenicity Studies

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

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

The default human body weight is 70 kg. The average body weights are shown above in Table 9. The derivations of the human cancer slope factors using these body weights are summarized below in Table 11.

Table 11. Derivation of CSF_{human} using multisite CSF_{animal} values and mean animal body weights for the studies and data presented in Tables 6, 7, 8, 9, 10

Publications	Sex/strain/species	Body weight (kg)	Tumor sites used in estimating potency	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
NTP (1987)	Male $B6C3F_1$ mice	0.0364	Combined alveolar/bronchiolar adenoma and carcinoma[1], Harderian gland papillary cystadenoma[1]	0.0294	0.19
	Female $B6C3F_1$ mice	0.0315	Combined alveolar/bronchiolar adenoma and carcinoma[2], Harderian gland papillary cystadenoma[1], Malignant lymphoma[2], Combined uterine adenoma and adenocarcinoma[1], Combined mammary adenocarcinoma and adenosquamous carcinoma[1]	0.0297	0.20
Snellings et al. (1981; 1984), Garman (1985)	Male F344 rats	0.386	Mononuclear cell leukemia[1], Testicular peritoneal mesothelioma[1], Brain glioma[1]	0.0247	0.091
	Female F344 rats	0.225	Mononuclear cell leukemia[1], Brain glioma[1]	0.0301	0.13
Lynch et al. (1984)	Male F344 rats	0.355	Mononuclear cell leukemia[1], Peritoneal mesothelioma[1], Brain glioma[1]	0.0186	0.070

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

Final Cancer Potency Estimation

The unit risk was based on data from the high quality human study involving an analysis of over 17000 workers in the US exposed to ethylene oxide (the NIOSH study[240,241]). This NIOSH human epidemiology study was deemed to be more sensitive than the rodent studies and was therefore used to derive the NSRL. The use of human data avoids the potential uncertainties involved in extrapolating risks from laboratory animal studies. Other key advantages of this study are the large sample size, high quality individual exposure data, lack of major confounders, longitudinal design, appropriate statistical analyses, and a relatively diverse study population. Evaluations by the original

[240] Steenland et al. (2003), full citation provided in footnote 11.
[241] Steenland et al. (2004), full citation provided in footnote 10.

study authors, US EPA, and OEHHA identified no major sources of bias, confounding or other errors in this study. US EPA has provided a thorough review of the other human studies of ethylene oxide and cancer, which generally had many fewer cancer cases and lower quality exposure and other data than the NIOSH study[242].

For both lymphoid and breast cancer, US EPA, in conjunction with the original NIOSH study authors, applied a number of exposure-response models to the NIOSH study data. Factors considered in model selection included overall fit, fit in the lower exposure regions, statistical significance, biologic plausibility, numbers of cancer cases, and model simplicity. Based on these considerations US EPA selected the two-piece linear spline model for its unit risk calculations. Some of the key variables and the results of these calculations are presented in Table 12.

Table 12. Summary of the variables and results used in the US EPA's cancer unit risk calculations for ethylene oxide

Variable/Result	Lymphoid cancer	Breast cancer	Total cancer
Species, study	Humans, NIOSH cohort	Humans, NIOSH cohort	–
Study reference	Steenland et al. 2004	Steenland et al. 2003	–
Study participants	17,530 men and women	5,139 women	–
Number of cases	53 lymphoid cancer deaths	233 incident breast cancer cases	–
Exposure-response model	Two piece linear spline knot at 1600 ppm-days	Two piece linear spline knot at 5750 ppm-days	–
β (per ppm-days)	7.58×10^{-4}	8.98×10^{-5}	–
β 95% CI	2.98×10^{-3}	1.84×10^{-4}	–
EC_{01} (ppm)	7.48×10^{-3}	1.38×10^{-2}	–
LEC_{01} (ppm)	1.90×10^{-3}	6.75×10^{-3}	–
Extrapolation	Linear	Linear	–
Unit risk based on adult exposure (per ppm)	5.26	1.48	6.1
Cancer slope factor (per mg/kg-day)	–	–	12

β, lower slope of the two-piece linear regression model; CI, confidence interval; EC_{01}, effective concentration associated with 1% extra risk; LEC_{01}, 95% (one-sided) lower confidence limit of the EC_{01}; ppm, parts per million; – , not applicable

[242] US EPA (2016a), full citation provided in footnote 3.

OEHHA has thoroughly reviewed the US EPA approach and evaluated a number of other approaches. OEHHA agrees with US EPA that the NIOSH study is of high quality and is the best available study for assessing the cancer risks of ethylene oxide. OEHHA also agrees with US EPA that the two-piece linear spline model is the best fitting and most accurate model for assessing the cancer risks of ethylene oxide at lower exposure concentrations. More recently, the US EPA reaffirmed that, "…since the issuance of the final [2016] assessment, there is no new scientific information that would alter EPA's derivation of the IRIS value or other aspects of the EPA IRIS assessment for ethylene oxide."[243] OEHHA was also unable to identify any new scientific information that would necessitate a change to the cancer unit risk based on adult exposure to ethylene oxide derived in the US EPA's 2016 risk assessment. Overall, OEHHA concludes the unit risk value of 6.1 per ppm (3.3×10^{-3} per μg/m^3; 12 per mg/kg-day) based on adult exposure is a scientifically sound and reliable estimate of the cancer risks of ethylene oxide.

Thus, the NSRL for ethylene oxide will be based on the cancer slope factor of 12 per mg/kg-day, derived by the US EPA[244] from the NIOSH study[245,246].

Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram body weight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the body weight for humans. When the calculation is for the general population, the body weight is assumed to be 70 kg[247]. The intake can be converted to a μg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

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

[243] US EPA (2022a), full citation provided in footnote 177.
[244] US EPA (2016a), full citation provided in footnote 3.
[245] Steenland et al. (2004), full citation provided in footnote 10.
[246] Steenland et al. (2003), full citation provided in footnote 11.
[247] Section 25703(a)(8).

As indicated previously, the human cancer slope factor for ethylene oxide derived from the NIOSH study is 12 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 0.058 µg/day.

Proposed Regulatory Amendment

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline and strikeout.

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

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
Ethylene oxide	~~2~~ 0.058
…	

Necessity

This proposed regulatory amendment would adopt an updated NSRL that reflects the currently available scientific knowledge about ethylene oxide, and conforms with the Proposition 65 implementing regulations. NSRLs provide assurance to the regulated community that exposures or discharges at or below these levels are considered not to pose a significant risk of cancer. This regulation is needed to convey that information to the public and the regulated population. Exposures at or below the NSRL are exempt from the warning and discharge requirements of Proposition 65[248].

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

In compliance with Government Code section 11346.3, OEHHA has assessed all the elements pursuant to sections 11346.3(b)(1)(A) through (D). In general, it is not possible

[248] Health and Safety Code sections 25249.9(b) and 25249.10(c).

to quantify any monetary values for this proposed regulatory action given that use of the NSRL is entirely voluntary and the NSRL only provides compliance assistance for businesses subject to the Act.

Creation or elimination of jobs within the State of California

This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. Ethylene oxide is listed under Proposition 65; therefore, businesses that manufacture, distribute, sell or use products with ethylene oxide in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of the chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Creation of new businesses or elimination of existing businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Expansion of businesses currently doing business within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Benefits of the proposed regulation to the health and welfare of California residents, worker safety, and the state’s environment

The NSRLs provide “safe harbor” values that aid businesses in determining if they are complying with the law. By updating the safe harbor levels, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the ethylene oxide emitted into the air from facilities or present in their product to a level that does

not cause a significant exposure, thereby providing a public health benefit to California residents and potentially reducing worker exposure.

Use of the NSRL is entirely voluntary for business compliance with the Act, and there is no method to measure whether this regulation will cause a decrease in the amount of the chemical released into the state's environment. By updating the safe harbor levels, the regulatory proposal may encourage businesses to lower the amount of the listed chemical emitted into the air or in their product to a level that does not cause a significant exposure, which may have a beneficial impact on the State's environment.

Benefits of the Proposed Regulation

The proposed regulatory amendment provides voluntary compliance assistance for businesses subject to the Act. In general, increasing compliance with the Act helps to protect the health and welfare of the California public, in line with the public health goal of Proposition 65. Updating this NSRL using the best available science also provides more accurate and current information about risk levels and a greater public health benefit to Californians.

Technical, Theoretical, and/or Empirical Studies, Reports, or Documents

The following documents were relied on by OEHHA for calculating the NSRL for ethylene oxide.

Reports, Federal Notice, and other related documents:

- Agency for Toxic Substances and Disease Registry (ATSDR 2022). Toxicological Profile for Ethylene Oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. August 2022. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf
- California Department of Health Services (CDHS 1987). Part B, Health Effects of Ethylene Oxide. Air Toxics Unit, Office of Environmental Health Hazard Assessment, California Department of Health Services, Berkeley, California.
- California Department of Health Services (CDHS 1988). Proposition 65 Risk-Specific Intake Levels, Ethylene Oxide, California Department of Health Services, Berkeley, California.

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- US Environmental Protection Agency (US EPA 2016a). Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) in Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC, EPA/635/R-16/350Fa. Available from: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=529970.
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- US Environmental Protection Agency (US EPA 2022a). Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. 40 CFR Part 63. [EPA-HQ-OAR-2018-0746; FRL-6494.1-02-OAR]. U.S. Environmental Protection Agency. Available at: https://www.federalregister.gov/documents/2022/12/21/2022-27522/reconsideration-of-the-2020-national-emission-standards-for-hazardous-air-pollutants-miscellaneous. Accessed: 01/07/23.
- US Environmental Protection Agency (US EPA 2022b). Summary of Public Comments and Responses for the Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. In: US Environmental Protection Agency. Office of Air Quality Planning and Standards Sector Policies and Programs Division (E-143-01) (ed). Available at: https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0200.

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Copies of these documents will be included in the regulatory record for this proposed action. These documents are available from OEHHA upon request.

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

OEHHA has determined there are no reasonable alternatives to the proposed regulatory action that would carry out the purposes of the Act. The NSRLs provide "safe harbor" values that aid businesses in determining if they are complying with the law. An alternative to the proposed amendment to Section 25705(b) would be to not adopt an updated NSRL for this chemical or to adopt an updated NSRL based on an alternative cancer potency estimate. However, either of these alternatives would result in a safe harbor level that is not scientifically supported. Failure to adopt this updated NSRL would leave the business community without the scientifically most appropriate "safe harbor" level to assist them in complying with Proposition 65. OEHHA has determined that there is no alternative to the proposed regulation that is less burdensome and equally effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute.

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

There are no significant costs that impact small businesses in compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by

its terms to businesses with 10 or more employees,[249] so it has no effect on very small businesses.

Evidence Supporting Finding of No Significant Adverse Economic Impact on Business

OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states because the proposed updated NSRL provides a voluntary “safe harbor” level for businesses to use when determining compliance with Proposition 65.

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

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

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