Air Toxics Hot Spots Program

Ethylene Oxide

Cancer Inhalation Unit Risk Factor

Technical Support Document for
Cancer Potency Factors
Appendix B

April 2023 Draft

Air and Site Assessment and Climate Indicators Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

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Technical Support Document for Cancer Potency Factors
Appendix B

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List of Abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AIC	Akaike Information Criterion
ATSDR	Agency for Toxic Substances and Disease Registry
β	Regression coefficient
BMDS	Benchmark Dose Modeling Software
BW	Body weight
CARB	California Air Resources Board
CAS	Chemical Abstracts Service
CDHS	California Department of Health Services
CF	Conversion factor
CI	Confidence interval
CSF	Cancer slope factor
CV	Coefficient of variation
CYP2E1	Cytochrome P450 2E1
DNA	Deoxyribonucleic acid
EC_{01}	Effective concentration associated with 1% extra risk
EC_{10}	Effective concentration associated with 10% extra risk
EH	Epoxide hydrolase
ET	Ethylene
EtO	Ethylene oxide
ET(OH)SG	S-(2-hydroxyethyl)glutathione
$ET(OH)_2$	Ethylene glycol
GSH	Reduced glutathione
GST	Glutathione-S-transferase
Hb	Hemoglobin
HEG	N7-(2-hydroxyethyl) guanine
HEMA	S-(2-hydroxyethyl)-mercapturic acid
HEV	N-(2-hydroxyethyl)-valine
HHS	United States Department of Health and Human Services, The
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk factor
LEC_{01}	95% (one-sided) lower confidence limit on the EC01
mg × h/L	Milligrams multiplied by hours per liter
mg/kg	Milligrams per kilogram
mg/kg-day	Milligrams per kilogram per day
mg/L	Milligrams per liter
mg/m^3	Milligrams per cubic meter
$\mu g/m^3$	Micrograms per cubic meter
µmol/L	Micromoles per liter
mm Hg	Millimeters of mercury
n	Number
NATTS	National Air Toxics Trends Stations
NIOSH	National Institute for Occupational Safety and Health
NSRL	No Significant Risk Level
NTP	National Toxicology Program, The
OEHHA	Office of Environmental Health Hazard Assessment, The
OR	Odds ratio
$(\mu g/m^3)^{-1}$	Per microgram per cubic meter
$(mg/kg\text{-}day)^{-1}$	Per milligram per kilogram per day
$(ppb)^{-1}$	Per part per billion
PBPK	Physiologically-based pharmacokinetic or toxicokinetic
pmol	Picomole
POD	Point of departure
ppb	Parts per billion
ppbv	Parts per billion by volume
ppm	Parts per million
ppm-days	Parts per million-days
ppm-years	Parts per million-years
Prop 65	Proposition 65 program
RBC	Red blood cell
RPTG	Richly-perfused tissue group
RR	Relative risk
SCAQMD	South Coast Air Quality Management District, The
SCE	Sister chromatid exchange
SD	Standard deviation
§	Section
SEER	Surveillance, Epidemiology, and End Results program
SMR	Standardized mortality ratio
TAC	Toxic Air Contaminant
TCEQ	Texas Commission on Environmental Quality
$t_{1/2}$	Blood elimination half-life
$t_{1/2\text{-}HEV}$	Half-life of HEV
TRI	Toxics Release Inventory
UAT	Urban Air Toxics
URE	Unit risk estimate
US EPA	United States Environmental Protection Agency, The

Preface

The Office of Environmental Health Hazard Assessment (OEHHA) is legislatively mandated to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code section 44360(b)(2)). In implementing this requirement, OEHHA derives inhalation unit risk factors (IURs) for carcinogenic Hot Spots air pollutants (CARB, 2023b). IURs are used to estimate lifetime cancer risks associated with inhalation exposure to carcinogens.

This draft document updates OEHHA's cancer unit risk factor for ethylene oxide under the Air Toxics Hot Spots Program. Ethylene oxide is identified a carcinogen under this program as well as under California's Proposition 65 (OEHHA, 2023).

OEHHA's current IUR for ethylene oxide of 8.8×10^{-5} per $\mu g/m^3$ (the same as 1.6×10^{-4} per part per billion) was derived when OEHHA was part of the California Department of Health Services (CDHS, 1987) and was based on animal cancer studies. Since then, the knowledge base has grown. The chemical is now widely recognized as a known human carcinogen (NTP, 2021; ATSDR, 2022; US EPA, 2016a; 2016b; IARC, 2012), and there is robust new evidence that enables the IUR to be updated.

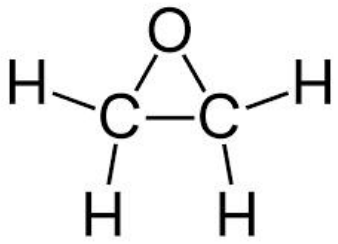
In 2016, US EPA updated its assessment for ethylene oxide and based its inhalation unit risk value on occupational studies (Steenland et al., 2003; Steenland et al., 2004) of 17,530 workers at sterilization facilities in the US (EPA, 2016a; 2016b). The US EPA's assessment received public comments and was peer-reviewed by its Science Advisory Board.

For this update, OEHHA reviewed the US EPA analysis, and considered key information on the pharmacokinetics and potential mechanisms of ethylene oxide carcinogenesis for the exposure-response analysis. OEHHA used the US EPA assessment as the primary source of studies published before 2016, and updated the literature review (Jan 2016-Jan 2023) to identify more recent studies relevant to the development of the IUR. After analyzing the most recent evidence, OEHHA updated its IUR to 3.3×10^{-3} per $\mu g/m^3$ (draft), utilizing potency parameters from the US EPA analysis.

The present document is being released for public comment, will be the subject of workshops in Northern and Southern California, and will be reviewed by the Scientific Review Panel on Toxic Air Contaminants. The comment period closes on May 22, 2023. Information on how to engage in the review process is contained on OEHHA's website: oehha.ca.gov.

Ethylene Oxide

CAS No: 75-21-8



I. PHYSICAL AND CHEMICAL PROPERTIES

(ATSDR, 2022; NCBI, 2023; NOAA, 2023)

Molecular formula:	C_2H_4O
Molecular weight:	44.05 grams per mole
Synonym:	epoxyethane, 1,2-epoxyethane, oxirane, dimethyl oxide
Description:	Colorless gas with a sweet, ether-like odor
Relative gas density:	1.49 (air = 1)
Specific gravity	0.8222 @ 50°C
Boiling point:	51.3°F @ 760 millimeters of mercury (mm Hg)
Vapor pressure:	1095 mm Hg @ 68°F; 1.095×10^3 mm Hg at 20°C
Solubility:	Soluble in benzene, acetone, ethanol, and ether; miscible with water (1×10^6 milligrams per liter (mg/L) @ 20°C)
Conversion factor:	1 part per million (ppm) = 1.82 milligrams per cubic meter (mg/m^3)

II. HEALTH ASSESSMENT VALUES

Inhalation Unit Risk Factor (IUR):	3.3×10^{-3} per microgram per cubic meter $(\mu g/m^3)^{-1}$; 6.1×10^{-3} per part per billion $(ppb)^{-1}$
Cancer Slope Factor (CSF):	12 per milligram per kilogram per day $(mg/kg\text{-}day)^{-1}$

III. MAJOR USES AND OCCURRENCE

Ethylene oxide (EtO) is used predominantly in the United States as a chemical intermediate in producing other industrial chemicals. In California, however, it is used primarily to sterilize medical and laboratory equipment and supplies and to fumigate agricultural products such as herbs and spices (CARB, 2022).

EtO emissions must be quantified under California's Air Toxics Hot Spots Program (CARB, 2023a) and reported under the United States Environmental Protection Agency's Toxics Release Inventory (TRI) program (US EPA, 2023c). There are at least 34 permitted EtO-emitting facilities in California (Ross, 2022)

Facility EtO emissions estimates are reported to the California Air Resources Board (CARB) by local air districts as part of the Air Toxics Hot Spots program. These inventory data are compiled from the California Emissions Inventory Data Analysis and Reporting System (CEIDARS) database and can be accessed using the publicly available facility search tool. The total EtO emissions in pounds, number of emissions sources (facilities), and maximum emissions reported for any facility are summarized by year for the last 10 inventory years (2011–2020) in Table 1 below. On average, the emissions are under 400 pounds per year, with a spike in 2014 due to a high emissions value reported by a single facility.

Table 1. Ethylene oxide (EtO) emissions from California facilities reporting to the California Air Resources Board for years 2011–2020 (CARB, 2022).

Year	Number of facilities	Total EtO Emissions (pounds)	Maximum EtO Emissions (pounds)
2011	64	1666	1016
2012	67	1289	646
2013	68	924	309
2014	56	5201	4620
2015	55	552	340
2016	48	433	265
2017	47	463	288
2018	48	471	341
2019	40	793	348
2020	33	556	391

The US EPA's TRI Toxics Tracker, a publicly available resource, was also used to access EtO emissions data for California. The total EtO emissions (pounds) are shown in Table 2 for the last 10 inventory years (2011–2020) for California facilities reporting to the TRI program. These emissions data are self-reported to TRI only by facilities meeting certain criteria (US EPA, 2023b). In 2021, US EPA changed the reporting process, requiring 29 additional medical sterilization facilities, including five in California, to begin reporting their EtO emissions to TRI (Ross, 2022). Consequently, these recent changes are not reflected in the data provided in Table 2.

Table 2. Ethylene oxide (EtO) emissions from California facilities reporting to US Environmental Protection Agency's Toxics Release Inventory (TRI) for years 2011–2020.

Year	Reported EtO Emissions (pounds)[a]
2011	1,083
2012	1,642
2013	1,228
2014	998
2015	1,109
2016	805
2017	15
2018	15
2019	15
2020	15

[(a)] The US EPA reported the emissions as "total releases" in pounds.

Non-occupational exposure to EtO results from cigarette smoke and ambient air. Mainstream cigarette smoke is reported to contain 7 mg EtO per cigarette (IARC, 2012). Background levels of EtO in ambient air result from a variety of minor non-point sources such as combustion of fossil fuels, release from consumer products (e.g., residues in fumigated food products and skin care products) (IARC, 2012; Kirman et al. 2021).

No California surveys examining statewide ambient EtO concentrations were found by OEHHA in the publicly available literature. However, EtO-related air monitoring conducted by the South Coast Air Quality Management District (SCAQMD) from summer 2022 to winter 2023 showed a background concentration range of 0.02–0.17 ppb in the South Coast Air Basin (SCAQMD, 2023a; 2023b). More localized monitoring near two medical sterilizer facilities revealed elevated EtO concentrations near the facilities, with concentrations ranging from undetectable to as high as 139 and 103 parts per billion by volume (ppbv) (SCAQMD, 2023a; 2023b). In comparison, the arithmetic mean background EtO level has been reported to be 0.16 ppb based on measurements

by US EPA from 2018–2019 in 18 rural and urban sites in eight states (KY, NJ, IL, UT, MI, AZ, WA, and MO; Kirman et al., 2021).

IV. CARCINOGENICITY

The available cancer studies in rats and mice and in humans were reviewed at different times by OEHHA (while as part of the California Department of Health Services; CDHS, 1987), US Department of Health and Human Services (HHS; NTP, 2021; ATSDR, 2022), US EPA (2016a; 2016b), and International Agency for Research on Cancer (IARC, 2012). Since OEHHA's 1987 Toxic Air Contaminant (TAC) document on EtO (CDHS, 1987), no new animal cancer bioassays on EtO have appeared in the peer-reviewed literature. However, several new cancer epidemiology studies were published. These studies were identified through a review of all the studies cited by US EPA (2016a)[1] after multiple rounds of literature searches, as well as a systematic search by OEHHA of the published scientific literature and technical reports from January 2016 to January 2023. In addition to the studies described by US EPA (2016a; 2016b), the literature search performed by OEHHA focused on key studies in five evidence streams: Human Cancer, Experimental Animal Cancer, Genotoxicity, ADME/Toxicokinetics, and Endogenous Formation. The search combined terms to identify EtO with complex strategies created for each evidence stream. Pubmed, Embase, Scopus, SciFinder-n, and Google Scholar were used.

Six rodent carcinogenicity studies of sufficient duration (Table 3) and three human epidemiological studies of EtO and cancer with quantitative exposure estimates (Table 7) were identified by OEHHA for consideration for quantitative dose-response analyses.

Rodent Carcinogenicity Studies

The available data from the rodent carcinogenicity studies (Table 3), discussed by IARC (2012), US EPA (2016a), and CDHS (1987; 1988) were reviewed by OEHHA. Overall, the two-year inhalation studies conducted by the National Toxicology Program (NTP, 1987) in male and female B6C3F_1 mice, Snellings et al. (1981, 1984) in male and female Fischer 344 rats, and Lynch et al. (1984) in male F344 rats, and the two-year gavage study by Dunkelberg (1982) in female Sprague-Dawley rats were sensitive studies compared to other animal studies in which tumors were observed.

[1] The literature searches for US EPA (2016a) included scientific literature published up to August 2016 (See US EPA, 2016b; Appendix J).

Table 3. Overview of long-term rodent carcinogenicity studies of ethylene oxide (EtO).

Sex, strain, and species	Route of administration	Exposure Duration	EtO Doses (mg/kg-day)	Purity of test material	Treatment-related tumor findings	Ref
Male Fischer 344 rats	Inhalation (chamber)	25 months	0, 3.13, 10.32, 31.27	99.9%	Mononuclear cell leukemia, testicular peritoneal mesothelioma, brain glioma	A
Female Fischer 344 rats	Inhalation (chamber)	25 months	0, 3.75, 12.38, 37.50	99.9%	Mononuclear cell leukemia, brain glioma	A
Male Fischer 344 rats	Inhalation (chamber)	104 weeks	0, 18.59, 37.18	99.7%	Mononuclear cell leukemia, peritoneal mesothelioma, brain glioma	B
Female Sprague-Dawley rats	Gavage	150 weeks	0, 2.20, 8.82	99.7%	Forestomach squamous cell carcinoma, forestomach fibrosarcoma	C
Male B6C3F$_1$ mice	Inhalation (chamber)	102 weeks	0, 18.32, 36.64	>99%	Alveolar/bronchiolar adenoma or carcinoma, harderian gland papillary cystadenoma	D
Female B6C3F$_1$ mice	Inhalation (chamber)	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	D

Abbreviations: mg/kg-day – milligrams per kilogram per day; Ref – Reference(s)

(A) Snellings et al. (1981; 1984) and Garman et al. (1985)

(B) Lynch et al. (1984)

(C) Dunkelberg (1982)

(D) The National Toxicology Program (NTP, 1987)

In the NTP (1987) studies in male and female $B6C3F_1$ mice, groups of 50 mice were exposed by inhalation to EtO concentrations of 0 (control), 50, or 100 ppm, 6 hours per day, 5 days per week for 102 weeks. According to NTP (1987), the animals received a total of 487 exposures throughout the study. The lifetime average daily EtO doses administered in the studies were calculated by OEHHA to be 0, 18.32, and 36.64 mg/kg-day, respectively, for male mice and 0, 19.21, and 38.42 mg/kg-day, respectively, for female mice. Survival was not affected by EtO treatment 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 (36.64 mg/kg-day)-dose group relative to the control ($p = 0.001536$), as well as a significant trend for the overall dose response (Table 4). In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in both the low (18.32 mg/kg-day)- and high-dose groups compared to the control ($p = 0.008121$ and $p = 0.01053$, respectively), with a significant trend overall (Table 4).

In female mice, statistically significant increases in the incidences of combined alveolar/bronchiolar adenoma or carcinoma ($p = 1.2 \times 10^{-5}$), malignant lymphoma ($p = 0.01085$), and combined uterine adenoma or carcinoma ($p = 0.0456$) were observed in the high (38.42 mg/kg-day)-dose group compared to the control, all with significant dose-response trends (Table 4). In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in both the low (19.21 mg/kg-day)- and high-dose groups ($p = 0.03428$ and $p = 0.02657$, respectively) with a significant trend (Table 4). A statistically significant increase in combined mammary adenocarcinoma or adenosquamous carcinoma was also observed in the low-dose female mice compared to the controls ($p = 0.02707$).

Table 4. Tumor incidences of treatment-related lesions in male and female B6C3F$_1$ mice administered ethylene oxide (EtO) by inhalation (NTP, 1987).[a]

Experiment	Tumor site and type	Tumor Incidence			Exact trend test *p*-value
		0 ppm EtO	50 ppm EtO	100 ppm EtO	
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

Abbreviation: NS – Not statistically significant ($p \geq 0.05$).

(a) The lifetime average daily EtO doses administered in the studies were calculated by OEHHA 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 exposed to 0 (control), 50, and 100 ppm EtO, respectively. Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined at a specified tumor site and alive at the time of first occurrence of the tumor. Treatment group tumor incidences with asterisks indicate statistically significant results from Fisher pairwise comparisons with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The exact trend tests were also conducted by OEHHA.

In the studies of male and female Fischer 344 rats by Snellings (1981; 1984), Garman (1985), and colleagues, groups of 120 rats were exposed to EtO by inhalation at

concentrations of 0 (2 groups; control), 10, 33, or 100 ppm, 6 hours per day, 5 days per week for 2 years. Snellings et al. (1981) reported that the animals received a total of 525 exposures throughout the studies. The lifetime average daily EtO doses administered in the studies were calculated by OEHHA to be 0, 3.13, 10.32, and 31.27 mg/kg-day, respectively, for male rats and 0, 3.75, 12.38, and 37.50 mg/kg-day, respectively, for female rats. Mortality appeared to increase in males and females in the high-dose groups (31.27 and 37.50 mg/kg-day, respectively) compared to controls after 22 months of exposure. However, this finding was not statistically significant.

A statistically significant increase in the incidence of mononuclear cell leukemia was observed in the mid (10.32 mg/kg-day)- and high (31.27 mg/kg-day)-dose groups compared to controls in the male rat study (p = 0.01935 and p = 0.03826 respectively), with a significant dose-response trend (Table 5). Statistically significant increases in the incidences of testicular peritoneal mesothelioma and brain glioma were also observed in high-dose male rats compared to controls (p = 0.02747 and p = 0.005341, respectively), along with significant trends (Table 5).

In female rats, a statistically significant increase in the incidence of mononuclear cell leukemia was observed in all treated groups compared to controls (p = 0.04522, p = 0.002217, and $p = 3.316 \times 10^{-7}$, respectively), with a significant dose-response trend (Table 5). A significant trend in brain glioma was also observed (Table 5).

Table 5. Tumor incidences of treatment-related lesions in male and female Fischer 344 rats administered ethylene oxide (EtO) by inhalation (Snellings et al. 1981, 1984; Garman et al. 1985).[a]

Experiment	Tumor site and type	Tumor Incidence				Exact trend test *p*-value
		0 ppm EtO	10 ppm EtO	33 ppm EtO	100 ppm EtO	
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	$p < 0.05$

[(a)] The lifetime average daily EtO doses administered in the studies were calculated by OEHHA 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 exposed to 0 (control), 10, 33, and 100 ppm EtO, respectively. 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 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). 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 (Garman et al., 1985). The control (0 ppm) 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): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The exact trend tests were also conducted by OEHHA.

In the Lynch et al. (1984) study in male Fischer 344 rats, groups of 80 rats were exposed to EtO by inhalation at concentrations of 0 (control), 50, or 100 ppm, 7 hours per day, 5 days per week for 104 weeks. The lifetime average daily EtO doses

administered in the studies were calculated by OEHHA to be 0, 18.59, and 37.18 mg/kg-day, respectively. Lynch et al. (1984) noted that body weights were statistically significantly decreased in all EtO-exposed groups ($p < 0.05$), and survival was significantly decreased in the high (37.18 mg/kg-day)-dose group ($p < 0.01$) compared to the control. A bacterial outbreak began eight months into the study. However, the animals continued the planned inhalation exposures other than a two-week period during the 16th month of the study. The study authors suggested that the outbreak alone and in combination with EtO exposure contributed to the decrease in survival (Lynch et al., 1984).

Statistically significant increases in the incidence of peritoneal mesothelioma (of testicular origin) and brain glioma were observed in the high-dose group ($p = 4.953 \times 10^{-5}$ and $p = 0.03226$, respectively), and a statistically significant increase in mononuclear cell leukemia was observed in the mid (18.59 mg/kg-day)-dose group compared to controls ($p = 0.02269$). Significant trends in peritoneal mesothelioma and brain glioma were also observed (Table 6).

Table 6. Tumor incidences of treatment-related lesions in Fischer 344 male rats administered ethylene oxide (EtO) by inhalation (Lynch et al. 1984).[a]

Tumor site and type	Tumor Incidence			Exact trend test *p*-value
	0 ppm EtO	50 ppm EtO	100 ppm EtO	
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*	$p < 0.05$

Abbreviation: NS – not statistically significant ($p \geq 0.05$).

[(a)] The lifetime average daily EtO doses administered in the studies were calculated by OEHHA to be 0, 18.59, and 37.18 mg/kg-day for rats exposed at 0 (control), 50, and 100 ppm, respectively. Tumor incidences are expressed as the number of tumor-bearing animals over the number of animals for which histopathological diagnosis was performed (Lynch et al., 1984). Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparisons with controls (conducted by OEHHA): * $p < 0.05$, *** $p < 0.001$. The Exact trend tests were also conducted by OEHHA.

The Dunkelberg (1982) study had significant uncertainties regarding the animal body weights, inability to adjust for intercurrent mortality[2], and twice-weekly bolus dosing regime[3]. Intercurrent mortality refers to deaths due to a cause unrelated to the tumors of interest. Dunkelberg (1982) reported increases in the incidences of forestomach squamous cell carcinoma and forestomach fibrosarcoma in female rats. The cancer incidences at EtO daily doses of 0 (control), 7.5, and 30 milligrams per kilogram of body weight (mg/kg BW) were 0/50, 8/50, and 29/50, respectively, for forestomach squamous cell carcinoma and 0/50, 0/50, and 2/50, respectively, for forestomach fibrosarcoma. The results for forestomach squamous cell carcinoma were statistically significant by pairwise comparison with control at 7.5 and 30 mg/kg BW ($p = 0.0029$ and $p = 5.4 \times 10^{-12}$, respectively) and by trend test using lifetime average daily doses of 0, 2.20, and 8.82 mg/kg BW ($p = 2.4 \times 10^{-12}$) but the study suffers from notable uncertainties for use in quantitative risk assessment.

Epidemiological studies

OEHHA identified three human epidemiological studies of ethylene oxide and cancer with quantitative exposure estimates in persons who were occupationally exposed (Steenland et al., 2003, 2004 (i.e., the NIOSH study); Swaen et al., 2009; and Mikoczy et al., 2011; Table 7 below). Given the available data from and discussion of these studies in US EPA's (2016a) EtO Integrated Risk Information System (IRIS) assessment, the studies were determined by OEHHA to be the most sensitive epidemiologic studies of sufficient quality. This determination considered such factors as the selection of the exposed and reference groups, reliable ascertainment of exposure, and completeness of follow-up, as well as biases and confounding factors.

The NIOSH study was determined to be the most sensitive epidemiologic study of sufficient quality for this quantitative risk assessment due to the 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 EtO exposure collected prior to cancer diagnosis, 5) diversity of data and subgroups (sex and race/ethnicity) which

[2] Dunkelberg (1982) reported increased mortality in the high (30 mg/kg BW)-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.

[3] Animals were dosed via gavage twice per week over a 150-week period, except for weeks 79–82, when dosing was interrupted due to the occurrence of pneumonia in several of the animals in the study.

allowed for exploratory sub-analyses of potentially susceptible populations, and 6) very high exposures incurred in the cohort which increased the sensitivity of the study to detect an effect.

Four epidemiological studies not included in the US EPA's IRIS assessment were identified by OEHHA (Garcia et al., 2015; Bulka et al., 2016; Hart et al., 2018; and Jones et al., 2023). These studies investigated associations between residential proximity to EtO-emitting facilities and increased cancer risk. Emissions data were obtained at the community level from US EPA's TRI (Bulka et al., 2016; Jones et al., 2023; US EPA, 2023a) and National Air Toxics Assessment (Garcia et al., 2015; Hart et al., 2018; US EPA, 2018) databases. While these community-based air pollutant studies can be useful for hazard identification, they were judged by OEHHA to be less useful for dose-response assessment of EtO compared to the occupational studies (Steenland et al., 2003 and 2004; Swaen et al., 2009; and Mikoczy et al., 2011) due to greater uncertainty in estimating individual exposures. This can result in non-differential exposure misclassification, and bias in risk estimates towards the null (Shy et al., 1978). Furthermore, there were lower exposure levels, fewer exposed cases, and potentially less exposure contrast in these community-based studies of EtO, decreasing the sensitivity of the studies to detect an effect.

Overall, the retrospective cohort study (Steenland et al., 2003; Steenland et al., 2004) by the National Institute for Occupational Safety and Health (NIOSH) was determined by OEHHA to be the most sensitive epidemiologic study of sufficient quality, considering such factors as the selection of the exposed and reference groups, reliable ascertainment of exposure, and completeness of follow-up, as well as biases and confounding factors.

Table 7. Overview of human epidemiological studies of ethylene oxide (EtO) and cancer with quantitative exposure estimates.

Population description	Exposure assessment method and levels	Key results	Comments	Refs
Population: National Institute for Occupational Safety and Health (NIOSH) cohort; >18,000 workers from 14 plants in 11 states exposed at least three months to EtO from the 1940s–1980s, with 461,000 person-years[a] 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. Cumulative exposure levels (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[b] (95% CIs[c]) for **lymphoid cancer mortality** in men by category of cumulative exposure (ppm-days) lagged[d] 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).	This is the largest existing cohort of EtO-exposed workers. The study included a 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 the 1) high quality of the exposure assessment; 2) absence of confounding co-exposures; 3) large cohort size and adequate statistical power; 4) information on EtO exposure collected prior to cancer diagnosis;	e

Abbreviations: CI – confidence interval; ppm – parts per million; ppm-days – parts per million-days; ppm-years – parts per million-years; SD – standard deviation.

(a) Person-years are an estimate of the actual years-at-risk that all persons contributed to a study (UNC, 2023).

(b) An odds ratio is the odds of disease in exposed persons divided by the odds of disease in unexposed persons. An odds ratio greater than 1.0 indicates that the exposure may increase the risk of cancer (NIH, 2023b).

(c) A confidence interval is a range around a measurement that conveys how precise the measurement is (NYDH, 2023).

(d) A lag period is a period before death or the end of follow-up during which any workplace EtO exposure that occurred is not included in the analysis. Lag periods are used to account for the fact that many occupationally or environmentally caused cancers are not diagnosed until many years after exposure begins (Selikoff et al., 1980; Archer et al., 2004; Marshall et al., 2007; Lipfert and Wyzga, 2019).

(e) US EPA (2016a), Steenland et al. (2004; analyses of mortality data), and Steenland et al. (2003; analyses of breast cancer incidence)

Table 7. Overview of human epidemiological studies of ethylene oxide (EtO) and cancer with quantitative exposure estimates (continued).

Population description	Exposure assessment method and levels	Key results	Comments	Refs
Population: NIOSH cohort (continued)	See above.	Odds ratios (95% CIs) 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). Odds ratios (95% CIs) for **breast cancer incidence** by category of cumulative exposure (ppm-days) lagged 15 years (categories: 0, >0–646, 647–2026, 2026–4919, 4919–14,620, >14,620 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).	5) diversity of data and subgroups (men and women, Blacks and whites) allowed for exploratory sub-analyses of potentially susceptible populations; and 6) very high exposures incurred in the cohort which increased the sensitivity of the study to detect an effect.	e

Abbreviations: CI – confidence interval; ppm-days – parts per million-days; NIOSH – National Institute for Occupational Safety and Health; Refs - references.
(e) US EPA (2016a), Steenland et al. (2004; analyses of mortality data), and Steenland et al. (2003; analyses of breast cancer incidence)

Table 7. Overview of human epidemiological studies of ethylene oxide (EtO) and cancer with quantitative exposure estimates (continued).

Population description	Exposure assessment method and levels	Key results	Comments	Refs
Population: Union Carbide cohort; 2063 male EtO workers exposed 1940–1988 with 75,316.2 person-years of observation. Follow-up until 2003.	Method: A matrix was developed to estimate cumulative EtO 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.	f
Population: Swedish sterilizers; 2171 male and female workers employed for at least one year in two plants in Sweden producing medical equipment sterilized with EtO (exposed 1925–1988). Follow-up until 2003.	Method: Cumulative exposure to EtO was estimated from plant specific job-exposure matrices combined with yearly statutory hygienic measurements. Levels: Cumulative exposure (ppm-years): mean = 2.92, median = 0.13.	No statistically significant excesses in cancers when compared to general population (external analyses). Internal analyses (i.e., within the study population) 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.	Exposures were much lower than in the NIOSH and Union Carbide cohorts, which decreases the ability to detect an effect.	g

Abbreviations: CI – confidence interval; NIOSH – National Institute for Occupational Safety and Health; ppm-years – parts per million-years; Refs - references.
(f) Swaen et al. (2009) [follow-up of Greenberg et al. (1990) and Teta et al. (1993)]
(g) Mikoczy et al. (2011) [follow-up of Hagmar et al. (1995) and Hagmar et al. (1991)]

Table 7. Overview of human epidemiological studies of ethylene oxide (EtO) and cancer with quantitative exposure estimates (continued).

Population description	Exposure assessment method and levels	Key results	Comments	Refs
Population: Swedish sterilizers (continued)	See above.	Incidence rate ratios (95% CIs) 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% CIs) 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)	See above.	g

Abbreviations: CI – confidence interval; ppm-years – parts per million-years; Refs - references.
(g) Mikoczy et al. (2011) [follow-up of Hagmar et al. (1995) and Hagmar et al. (1991)]

NIOSH study

The NIOSH retrospective cohort study (Steenland et al., 2003; Steenland et al., 2004) used by US EPA to calculate the 2016 adult-exposure-based EtO IRIS IUR ("US EPA's IUR" hereafter) was thoroughly evaluated by OEHHA. The study involved more than 18,000 workers exposed to EtO at 14 US sterilization facilities. 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 EtO-exposed workers were involved with sterilizing medical supplies, treating spices, and manufacturing and testing of medical sterilizers. Mortality (including lymphoid cancer mortality) and breast cancer incidence were assessed. The cohort was assembled by NIOSH and included all employees who worked at one of the included facilities for at least 3 months for the mortality analyses or 12 months for the breast cancer incidence analyses. Each participant's EtO 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 were acquired between 1976 and 1985 from 18 different sterilization facilities, including 2700 individual time-weighted exposure values for workers' personal breathing zones. Further details on the exposure model can be found elsewhere (Hornung et al., 1994; Steenland et al., 2003; Steenland et al., 2004; US EPA, 2016a). Cancer or mortality follow-up was through December 31, 1998, the date of death or breast cancer diagnosis, or the date of loss to follow-up, whichever was earlier.

The NIOSH study was judged by US EPA 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 use of internal comparison groups. The NIOSH study was also reviewed by OEHHA, using the Bradford-Hill guidelines for causal inference and NTP's risk of bias tool (Hill, 1965; NTP, 2019), and determined to be 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 EtO exposure levels) were 0.90 (95% confidence interval (CI), 0.88–0.93) and 0.98 (95% CI, 0.92–1.03), respectively

(Steenland et al., 2004). An SMR is a ratio of the number of deaths observed in a study population over a period of time to the number that would be expected over the same period if the study population had the same rates as the standard population (INED, 2023). A total of 53 deaths due to lymphoid cancer (International Classification of Diseases 9th revision codes 200, 202, 203, and 204) were identified by the study. Lymphoid cancer was a particular focus of this study since it was shown to be elevated in an earlier analysis of this cohort (Stayner et al., 1993).

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 EtO-associated relative risks (RRs) were elevated in both sexes, and the difference between sexes was not statistically significant. Relative risk is the probability of an event occurring in an exposed group divided by the probability of that event occurring in a non-exposed group (Tenny and Hoffman, 2022). In initial analyses, results were calculated by the NIOSH researchers using different lag periods, and 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 EtO exposure that occurred is not included in the analysis. Lag periods are used to account for the fact that many occupationally or environmentally caused cancers are not diagnosed until many years after exposure begins (Selikoff et al., 1980; Archer et al., 2004; Marshall et al., 2007; Lipfert and Wyzga, 2019).

The results for lymphoid cancer mortality using a 15-year lag and an internal comparison group are shown in Table 8. 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 (McNamee, 2003).

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 8, odds ratios (ORs) were greater than 1.0 in all non-reference categories of exposure. An odds ratio greater than 1.0 indicates that the exposure may increase the risk of cancer (NIH, 2023). The ORs increased from the lowest (>0–1,200 ppm-days; OR = 1.75) to the second lowest (1201–3680 ppm-days; OR = 3.15) non-reference exposure category and appeared to plateau in the other exposure categories. Such plateaus may be due to factors like the depletion of susceptible subpopulations, mismeasurement at higher exposures, or healthy worker survivor effect and were noted by US EPA (2016b) to have been seen for other carcinogens. The NIOSH researchers noted that peak and average exposures did not predict cancer risk as

well as cumulative exposure although detailed results for these metrics were not provided.

Table 8. Odds ratios for lymphoid cancer mortality by categories of cumulative ethylene oxide (EtO) exposure, males and females combined, 15-year exposure lag (US EPA, 2016a)

Cumulative EtO 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
3681–13,500	2.44	0.80–7.50	10
>13,500	3.00	1.02–8.45	13

Abbreviations: CI – confidence interval; N – number of lymphoid cancer deaths; ppm – parts per million; ppm-days – parts per million-days.

(a) 15-year exposure lag

(b) Adjusted or matched on age, sex, and race

Breast Cancer Incidence

The breast cancer portion of the NIOSH study (Steenland et al., 2003) involved 7576 women and 319 cases of incident breast cancer. 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 US EPA's exposure-response analyses were limited to the 5139 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. With carcinoma *in situ*, abnormal (cancer) cells are found only in the place where they first formed (i.e., they haven't spread to other parts of the body). 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 (the number of births carried to a viable gestational age), and family history of breast cancer. Information on body 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 the Steenland et al. (2003) study. As noted above, the study was deemed by US EPA to be of "high quality." OEHHA's evaluations of the study led to the same conclusion.

The NIOSH study results for breast cancer incidence are presented in Table 9. The average duration of exposure was 10.7 years, and the median cumulative EtO 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 reference exposure category is the unexposed group/group with no EtO exposure and an OR of 1. All other groups are compared to this group. The numbers of cases in the other exposure categories were not provided. However, given that the standard errors for the ORs in these other categories were very similar, the number of cases in each of these categories (not reported) was likely similar as well (e.g., approximately 34–35 cases each). As shown in Table 9, the ORs for breast cancer were greater than 1.0 in all non-reference categories except the second from the lowest (647–2026 ppm-days). The upper CI of 1.60 for the OR in this category highlights the possibility that RRs could be elevated in this category as well. The OR in the highest exposure category (>14,620 ppm-days) was statistically significant (OR = 1.87; 95% CI, 1.12–3.10).

Table 9. Odds ratios for breast cancer incidence in females by categories of cumulative ethylene oxide (EtO) exposure, 15-year exposure lag (Steenland et al., 2003.

Cumulative EtO 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
4919–14,620	1.42	0.88–2.29
>14,620	1.87	1.12–3.10

Abbreviation: CI – confidence interval; ppm-days – parts per million-days

(a) 15-year exposure lag

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

Toxicokinetics

The toxicokinetics (absorption, distribution, metabolism, and excretion) of EtO have been reviewed in recent reports by US EPA (2016a) and the Agency for Toxic Substances and Disease Registry (ATSDR, 2022). Much of the current understanding regarding the toxicokinetics of EtO has been gained from studies of rodents exposed to EtO via inhalation, e.g., Brown et al. (1996; 1998). However, occupational studies of inhalation-exposed workers (Brugnone et al., 1985; 1986) and *in vitro* examinations of inter-species differences (Csanády et al., 2000; Fennell and Brown, 2001) have provided additional insights into the toxicokinetics of EtO.

The overall literature indicates that inhaled EtO is efficiently absorbed into the blood through the respiratory tract (US EPA, 2016a). The ventilation rate of the exposed individual and the EtO air concentrations are the primary factors affecting the uptake of inhaled EtO due to its solubility in blood (IARC, 2008). Following absorption, EtO is rapidly distributed to all tissues, readily binding to proteins (e.g., hemoglobin; Hb) and deoxyribonucleic acid (DNA) in tissues throughout the body (US EPA, 2016a). EtO metabolism occurs via two pathways (hydrolysis and glutathione [GSH] 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), is proposed to contribute to approximately 80%, 40%, and 20% of the EtO metabolism in humans, rats, and mice, respectively. This metabolic pathway leads to the stepwise 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 GSH conjugation of EtO 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). GST-mediated metabolism rates are nearly two orders of magnitude faster than EH-mediated ones in the rodent liver and approximately two-fold faster in the human liver (Filser and Klein, 2018). Thus, rats and mice may be more likely to experience GSH depletion, decreased capacity to rapidly detoxify EtO, and increased EtO concentrations in blood relative to humans at exposure concentrations >100 ppm (182 mg/m^3; Filser and Klein, 2018).

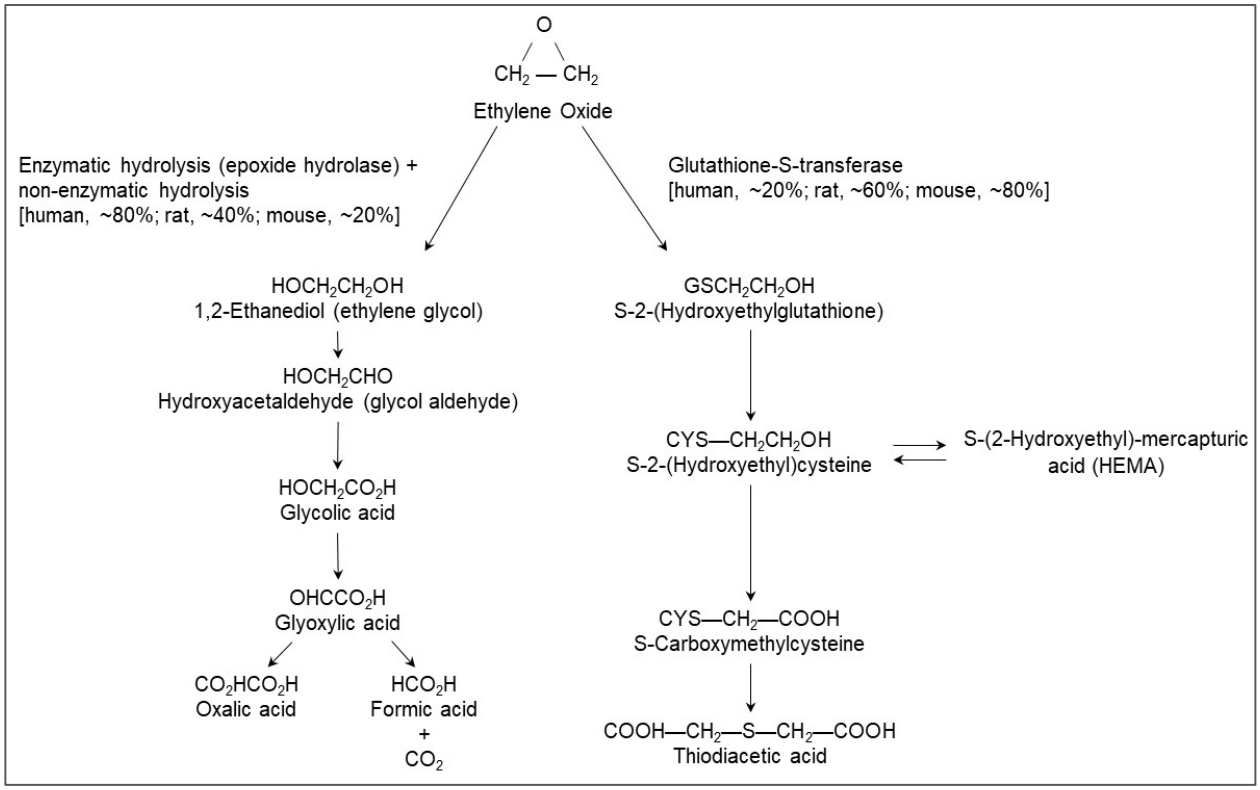


Figure 1. Proposed metabolic scheme for ethylene oxide. Adapted from IARC (2008) and ATSDR (2022).

Elimination of EtO is thought to follow first-order kinetics (Filser and Bolt, 1984) for exposures up to 200 ppm (365 mg/m^3). Thus, at ≤200 ppm (365 mg/m^3), EtO elimination depends upon its concentration in the body, and a constant fraction of EtO is eliminated per unit of time. EtO elimination half-lives ($t_{1/2's}$) 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), rats exposed at 100 ppm (182 mg/m^3) for 4 hours (Brown et al., 1996; Csanády et al., 2000) , and mice exposed at 1 ppm (1.8 mg/m^3) for 1 hour (Ehrenberg et al., 1974) or 100 ppm (182 mg/m^3) for 4 hours (Csanády et al., 2000), respectively. Cumulatively, these studies suggest to OEHHA that EtO is eliminated faster in rats and mice than humans at exposure concentrations ≤100 ppm (182 mg/m^3).

Physiologically-based pharmacokinetic or toxicokinetic (PBPK) models of EtO have shown comparable blood concentrations across humans, rats, and mice over a limited exposure range (Csanády et al., 2000; Fennell and Brown, 2001). The model simulations of peak blood EtO concentrations and areas under the curves (AUCs, i.e., the total chemical exposures reaching the blood over time) in humans, rats, and mice exposed at ≤100 ppm (182 mg/m^3) are approximately equal and linearly related to the inhaled EtO concentrations (Fennell and Brown, 2001; US EPA, 2016a).

The one PBPK model published after the US EPA's EtO IRIS assessment (2016a; 2016b) is that of Filser and Klein (2018; Figure 2 below). In this PBPK model, most of the parameter values were obtained from the literature, calculated, allometrically scaled across species, or assumed to be tissue- or species-independent. Data sets were taken from several past studies on human toxicokinetics (Brugnone et al., 1986; Filser et al., 2013) and Hb- or DNA-adduct formation post EtO exposure (Duus et al., 1989; Lewalter, 1996; Angerer et al., 1998; Boogaard et al., 1999; Yong et al., 2001) for model validation.

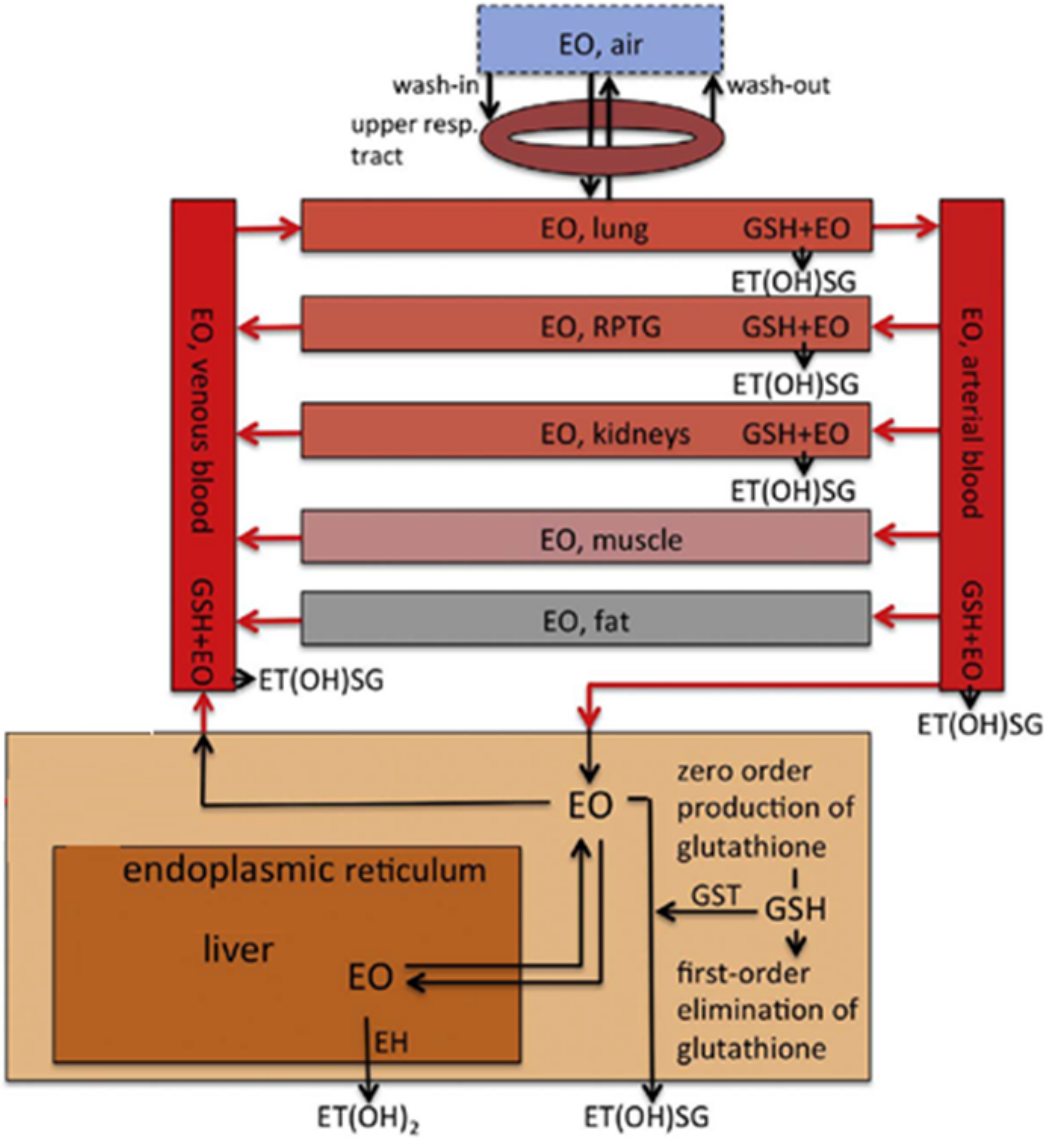


Figure 2. Schematic structure of the PBPK model for inhaled ethylene oxide. The diagram was reproduced from Filser and Klein (2018; Figure 1) with modifications. Compartments in solid lines are characterized by defined volumes; the air compartment (dotted lines) can have a defined volume or can be infinitely large, depending on the exposure condition. Symbols: Red arrows – transport in the blood; black arrows – uptake or elimination. Abbreviations: EH – epoxide hydrolase (microsomal); EO – ethylene oxide, abbreviated "EtO" elsewhere in this document; ET – ethylene; ET(OH)SG – S-(2-hydroxyethyl)glutathione; $ET(OH)_2$ – ethylene glycol; GSH – glutathione (reduced); GST – glutathione S-transferase (cytosolic); PBPK – physiologically-based pharmacokinetic/toxicokinetic; RPTG – richly perfused tissue group.

The predicted blood EtO concentrations, adduct levels, and ratio of EtO in exhaled versus inhaled air over time agreed with published data. See, for example, Figures 3 and 4 below.

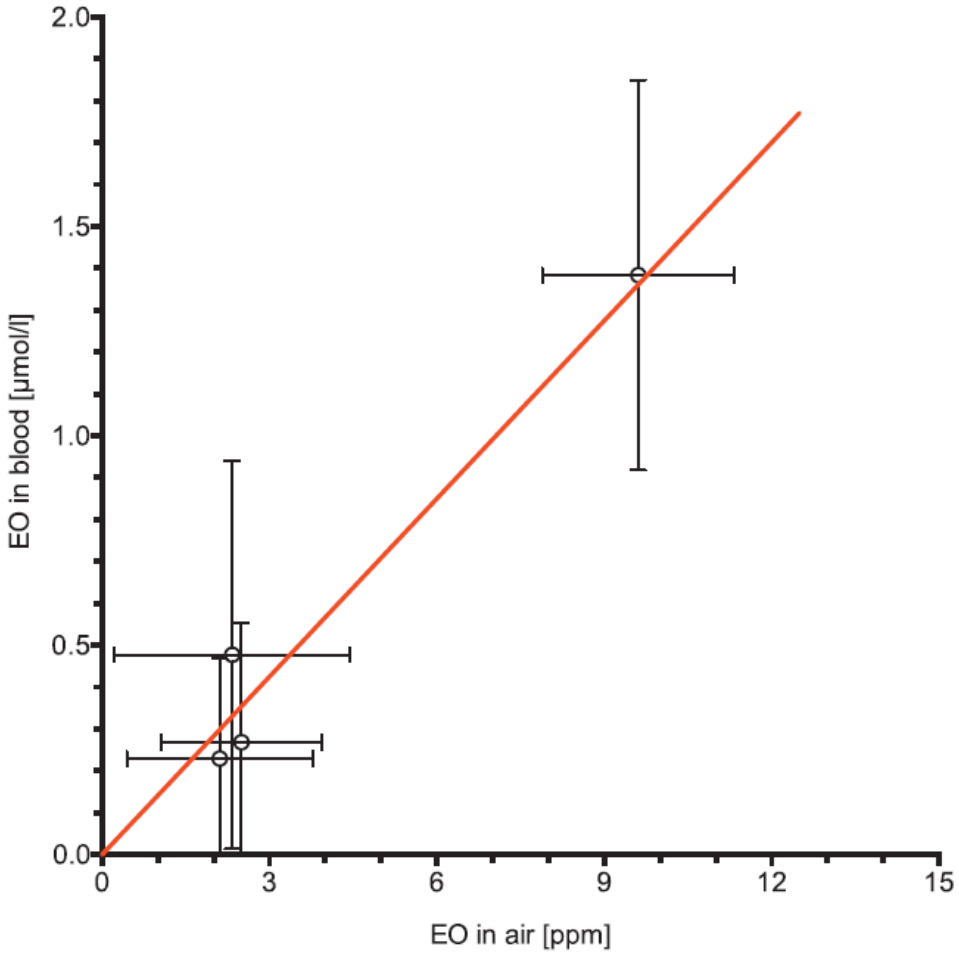


Figure 3. Ethylene oxide concentrations in venous blood of humans exposed to atmospheric ethylene oxide. The graph was reproduced from Filser and Klein (2018; Figure 3). Circles and error bars represent means ± standard deviations (n = 9) of the data measured in workers for 4 hours and 8 hours of 8-hour workshifts in a hospital sterilizer unit (Brugnone et al., 1986). The solid diagonal red line represents the curve obtained by the Filser and Klein (2018) PBPK model, assuming a 70-kg BW and an 8-hour exposure period. The modeled curve has the same slope as a linear regression of the measured data. Abbreviations: BW – body weight; EO – ethylene oxide, abbreviated "EtO" elsewhere in this document; kg – kilogram; µmol/l – micromoles per liter; n – number; PBPK – physiologically-based pharmacokinetic/toxicokinetic; ppm – parts per million.

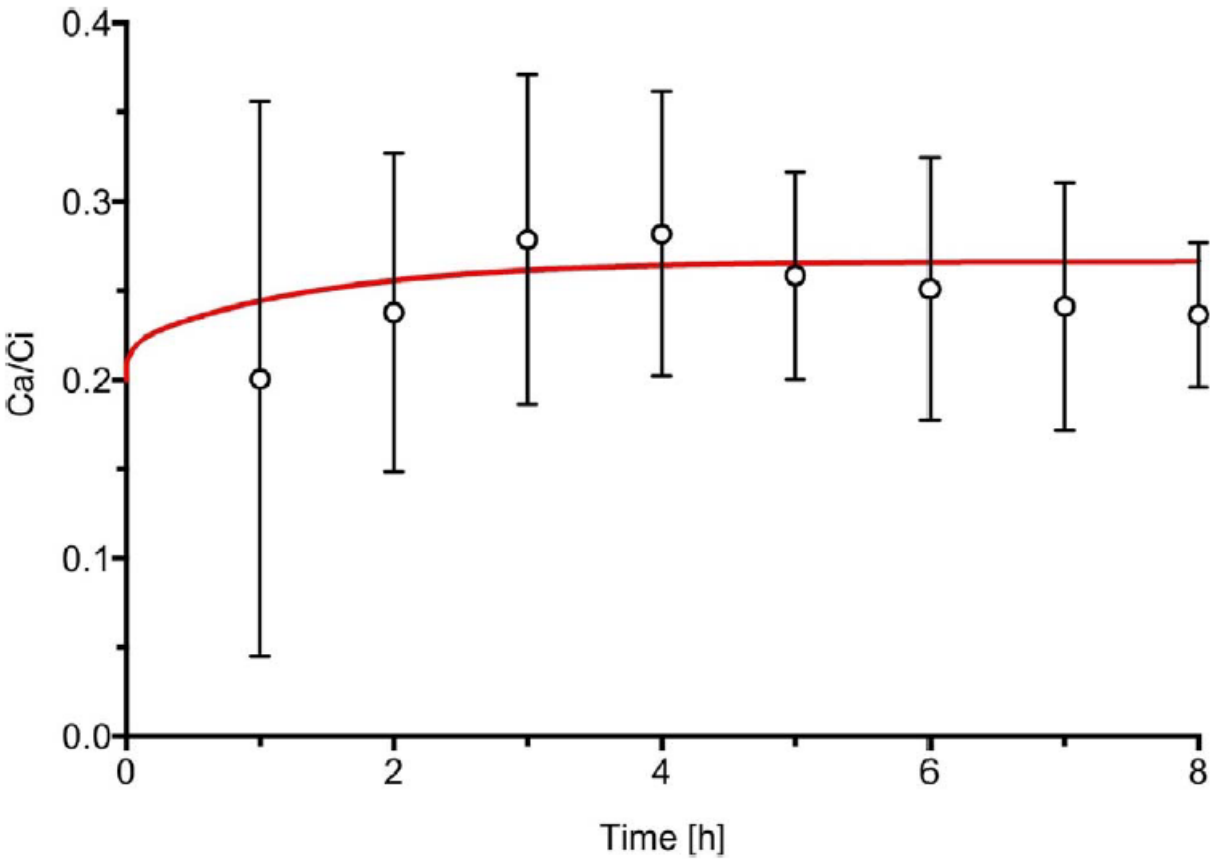


Figure 4. Ratio of ethylene oxide (EtO) in the exhaled alveolar air (Ca) to EtO in the breathing area (Ci) as a function of time. The graph was reproduced from Filser and Klein (2018; Figure 9). The ratios were measured in 10 humans occupationally exposed to EtO (Brugnone et al., 1985) and graphed by Filser and Klein (2018) as circles with error bars (means ± SDs) for comparison to the modeled curve for a subject with a 70-kg BW. Abbreviations: BW – bodyweight; kg – kilogram; SD – standard deviation.

The PBPK model was consistent with previous findings by Fennell and Brown (2001). Filser and Klein (2018) reported that according to their PBPK model, the GST-mediated pathway would decrease in favor of the EH-mediated one in mice and rats at EtO concentrations ≥200 ppm (365 mg/m^3). This GSH-depletion-mediated change was more evident in the mouse than in the rat (Figure 5). For example, assuming that GST and EH accounted for 100% of the total enzyme-mediated EtO metabolism, Filser and Klein (2018) reported that over an exposure range of 0.5–500 ppm (0.91–911 mg/m^3), model-predicted GST-mediated metabolism dropped by 33% and 21% in the mouse and rat, respectively. Concurrent increases of 33% and 21% were predicted for EH-mediated metabolism in the mouse and rat, respectively. In contrast, human exposures of 0.5–500 ppm (0.91–911 mg/m^3) produced a minor (0.8%)

increase in GST-mediated metabolism (Figure 5) and a decrease in EH-mediated metabolism.

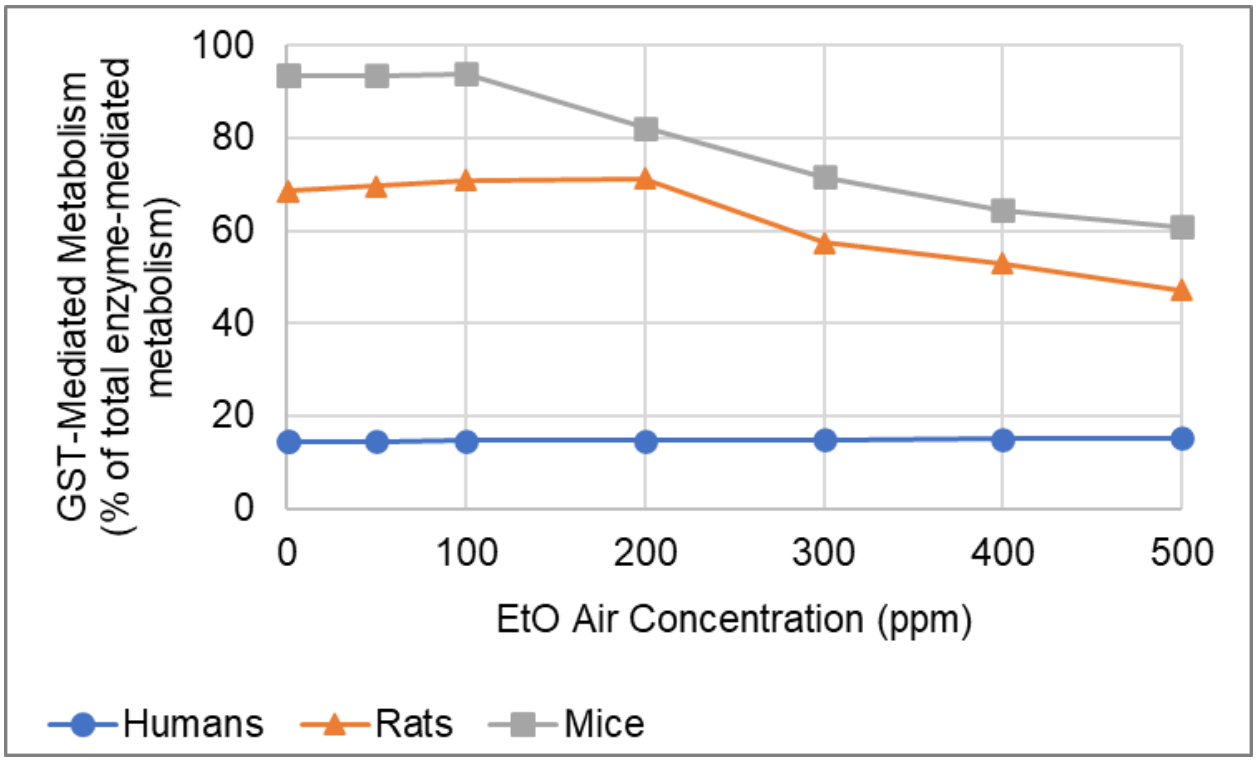


Figure 5. Physiologically-based toxicokinetic model predictions for the effect of EtO exposure concentration on the percentage of EtO metabolized by GST. Adapted from Filser and Klein (2018, Table 8). Corresponding EH-mediated metabolism not shown. Abbreviations: EH – epoxide hydrolase enzyme; EtO – ethylene oxide; GST - glutathione-S-transferase enzyme; ppm – parts per million.

Another notable finding was related to individuals with a *GSTT1*0* genotype. The *GSTT1*0* genotype is a deletion polymorphism in the *GSTT1* gene, resulting in a lack of GSTT1 activity. Citing research by Bolt and Thier (2006), Filser and Klein (2018) stated that approximately 10–62% of the population, depending on race and ethnicity, may have a *GSTT1*0* genotype. The PBPK model predicted an 11% increase in the N-(2-hydroxyethyl)-valine (HEV) adduct levels of *GSTT1*0* carriers relative to individuals with the normal *GSTT1* gene when exposed under identical conditions to 1 ppm of EtO. HEV adducts result from EtO alkylation of valine in Hb. However, given EH- and GST-mediated EtO metabolism were predicted to account for approximately 85–86% and 14–15%, respectively, in a modeled 70-kg individual exposed for 6 hours to 0.5–500 ppm EtO, the authors considered GST-mediated EtO elimination in humans to be quantitatively minor relative to that of EH.

Endogenous Production of Ethylene Oxide

Endogenous production of EtO is known to result from ethylene metabolism in humans and other mammals (Filser et al., 2013). 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 (Csanády et al., 2000). Thus, all species and individuals are likely to be exposed to EtO endogenously, irrespective of their exogenous exposures to EtO in the air (Kirman et al., 2021).

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 EtO (endogenous + exogenous). Kirman et al. (2021) showed background exposures to EtO and ethylene in ambient air alone are insufficient to account for HEV levels seen in non-smokers, and endogenous EtO production contributes more to non-smoker HEV levels than ambient EtO and ethylene exposures do. The EtO 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, EtO 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).

Kirman et al. (2021) cited data on HEV adducts in smokers and non-smokers to argue that the cancer potency of EtO is low at low exposure levels. Their argument rested on a supposed lack of association between tobacco smoking and either lymphoid cancer or breast cancer, which they stated would be inconsistent with mean HEV adduct levels that are 7.5-fold higher in smokers than in non-smokers. IARC (2012), however, found 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). The study found an association between current smoking and non-Hodgkin lymphoma in women (RR = 1.37, 95% 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). This study found associations between tobacco smoking and Hodgkin lymphoma (1.45 per 10 cigarettes/day, 95% CI = 1.22–1.72) and mature T-cell malignancies (1.38 per 10 cigarettes/day, 95% CI = 1.10–1.73). These large-cohort findings support the plausibility of increased cancer risks from low concentrations of EtO.

While the hemoglobin adducts such as the HEV resulting from endogenous and exogenous EtO may serve as sensitive markers of EtO exposure, the paucity of data on their relationship with the relevant DNA adducts makes it a limiting factor for use in risk assessment (Rietjens et al., 2021). Alternatively, using the HEV levels to back-calculate endogenous-equivalent air concentrations of EtO is untenable at present as there are no relevant toxicokinetic models or data to support it. In this regard, ATSDR (2022) concluded that data are not available to demonstrate that background levels in non-smokers are direct indicators of internal, endogenous EtO exposures. Despite these limitations, Kirman et al. (2021) converted the background HEV levels in non-smokers to endogenous-equivalent air concentrations based on a relationship between HEV levels and air concentrations of EtO observed at occupational exposure levels. They concluded that the average endogenous HEV level in non-smokers is equivalent to an air concentration of 2.7 ppb. The dose-response relationship for endogenous EtO exposures might be different from the dose-responses seen with ambient exposures, possibly sublinear but ultimately unknown (US EPA, 2016a).

Genotoxicity

Studies on the genotoxicity of EtO have been reviewed by CDHS (1987), US EPA (2016a), several IARC monographs (1994; 2008; 2012), and ATSDR (2022). These studies were conducted in various *in vitro* and *in vivo* systems, with and without metabolic activation, and some were observational studies in exposed workers. US EPA (2016a) has summarized the numerous papers investigating the genotoxicity of EtO and concluded 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 (2016a) 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.”

IARC (2012) summarizes the evidence (shown in Table 10) and states the following regarding the genotoxicity of EtO:

> "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 hemoglobin 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 10. 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

Abbreviations: NR – not reported

(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

In its most recent toxicological profile for EtO, ATSDR (2022) 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 (Zeljezic et al., 2016) and one in children (Carlsson et al., 2017)) and a third study in Big Blue mice (Manjanatha et al., 2017). In the Zeljezic et al. (2016) study, workers exposed to a mixture of chemicals, including EtO, 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 ($p < 0.05$). The strict use of personal protective equipment for eight months diminished the levels of micronuclei and DNA damage (measured by comet assay) in the peripheral blood lymphocytes of the workers. The Carlsson et al. (2017) study was conducted using peripheral blood samples (n = 51) collected from school-age children by the Swedish National Food Agency. The study found that the frequency of micronuclei formation was positively associated with levels of EtO Hb adducts in erythrocytes (red blood cells). The Manjanatha et al. (2017) publication reported additional data from an earlier study (Parsons et al., 2013) conducted in Big Blue mice and found a statistically significant increase in the mutational frequency of the cll gene in lung tissues from mice exposed for 8 or 12 weeks to 200 ppm EtO via inhalation. Findings from these additional studies are consistent with the overall evidence for the genotoxicity of EtO.

V. CANCER HAZARD EVALUATION

Evaluations of the carcinogenicity of EtO undertaken by national and international health agencies point towards the same conclusion, evidence base, and mechanism of carcinogenicity.

- IARC (2012) concluded that EtO is “carcinogenic to humans” based on limited evidence in humans and sufficient evidence in animals supported by strong evidence of a genotoxic mechanism.
- EtO has been listed in the NTP’s Report on Carcinogens since 1985 and is now considered “known to be a human carcinogen” (NTP, 2021).
- US EPA (2016a) concluded with high confidence that EtO is “carcinogenic to humans” based on strong (but less than conclusive) epidemiological evidence, extensive evidence in animals, clear evidence of genotoxicity with a mutagenic mode of action, and strong evidence that key precursor events are anticipated to occur in humans and progress to tumors.

The present assessment agrees with the conclusions of these three agencies regarding the carcinogenicity of EtO.

VI. QUANTITATIVE CANCER RISK ASSESSMENT

For conducting a quantitative cancer risk assessment for EtO, human epidemiological studies are more relevant and sensitive than animal studies. In this regard, OEHHA concurred with US EPA’s approach and conclusions that the NIOSH study (Steenland et al., 2003; Steenland et al., 2004) is of high quality and is the best available study for conducting exposure-response analyses (US EPA 2016a; 2016b). As presented in the sections below, the US EPA concluded that a two-piece linear spline model is the best fitting and most accurate model for assessing the lower-exposure (general population) cancer risks of EtO. 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.” OEHHA was also unable to identify any new scientific information that would necessitate a change to the US EPA’s IUR. As such, the present update of OEHHA’s EtO IUR is based on US EPA’s 2016 analysis of the exposure-response relationship for EtO and the combined adult-exposure-based IUR for lymphoid cancer and breast cancer, as described below.

The process US EPA used to calculate the EtO cancer IUR was described as follows (US EPA, 2016a):

> “The unit risk estimates for cancer mortality and incidence were based on the human data from the NIOSH study (Steenland et al., 2003; Steenland et al., 2004). 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)[4] 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 lymphoid cancer unit risk estimate of 2.9×10^{-3} per $\mu g/m^3$ (5.3×10^{-3} per ppb), as cancer incidence estimates are generally preferred over mortality estimates."[5]

"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 $\mu g/m^3$ (1.5×10^{-3} per ppb) was obtained for breast cancer incidence. A unit risk estimate for breast cancer mortality

[4] Conversion equation: 1 ppm = 1830 $\mu g/m^3$

[5] Excess mortality is the difference between the observed number of deaths and expected number of deaths in a specific time period.

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 $\mu g/m^3$ (6.1×10^{-3} per ppb)."

Lymphoid Cancer Exposure-Response and IUR Calculations

The 1998 follow-up NIOSH study results for lymphoid cancer mortality were first published by the Steenland et al. in a peer-reviewed scientific journal in 2004. Since then, US EPA contracted with the study authors to perform additional exposure-response modeling and other analyses on these data (US EPA, 2016a). 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 8 where RR estimates initially increase with increasing exposure but tend to plateau at higher exposures. Focusing on individual data instead of categorical data, good fit in the lower-exposure ranges, parsimony, biologic plausibility, and other statistical considerations, US EPA (2016a; 2016b) concluded that a two-piece linear regression spline model with a knot at 1600 ppm-days (Figure 6) provided the best biologically plausible fit to the underlying NIOSH study data, especially in the lower exposure region. Other models, including the log-linear models (e.g., Cox regression) and the models using categorical data or exposure transformations, generally resulted in slopes that appeared to dramatically over- or under-predict the actual study results, especially in the lower-exposure ranges.

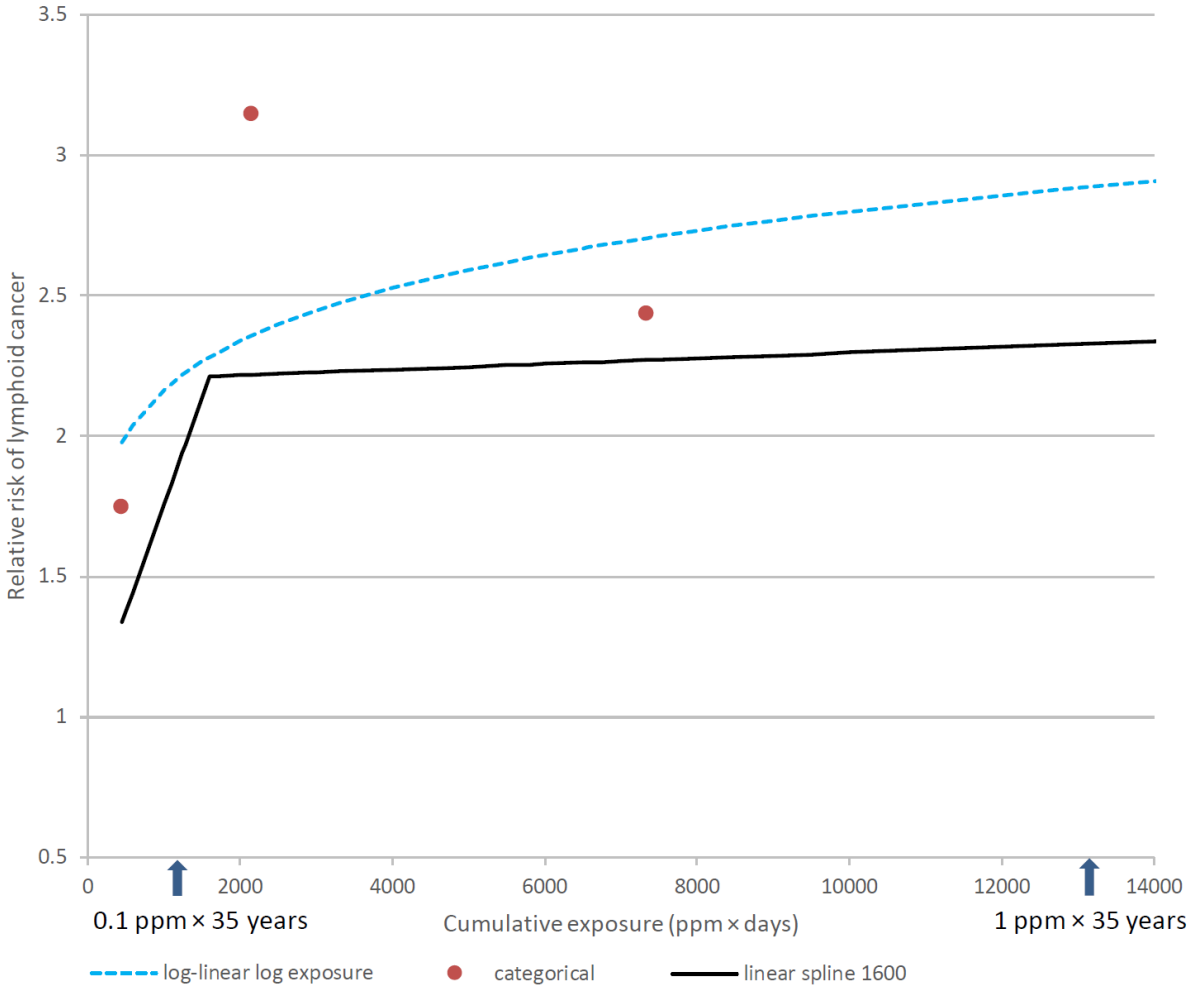


Figure 6. Relative risk estimates for lymphoid cancer from occupational ethylene oxide (EtO) exposures (with 15-year lag). The figure was modified from US EPA (2016a, Figure 4-9) by OEHHA to show the key below the graph. "Lymphoid cancer models: log cumulative exposure Cox regression model; categorical results; two-piece linear spline model with knot at 1600 ppm × days. [Note that, with the exception of the categorical results, the various models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of relative risk values (i.e., along the y-axis). They are, however, comparable in terms of general shape.]" OEHHA notes that there appear to be a couple of missing categorical data points from the original study. Additionally, the weaknesses of the log model aren't clear from the graph, so the log-linear-log line is somewhat deceptive.

Sensitivity analyses examining different knots in the two-piece spline model resulted in higher Akaike Information Criterion (AIC)[6] scores (e.g., 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. Excess relative risk is the relative risk minus 1.

Several exposure-response models were evaluated by OEHHA using the publicly available categorical data provided in the Steenland et al. (2004) publication or US EPA (2016a) EtO IRIS document. These models included weighted linear regressions, weighted least squares regressions, and generalized least squares regressions (Orsini et al., 2006; Lash et al., 2021). These involved 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 evaluated fit the underlying NIOSH study data better than the two-piece linear spline model selected by US EPA (2016a). OEHHA also considered running various exposure-response analyses using US EPA's Benchmark Dose Software (BMDS; Davis, 2011). However, the available data were presented as ORs, calculated by matching 100 randomly selected controls to each lymphoid cancer death. Although this methodology provides efficient and reliable estimates of relative risk (Steenland and Deddens, 1997), these ORs cannot be readily used in the BMDS, which requires information on absolute risks or rates. After an extensive and thorough evaluation of several 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 EtO. OEHHA evaluated the possibility that workers in the NIOSH cohort who had exposures of high intensity but low duration may have caused some bias or other form of exposure misclassification that affected the middle categories of cumulative exposure. Overall, little evidence of major bias or impacts on cancer unit risk estimates was identified. Further details on this particular analysis can be found in the "Additional Evaluations of Bias" section of the present document.

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[6] AIC values are estimators that allow for qualitative comparison of a group of models using a similar fitting method (continuous, in this case). When multiple usable models are found for the same data set, the model with the lowest AIC would be the presumptive better model (US EPA, 2012).

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 life-table approach was used because it considers other causes of mortality and accounts for the fact that baseline rates of lymphoid cancer vary by age. The occupational exposure levels reported by Steenland et al. (2004) were converted to lifetime (70-year) environmental exposure levels by adjusting for the amount of air breathed in per day (20 versus 10 m^3) 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 exposure-response relationship for lymphoid cancer incidence was assumed by US EPA to be 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 (Howlader et al., 2014). The analysis resulted in an EC_{01} and LEC_{01} of 7.48×10^{-3} and 1.90×10^{-3} ppm, respectively, and a cancer IUR for lymphoid cancer incidence of **$5.26\ (ppm)^{-1}$**. OEHHA replicated these life-table and IUR calculations and obtained the same result.

Breast Cancer Exposure-Response and IUR Calculations

The exposure-response models for breast cancer presented in Steenland et al. (2003) or US EPA (2016a) 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 rationale described 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 (Figure 7). Models using peak and average exposure did not fit the data as well. Model fits 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 (US EPA, 2016a; 2016b).

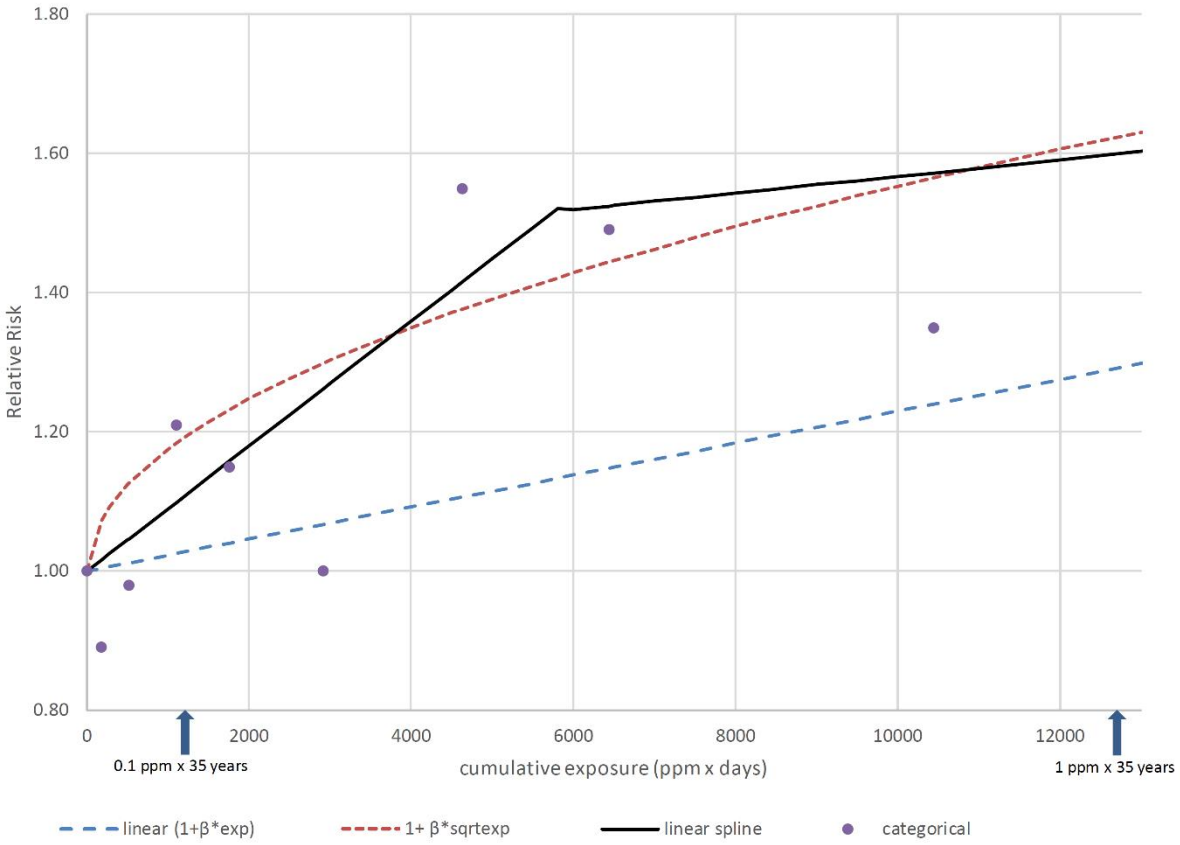

Figure 7. Relative Risk (RR) estimates for breast cancer incidence from occupational ethylene oxide (EtO) exposures (with 15-year lag). The figure was modified from US EPA (2016a, Figure 4-10) by OEHHA to show the key below the graph. Breast cancer models: linear two-piece spline model, with knot at 5,750 ppm × days; linear square-root cumulative exposure model; (continuous exposure) linear model; categorical results (deciles). [Note that the various models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values (i.e., along the y-axis). They are, however, comparable in terms of general shape.]

As with lymphoid cancer mortality, OEHHA evaluated several exposure-response models using the published publicly available categorical data, and none of the

models 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 EtO.

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 (ppm)$^{-1}$.**

Total Cancer Risk Estimates and Derivation of the IUR for EtO

US EPA combined the cancer unit risk estimates for lymphoid (both sexes) and breast cancer (females), stating the following.

> "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 final combined cancer IUR estimate of **6.1 (ppm)$^{-1}$** [6.1×10^{-3} per (ppb)$^{-1}$; 3.3×10^{-3} per (μg/m^3)$^{-1}$], with lymphoid cancer contributing about 75–80% of the total. The corresponding cancer potency factor, also known as cancer slope factor (CSF), is 12 per mg/kg-day (mg/kg-day)$^{-1}$ and is calculated from the total cancer IUR using the following equation (OEHHA, 2009):

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

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 (1 mg = 1000 μg).

The IUR describes the excess cancer risk associated with inhalation exposure to an EtO concentration of 1 μg/m^3; the CSF describes the excess cancer risk associated with exposure to 1 mg of EtO per kg BW (OEHHA, 2009).

The ethylene oxide cancer potency estimate derived from the NIOSH epidemiological study is based on excess risk. In other words, the human IUR expresses risk over and above the background risk. The IUR and CSF express cancer risk over and above the background risk. The background risk includes cancer risk due to endogenous EtO exposures. Thus, in the case of the EtO, the IUR and CSF are meant for use in computing risk levels associated with non-zero exogenous exposures (i.e., > 0 ppm or 0 mg/kg-day).

Overall, US EPA (2016a) calculated an adult-exposure-only IUR of 6.1 $(ppm)^{-1}$ [6.1 × 10^{-3} $(ppb)^{-1}$; CSF = 12 $(mg/kg\text{-}day)^{-1}$] combining lymphoid cancer in males and females and breast cancer in females. This IUR was based on data from a high-quality human epidemiological study involving an analysis of over 17,000 workers in the US exposed to EtO (Steenland et al., 2003; 2004). US EPA provided a thorough review of the other human studies of EtO and cancer (Table 7), which generally had many fewer cancer cases and lower quality exposure and other data compared to the NIOSH study (US EPA, 2016a).

For lymphoid and breast cancer, US EPA, in conjunction with the original NIOSH study authors, applied several 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 IUR calculations. Some of the key variables and the results of these calculations are presented in Table 11.

Table 11. Summary of the variables and results used in US EPA's cancer unit risk calculations for ethylene oxide (EtO).

Variable/Result	Lymphoid cancer	Breast cancer	Total cancer
Species, study	Humans, NIOSH cohort	Humans, NIOSH cohort	NA
Study reference	Steenland et al. 2004	Steenland et al. 2003	NA
Study participants	17,530 men and women	5,139 women	NA
Number of cases	53 lymphoid cancer deaths	233 incident breast cancer cases	NA
Exposure-response model	Two-piece linear spline knot at 1600 ppm-days	Two-piece linear spline knot at 5750 ppm-days	NA
β (per ppm-days)	7.58×10^{-4}	8.98×10^{-5}	NA
β 95% CI	2.98×10^{-3}	1.84×10^{-4}	NA
EC_{01} (ppm)	7.48×10^{-3}	1.38×10^{-2}	NA
LEC_{01} (ppm)	1.90×10^{-3}	6.75×10^{-3}	NA
Extrapolation	Linear	Linear	NA
Unit risk $(ppm)^{-1}$	5.26	1.48	6.1
Cancer slope factor $(mg/kg\text{-}day)^{-1}$	NA	NA	12

Abbreviations: β [beta] – 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}; $(mg/kg\text{-}day)^{-1}$ – per milligram per kilogram per day; $(ppm)^{-1}$ – per part per million; ppm – parts per million; NA – not applicable.

Additional Evaluations of Bias

Several quantitative and qualitative evaluations were performed by OEHHA to assess potential biases and errors in the NIOSH study (Steenland et al., 2003; 2004). Exposure misclassification and the healthy worker effect were of particular focus for OEHHA. With regards to exposure misclassification, a validated exposure model was used by the NIOSH study authors, accounting for 85% of the variance in an independent set of EtO sampling data. This level of variance is generally considered very good for retrospective exposure models of this type (Hornung et al., 1994). 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. 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. 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 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 IUR calculations or the generalizability of the NIOSH findings.

Further, two aspects of the healthy worker effect, the healthy hire effect and the healthy worker survivor effect, were evaluated by OEHHA (Arrighi and Hertz-Picciotto, 1994). 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 (2016a; 2016b) 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 (Park, 2020). Adjustment for employment duration in mortality analyses resulted in statistically significant and stronger associations between cumulative EtO exposure and female breast cancer and hematopoietic cancer (Park, 2020). Importantly though, US EPA used the lower slope of a two-piece regression spline for

its IUR calculations, and this slope was heavily influenced by workers in the lower, not higher, cumulative exposure categories. In addition, OEHHA performed several 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 IURs.

On the topic of exposure assessment, Bogen et al. (2019) have suggested that exposures occurring prior to 1978, the first year that EtO sampling data were available for the NIOSH cohort, may have been dramatically under-predicted by the NIOSH exposure model. However, as noted by these authors, several 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 to OEHHA.

EtO IUR Values Developed by TCEQ

In 2020, the TCEQ published a risk assessment document for EtO in which they calculated an upper-bound cancer IUR of 2.5×10^{-3} per $(ppm)^{-1}$ unadjusted for age (TCEQ, 2020). This IUR is markedly lower than the corresponding adult-exposure-based value of 6.1 $(ppm)^{-1}$ [6.1×10^{-3} $(ppb)^{-1}$] established by the US EPA (2016a), 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" (US EPA 2022a; 2022b)

TCEQ's exclusion of breast cancer

Both the TCEQ (2020) and the US EPA (2016a) IUR calculations were based on findings from the NIOSH cohort of US sterilization workers (Steenland et al., 2003; 2004), and both included risks of lymphoid cancer. However, while the US EPA's IUR calculations also included breast cancer, the TCEQ's did not. TCEQ's decision not to include breast cancer appears to OEHHA to be based primarily on two recent meta-analyses (Marsh et al., 2019; Vincent et al., 2019) and a recent cross-sectional study (Jain, 2020), all of which reportedly did not find strong evidence of an association between EtO exposure and breast cancer incidence. However, in its review of these studies, US EPA (2022a) 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 (2022a), these two decisions by the meta-analyses authors (Marsh et al., 2019; Vincent et al., 2019) led to the exclusion of the strongest evidence linking EtO to breast cancer, including the positive findings from the high quality NIOSH cohort. OEHHA also reviewed these two meta-analyses and agrees with the US EPA that the two issues mentioned above are major flaws, and the meta-analyses by Marsh, Vincent, and their respective colleagues cannot be used to justify the exclusion of breast cancer in EtO IUR calculations. In its review of the cross-sectional study by Jain (2020), US EPA (2022a) identified several flaws, including the mischaracterization of an EtO 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 EtO exposure 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 of breast cancer" (US EPA, 2022a). OEHHA reviewed the Jain et al. (2020) study and agrees with US EPA's conclusions that this study also cannot be used to support the assertion that EtO does not cause breast cancer.

Overall, US EPA (2022a) 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 [was] 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 EtO exposure and breast cancer. Residential proximity to an EtO-emitting facility was significantly associated with *in situ* breast cancer in the NIH-AARP cohort (Jones et al., 2023, Table 3). For example, a hazard ratio (95% CI) of 1.13 (1.01–1.27) was reported with proximity within 10 kilometers. A hazard ratio is a measure of how often cancer occurs in one group compared to how often it happens in another group, over time (NIH, 2023a). There was also a weak, albeit non-significant, association with invasive breast cancer in the Nurse's Health Study II cohort (Hart et al., 2018), which estimated exposure

using census tracts. These studies lend support to the breast cancer findings in the NIOSH cohort, despite their limitations and uncertainties in characterizing individual exposure. Overall, OEHHA agrees that breast cancer should be included in the cancer unit risk calculations.

TCEQ's dose-response model

The other major reason why US EPA (2022a) rejected TCEQ's (2020) EtO cancer IUR was the dose-response model used by TCEQ. While US EPA used a two-piece linear regression spline model, TCEQ used a Cox Proportional Hazards model. US EPA (2016a; 2016b) also evaluated the Cox Proportional Hazards model but found that it provided a very poor fit to the NIOSH cohort data, especially in the lower-exposure region more relevant for the general population. As noted by US EPA (2022a):

> "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 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 EtO 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 the best and most appropriate fit to the underlying NIOSH data.

TCEQ's "reality check"

TCEQ (2020) provided several "reality check" calculations to justify their model selection. However, these calculations involved several flaws that limited their usefulness. In its main "reality check," TCEQ estimated the numbers of cases expected in the NIOSH cohort using standardized 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 (2022a), 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:

> "…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 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" (US EPA, 2022a).
>
> "Differences between cancer rates in a specific cohort and national rates may result from differences in population (non-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" (US EPA, 2022b).
>
> "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" (US EPA, 2022b).

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 EtO risk assessment can be found elsewhere (US EPA, 2022a; 2022b).

VII. CONCLUSIONS

The evaluation of animal and epidemiological cancer studies for EtO indicates that human epidemiological studies are more relevant and sensitive than animal studies for deriving an IUR. In this regard, the NIOSH study (Steenland et al., 2003; 2004) is the best available study for conducting exposure-response analysis for EtO. OEHHA

agrees with the two-piece linear spline model selected by US EPA (2016a) for deriving the cancer IUR for EtO, as OEHHA did not find another model to provide better fit to the underlying data. OEHHA was also unable to identify any new scientific information that would necessitate a change to the US EPA's IUR. As such, the present update of OEHHA's existing EtO IUR (CDHS, 1987) is consistent with US EPA's analysis of the EtO exposure-response relationship and the combined IUR for breast cancer and lymphoid cancer.

Overall, OEHHA concludes that the IUR value of 3.3×10^{-3} $(\mu g/m^3)^{-1}$ [6.1×10^{-3} $(ppb)^{-1}$] is a scientifically sound and reliable estimate of the cancer risks of EtO.

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