Air Toxics Hot Spots Program

Ethylene Oxide

Cancer Inhalation Unit Risk Factor

Technical Support Document for
Cancer Potency Factors
Appendix B

Public Review Draft

May 2026

Ethylene Oxide

Air and Site Assessment and Climate Indicators Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

Page Intentionally Left Blank

Ethylene Oxide

Cancer Inhalation Unit Risk Factor

Technical Support Document for
Cancer Potency Factors
Appendix B

May 2026 Draft

Prepared by the
Office of Environmental Health Hazard Assessment

Kristina Thayer, Ph.D., Director

Contributors, in alphabetical order

Jordan Aron, Ph.D.
Vanessa Cheng, Ph.D.
Sarah Elmore, Ph.D.
Nancy Firchow, M.L.S.
Neela Guha, Ph.D.
Gwendolyn Osborne, M.D., MPH
Homa Sadeghi, Ph.D.
Rose Schmitz, M.S.
Molly Schwalb, Ph.D., MPH
Rona M. Silva, Ph.D.
Craig Steinmaus, M.D., MPH
Feng C. Tsai, Ph.D., M.S.

Technical Reviewers, in alphabetical order

Kannan Krishnan, Ph.D.
Martha Sandy, Ph.D., MPH
Meng Sun, Ph.D., M.S.
Rima Woods, Ph.D.

Executive Reviewers

Kimberly Gettmann, Ph.D.
David Edwards, Ph.D.

Page Intentionally Left Blank

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

ADME	Absorption, Distribution, Metabolism, or Elimination
AIC	Akaike Information Criterion
ATSDR	The Agency for Toxic Substances and Disease Registry
β	Regression coefficient
BMDS	Benchmark Dose Modeling Software
BW	Body weight
Ca/Ci	Ratio of EtO in the exhaled alveolar air to EtO in the breathing area (Ci)
CARB	The California Air Resources Board
CAS	Chemical Abstracts Service
CDHS	The California Department of Health Services
CF	Conversion factor
CI	Confidence interval
CSF	Cancer slope factor
DNA	Deoxyribonucleic acid
EC_{01}	Effective concentration associated with 1% extra risk
EH	Epoxide hydrolase
EtO	Ethylene oxide
ET(OH)SG	S-(2-hydroxyethyl)glutathione
$ET(OH)_2$	Ethylene glycol
GSH	Reduced glutathione
GST	Glutathione-S-transferase
HARP	Hot Spots Analysis and Reporting Program
Hb	Hemoglobin
HEMA	S-(2-hydroxyethyl)-mercapturic acid
HEV	N-(2-hydroxyethyl)-valine
HEVL	N-(2-hydroxyethyl)-L-valyl-L-leucine
HHS	The United States Department of Health and Human Services
IARC	The 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 EC_{01}
MDL	Method Detection Limit
mg/kg	Milligrams per kilogram of body weight
mg/kg-day	Milligrams per kilogram of body weight per day
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
MOA	Mechanism of action
n	Number
NATA	National Air Toxics Assessment program, US EPA
NHANES	National Health and Nutrition Examination Surveys
NIH-AARP	National Institutes of Health-Americal Association of Retired Persons
NIOSH	The National Institute for Occupational Safety and Health
NP	Not provided
NS	Not statistically significant
NTP	The National Toxicology Program,
OEHHA	The Office of Environmental Health Hazard Assessment
OR	Odds ratio
$(mg/kg\text{-}day)^{-1}$	Per milligram per kilogram of body weight per day
$(\mu g/m^3)^{-1}$	Per microgram per cubic meter
$(ppb)^{-1}$	Per part per billion
PBPK	Physiologically-based pharmacokinetic or toxicokinetic
PECO	Populations, Exposures, Comparators, and Outcomes
pmol	Picomole
ppb	Parts per billion
ppm	Parts per million
ppm-days	Parts per million-days
ppm-years	Parts per million-years
RBC	Red blood cell

List of Abbreviations (continued)

Ref	References
RPTG	Richly-perfused tissue group
RR	Relative risk
SCAQMD	The South Coast Air Quality Management District
SCE	Sister chromatid exchange
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results program
SMR	Standardized mortality ratio
TCEQ	The Texas Commission on Environmental Quality
TIAB	Title and abstract (search)
TRI	Toxics Release Inventory, US EPA
UAT	Urban Air Toxics
UCC	Union Carbide Corporation
URE	Unit risk estimate
US EPA	The United States Environmental Protection Agency
WOS	Web of Science

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. IURs are used to estimate lifetime cancer risks associated with inhalation exposure to carcinogens.

The present draft proposes an update to OEHHA's IUR for ethylene oxide (EtO) under the Air Toxics Hot Spots Program. OEHHA's current EtO IUR of 8.8×10^{-5} per microgram per cubic meter (μg/m^3; 1.6×10^{-4} per part per billion; ppb) was derived using animal cancer studies when OEHHA's predecessor organization was a part of the California Department of Health Services. Since then, the knowledge base has grown. The chemical is now widely recognized as a known human carcinogen, and there is robust new evidence that enables the IUR to be updated.

In 2016, the US Environmental Protection Agency (US EPA) updated its assessment for EtO and based its IUR estimates on occupational studies of workers at sterilization facilities in the US. The US EPA assessment received public comments and was peer-reviewed by its Science Advisory Board.

OEHHA reviewed US EPA's analysis and considered key information on the pharmacokinetics and potential mechanisms of EtO's carcinogenesis for the exposure-response analysis. OEHHA used US EPA's assessment as the primary source of studies published before 2016 and updated the literature review to identify more recent studies relevant for developing the IUR. OEHHA proposed the updated IUR of 3.3×10^{-3} per μg/m^3 (6.1×10^{-3} per ppb), based on US EPA's analysis and, on April 7, 2023, released a draft updated IUR document to solicit public comments. The comment period closed on June 14, 2023. Submitted comments can be viewed on OEHHA's EtO Comment Submission page (oehha.ca.gov/comments).

OEHHA is now releasing the present draft for additional public comments. This draft considers the previous public comments received and includes literature from January 2016 to April 2026. Notably, OEHHA revised its proposed updated EtO IUR to 3.0×10^{-3} (μg/m^3)$^{-1}$ [5.5×10^{-3} (ppb)$^{-1}$] in the present draft. The updated IUR value of 3.0×10^{-3} (μg/m^3)$^{-1}$ [5.5×10^{-3} (ppb)$^{-1}$] corresponds to US EPA's "adult-based" unit risk estimate for lymphoid and breast cancers combined. This adult-based unit risk value was derived by US EPA and allows for the calculation of age-group-specific cancer risk.

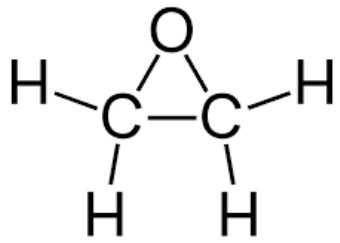
Given the update to the IUR, the previously proposed Cancer Slope Factor (CSF), 12 per milligram per kilogram of body weight per day ((mg/kg-day)$^{-1}$), was updated to 11 (mg/kg-day)$^{-1}$.

For Hot Spots health risk assessments, OEHHA's currently proposed updated EtO IUR of 3.0×10^{-3} (µg/m^3)$^{-1}$ [5.5×10^{-3} (ppb)$^{-1}$] will facilitate the calculation of lifetime or age-group-specific cancer risk estimates based on OEHHA's Age Sensitivity Factors when integrated into the Hot Spots Analysis and Reporting Program (HARP).

The present document will be the subject of public workshops in Northern and Southern California before being reviewed by the Scientific Review Panel on Toxic Air Contaminants. This second public comment period closes on June 29, 2026. Information on how to engage in the review process is contained on OEHHA's website: oehha.ca.gov.

Ethylene Oxide

Chemical Abstracts Service (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
Synonyms:	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
Atmospheric Half-Life:	69–149 days (estimated; degradative oxidation via free-radical formation)
Solubility:	Soluble in benzene, acetone, ethanol, and ether; miscible with water (1×10^6 milligrams per liter @ 20°C)
Conversion factor:	1.82 micrograms per cubic meter ($\mu g/m^3$) = 1 part per billion (ppb)

II. HEALTH ASSESSMENT VALUES

Inhalation Unit Risk Factor (IUR)[1]:	3.0×10^{-3} per µg/m^3 [(µg/m^3)$^{-1}$]; 5.5×10^{-3} per ppb [(ppb)$^{-1}$]
Cancer Slope Factor (CSF):	11 per milligram per kilogram of body weight per day ((mg/kg-day)$^{-1}$)

III. MAJOR USES AND OCCURRENCE

Ethylene oxide (EtO) is primarily used to sterilize medical and laboratory equipment and as a chemical intermediate in a wide range of commercial and industrial products (CARB, 2026). Other potential sources of EtO include fires (residential wood combustion and wildfires), incomplete combustion from mobile sources, off gassing from previously sterilized equipment at warehouses or storage facilities, cigarettes and vaping, endogenous sources and other biological mechanisms, consumer products, and fumigation of herbs and spices (historically and outside of California).

EtO emissions must be quantified for applicable facilities under California's Air Toxics Hot Spots Program (CARB, 2023a) and the Criteria and Toxics Reporting (CTR) Regulation, and reported under the US Environmental Protection Agency's (US EPA) Toxics Release Inventory (TRI) program (US EPA, 2023c).

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 and CTR Regulation. 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 (lbs), number of emissions sources (facilities), and maximum emissions reported for any facility are summarized by year for the last 14 inventory years (2011–2024) in Table 1 below, based on data from CARB's facility search tool. The total and maximum emissions were generally under 4000 lbs per year (433–5201 lbs and 265–4620 lbs, respectively), except for a spike in 2014 due to a high emissions value reported by a single facility, which may reflect a reporting error; however, this could not be verified as the facility has since shut down.

[1] The currently proposed IUR and CSF were updated from 3.3 ×10^{-3} (µg/m^3)$^{-1}$ [6.1 × 10^{-3} (ppb)$^{-1}$] and 12 (mg/kg-day)$^{-1}$, respectively, to facilitate age-specific cancer risk estimates in Hot Spots health risk assessments. The previously proposed IUR and CSF were presented in OEHHA's April 2023 draft document.

Table 1. EtO emissions from California facilities reporting to the California Air Resources Board for years 2011–2024. (CARB, 2026).

Year	Number of Facilities	Total EtO Emissions (lbs)[a]
2011	64	1666
2012	67	1289
2013	68	924
2014	60	5203
2015	56	552
2016	52	433
2017	47	463
2018	48	471
2019	42	793
2020	33	556
2021	33	955
2022	42	585
2023	54	509
2024[c]	386	499

(a) Total emissions is the sum of emissions in pounds (lbs) from all reporting facilities for the year.
(b) The maximum emissions value is from the highest-emitting facility in a given year.
(c) Preliminary data provided by CARB. Of the 386 facilities, 369 reported below 1 pound with the highest source being 173.78 pounds. The large increase in the reported facilities in 2024 is mostly due to the 2022 amendment of reporting regulations, including CTR and Emission Inventory and Guidelines (EICG). Data from 2024 will be made publicly available after data quality has been evaluated by CARB.

US EPA's TRI Explorer, a publicly available resource, was also used by OEHHA to access EtO emissions data for California. Total EtO emissions are shown in Table 2 for the last 14 inventory years available (2011–2024) 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). These recent changes are reflected in the value for 2022 provided in Table 2.

Table 2. EtO emissions from California facilities reporting to US EPA's Toxics Release Inventory (TRI) for years 2011–2024.

Year	Number of Facilities	Reported EtO Emissions (lbs)[a]
2011	3	1083
2012	3	1642
2013	3	1228
2014	3	998
2015	3	1109
2016	3	805
2017	1	15
2018	1	15
2019	1	15
2020	1	15
2021	2	31
2022	8	505
2023	8	413
2024	8	920

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

Non-occupational exposure to EtO results from smoke and ambient air. Mainstream tobacco smoke is reported to contain 7 µg EtO per cigarette (IARC, 2004; Kenwood et al., 2021). Background EtO levels in ambient air result from a variety of minor non-point sources such as water-logged soil, combustion of fossil fuels, and release from consumer products (e.g., residues in fumigated food products and skin care products; IARC, 2008; IARC, 2012; Kirman et al., 2021; Kirman et al., 2025), while background EtO levels in the body can come from physiological processes (e.g., ethylene metabolism).

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 2024 showed an urban background concentration range of 0.06–0.2 µg/m^3 (0.03–0.11 ppb) in the South Coast Air Basin (SCAQMD, 2024a; 2024b). The most recent complete year of SCAQMD's monitoring data available from US EPA's database[2] was 2024, which showed the ambient outdoor air EtO levels ranged from 0.05 to 0.23 µg/m^3 (0.03 to 0.13 ppb) with a mean of 0.11 µg/m^3 (0.06 ppb) in Los Angeles. In 2024, ambient EtO levels ranged from 0.04 to 0.45 µg/m^3 (0.02 to 0.25 ppb) with a mean of 0.13 µg/m^3 (0.07 ppb) in Riverside, CA[3] (US EPA, 2025). For that year, out of 57 measurements in Los Angeles, 24 samples were below the method detection limit (MDL), and similarly, out of 50 samples in Riverside, 19 samples were below the MDL.[4]

More localized monitoring near two medical sterilizer facilities in the South Coast Air Basin revealed elevated EtO concentrations near the facilities, with concentrations ranging from undetectable to as high as 240 and 118 parts per billion by volume (SCAQMD, 2024a; 2024b).

The nationwide mean EtO mixing ratio[5] (ambient mass concentrations and/or volume mixing ratios) has been reported to be 0.136 µg/m^3 (0.075 ppb) based on data collected from 76 individual EPA monitoring sites in 22 states between 2018 and 2024 (Robinson et al., 2025). Previously, the arithmetic mean background EtO level was reported to be 0.29 µg/m^3 (0.16 ppb) based on measurements by US EPA from 2018–2019 in 18 rural

---

[2] https://www.epa.gov/outdoor-air-quality-data/monitor-values-report-hazardous-air-pollutants

[3] The outdoor air quality monitoring data for Riverside, CA in 2024 included fewer than 75% of the expected measurements. The most recent year with complete monitoring data for EtO was 2023, in which the EtO levels ranged between 0.04 to 0.22 µg/m^3 (0.02 to 0.12 ppb) with a mean concentration was 0.10 µg/m^3 (0.05 ppb). Out of 57 samples in Riverside, 33 samples were below the MDL of 0.02 µg/m^3 (US EPA, 2025).

[4] The maximum federal MDL which is the default MDL associated with each instrument and method, for EtO in 2024 was 0.12 µg/m^3 (0.07ppb) and the maximum Alternate MDL which is a value provided by the reporting agency for the specific concentration was 0.023 µg/m^3 (0.013 ppb). Whenever available, an Alternate MDL was used instead of federal MDL.

[5] EtO mixing ratio is the amount of EtO relative to the total amount of air.

and urban sites in eight states (KY, NJ, IL, UT, MI, AZ, WA, and MO; Kirman et al., 2021).

A decrease in EtO mixing ratios was observed based on EtO mixing ratios compiled from 24-hours integrated canister samples collected from monitoring sites across 22 states between 2018 and 2024 (Robinson et al., 2025). The aggregated annual EtO levels (from all included sites) declined from 0.335 μg/m^3 (0.185 ppb) in 2019 to 0.118 μg/m^3 (0.065 ppb) in 2024. However, the year-over-year trend for individual sites showed mixed results, where 52% of the monitoring sites only showed an overall decrease in EtO emission. This study found that EtO mixing ratios were higher in summer compared to winter. As expected, high emitter-near-source monitoring sites[6] had higher median and mean values compared to other land uses categories, including low emitters-near-source, mid-range[7], urban, suburban, and rural sites. There was no significant difference in the mean EtO ambient levels in the low emitters-near-source, and mid-range sites, however there were significant differences between those sites compared to suburban and rural sites. Ambient EtO levels were positively correlated with temperature (Robinson et al., 2025). EtO mixing ratios were higher for wildfire-impacted days than non-wildfire days with controlling for temperatures (Robinson et al., 2025). The study authors suggested that traffic is not a major source of EtO because no significant difference in EtO levels was observed between weekdays and weekends. About twenty percent of the data were reported to be below the MDL. The study authors highlighted the potential uncertainty in accuracy of these background levels (Robinson et al., 2025).

IV. LITERATURE SEARCH AND STUDY EVALUATIONS

In 2016, US EPA's Integrated Risk Information System (IRIS) published a comprehensive review of the scientific literature on the potential carcinogenic effects of EtO (US EPA, 2016a). OEHHA evaluated US EPA's review and concluded it provided a complete and accurate assessment of the relevant literature published up to that time. From the US EPA (2016a, 2016b) assessment, OEHHA identified three human epidemiological studies of EtO and cancer with quantitative exposure estimates in persons who were occupationally exposed (Steenland et al., 2003, 2004 (i.e., the

[6] High emitter-near-source monitoring sites are monitoring sites located within 2 kilometers of point sources that their EtO emissions were within the upper quartile of all EtO emitters in the US EPA's National Emissions Inventory or TRI (Robinson et al., 2025).

[7] Mid-range monitoring sites are sites between 2–10 kilometers from the emission source (Robinson et al., 2025).

NIOSH study); Swaen et al., 2009 (i.e., the Union Carbide study); and Mikoczy et al., 2011 (i.e., the Sweden study).[8]

Thus, OEHHA focused its new literature screening efforts on identifying studies published since the 2016 US EPA review. In addition, because EtO is already recognized as a known or likely human carcinogen (IARC, 2012; NTP, 2021; TCEQ, 2020a; US EPA, 2016a), OEHHA also focused its assessment efforts on studies of EtO and cancer, and more specifically, on information that could help quantify the exposure-response relationship between EtO and cancer.

Literature search strategy and Populations, Exposures, Comparators, and Outcomes criteria

OEHHA undertook two separate literature search efforts for this review. One involved identifying epidemiological studies and the other involved identifying animal cancer studies and key supplemental material (i.e., mechanistic; Absorption, Distribution, Metabolism, or Elimination (ADME) materials). The following electronic databases were included in these searches:

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- Embase
- Scifinder

The keywords used in these searches included “ethylene oxide” and its common synonyms. The search for epidemiologic studies also included keywords used to identify epidemiologic research including terms such as “case-control”, “cohort”, or “standardized mortality ratio”. The search for animal studies included similar terms for EtO as well as terms for various cancer outcomes. A detailed list of the keywords used in these searches is provided in Attachment A. No language restrictions were applied in the searches.

The literature searches performed by OEHHA were conducted in October (for human evidence) and November (for animal evidence) 2025 and were restricted to studies

[8] These epidemiologic studies are described by US EPA in their report (2016a; 2016b) as being without major flaws and potentially useful for dose-response. These studies also underwent detailed study evaluations by OEHHA.

published after January 1, 2016. Literature searches were also conducted in April 2026, shortly before public release of this draft assessment.

Additional studies identified in the April 2026 searches were only fully incorporated into the assessment if they met the Populations, Exposures, Comparators, and Outcomes (PECO) criteria and would have a material impact on the assessment conclusions (i.e., impact the IUR value). The full list of studies identified during the April update that met the screening criteria or tagged as supplemental relevant information are provided in Attachment B with a brief rationale for why studies not cited in the assessment were not considered to have a material impact on the IUR. In addition to the electronic database searches, the following sources were also searched in an effort to identify studies that may have been missed during the electronic database searches:

- Bibliographies of all relevant publications identified during the literature searches
- Recent review publications
- Relevant government reports (e.g., US EPA, Agency for Toxic Substances and Disease Registry (ATSDR), Texas Commission on Environmental Quality (TCEQ))

A set of PECO criteria were used to help identify potentially relevant studies during the literature searches. These criteria are presented in Table 3. Studies that did not meet these PECO criteria but contained potentially relevant supplemental material were also tracked during the literature screening process as outlined in Attachment A. Studies categorized as supplemental material included studies in non-mammalian species, *in vitro* studies, in silico models, and physiologically-based pharmacokinetic/toxicokinetic (PBPK) studies, non-PECO routes of exposure (e.g., intraperitoneal injection, oral administration), exposure assessment or characterization (no health outcome) studies, and human case reports or case series.

Table 3. Populations, Exposures, Comparators, and Outcomes (PECO) criteria.

Populations	**Human:** Studies of any population and life stage (occupational or general population, including children and other sensitive populations) **Animal:** Non-human mammalian animal species of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages)
Exposures	Relevant forms: EtO (CAS 75-21-8), synonyms or occupations associated with EtO use (e.g., working in sterilization facilities) **Human:** Any quantitative exposure to EtO via inhalation as determined by controlled exposure, measured concentration of EtO in contact medium (i.e., air), biomarkers of exposure (e.g., serum levels), or occupation in a job involving EtO exposure **Animal:** Any quantitative exposure to EtO via inhalation of at least 1 year. Studies involving exposures to mixtures will be included only if they include an arm with exposure to EtO alone.
Comparators	**Human:** Studies reporting effect measures (e.g., incidence rates, relative risk, standardized mortality ratio, odds ratio) based on a comparison or referent population exposed to lower levels, or no exposure/exposure below detection limits of EtO, or cancer cases versus controls, or a repeated measures design. Case series or case reports will be marked as supplemental if relevant **Animal:** A concurrent control group exposed to vehicle-only treatment or untreated control (control could be a baseline measurement in repeated measure studies)
Outcomes	Cancer outcomes

Abbreviation: CAS – Chemical Abstracts Service (number).

All records identified in the literature searches were evaluated for whether they met the PECO criteria by two independent reviewers, first at the title and abstract (TIAB) level and then at the full-text level using structured forms in Excel (for human evidence) or DistillerSR (Evidence Partners, 2025) (for animal evidence or supplemental material).

Screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer, if needed. A pilot screening effort was undertaken to confirm clarity of the screening criteria and adjust instructions.

During TIAB screening, records with no abstract are initially evaluated based on title relevance (title should indicate clear relevance). Eligibility status of non-English studies was assessed using online translation tools or engagement with a native speaker.

Full-text copies of records marked as “included” or “unclear” during TIAB evaluations were obtained and independently assessed by two screeners to confirm they met the PECO criteria. References that could not be procured within 45 days of attempt were determined to be unavailable. Rationales for excluding studies were documented (e.g., study did not meet PECO, full-text not available). Fee-based translation services for non-English studies are typically reserved for studies that were anticipated as being useful for toxicity value derivation. When there were multiple publications using the same or overlapping data or study populations, all publications were included at this stage of the literature search process.

In addition to failure to meet PECO criteria, epidemiological and toxicological studies may have been excluded during this stage of the literature search process due to critical reporting limitations. Although these reporting limitations are more commonly identified during subsequent phases of the assessment (e.g., data extraction of methods/results or study quality or risk of bias evaluation), studies can also be excluded during this stage of the assessment if critical reporting limitations are identified in the full-text reviews described above. Regardless of when these limitations are identified, exclusions based on full-text content are documented at the level of full-text exclusions in literature flow diagrams with a rationale of “critical reporting limitation.” Critical reporting information for different study types are summarized below. For each piece of information, if the information can be inferred (when not directly stated) for an exposure/endpoint combination, the study should be included.

Critical reporting information for epidemiologic studies:

- Sample size
- Exposure characterization and/or measurement method
- Outcome ascertainment method
- Study design

Critical reporting information for animal studies:

- Species
- Test article name
- Level and duration of exposure
- Route of exposure

Study evaluations

Once the literature searches and PECO screening procedures described above were complete, all publications meeting the PECO criteria underwent a further study evaluation process. The goal of this process was to identify those studies most likely to contribute to assessing the exposure-response relationship between EtO and cancer. Since no new animal cancer bioassays were identified in OEHHA's literature searches, the following text describes the processes used to evaluate human epidemiologic studies. OEHHA's detailed approach to these study evaluations is presented in Attachments C, D, and E and was developed using a variety of risk of bias and study evaluation tools and reports, including those from the National Toxicology Program's (NTP) Risk of Bias Tool (NTP, 2015; NTP, 2019), the NTP Report on Carcinogens Handbook (NTP, 2025), the Cochran Collaboration (Higgins et al., 2024a; Higgins et al., 2024b), the US EPA ORD Handbook for Developing IRIS Assessments (US EPA, 2022c), and others (Axelson, 1978; Breslow and Day, 1987; Greenland, 1998a; Greenland, 1998b; Hill, 1965; Schlesselman, 1978).

The study evaluation process involved two main steps. In the first step, all studies identified in OEHHA's literature search that met the PECO criteria underwent an initial screening assessment ("initial screening"). The goal of this step was to apply a basic set of preliminary screening criteria that would help to identify and exclude those studies with obvious and serious limitations precluding their use for exposure-response analysis. In the second step, all studies that met the initial screening criteria then underwent a set of more comprehensive and detailed evaluations with the goal of identifying the study or studies that would ultimately be the most useful for exposure-response and IUR development.

The following factors were considered in the "initial screening" step:

- Study designs, and specifically whether the study design can be used to establish temporality (i.e., that the exposure preceded the outcome)
- The general validity and relevance of the methods used to assess exposure and outcome
- Whether the study included consideration or analyses of confounding
- The presentation of information or results on exposure-response

This step was considered an "initial screening" evaluation since the purpose was to exclude those studies with obvious and easily identifiable serious limitations that would preclude their use in IUR development and thus preclude the need for further in-depth analyses. "Serious" limitations were those that raised important concerns about the

overall validity of the study's results or about the study's overall utility for exposure-response assessment. The primary reasons why studies would be excluded at this step and not be considered for the next evaluation step include a failure to provide adequate evidence that the exposure preceded the outcome (i.e., temporality), obvious and serious limitations in the methods used to assess exposure or outcome, a high likelihood or overall lack of consideration of confounding, or a lack of information on exposure-response.

The second step of the study evaluation process involved more in-depth evaluations of the studies that met the "initial screening" criteria. The goal of this step was to systematically determine which study or studies with exposure-response information were the most valid and most useful for final exposure-response and IUR calculations. The following key factors were considered in this step:

- Participant selection methods and participation rates
- Details on the quality and validity of the exposure assessment
- Details of the quality and validity of the outcome assessment
- Statistical power considerations, including sample sizes and the range of exposure
- The appropriateness and completeness of the statistical analyses
- Consideration of appropriate lag or latency periods
- The clarity of the results and the possibility of selective reporting
- Detailed and thorough evaluations of confounding
- The quality, thoroughness, and relevance of the exposure-response information
- The potential for conflicts of interest
- Other factors that make a study preferred in the context of IUR development (e.g., inclusion of both sexes)

A full list of the factors used in these evaluations, and the general guidelines used for applying evaluation ratings, are provided in Attachments D and E.

V. CARCINOGENICITY STUDIES

The available cancer studies in rodents and in humans were reviewed in several authoritative evaluations over the years, including 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). The CDHS 1987 review was conducted under the Toxic Air Contaminant program by OEHHA's predecessor organization within CDHS. Since the CDHS document on EtO (CDHS, 1987), no new animal cancer bioassays on EtO have appeared in the peer-reviewed literature. However, several cancer epidemiology studies have been published since then.

The studies for OEHHA's current review were identified as described in the Literature Search section above.

Six rodent carcinogenicity studies of sufficient duration (i.e., >18 months; Table 4) and three human epidemiological studies of EtO and cancer with quantitative exposure estimates (Table 8) were identified by OEHHA for consideration for quantitative dose-response analyses. These studies are discussed in the following two sections. All of the rodent carcinogenicity studies in Table 4 were performed with an exposure duration of approximately two years or longer.

Rodent Carcinogenicity Studies

No new animal cancer studies (other than the original set of animal studies identified by OEHHA in 2023) were identified by the recent systematic literature screening to be suitable for dose-response assessment. A summary of the literature search for animal carcinogenicity studies published between January 1, 2016, and April 10, 2026 is shown in Figure 1. Briefly, 249 unique studies were identified from searching databases. First, titles and abstracts were screened against the PECO criteria (Attachment A). Five publications were advanced to full-text screening because they appeared to meet the PECO criteria (or were "unclear" based on the title/abstract content). The five studies were ultimately tagged as relevant supplemental information during the full-text screening given the lack of information needed for dose-response assessment.

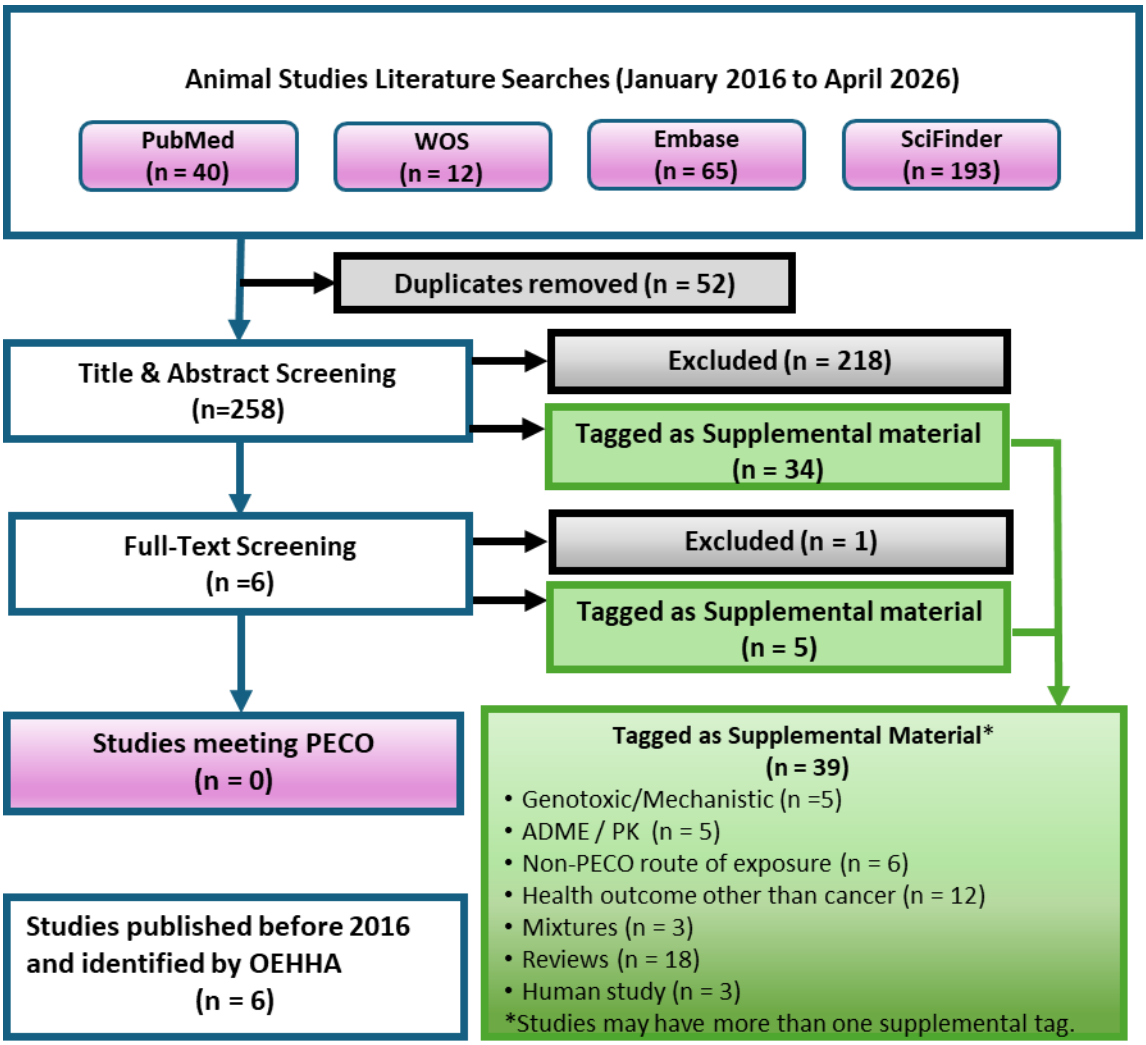


Figure 1. Results of OEHHA's literature search of animal studies of EtO and cancer published between January 1, 2016, and April 10, 2026.
Abbreviations: ADME – Absorption, Distribution, Metabolism, and Elimination; n – number; PECO – Populations, Exposures, Comparators, and Outcomes; PK – pharmacokinetic; WOS – Web of Science.

The available data from the rodent carcinogenicity studies of sufficient duration were reviewed by OEHHA (Table 4). These studies, listed below, were published before our

updated literature search covering 2016–2026[9], and no more recently conducted rodent carcinogenicity studies were identified (Figure 1).

- Inhalation studies conducted by the National Toxicology Program (NTP, 1987) in male and female $B6C3F_1$ mice
- Inhalation studies conducted by Snellings et al. (1981, 1984) and Garman et al. (1985) in male and female Fischer 344 rats
- Inhalation study by Lynch et al. (1984) in male F344 rats
- Gavage study by Dunkelberg (1982) in female Sprague-Dawley rats

The results of these studies are presented below.

[9] A literature search update in April 2026 did not identify any additional animal carcinogenicity studies to be included.

Table 4. Overview of long-term rodent carcinogenicity studies of 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 B6C3F$_1$ mice	Inhalation (chamber)	102 weeks	0, 18.32, 36.64	>99%	Alveolar/bronchiolar adenoma or carcinoma, harderian gland papillary cystadenoma	A
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	A
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	B
Female Fischer 344 rats	Inhalation (chamber)	25 months	0, 3.75, 12.38, 37.50	99.9%	Mononuclear cell leukemia, brain glioma	B
Male Fischer 344 rats	Inhalation (chamber)	104 weeks	0, 18.59, 37.18	99.7%	Mononuclear cell leukemia, peritoneal mesothelioma, brain glioma	C
Female Sprague-Dawley rats	Gavage	110 weeks	0, 2.08, 8.34	99.7%	Forestomach squamous cell carcinoma, forestomach fibrosarcoma	D

Abbreviations: mg/kg-day – milligrams per kilogram of body weight per day; Ref – Reference(s)
* Calculated by OEHHA.
(A) The National Toxicology Program (NTP, 1987)
(B) Snellings et al. (1981; 1984) and Garman et al. (1985)
(C) Lynch et al. (1984)
(D) Dunkelberg (1982)

In the NTP (1987) studies in male and female B6C3F$_1$ mice, groups of 50 mice were exposed by inhalation to EtO at 0, 91, or 182 mg/m^3 (0, 50, or 100 ppm; control, low dose, or high dose, respectively), 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-dose group (100 ppm or 36.64 mg/kg-day) relative to the control (p = 0.002), as well as a significant trend for the overall dose response (Table 5). In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in the low-dose (50 ppm or 18.32 mg/kg-day) and high-dose groups compared to the control (p = 0.008 and p = 0.011, respectively), with a significant trend overall (Table 5).

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 = 0.046) were observed in the high-dose group (100 ppm or 38.42 mg/kg-day) compared to the control, all with significant dose-response trends (Table 5). In addition, a statistically significant increase in the incidence of Harderian gland papillary cystadenoma was observed in both the low-dose (50 ppm or 19.21 mg/kg-day) and high-dose groups (p = 0.034 and p = 0.027, respectively) compared to the control with a significant trend (Table 5). 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 = 0.027).

Table 5. Tumor incidences of treatment-related neoplastic lesions in male and female B6C3F1 mice administered EtO by inhalation (NTP, 1987)[a].

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

Abbreviation: NS – not statistically significant ($p \geq 0.05$); ppm – part(s) per million.

[(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 0 (2 groups), 10, 33, or 100 ppm (control, low, mid, and high dose, respectively), 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-dose (33 ppm or 10.32 mg/kg-day) and high-dose (100 ppm or 31.27 mg/kg-day) groups compared to controls in the male rat study (p = 0.019 and p = 0.038 respectively), with a significant dose-response trend (Table 6). 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 = 0.027 and p = 0.005, respectively), along with significant trends (Table 6).

In female rats, a statistically significant increase in the incidence of mononuclear cell leukemia was observed in all treated groups compared to controls (p = 0.045, p = 0.002, and $p = 3.3 \times 10^{-7}$, for the low-, mid-, and high-dose groups, respectively), with a significant dose-response trend (Table 6). A significant trend in brain glioma was also observed (Table 6).

Table 6. Tumor incidences of treatment-related neoplastic lesions in male and female Fischer 344 rats administered 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	10 ppm	33 ppm	100 ppm	
Male rats	Mononuclear cell leukemia	13/97	9/51	12/39*	9/30*	$p < 0.05$
	Testicular peritoneal mesothelioma	2/97	2/51	4/39	4/30*	$p < 0.05$
	Brain glioma	1/181	0/92	3/85	6/87**	$p < 0.001$
Female rats	Mononuclear cell leukemia	11/116	11/54*	14/48**	15/26***	$p < 0.001$
	Brain glioma	0/187	1/94	2/90	2/78	$p < 0.05$

[(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 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 Lynch et al. (1984) study in male Fischer 344 rats, groups of 80 rats were exposed to EtO by inhalation at concentrations of 0, 50, or 100 ppm (control-, low-, and high-dose, respectively), 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

significantly decreased in all EtO-exposed groups ($p < 0.05$) and survival was significantly decreased in the high-dose group (37.18 mg/kg-day; $p < 0.01$) compared to the control group. 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 incidences of peritoneal mesothelioma (of testicular origin; $p = 5.0 \times 10^{-5}$) and brain glioma ($p = 0.032$) were observed in the high-dose group (100 ppm or 37.18 mg/kg-day) compared to controls, and a statistically significant increase in mononuclear cell leukemia was observed in the low-dose group (50 ppm or 18.59 mg/kg-day) compared to controls ($p = 0.023$). Significant trends in peritoneal mesothelioma and brain glioma were also observed (Table 7).

Table 7. Tumor incidences of treatment-related neoplastic lesions in Fischer 344 male rats administered EtO by inhalation (Lynch et al., 1984)[a].

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

Abbreviation: NS – not statistically significant ($p \geq 0.05$); ppm – parts per million.

[(a)] 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.

In the Dunkelberg (1982) study, groups of 50 female Sprague-Dawley rats were administered either 0, 7.5, or 30 milligrams per kilogram of body weight (mg/kg) EtO dissolved in salad oil via gavage twice weekly for a total of 214 exposures. The study duration was 150 weeks. The lifetime average daily doses of EtO administered in the study were calculated to be 0, 2.08, and 8.34 mg/kg-day, respectively. The study authors

noted that the rats in the 8.34-mg/kg-day group died earlier from tumors compared to controls. No additional issues in survival were noted.

Dunkelberg (1982) reported increases in the incidences of forestomach squamous cell carcinoma and forestomach fibrosarcoma in female rats. The cancer incidences at EtO doses of 0 (control), 7.5, and 30 mg/kg on each dosing day 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 ($p = 0.003$ and $p = 5.4 \times 10^{-12}$, respectively) and by trend test using lifetime average daily oral doses of 0, 2.08, and 8.34 mg/kg ($p = 2.4 \times 10^{-12}$). However, this study of the oral route was not considered further for developing an inhalation IUR for EtO, as human epidemiological studies and animal carcinogenicity studies with inhalation exposures were available.

Epidemiological Studies

OEHHA's literature search and PECO screening results

A summary of the results of OEHHA's literature search is shown in Figure 2. Briefly, 1814 non-duplicate publications were identified in the electronic database searches. After the other literature (e.g., bibliographies, reviews, reports) searches, TIAB search, and full text screening, 12 publications were found that met the PECO criteria (Attachment A).[10] Details on these 11 publications are provided in Attachment C. Nine of these publications (Bulka et al., 2016; Chen, 2018; Chen et al., 2024; Ish et al., 2025; Jain, 2020; Jones et al., 2023; Kelly-Reif et al., 2025; Park, 2020; Valdez-Flores et al., 2025) were identified from the electronic database searches. The remaining two publications (Garcia et al., 2015; Hart et al., 2018) were identified in the bibliography searches. One of these (Garcia et al., 2015) was published prior to 2016 but was not included in US EPA's review. The major reasons why publications were excluded at the PECO stage during OEHHA's screening were that they did not involve human exposure and cancer risk, or they were studies of the chemistry of EtO or related agents.

[10] This includes the 11 publications shown in Figure 2 and one additional publication that became available in March 2026 – Picciotto et al. (2026).

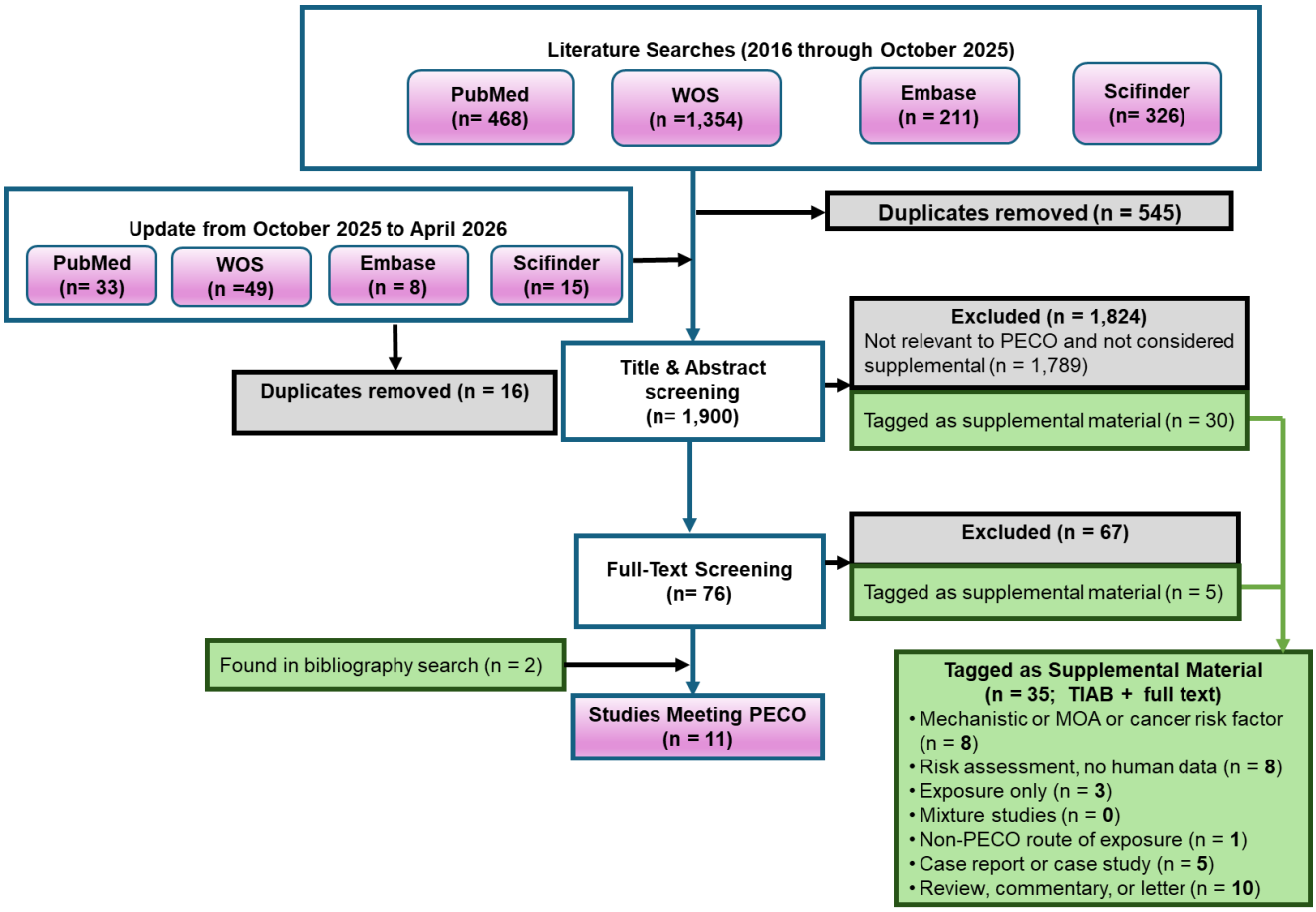


Figure 2. Results of OEHHA's literature search and PECO screening of epidemiologic studies of EtO and cancer.
Abbreviations: MOA – mechanism of action; PECO – Populations, Exposures, Comparators, and Outcomes; TIAB – title and abstract search; WOS – Web of Science.

Initial screening results

All of the 11 publications identified from OEHHA's literature search as meeting the PECO criteria were evaluated using the initial screening factors provided above. The results of these evaluations are shown in Attachment C. The study designs of these publications were ecological (n = 2), cross-sectional (n = 1), and longitudinal cohort (n = 8). Both of the ecologic studies reported some evidence of an association between EtO and either diffuse large B-cell lymphoma (Bulka, 2016) or breast cancer (Chen, 2018); although, the effect sizes were small in both studies (e.g., relative risk (RR) estimates <1.10; Attachment C). Importantly, both studies had major limitations that precluded their use for exposure-response assessment and IUR calculations. These limitations included the inadequate consideration of confounding, use of very broad and non-specific exposure

metrics, ecologic nature of the outcome data, and use of a study design that did not account for temporality.

The cross-sectional study by Jain (2020) was also excluded from further consideration for IUR development. In this study, data from the 2013–2016 National Health and Nutrition Examination Surveys (NHANES) were used to evaluate associations between "concentrations of EtO in whole blood" and whether participants reported that they had ever been told by a health care professional that they had cancer. Multiple cancer types were assessed including breast cancer. Results for lymphoid cancer were not reported. Overall, clear associations were not identified. However, the process of carcinogenesis from initiation to diagnosis has a very long latency, and cross-sectional cancer studies like this, which measure exposure and disease near the same time-point, generally cannot be used to establish temporality (i.e., that the exposure preceded the disease; Savitz and Wellenius, 2023). This is important since establishing temporality is a critical component of causal inference (Hill, 1965). Another weakness of the Jain (2020) study included concerns about whether the exposure variable (which was poorly described but appears to be based on hemoglobin (Hb) adduct and not actual EtO concentrations) was a reliable or accurate indicator of biologically relevant EtO exposure (Lin, 2025). Other weaknesses included uncertainty about the specificity of the self-reported cancer outcomes and the lack of clear exposure-response information. Overall, for all the reasons given above, it was determined that the Jain (2020) study could not be used for accurately assessing EtO-cancer exposure-response.

The eight remaining publications involved studies that utilized longitudinal cohort designs. These studies leveraged data from either population-based cohorts (the Nurses' Health Study (Chen, 2024; Hart, 2018), the California Teachers Study (Garcia, 2015), the Sister Study (Ish, 2025), or the National Institutes of Health-Americal Association of Retired Persons (NIH-AARP) Diet and Health Study (Jones, 2023)) or occupationally exposed cohorts (the National Institute for Occupational Safety and Health (NIOSH) cohort (Kelly-Reif, 2025; Park, 2020) or the Union Carbide Corporation (UCC) cohort (Valdez-Flores, 2025). The population-based cohorts based their exposure assessments on community-level EtO emissions from US EPA's TRI (Ish, 2025; Jones, 2023) or National Air Toxics Assessment (Chen, 2024; Garcia, 2015; Hart, 2018) database. The cancers investigated in these population-based cohorts included lymphoma, multiple myeloma, and breast cancer. Briefly, none of these five publications reported a clear association between EtO and these cancers, with RR estimates near 1.0 in all studies (Attachment C). While community-based air pollutant studies like these can potentially provide supportive information for hazard identification, these five publications were judged by OEHHA to be less useful than the occupational studies for exposure-response assessment due to their greater uncertainty in estimating individual EtO exposures. More specifically, it is unknown whether the TRI or National Air Toxics Assessment program (NATA), which are

based primarily on weather data and/or industrial emissions, can be used to provide accurate estimations of EtO exposure at an individual level. Importantly, adequate validation studies addressing this issue have not been done for either database. Errors in assessing exposure at the individual level can result in non-differential exposure misclassification, and this can bias RR estimates towards the null (i.e., towards finding no association; Greenland, 1998a). Furthermore, because these studies involved exposure levels seen in the general population, the range of exposure in these studies was generally much less than the exposure ranges seen in the occupational cohorts. The low, and generally narrow range of EtO exposure seen in these population-based studies likely decreased their sensitivity or statistical power to detect associations. Based on all these cumulative weaknesses, none of the recent population-based studies identified in OEHHA's literature search were considered further for exposure-response or IUR determinations.

The remaining three publications (Park, 2020; Kelly-Reif, 2025; Valdez-Flores, 2025) involved occupationally exposed populations, and all were either extensions or re-analyses of occupational cohorts used in publications previously identified by US EPA (i.e., published before 2016). The publication by Kelly-Reif et al. (2025) was an extended follow-up of breast cancer mortality in the NIOSH cohort of US sterilization workers which is discussed in detail below. The publication by Park (2020) also involved the NIOSH cohort, but the primary goal of this article was to evaluate the healthy worker survivor effect[11]. Because the Park (2020) article involved an incomplete and potentially biased method for this evaluation, it was not considered further for IUR calculations. More specifically, Park (2020) attempted to "reduce survivor bias" in the NIOSH analyses of EtO and cancer by including employment duration as a variable in their regression models. However, because employment status can be related to both EtO exposure and cancer outcomes, this method may introduce collider bias. More in-depth descriptions of this bias are provided elsewhere (Buckley, 2015; Picciotto, 2015; Picciotto et al., 2026), and further discussion of the healthy worker effect is provided below (in the section labeled "Additional Evaluations of Bias"). The third publication (Valdez-Flores, 2025) was a follow-up extension of the UCC cohort study in US chemical plant workers. This publication is also discussed in detail below.

[11] The healthy worker survivor effect is based on the finding that long-term workers generally have lower mortality rates than those who leave work earlier. This effect also tends to bias relative risk estimates downwards and generally affects workers in the higher categories of cumulative exposure. According to Picciotto et al. (2026), this phenomenon "sometimes leads to estimates suggesting that the exposure is beneficial, but even in less extreme examples, the healthy worker survivor effect results in underestimates of harmful effects".

Overall, OEHHA identified two publications in its literature search and initial screening evaluations that provided potentially useful information for exposure-response assessment (Kelly-Reif, 2025; Valdez-Flores, 2025). Although several new ecologic or general population studies were identified from the literature searches and PECO screening, for the reasons given above (temporality could not be established, limited exposure information, potential confounding, low statistical power), none of these provided relevant or useful information for IUR development. The results from the new publications on the NIOSH (Kelly-Reif et al., 2025) and UCC (Valdez-Flores et al., 2025) occupational cohorts supported previously published results from these same cohorts. That is, as in a 2003 publication from the NIOSH cohort (Steenland, 2003), the more recent NIOSH publication by Kelly-Reif et al. (2025) also found evidence linking EtO to breast cancer. Likewise, as in a 2009 publication from the UCC cohort (Swaen, 2009), the more recent publication by Valdez-Flores et al. (2025) also found no clear evidence of an association between EtO and lymphoid cancer. Overall, both the Kelly-Reif et al. (2025) and the Valdez-Flores et al. (2025) publications met the initial screening criteria described above, and both were advanced to the full detailed study evaluation stage.

In its review of US EPA's 2016 risk assessment, OEHHA identified four publications that appeared preliminarily to be without obvious and serious limitations and provided some information on exposure-response. Three of these were from the NIOSH (Steenland, 2004; Steenland, 2003) and UCC cohorts (Swaen, 2009) and published before 2016. An additional publication was from a longitudinal cohort study of EtO-exposed workers from two sterilization facilities in Sweden (Mikoczy, 2011). Overall, based on both its updated literature search and its evaluation of US EPA's 2016 review, OEHHA identified six publications (Mikoczy, 2011; Steenland, 2004; Steenland, 2003; Swaen, 2009; Valdez-Flores, 2025; Kelly-Reif, 2025) from three occupational cohorts (NIOSH, UCC, and Sweden) that were eligible for full detailed study evaluation. Descriptions of each of these cohorts and their key results are provided in Table 8.

642 **Table 8. Overview of human epidemiological cohorts examining EtO and cancer eligible for detailed study**
643 **evaluation.**

Cohort description	Exposure assessment methods and levels	Key results	Comments
National Institute for Occupational Safety and Health (NIOSH) cohort; initially >18,000 workers and 14 US sterilization plants; worked between 1940s–1980s; follow-up through 1998 (or 2021 for breast cancer mortality); described by Kelly-Reif et al. (2025), Steenland et al. (2004), and Steenland et al. (2003).	Multiple regression exposure model incorporating information on workplace air measurements (2700 measurements in 1976–1985), sterilization unit size, engineering controls, timing of sterilization, product type, calendar year, and historical process changes. Mean (± SD) cumulative exposures of 13,797 ppm-days (± 31,974) in men and 6643 ppm-days (±13,943) in women; median in both sexes of 2044 ppm-days.	Odds ratios (95% CIs) for **lymphoid cancer mortality** in both sexes combined were 1.00, 1.75 (0.59–5.25), 3.15 (1.04–9.49), 2.44 (0.80–7.50), and 3.00 (1.02–8.45) for cumulative exposures lagged 15 years of 0; >0–1200; 1201–3680; 3681–13,500; and >13,500 ppm-days, respectively. Odds ratios (95% CIs) for **breast cancer incidence** were 1.00, 1.06 (0.66–1.71), 0.99 (0.61–1.60), 1.24 (0.76–2.00), 1.42 (0.88–2.29), and 1.87 (1.12–3.10) for cumulative exposures lagged 15 years of 0; >0–647; 647–2026; 2026–4919; 4919–14,620; and >14,620 ppm-days, respectively. Odds ratios (95% CIs) for **breast cancer mortality** were 1.00, 2.57 (0.94–7.64), 3.07 (1.02–9.71), 2.04 (0.79–5.89), 4.30 (1.59–12.85), 4.40 (1.33–15.15), and 4.67 (1.40–16.05) for cumulative exposures lagged 20 years of 0; >0–500; >500–1000; >1000–5000; >5000–15,000; >15,000–25,000; and >25,000 ppm-days, respectively.	Most suitable epidemiologic study for exposure-response quantification due to its large size, good statistical power, high quality exposure data, appropriate follow-up, lack of obvious confounding variables, inclusion of both sexes, wide range of exposure, and thorough exposure-response analyses.

644 Abbreviations: CI – confidence interval; ppm-days – parts per million-days; SD – standard deviation; US – United States.

645

Table 8. Overview of human epidemiological cohorts examining EtO and cancer eligible for detailed study evaluation (continued).

Cohort description	Exposure assessment methods and levels	Key results	Comments
Union Carbide Corporation (UCC) cohort; 2053 male chemical plant workers; worked between 1940–1988; follow-up through 2013; described by Swaen et al. (2009) and Valdez-Flores et al. (2025).	Exposure matrix using workplace air measurements, department records and manuals, air levels from other facilities, unclear exposure estimates, and employee and expert interviews, broadly classified into 3 exposure levels for 4 time periods Mean cumulative exposure of 24,513 ppm-days (SD not provided); median of 7480 ppm-days	Rate ratios (95% CIs) for **lymphoid cancer mortality** were 1.00, 2.04 (0.59–7.07), 0.81 (0.23–2.81), 1.48 (0.43–5.15), and 0.70 (0.20–2.43) for cumulative exposures of 0.00–2502; 2502–5094; 5094–14,949; 14,949–26,920; and >26,920 ppm-days, respectively.	Limited exposure model validation; no females and no results for female breast cancer; small sample sizes; limited results regarding lag periods; possible co-exposures.

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

Table 8. Overview of human epidemiological cohorts examining EtO and cancer eligible for detailed study evaluation (continued).

Cohort description	Exposure assessment methods and levels	Key results	Comments
Swedish cohort; 2171 medical equipment sterilization workers; worked between 1925–1988; follow-up through 2003; described by Mikoczy et al. (2011).	Plant specific job-exposure matrices combined with yearly statutory workplace air measurements after 1985 Mean cumulative exposure of 1066 ppm-days (SD not provided); median of 47.45 ppm-days	Rate ratios (95% CIs) for **lymphohematopoietic cancer incidence** were 1.00, 1.17 (0.36–3.78), 0.92 (0.28–3.05) for cumulative exposures of 0–47.45, >47.45–76.65, and >76.65 ppm-days, respectively. Rate ratios (95% CIs) for **breast cancer incidence** were 1.00, 2.76 (1.20–6.33), 3.55 (1.58–7.93) for cumulative exposures of 0–47.45, >47.45–76.65, and >76.65 ppm-days, respectively.	Relatively low and narrow exposure range; few lymphohematopoietic cancers (n = 18); results for lymphoid cancer not provided; provides some evidence of increased breast cancer risks at relatively low EtO exposure levels.

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

Detailed study evaluation results

Based on the literature search and screening evaluations described above, as well as on OEHHA's review of the 2016 US EPA EtO risk assessment (US EPA, 2016a; 2016b), OEHHA identified six publications from three occupational cohorts that were considered potentially useful for IUR development. As such, the publications from these three cohorts were advanced to full study evaluation. As noted above, these included publications from the NIOSH (Kelly-Reif et al., 2025; Steenland et al., 2003; Steenland et al., 2004) and UCC (Swaen et al., 2009; Valdez-Flores et al., 2025) cohorts, as well as a publication from a cohort study of workers from two sterilization facilities in Sweden (Mikoczy et al., 2011; Table 8). For simplicity, publications from the same cohort and involving the same underlying study design are collectively referred to as coming from the same "study".

Each of these three cohort studies underwent detailed study evaluations in order to determine which study or studies were the most useful and valid for exposure-response and IUR calculations. The results of these evaluations are provided in Attachment D and summarized in Figure 3. Overall, of these three cohort studies, the NIOSH retrospective cohort studies of lymphoid cancer mortality and breast cancer incidence (Steenland et al., 2003; Steenland et al., 2004) were determined by OEHHA to be of high study quality and the most sensitive and valid epidemiologic studies for IUR calculations. The recent (Kelly-Reif et al., 2025) analysis of breast cancer mortality in the NIOSH cohort was important in that it provided strong supportive evidence that EtO is causally related to breast cancer. However, the previous (Steenland et al., 2003) NIOSH results on breast cancer incidence were selected for the IUR calculations rather than the mortality results since the focus of the lifetable analyses and IUR calculations was on cancer incidence. Cancer incidence is typically preferred over cancer mortality for IUR calculations because it is usually a more sensitive metric of overall cancer occurrence. The UCC cohort study (Swaen et al., 2009; Valdez-Flores et al., 2025) and the cohort study of Swedish sterilization workers (Mikoczy et al., 2011) were determined by OEHHA to be of overall lower study quality than the NIOSH cohort study (Figure 3 and Attachment D).

The NIOSH cohort study selected by OEHHA is the same study used by US EPA (2016a) for its IUR calculations. The design of this study and its results are described in detail in the following sections. This is then followed by a more thorough discussion of the detailed study evaluation results and the rationale for why this study was selected over other studies for OEHHA's exposure-response and IUR calculations.

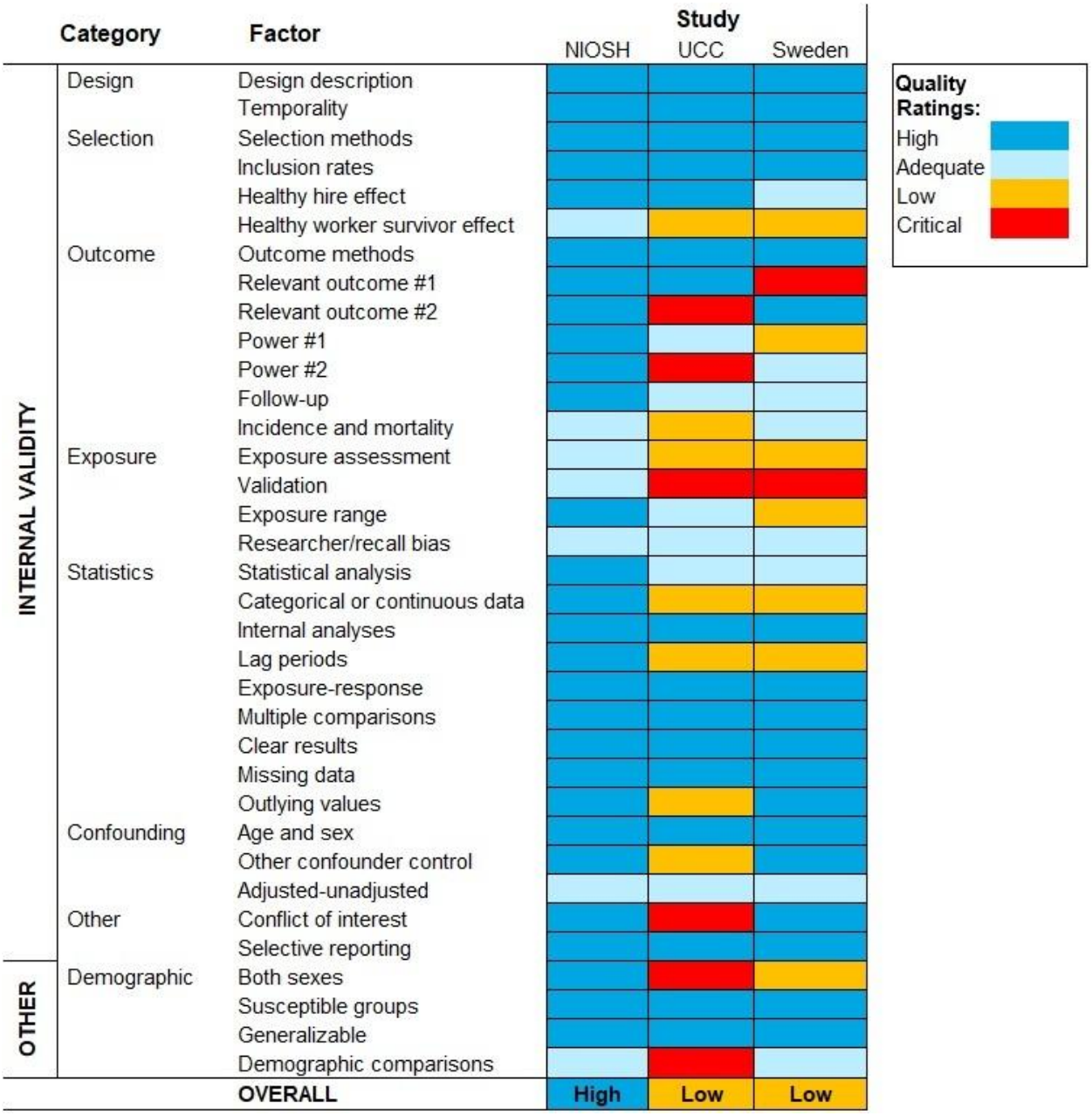


Figure 3. Detailed evaluations of the epidemiologic studies considered for exposure-response and IUR calculations.

References: NIOSH (Kelly-Reif et al., 2025; Steenland et al., 2003; Steenland et al., 2004); UCC (Swaen et al., 2009; Valdez-Flores et al., 2025); Sweden (Mikoczy et al., 2011). Further details on these evaluations and ratings are provided in Attachments D and E.

The NIOSH cohort study

The NIOSH study was a retrospective longitudinal cohort study initially involving more than 18,000 workers exposed to EtO at 14 US sterilization facilities (Kelly-Reif et al., 2025; Steenland et al., 2003; Steenland et al., 2004). One of the smaller facilities lacked exposure estimates (n = 705; 4% of the cohort) and was excluded, leaving 17,530 male (n = 7645) and female (n = 9885) workers for the exposure-response analyses. Most EtO-exposed workers were involved with sterilizing medical supplies, treating spices, and manufacturing and testing medical sterilizers. The workers were not highly exposed to any other known carcinogen at these facilities. In the 2003 and 2004 publications from this cohort, cancer mortality, including lymphoid and breast cancer mortality, and breast cancer incidence were assessed with longitudinal follow-up through 1998 and an average follow-up of approximately 25 years (Steenland et al., 2004; Steenland et al., 2003). More recently, results for breast cancer mortality with an additional 23 years of follow-up (through 2021) were reported (Kelly-Reif et al., 2025). The cohort was assembled by NIOSH and included all employees who worked at one of the included facilities for at least 12 months for breast cancer mortality and incidence or 3 months for lymphoid cancer mortality. 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 and included 2700 individual time-weighted average exposure values for workers' personal breathing zones. Estimates of annual exposure based on model results showed that median EtO exposure levels in the cohort's non-cancer control participants (the very large majority of all participants) were about 11 mg/m^3 (6 ppm) in the early 1950s and roughly 0–4 mg/m^3 (0–2 ppm) after that time (Figure 4). As shown in Figure 4, annual median EtO exposures were generally higher in lymphoid cancer cases than in non-cancer controls. For those exposed to the highest EtO levels, the 95^{th} percentile of the annual EtO exposure levels appeared to have peaked during three separate periods—around 1952, 1960, and 1972 (data not shown in Figure 4)—and as with the median levels, were generally higher in lymphoid cancer cases than in controls. Further details on the exposure model and modeled exposure levels can be found elsewhere (Hornung et al., 1994; Steenland et al., 2003; Steenland et al., 2004; US EPA, 2016a; US EPA, 2016b). Elevated risks of both lymphoid cancer and breast cancer associated with EtO exposure were identified in these studies, and detailed descriptions of these results are provided in the following sections.

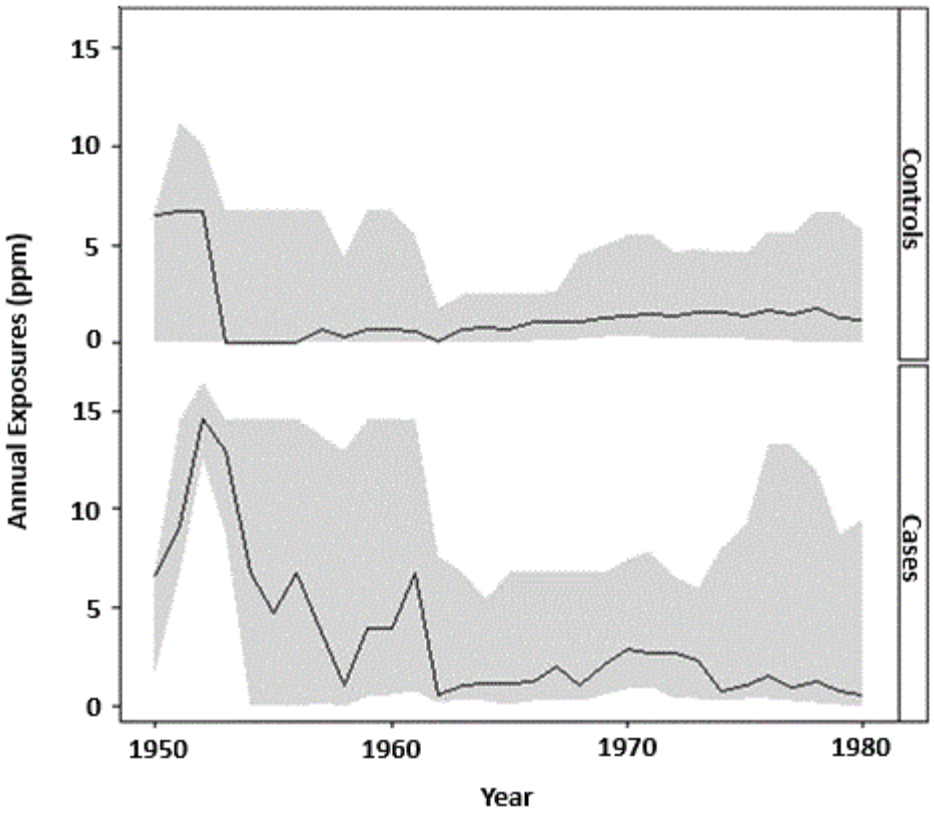


Figure 4. Estimated annual EtO exposures (ppm) experienced by lymphoid cancer cases and controls in the NIOSH cohort participants while working. Figure from US EPA (2016b, Figure D-22). Medians (dark line) and interquartile ranges (gray shaded area). Axis labels were enlarged by OEHHA for greater accessibility.

Lymphoid Cancer Mortality Analyses and Results

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" (Celentano and Szklo, 2019). In this case, the standard population was the general US population categorized into groups by age and sex. A total of 53 deaths due to lymphoid cancer (International Classification of Diseases 9th revision codes 200, 202, 203, and 204) were identified. Lymphoid cancer was a

particular focus of this study since it was shown to be elevated in an earlier analysis (Stayner et al., 1993) of this cohort.

Each lymphoid cancer death was matched to 100 randomly selected controls based on race, sex, and date of birth. Age was the time variable in the regression analyses, effectively matching on age. In addition, as per the authors, “Matching on date of birth, in combination with the use of age as the time variable to form risk sets was equivalent to matching on calendar time” (Steenland et al., 2004; Steenland et al., 2003). No other major potential confounding variables were identified. Males and females were combined in the final exposure-response analyses since EtO-associated RRs were elevated in both sexes, and the difference in these RRs between sexes was not statistically significant. In general terms, 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 or lesser exposed group (Gordis, 2014). In the 2004 publication by Steenland et al., the results were calculated using different lag periods, and the best fitting exposure-response models were found to be those that used a 15-year exposure lag. A lag period is used to account for the fact that there is a period of time between when an exposure first initiates a cancer (i.e., the time when a single or a relatively small number of cells undergo the first steps of malignant transformation) and the time that the cancer is large or diffuse enough to be diagnosed (e.g., becomes detectable or is detected using standard diagnostic procedures). This period is commonly several years or more and may even be several decades or longer for some exposures and some cancer types (Archer et al., 2004; Lipfert and Wyzga, 2019; Marshall et al., 2007; Selikoff et al., 1980). When a 15-year lag period is used, all EtO exposures at the included facilities occurring in the 15 years before cancer diagnosis or cancer mortality in cancer cases (and at the same time in the matched risk set of non-cancer controls) are set to zero under the assumption that exposure during this time was unlikely to have caused the cancer being studied.

The results for lymphoid cancer mortality using a 15-year lag and an internal comparison group are shown in Table 9. Internal comparisons between exposure subgroups within a cohort are conducted to better control for confounding since lifestyle and general health status (potential confounders) may be more similar within the cohort than when compared to the general population (McNamee, 2003).

The average duration of exposure in the study participants was 8.7 years, the average follow-up was 26.8 years, and the average cumulative exposure was 9818.5 ppm-days. As seen in Table 9, odds ratios (ORs) for lymphoid cancer mortality were greater than 1.0 in all non-reference categories of exposure. An odds ratio greater than 1.0 indicates that exposure may increase the risk of cancer (Gordis, 2014). The

ORs increased from the lowest (>0–1200 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 higher exposure categories. Such attenuation at higher exposure levels is fairly common in occupational epidemiology cancer studies and may be due to factors such as the depletion of susceptible subpopulations, saturation of key enzyme systems, mismeasurement of exposures, use of cumulative exposure metrics, or the healthy worker survivor effect (Stayner et al., 2003). Further discussion of this plateaued type of exposure-response pattern is provided below. The NIOSH researchers noted that peak and average exposures did not predict cancer risk as well as cumulative exposures; although, detailed results for these metrics were not provided.

Table 9. Odds ratios for lymphoid cancer mortality in the NIOSH cohort by categories of cumulative EtO exposure, with males and females combined and a 15-year exposure lag (US EPA, 2016a).

Cumulative EtO exposure (ppm-days)	Odds ratio[a]	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; NIOSH – National Institute for Occupational Safety and Health.

[(a)] Cases and controls were matched on date of birth, sex, and race. Age was the time variable in the regression analysis, effectively matching on age. Matching on date of birth, in combination with the use of age as the time variable to form risk sets, was equivalent to matching on calendar time.

Breast Cancer Incidence and Mortality Analyses and Results

The breast cancer incidence portion of the NIOSH study involved 7576 women and 319 cases of incident breast cancer (Steenland et al., 2003). This part of 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. Some 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). However, they can progress to invasive tumors. The advantages of limiting the analyses to those with interviews were the availability of interview information on other breast cancer risk factors (e.g., potential confounding variables) and a more complete case ascertainment (since several breast cancer cases (n = 44) were identified by interview alone). Interview rates were reasonably similar among cases and controls (73% versus 68%, respectively; Steenland et al., 2003), suggesting that major upward bias to the RR estimates due to differences between case and control participation rates was unlikely. This is especially true if short-term workers (who may have had lower cumulative exposures) were more difficult to locate and therefore less likely to be interviewed. 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 this study and therefore unlikely to have caused important confounding (Axelson, 1978). As noted above, this study was deemed by US EPA (2016b) to be of "high quality." OEHHA's detailed evaluations of this study led to the same conclusion (Attachment D and Figure 3).

The NIOSH study results for breast cancer incidence are presented in Table 10. The average duration of exposure was 10.7 years, and the median cumulative EtO exposure was 3139 ppm-days. In models using a 15-year lag, there were 62 breast cancer cases in the reference exposure category. The reference exposure category is the group in which exposures were lagged out, yielding a zero exposure and an assigned 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 of the ORs in these other categories were very similar, the number of cases in each of these categories was likely similar as well (e.g., approximately 34–35 cases each). As shown in Table 10, 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 end of the 95% CI of 1.60 for the OR in this category highlights the possibility that risks 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 10. Odds ratios for breast cancer incidence in the NIOSH cohort by categories of cumulative EtO exposure, in females, 15-year exposure lag (Steenland et al., 2003).

Cumulative EtO exposure (ppm-days)	Odds ratio[a]	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

Abbreviations: CI – confidence interval; NIOSH – National Institute for Occupational Safety and Health.

[(a)] Adjusted for year of birth, parity, and family history of breast cancer; matched on age (by using age as the time variable in the regression analyses) and race.

Recently, an updated analysis of breast cancer mortality using the NIOSH cohort was published (Kelly-Reif et al., 2025). This analysis extended the follow-up period from 1998–2021 compared to the previous mortality assessment (Steenland et al., 2004). There were 181 breast cancer deaths overall and 111 breast cancer deaths with interview data. The best fitting model for these mortality data had a 20-year lag period. Standardized mortality ratios for breast cancer (with a 20-year exposure lag), using the general US population as the reference group, were all <1.5 and not statistically significant. However, rate ratios for analyses using an internal reference group were all above 1.0 compared to the reference category and statistically significant at most exposure levels. More specifically, rate ratios for cumulative exposures with a 20-year lag of >0–500; >500–1000; >1000–5000; >5000–15,000; >15,000–25,000; and >25,000 ppm-days in those with interview data were 2.57 (95% CI = 0.94–7.64), 3.07 (95% CI = 1.02–9.71), 2.04 (95% CI = 0.79–5.89), 4.30 (95% CI = 1.59–12.85), 4.40 (95% CI = 1.33–15.15), and 4.67 (95% CI = 1.40–16.05), respectively. Similar results were seen in analyses involving all breast cancer deaths (i.e., those with and without interviews). Overall, this study provided strong evidence for an association between EtO and breast cancer mortality. As noted above, these particular results were not used in US EPA's or OEHHA's final IUR calculations since the focus of these calculations was on cancer incidence rather than cancer mortality. However, these findings are important in that they support the NIOSH findings for

breast cancer incidence and add strong additional evidence that EtO is causally linked to breast cancer.

Toxicokinetics

The toxicokinetics (absorption, distribution, metabolism, and elimination) of EtO have been reviewed by IARC (2008), US EPA (2016a), and 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). The levels of N-(2- hydroxyethyl)valine (HEV) adducts resulting from EtO alkylation of valine in Hb have been widely reported in rodents and humans. While HEV is recognized as a useful biomarker of occupational EtO exposure in worker studies, its use as an indicator at low ambient environmental EtO exposures is not straight forward due to the influence of confounding EtO exposure sources and polymorphic enzymes involved in EtO metabolism (Lin et al., 2025; see the Endogenous Production of EtO section).

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 5; 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

915 thiodoacetic acid (Figure 5; IARC, 2008; ATSDR, 2022). GST-mediated metabolism
916 rates are nearly two orders of magnitude faster than EH-mediated ones in the rodent
917 liver and approximately two-fold faster in the human liver (Filser and Klein, 2018).
918 Non-enzymatic, spontaneous conjugation of EtO with GSH occurs in all body
919 compartments, except muscle and fat, at a similar rate in both rodents and humans
920 (Fennel and Brown 2001, Filser and Klein, 2018).

921

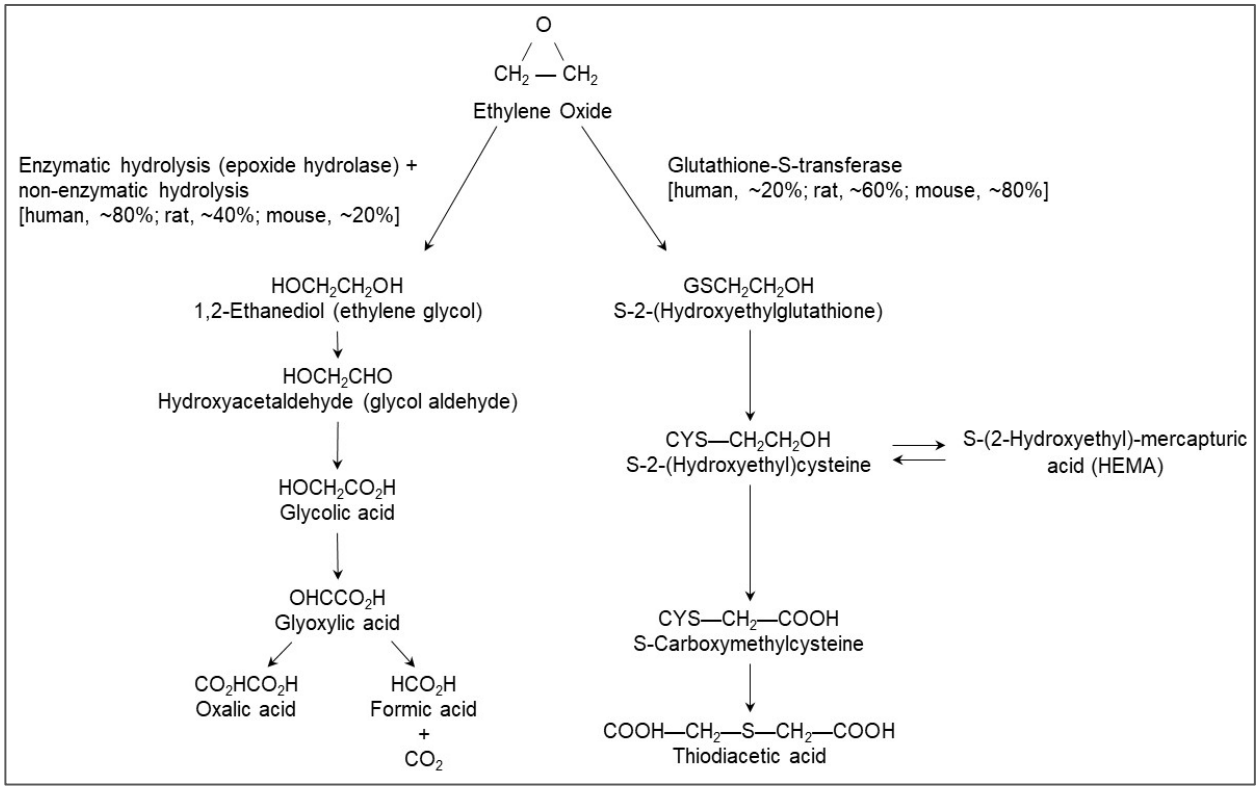


Figure 5. Proposed metabolic scheme for EtO. Adapted from IARC (2008) and ATSDR (2022).

Overall elimination of EtO is thought to follow first-order kinetics (Filser and Bolt, 1984) for exposures up to 365 mg/m^3 (200 ppm). Thus, at ≤365 mg/m^3 (200 ppm), 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 in blood of approximately 40 minutes, 10–19 minutes, and 9 minutes were determined for humans exposed occupationally at 1.8 mg/m^3 (1 ppm; Hattis 1987; Filser et al., 1992), rats exposed at 182 mg/m^3 (100 ppm) for 4 hours (Brown et al., 1996; Csanády et al., 2000), and mice exposed at 1.8 mg/m^3 (1 ppm) for 1 hour (Ehrenberg et al., 1974) or 182 mg/m^3 (100 ppm) for 4 hours (Csanády et al., 2000), respectively. Taken together, these studies indicate that EtO is eliminated faster in rats and mice than humans at exposure concentrations ≤182 mg/m^3 (100 ppm).

Physiologically-based pharmacokinetic or toxicokinetic (PBPK) models of EtO have shown comparable steady-state blood concentrations across humans, rats, and mice for exposure concentrations up to 100 ppm (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 ≤182 mg/m^3 (range = 1.8–182 mg/m^3;

1–100 ppm) were approximately equal and linearly related to the inhaled EtO concentrations (Fennell and Brown, 2001; US EPA, 2016a).

In the PBPK model of Filser and Klein (2018; Figure 6 below), 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.

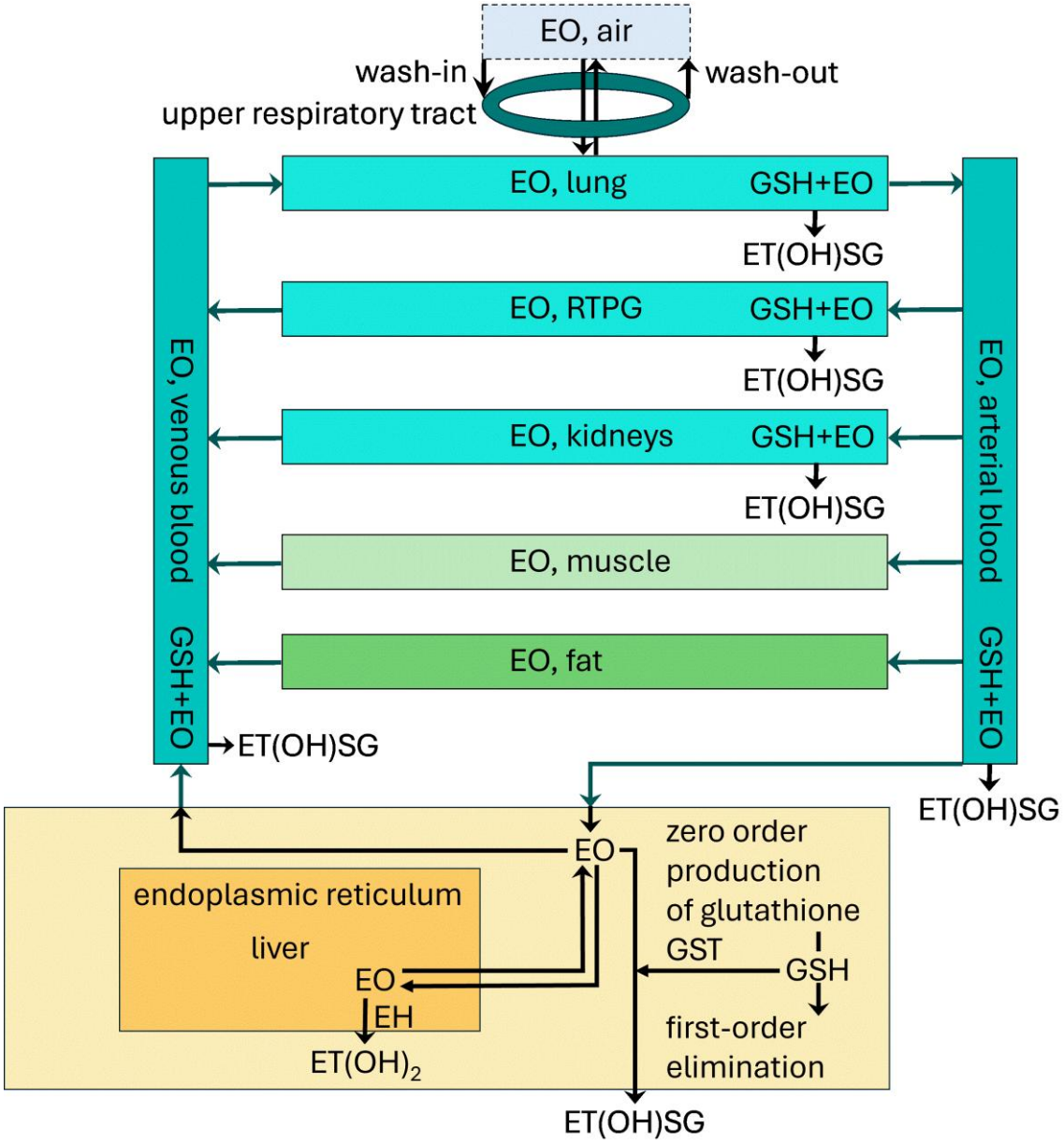


Figure 6. Schematic structure of the PBPK model for inhaled EtO.
The diagram was reproduced from Filser and Klein (2018, Figure 1) with modifications by OEHHA to ensure adequate color contrast, meeting Web Content Accessibility Guidelines. Compartments in solid lines are characterized by defined volumes; the air compartment (dotted lines) can have a defined volume or can be infinitely large, depending on the exposure condition. 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 7 and 8 below.

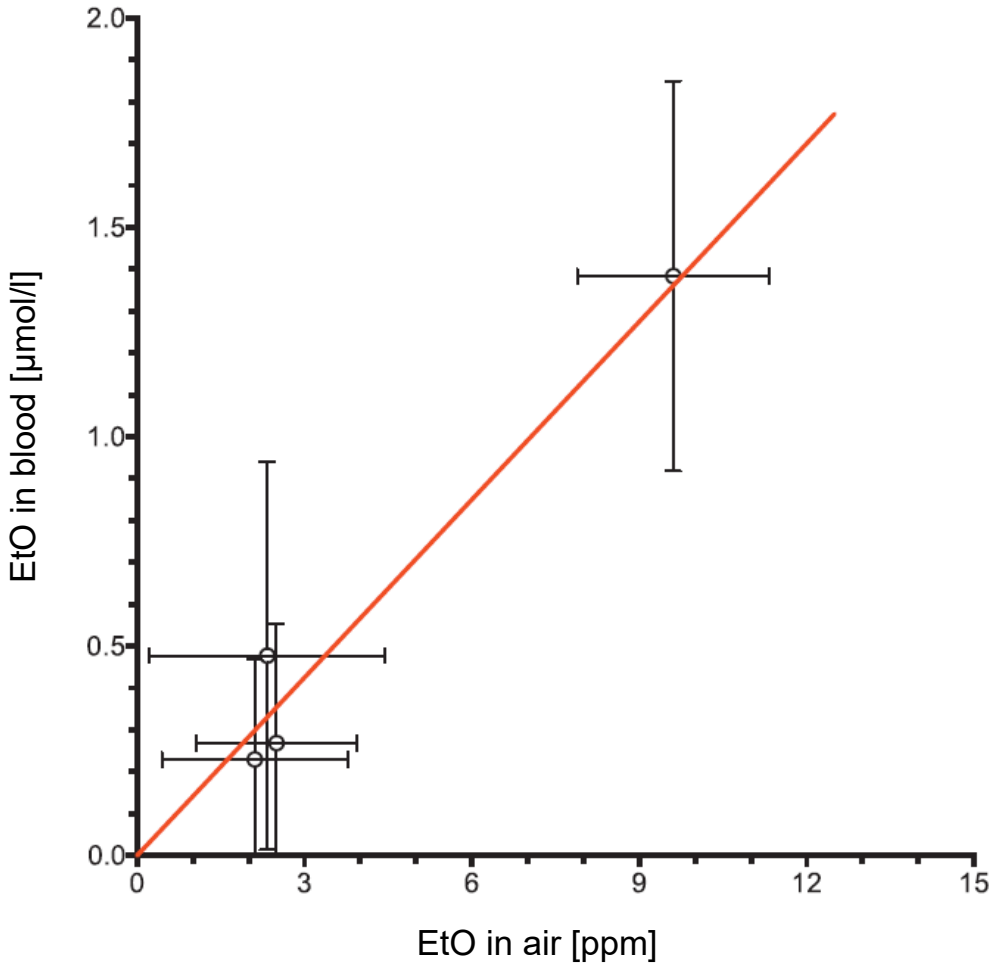


Figure 7. EtO concentrations in venous blood of humans exposed to atmospheric EtO.
The graph was reproduced from Filser and Klein (2018, Figure 3). Circles and error bars represent means ± standard deviations (n = 9) of the data measured in workers for 4 hours and 8 hours of 8-hour workshifts in a hospital sterilizer unit (Brugnone et al., 1986). The solid diagonal red line represents the model fit obtained by the Filser and Klein (2018) PBPK model, assuming a 70-kg BW and an 8-hour exposure period. The modeled line has the same slope as a linear regression of the measured data. Abbreviations: BW – body weight; kg – kilogram; µmol/l – micromoles per liter; n – number; PBPK – physiologically-based pharmacokinetic/toxicokinetic; ppm – parts per million.

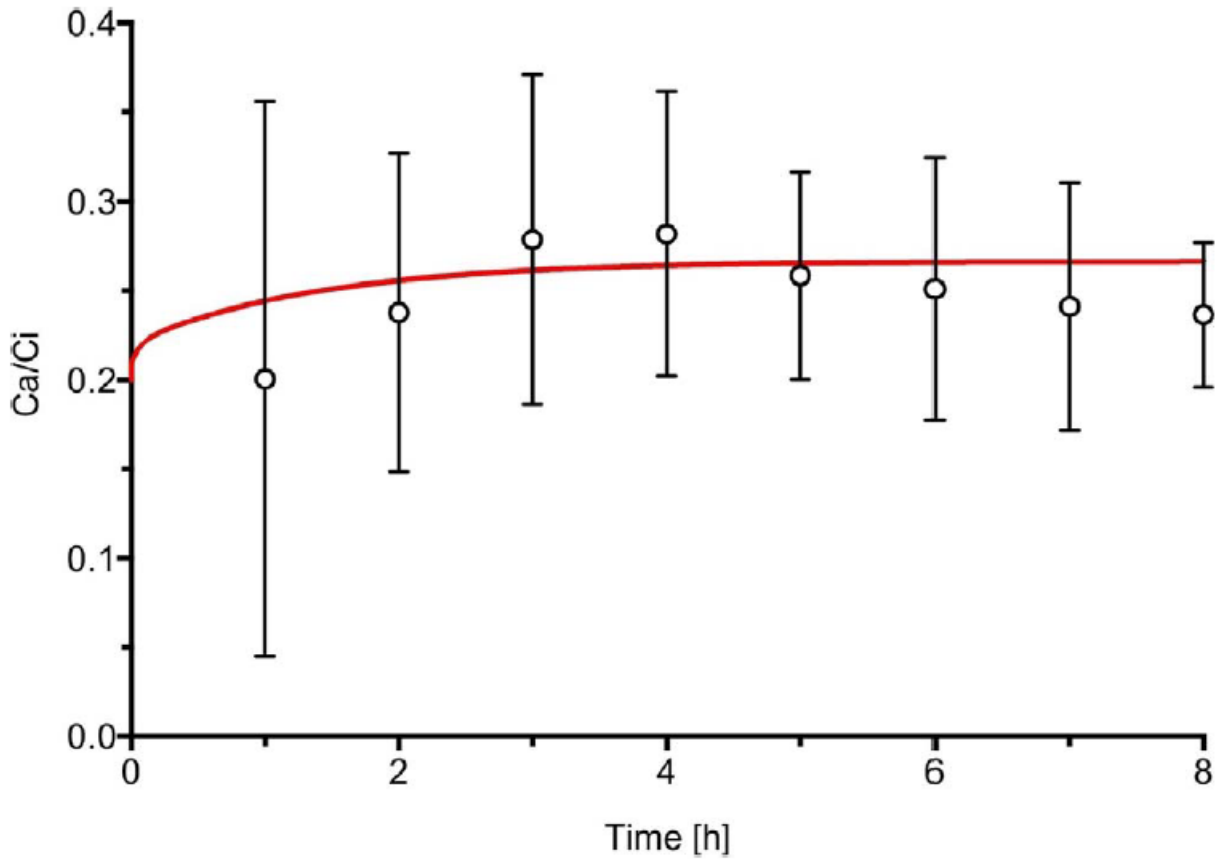


Figure 8. Ratio of EtO in the exhaled alveolar air (Ca) to EtO in the breathing area (Ci) as a function of time (hours).

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). It is also consistent with EtO elimination occurring via a slower hydrolysis process as tissue GSH is depleted, leading to a greater-than-linear increase in blood EtO concentrations (US EPA, 2016a). Relatedly, Filser and Klein (2018) reported that according to their PBPK model, the GST-mediated pathway would decrease in favor of the EH-mediated pathway in mice and rats at EtO concentrations ≥365 mg/m^3 (200 ppm). This GSH-depletion-mediated change was more evident in the mouse than in the rat (Figure 9). 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 0.91–911 mg/m^3 (0.5–500 ppm), 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, for humans, the model predicted that over an exposure range of 0.91–911 mg/m^3 (0.5–500 ppm), a minor (0.8%) increase in GST-mediated metabolism would occur (Figure 9), accompanied by a decrease in EH-mediated metabolism.

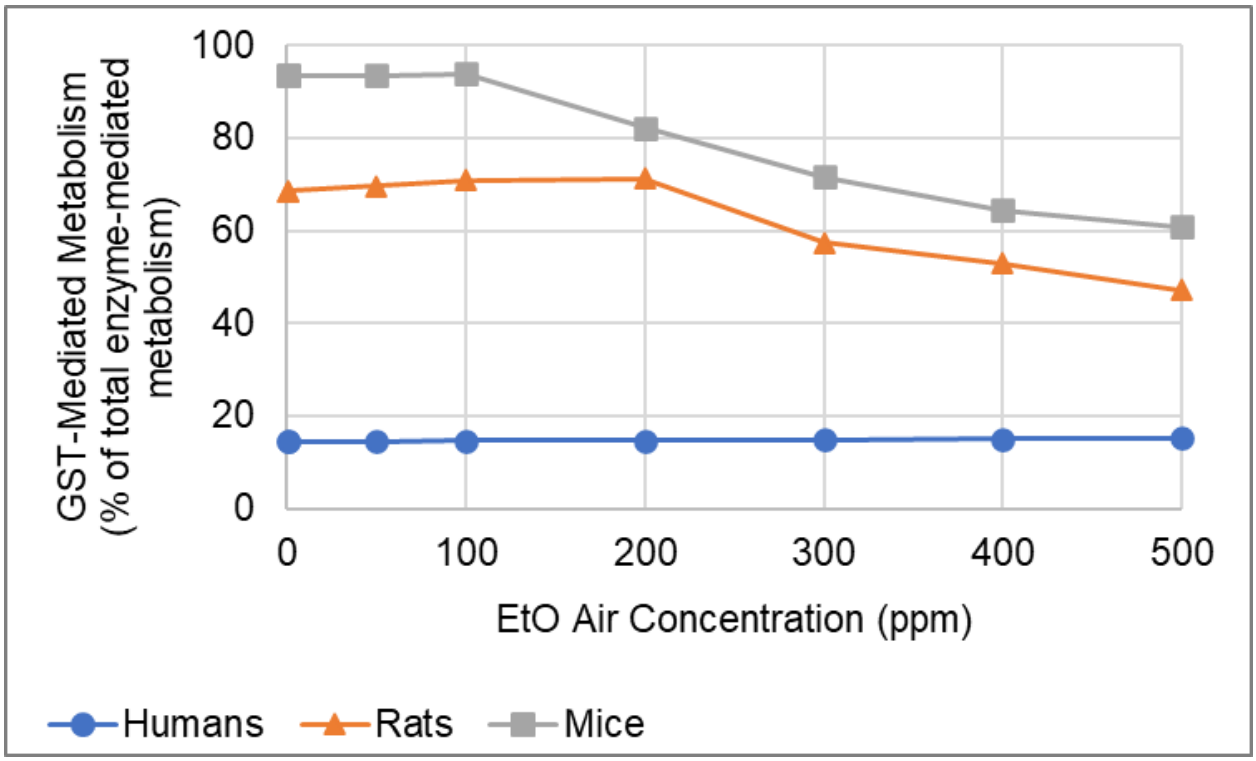


Figure 9. Physiologically-based toxicokinetic model predictions for the effect of EtO exposure concentration on the percentage of EtO metabolized by GST. Adapted from Filser and Klein (2018, Table 8). Corresponding EH-mediated metabolism is not shown. Abbreviations: EH – epoxide hydrolase enzyme; GST - glutathione-S-transferase enzyme; ppm – parts per million.

Another notable finding was related to the HEV levels in 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 HEV adduct levels of *GSTT1*0* carriers relative to individuals with the normal *GSTT1* gene when exposed under identical conditions to 1.8 mg/m^3 (1 ppm) of EtO. However, given EH- and GST-mediated EtO metabolism was predicted to account for approximately 85%–86% and 14%–15%, respectively, in a

modeled 70-kg individual exposed for 6 hours to 0.91–910 mg/m^3 (0.5–500 ppm) EtO, Filser and Klein considered GST-mediated EtO elimination in humans to be quantitatively minor relative to that of EH.

More recently, a toxicokinetic model was developed to simulate levels of HEV and elimination of its urinary cleavage product, *N*-(2-hydroxyethyl)-L-valyl-L-leucine (HEVL) (Mráz et al., 2024). However, no comparison of model simulations with human data was performed, and the model also didn't differentiate between endogenous and external exposure to EtO.

Endogenous Production of EtO

Background EtO exposures come from endogenous physiological and ambient environmental (exogenous) sources, such as ethylene metabolism in the body and EtO emissions from natural background sources (e.g., water-logged soil) and anthropogenic sources (e.g., vehicle exhaust and other combustion sources; IARC, 2008). 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 Hb; 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).

Endogenous ethylene production rates of 2.8 nmol/hr in Sprague-Dawley rats and 32 nmol/h in humans have been calculated (Filser et al., 1992; IARC, 1994). Validated models or measurements of EtO production from endogenous ethylene in animals or humans are not available. However, measurements of HEV adducts provide unequivocal scientific support to the presence of endogenous EtO exposure sources in both animals and humans (Rietjens et al., 2022). Background HEV levels ranging from 8.3–100 pmol/g Hb in mice, 25–50 pmol/g Hb in rats[12] and 8.3–656 pmol/g Hb in humans (healthy non-smokers with "no or negligible exogenous EtO exposure") have been reported (Kirman et al., 2021, 2025). These authors also reported an arithmetic mean HEV level of 22.9 pmol/g Hb in human nonsmokers. In smokers, HEV levels were higher by up to an order of magnitude (mean = 187 pmol/g Hb; range = 8.59–1460 pmol/g Hb).

[12] The values for rats and mice are given as ranges of arithmetic means from each strain/study group. For details, see Table 2 of Kirman et al. (2021).

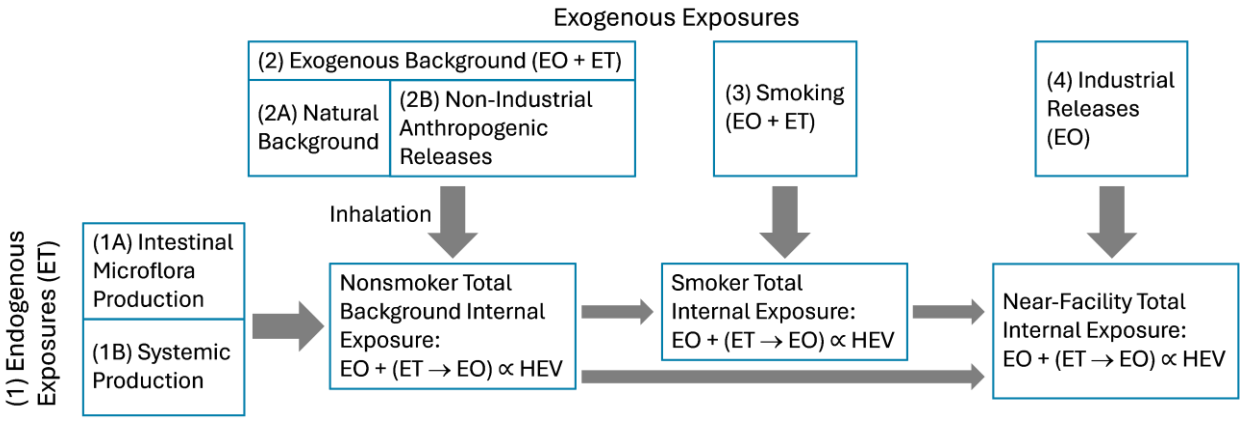


Figure 10. Conceptual model for exposure pathways contributing to total EtO exposure based on HEV biomarker burden.
The figure was reproduced from Kirman et al. (2025, Figure 1). OEHHA modified the font for greater accessibility. Abbreviations: EO – ethylene oxide (abbreviated EtO elsewhere in this document); ET – ethylene; HEV – N-(2-hydroxyethyl)-valine; ∝ - proportional to.

As shown in Figure 10, measurements of HEV levels in humans or other species reflect both direct exposure to EtO (endogenous + exogenous) and EtO burden through conversion of ethylene (endogenous + exogenous). The usefulness of HEV levels in predicting endogenous production of ethylene or EtO in humans is uncertain at present as there are no validated toxicokinetic models or data to support it. Despite this deficiency, Kirman et al. (2021; 2025) derived endogenous-equivalent values (i.e., “endogenous levels normally found within the body expressed in terms of exogenous exposures”) using a quantitative relationship between HEV levels and exogenous EtO exposures based on occupational exposure studies (Table 11). The conversion factor derived from occupational exposures to EtO (11.3 pmol/g Hb per ppb EtO) was used by these authors to predict HEV levels associated with low ambient EtO exposures and HEV levels associated with endogenous EtO levels down to zero. Thus, by applying the linearity assumption through the three dose regions (i.e., endogenous, ambient, and occupational exposures), Kirman et al. used the same conversion factor for interpreting HEV levels across a broad range of EtO exposures. These authors also attributed HEV levels to endogenous EtO sources based on a subtraction method (i.e., total HEV levels minus HEV resulting from exogenous ethylene and exogenous EtO). In other terms, the portion (93%) of total background HEV levels in non-smokers that was unexplained and unaccounted for by the exogenous ethylene and EtO was “attributed” to endogenous EtO sources.

Table 11. Equivalent exposure concentrations of EtO in air corresponding to total and endogenous hemoglobin adduct burdens in non-smoking and smoking populations in the United States.

Group	Percentile	Total HEV Burden [pmol HEV/g Hb]	HEV Burden Attributed to Endogenous Pathways [pmol HEV/g Hb (90% CI)]	Total Equivalent EtO Exposure, Corresponding to Total HEV [ppb, Continuous (90% CI)]	Endogenous Equivalent EtO Concentration, Corresponding to Endogenous HEV [ppb, Continuous (90% CI)]
Non-smokers	1st	5.8	3.7 (1.8–5.1)	0.9 (0.3–1.3)	0.7 (0.1–1.1)
	50th	19.7	17.6 (15.7–19)	3 (1.1–4.5)	2.8 (0.9–4.3)
	99th	76.9	74.8 (72.9–76.2)	11.7 (4.2–17.5)	11.5 (4–17.3)
Smokers	1st	13.4	NP	1.2	NP
	50th	154.4	NP	13.7	NP
	99th	660.0	NP	58.4	NP

The table was created with selected data from Kirman et al. (2025; Tables 6 and 7) with modifications. Data are shown only for the 1st, 50th, and 99th percentiles for total HEV burden. Abbreviations: CI – confidence interval; g – gram; Hb – hemoglobin; HEV – N-(2-hydroxyethyl)-valine; NP – not provided; pmol – picomole; ppb – parts per billion.

In contrast to Kirman et al.'s back-calculation and subtraction approach, Lin et al. (2025) took a forward dosimetry approach, using the endogenous production rate of ethylene as an input to a toxicokinetic model to calculate HEV levels and exhaled breath ethylene levels. By integrating the previously reported endogenous ethylene production rates (range = 0–68 nmol/h) within the PBPK model (Filser and Klein 2018), Lin et al. (2025) simulated HEV levels for ambient ethylene exposures ranging from 0–100 ppb. In this study, endogenous ethylene production was provided as an input to arterial blood, rather than as tissue-specific rates (which are not known with certainty), thus potentially impacting the hepatic first pass and resulting HEV predictions. As per their model, an average HEV level of 1.6 pmol/g Hb was predicted in an adult producing ethylene internally at 32 nmol/h. This could not explain the HEV levels in non-smokers (22.9 pmol/g Hb), thus implying the presence of other, unidentified HEV sources.

The analyses of the HEV levels in non-smokers both by Kirman et al. (2025) and Lin et al. (2025) indicate that only a small proportion is accounted for by known, ambient concentrations of ethylene and EtO, and that the remaining large part of the background HEV levels in non-smokers remains unaccounted for. While Kirman et al. (2025) attributed the entirety of the unaccounted HEV to endogenous production of EtO, Lin et al. (2015) attributed this to unidentified source(s) of HEV in the body or in the environment. Given the state of knowledge and models regarding the (i) tissue-specific production rate for ethylene, (ii) fraction of endogenously-produced ethylene converted to EtO, and (iii) lack of a validation dataset for endogenous EtO versus HEV levels, OEHHA recognizes the uncertainty regarding the relative contribution of endogenous sources of ethylene and EtO to the background levels of HEV in non-smokers (i.e., 8.27–656 pmol/g Hb). However, this uncertainty regarding the relative contribution of endogenous EtO sources to background HEV levels does not impact the derivation of the IUR, which is based on extra risk above endogenous and ambient background exposures to EtO (see Section VII. Quantitative Cancer Risk Assessment).

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) summarized the evidence (shown in Table 12) and stated 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 12. Comparison of the evidence for key events—cytogenetic, genetic, and related changes—induced by EtO 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 toxicological profile for EtO, ATSDR (2022) concluded,

> "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 RBCs. 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 cII gene in lung tissues from mice exposed for 8 or 12 weeks to 364 mg/m^3 (200 ppm) EtO via inhalation. Findings from these additional studies are consistent with the overall evidence for the genotoxicity of EtO.

VI. 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.
- 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.

- NTP listed EtO in the Report on Carcinogens since 1985 and considers EtO "known to be a human carcinogen" (NTP, 2021).

OEHHA agrees with the conclusions of these agencies regarding the carcinogenicity of EtO. With regard to other states' agencies, TCEQ (2020a) has determined that EtO is "likely to be carcinogenic to humans" based on insufficient human data, but with sufficient animal data and a putative mutagenic mode of action.

VII. QUANTITATIVE CANCER RISK ASSESSMENT

Study Selection

Results from the NIOSH epidemiologic cohort study reviewed above were selected as the basis of OEHHA's quantitative cancer risk assessment of EtO. This study was judged by US EPA (2016a) 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 time, absence of known confounding exposures, multiple study locations, and use of internal comparison groups. The NIOSH study was also reviewed by OEHHA and determined to be of high quality and unlikely to be affected by important bias or confounding. The results of OEHHA's detailed evaluations of this study are shown in Figure 3 and Attachment D and are discussed in further detail below.

Overall, OEHHA identified several key advantages of using the NIOSH study over other studies for the exposure-response and IUR calculations. These advantages included the following.

- Large sample size (n = 17,530 participants) and good statistical power
- High quality individual exposure data with appropriate model validation
- Appropriate follow-up period (i.e., average follow-up of 26.8 years)
- Lack of obvious major confounding variables
- Longitudinal design
- High participant follow-up rates
- Sound methodology and thorough statistical analyses

- Comprehensive assessment of exposure lag periods
- Inclusion of both males and females
- Relevant cancer types (lymphoid and breast cancers)
- Wide range of cumulative EtO exposures (average = 9818.5 ppm-days; SD = 23,980 ppm-days)
- Availability of appropriate and thorough exposure-response analyses and results

The NIOSH human epidemiology study (Steenland et al., 2003; Steenland et al., 2004; US EPA, 2016a; US EPA, 2016b) was selected by OEHHA for deriving the IUR over data from rodent studies because it is considered a high-quality study, it is more sensitive than the rodent studies, and it avoids the uncertainties associated with interspecies extrapolation. As discussed above and shown in Table 8 and Attachment D, OEHHA identified two other human epidemiologic studies that presented exposure-response data on EtO and cancer. This included a study from the UCC cohort of chemical production facility workers in the US and a study of workers from two plants in Sweden producing medical equipment sterilized with EtO. Both of these studies involved longitudinal designs and follow-up periods that were similar to or longer than the NIOSH cohort study. In addition, both included internal analyses which likely helped limit any bias from the healthy hire effect. Despite these strengths, however, both the UCC and the Sweden studies had important limitations which led to OEHHA's decision not to use these studies for exposure-response assessment (Attachment D and Figure 3). For example, both had much smaller sample sizes than the NIOSH cohort (approximately 2100 people in each of these two studies versus over 17,000 people in the NIOSH cohort). The relatively small sample sizes of these two studies likely limited their ability to identify statistically significant effects. The Swedish study had several other important weaknesses. For example, this study only included 18 lymphohematopoietic cancers. This relatively small number can limit the researcher's ability to perform certain sensitivity analyses or to thoroughly evaluate exposure lag periods. Another weakness of this study is that separate analyses of lymphoid cancers were not done. This is important because these were the cancer types in which the strongest associations were seen in the NIOSH cohort study. Another limitation of the Swedish study was that the methods used to assign individual exposures, and the data used to attempt to validate these methods were limited and unclear. For example, the validation procedures used in this study were based on Hb adducts rather than actual measurements of EtO exposure. In addition, these procedures only included small numbers of individuals (e.g., n = 8 exposed participants) and were based on very broad and relatively insensitive categorizations of exposure (e.g., EtO exposure >0.4 mg/m^3 (0.2 ppm)

versus lower levels; Hagmar et al., 1991). Another weakness of the Swedish study was that cumulative exposure levels (median = 47.45 ppm-days; 75th percentile = 80.3 ppm-days) were much lower than those in the NIOSH cohort. These low exposure levels may have limited the ability of this study to identify clear associations for some cancer types, especially relatively rare cancers like lymphoid cancer.

The UCC cohort study also had several limitations that precluded its use in IUR development. For example, the exposure modeling used in this study had several potential weaknesses. These included limited air monitoring data; fairly extensive use of EtO measurements from facilities that were not part of the study (including some that were not in the US); and unclear and insensitive estimates of exposure for several exposure groups and calendar years (Swaen et al., 2009). In addition, appropriate validation data were not reported. Thus, the accuracy of the exposure modeling used in this study is unknown. Errors in exposure assessment, if similar between case and control groups, can bias relative risk estimates towards the null (i.e., towards finding no effect). Another potential weakness of the UCC study is that a variety of other chemical exposures were known to have occurred in the UCC chemical production facilities, raising concerns about potential confounding (Greenberg et al., 1990). In addition, the UCC study only included male workers, so female breast cancer could not be assessed. For lymphoid cancer, the UCC cohort study only included 25 cases. This number was likely too small to thoroughly and precisely evaluate exposure lag periods, and the resulting analyses assessing these lags were limited.

Overall, OEHHA concurred with US EPA's conclusions that the NIOSH study is of high quality and is the best available study for conducting exposure-response analyses for IUR development (US EPA, 2016a; 2016b). US EPA also 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" (US EPA, 2022a; 2022b). As noted above, OEHHA did not identify any new scientific information in its updated literature search that would necessitate a change to US EPA's selection of the NIOSH study for its IUR calculations. As such, the present update of OEHHA's EtO IUR is based on the same NIOSH study data used by US EPA to calculate its unit risk estimate for lymphoid and breast cancer. The following sections describe the procedures and methods used to calculate US EPA's and OEHHA's IUR.

Lymphoid Cancer Exposure-Response and IUR Calculations

Introduction

The NIOSH study results for lymphoid cancer mortality with follow-up through 1998 were first published by Steenland et al. in a peer-reviewed scientific journal in 2004 (Steenland et al., 2004). Since then, US EPA contracted with the study authors to perform additional exposure-response modeling and other analyses of these data (US EPA, 2016a; 2016b). This work included performing linear and log-linear exposure-response models; weighted linear regressions of categorical odds ratios; 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 EtO exposure); and multiple sensitivity analyses.

The results of the various models applied to the NIOSH cohort data for lymphoid cancer in US EPA's 2016 assessment are shown in Figure 11. As seen in this figure, the models vary greatly in their overall shape (e.g., linear versus non-linear), steepness, and estimated RRs, especially in the lower exposure region (e.g., <1600 ppm-days). This variability is primarily due to the underlying equations inherent in each model. The purple dots in Figure 11 represent the categorical odds ratios, which are also presented in Table 9. Other than the model used to generate the categorical ORs and the weighted linear regression model that used these categorical ORs, all other models shown in Figure 11 are based on individual-level continuous data. This includes the two-piece linear spline model with a knot at 1600 ppm-days ultimately selected by US EPA and OEHHA for their IUR calculations. This model is represented by the dashed red line labeled as "linspline1600" in the Figure 11 key and identified with a box labeled as "US EPA/OEHHA." The figure also includes the Cox Proportional Hazards (CPH) log-linear model used by the TCEQ (2020a) to calculate their IUR. This model is represented by the lower solid light blue line labeled as "e^(β*exp)" in the Figure 11 key and identified with a box labeled as "TCEQ." This model is sometimes referred to as the "standard CPH model" (Valdez-Flores et al., 2025). Two important points can be easily seen in Figure 11. First, the two-piece linear spline model used by OEHHA and US EPA corresponds more closely—both in shape and in estimated risk levels at lower exposures—to the categorical ORs than does the standard CPH model used by TCEQ. Second, at lower exposures, the risks predicted by the standard CPH model used by the TCEQ are dramatically lower than those predicted by the categorical ORs, the two-piece linear spline model, and almost every other model evaluated. This latter point is especially important since the primary goal of the IUR derivation process is to

estimate risks at lower, environmentally relevant exposure levels. In the following section, a detailed justification is provided for why US EPA and OEHHA selected the two-piece linear spline model with a knot at 1600 ppm-days over the other models, including the standard CPH model, for its IUR calculations.

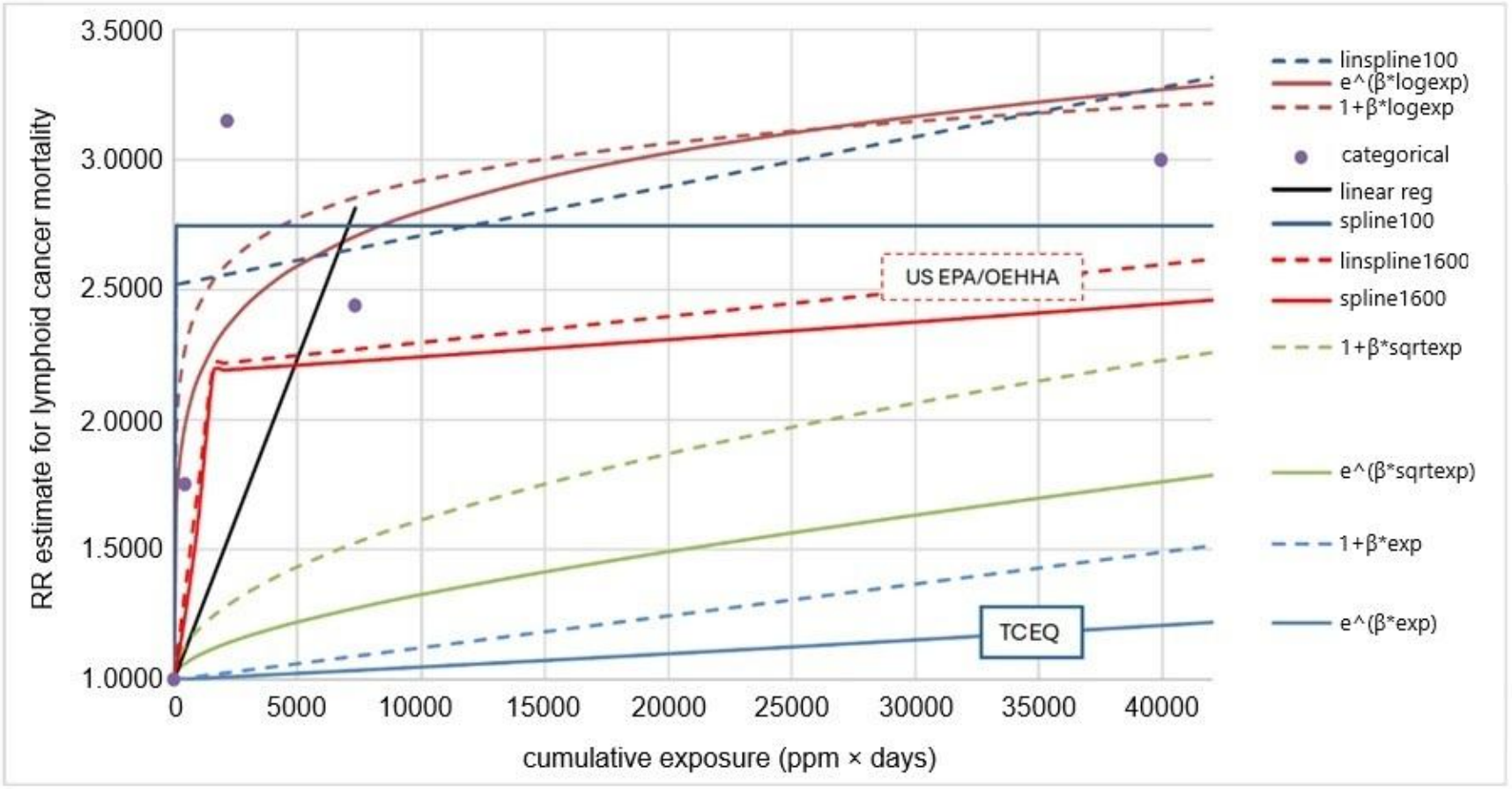


Figure 11. Exposure-response models for lymphoid cancer mortality versus occupational cumulative exposure in the NIOSH cohort, in males and females combined, 15-year exposure lag.

This figure was modified from US EPA Figure 4-3 (2016a) by OEHHA to enlarge the font size and roughly align each model label in the figure key with the last portion of its respective model. Models shown in this figure are: linspline100: two-piece linear spline model with knot at 100 ppm-days; e^(β*logexp): relative risk (RR) = $e^{(\beta \times \ln(\text{exposure}))}$; 1 + β*logexp: RR = 1 + (β × ln(exposure)); categorical: RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures, plotted at the mean cumulative

exposure for each category; linear reg: weighted linear regression of the categorical results, excluding the highest exposure group to alleviate some of the plateauing at higher exposures; spline100: two-piece log-linear spline model with knot at 100 ppm-days; linspline1600: two-piece linear spline model with knot at 1,600 ppm-days (model used by US EPA (2016a) and OEHHA); spline1600: two-piece log-linear spline model with knot at 1,600 ppm-days; 1 + β*sqrtexp: RR = 1 + (β × sqrt(exposure)); e^(β*sqrtexp): RR = $e^{(\beta \times \sqrt{exposure})}$; 1 + β*exp: RR = 1 + (β × exposure); e^(β*exp): RR = $e^{(\beta \times exposure)}$ (model used by TCEQ (2020a)). The models used by TCEQ (2020a), US EPA (2016a), and OEHHA (for this document) are labeled in boxes in the figure. Note that, with the exception of the categorical results and the linear regression modeling of the categorical results, the different 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.

Model Selection

The following general principles were recommended by US EPA's EtO Science Advisory Board for exposure-response model selection and were used by US EPA in its model selection process (US EPA, 2015; 2016a).

- The use of individual level continuous exposure data over categorical data
- Prioritizing the specific fit of the model at lower exposure levels rather than the overall fit of the model at high and low exposure levels combined. This principle is particularly important since some models appear to dramatically underestimate risks at lower exposures.
- Parsimony
- Not solely relying on Akaike Information Criteria (AIC) scores for model fit
- Biological plausibility and statistical considerations

OEHHA reviewed these principles and agrees that they provide a sound and valid approach to model selection. Another factor used by US EPA and OEHHA in the model selection process was visual fit; that is, a visual comparison of the continuous data model results to the categorical ORs. As described below, OEHHA judged these categorical ORs to be based on high quality data, calculated using sound statistical methods, and unlikely to be affected by major confounding or bias. As can be seen by the categorical ORs presented in Table 9 and in Figure 11, the NIOSH cohort results for lymphoid cancer appear to have a "supra-linear" shape (Crump, 2006). That is, the risks appear to rise fairly steeply in the lower exposure range and then attenuate or plateau at higher exposure levels. The exact reason for this attenuation in this study is unknown. However, this exposure-response shape is commonly seen in occupational epidemiology studies, and there are several plausible reasons explaining this effect. As mentioned earlier, these include the healthy worker survivor effect, depletion of susceptible people at high exposure levels, misclassification of exposure, saturation of key enzyme systems or other processes involved in cancer development, the use of cumulative exposure metrics, and competing risk factors (Stayner et al., 2003). Further discussion of this issue is provided below.

Several models evaluated by the NIOSH researchers involved two-piece linear or two-piece log-linear spline models (Figure 11). Two-piece spline models can be particularly useful for exposure-response data that exhibit a "supra-linear" shape since they allow the placement of a "knot" at some point within the exposure range and calculation of separate exposure-response slopes above and below this knot

(i.e., the calculation of separate slopes for the higher and lower portions of the exposure range). With respect to the NIOSH lymphoid cancer data, this allows for the calculation of one slope for the lower part of the exposure range where the risks appear to rise steeply and a separate slope for the upper part of the exposure range where the risks appear to rise less steeply or plateau. Allowing for two separate slopes like this helps prevent a situation in which the higher exposure data has an overly influential effect on the risks that are estimated at lower exposure levels.

A key consideration when using a two-piece spline model is the location of the knot. The NIOSH study authors and US EPA evaluated a range of different knots and found that the lowest AIC score (generally indicative of a good statistical fit) occurred with the knot at a cumulative EtO exposure of 100 ppm-days (US EPA, 2016a; 2016b). However, it was found that the model with a knot at 1600 ppm-days also had a relatively low AIC score, one that was reasonably close to that of the model using a knot at 100 ppm-days (462.1 versus 461.4, respectively). US EPA ultimately selected the model with a knot at 1600 ppm-days for several reasons. First, there were no exposed cases with EtO exposures below 100 ppm-days. This means that the exposure-response slope below the 100 ppm-days knot was largely determined by the higher exposure part of the exposure-response curve. This is inconsistent with the ultimate goal of this modeling process, which is to accurately estimate the risks at lower, not higher, exposures. In contrast, there were 13 lymphoid cancer deaths below the knot at 1600 ppm-days. This larger number allows for a more precise estimation of low exposure risks. Another important reason US EPA selected the knot at 1600 versus 100 ppm-days was that the latter led to an implausibly steep slope below the knot. This can be seen in Figure 11, which shows that the exposure-response slope for the knot at 100 ppm-days (the dashed darker blue line labeled as “linspline100” in the figure key) is nearly vertical below the knot. This very steep slope led to implausibly high risk estimates below the knot (i.e., in the lower exposure range).

While US EPA ultimately selected the two-piece linear spline model with a knot at 1600 ppm-days, a variety of other models were also evaluated. One of these was a two-piece log-linear spline with a knot at 1600 ppm-days (the solid red line labeled as “spline1600” in Figure 11). While this model had a similar AIC score and *p*-value as the linear two-piece spline model with a knot at 1600 ppm-days, the linear model was preferred over the log-linear model because the former allowed for a more straightforward and simpler (i.e., parsimonious) linear low-dose extrapolation. A key advantage of the linear model over the log-linear model is that with the linear model, the unit risk estimate does not depend on the risk level chosen as the point of departure.

Several other models were evaluated by the NIOSH researchers and US EPA (US EPA, 2016a; 2016b). The models with a logged exposure variable (i.e., the upper solid and dashed red lines labeled as "e^(β*logexp)" and "1 + β*logexp", respectively, in the Figure 11 key), while providing relatively good AIC scores and the lowest *p*-values (e.g., 0.02), were not selected for IUR development by US EPA or OEHHA because these models resulted in exposure-response curves that were very steep in the lower exposure regions. This can be easily seen in Figure 11. This extreme steepness would have led to implausibly high unit risk estimates if these models were used as the basis of the IUR calculations. Models with a square root transformation of the exposure variable (the solid and dashed green lines labeled as "e^(β*sqrtexp)" and "1 + β*sqrtexp", respectively, in the Figure 11 key) did not provide a marked improvement in fit over the two-piece linear spline model either statistically or when visually compared to the categorical ORs. The standard CPH model (the lowest solid blue line labeled "e^(β*exp)" in the Figure 11 key and identified with a box labeled "TCEQ") had a higher AIC score (464.4) and a higher *p*-value (0.22) than all the other models. In addition, it did not exhibit the "supra-linear" shape exhibited by the categorical ORs and by the statistically better fitting models. As noted above, a key criterion for model selection was the model fit in the lower exposure region (i.e., the region most relevant for lower environmental exposures). As can be seen in Figure 11, the standard CPH model dramatically underestimates low exposure risks when compared to the categorical ORs and all the better-fitting models. This lack of fit in the lower exposure region highlights the critical limitation of using the standard CPH model for estimating low exposure EtO risks.

As noted above, an important consideration in US EPA's model selection was the shape of the exposure-response curve. The two-piece linear spline model selected by US EPA and OEHHA is generally consistent with a "supra-linear" shape, and there was a variety of evidence to support the use of a model with this shape. Importantly, as previously noted, the categorical ORs, which appear to rise steeply at lower exposure levels and then somewhat attenuate at higher exposure levels, also had this same general exposure-response pattern. Although categorical analyses are sometimes criticized because they can lead to a loss of precision, they can also have several important advantages. For example, they may be less impacted by outlying values than analyses involving continuous data. In addition, categorical analyses are generally less dependent on the inherent form of the underlying model equations, which in some cases may not provide a good fit to the underlying data when individual level continuous data are used. The categorical ORs presented by Steenland et al. (2004) and shown in Figure 11 were calculated using standard, widely accepted methods. OEHHA thoroughly evaluated the statistical approach (and associated sensitivity analyses) used to generate these ORs and found that these ORs are unlikely to have been affected by any major bias. [Detailed evaluations of

bias are provided below.] Overall, given the high likelihood that the categorical ORs are valid and without major bias, the fact that the categorical ORs exhibit a "supra-linear" exposure-response pattern provides strong support for using a continuous data model that also has this same supra-linear shape.

There are several other pieces of information supporting the "supra-linear" nature of the NIOSH cohort lymphoid cancer results (i.e., the attenuation of the slope at higher exposure levels). First, this pattern is common in occupational epidemiology. Stayner et al. (2003) provide several examples in which this same exposure-response pattern has been seen in other occupational cohorts. Because it is fairly common, it is not surprising that this pattern is also seen in the NIOSH cohort. This general pattern was also seen in the NIOSH cohort findings for breast cancer incidence and breast cancer mortality, highlighting the consistency of this general exposure-response pattern within this study. Second, the statistically best fitting models in terms of both AIC scores and *p*-values (the linear models with the exposure variable logged) also had this same general shape. While these particular models were not selected for the reasons discussed above, the fact that they provided a good statistical fit to the NIOSH data adds further support that the NIOSH lymphoid cancer findings truly are "supra-linear." Another piece of evidence supporting a supra-linear shape comes from the analyses presented by US EPA (2016b) in which they removed a progressively larger percentage of the higher exposure data from the standard CPH modeling of the NIOSH lymphoid cancer data. Here, they found that when the upper 5%, 10%, 20%, 30%, 40%, and 55% of the highest exposures were removed, the exposure-response slope increased by 0.4, 1.7, 7.9, 5.6, 26.7, and 113.7 times, respectively (US EPA, 2016b). Increases like this are more consistent with an underlying "supra-linear" exposure-response pattern than with a pattern that is more linear or sub-linear in shape. For completeness, OEHHA evaluated several additional exposure-response models using the publicly available categorical data provided in Steenland et al. (2004) or US EPA's evaluation (US EPA, 2016a). These additional models are not shown in Figure 11 but included weighted linear regressions, weighted least squares regressions, and generalized least squares regressions (Greenland and Longnecker, 1992; Orsini et al., 2006; Rothman, 1986). They 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 these models fit the underlying NIOSH study data visually or statistically 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 et al., 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 incidence and sample size. Overall, after an extensive and thorough evaluation of multiple different models and methodologies, OEHHA concluded that 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 also considered the two-piece linear spline biologically plausible. That is, because EtO is a direct acting genotoxic carcinogen, dose-response functions that are linear at low doses are considered most plausible. And, as mentioned above, the plateauing or attenuation of the ORs at higher exposure levels seen in the NIOSH findings has been observed in a number of other studies of occupational carcinogens and there are several reasonable and plausible explanations for this pattern (Stayner et al., 2003).

Lymphoid Cancer IUR Calculations

OEHHA concurred with US EPA's selection of the lower portion of the two-piece linear spline model with a knot at 2912 $\mu g/m^3$ (1600 ppm) for its IUR calculations for the reasons given above. The lower slope was used since the ultimate goal of these IUR calculations is to estimate risks at lower exposures. The lower slope of the two-piece spline model (i.e., the exposure-response slope below the knot at 2912 $\mu g/m^3$; 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. US EPA (2016a) entered this slope and its 95% upper bound into 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 exposures 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 per year). The EC_{01} and its one-sided lower 95% confidence bound (the LEC_{01}) for lymphoid cancer mortality were 1.98×10^{-2} and 5.03×10^{-3} ppm, respectively. Using the same basic approach, EC_{01} and LEC_{01} values were also developed for lymphoid cancer incidence. Here, the exposure-response relationship for EtO and lymphoid cancer incidence was assumed to be the same as that identified in the NIOSH study 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). This analysis resulted in an EC_{01} and LEC_{01} for lymphoid cancer incidence of 7.48×10^{-3} and 1.90×10^{-3} ppm, respectively, and a cancer inhalation unit risk estimate for lymphoid cancer incidence of 5.26 $(ppm)^{-1}$. OEHHA replicated these calculations and obtained the same result. As this unit risk estimate was derived under the assumption that lymphoid cancer relative risk is independent of age and did not account for increased early-life susceptibility to cancer, US EPA performed an alternate life-table analysis to obtain an "adult-exposure-only" unit risk estimate (US EPA, 2016a; 2016b). In the alternate analysis, exposure to EtO began at age 16 years instead of at birth, and the resulting estimate was then rescaled to a 70-year lifetime. OEHHA concurs with this approach. This alternative approach resulted in an "adult-based" unit risk estimate for lymphoid cancer of 2.61×10^{-3} $(\mu g/m^3)^{-1}$ or 4.78×10^{-3} $(ppb)^{-1}$.

Breast Cancer Exposure-Response and IUR Calculations

Introduction and Model Selection

Similar to what was described above for the NIOSH lymphoid cancer mortality findings, a variety of different models were also evaluated for the NIOSH breast cancer incidence findings (Steenland et al., 2003; US EPA, 2016a; 2016b). These included a combination of linear and log-linear models, models using continuous or categorical exposure data, two-piece spline models, models with and without exposure variable transformation, and models using different exposure metrics (e.g., cumulative exposure, exposure duration, average, and peak). US EPA ultimately selected the two-piece linear spline model involving individual exposure data, cumulative exposure, a 15-year exposure lag, and a knot at 5750 ppm-days (Figure 12).

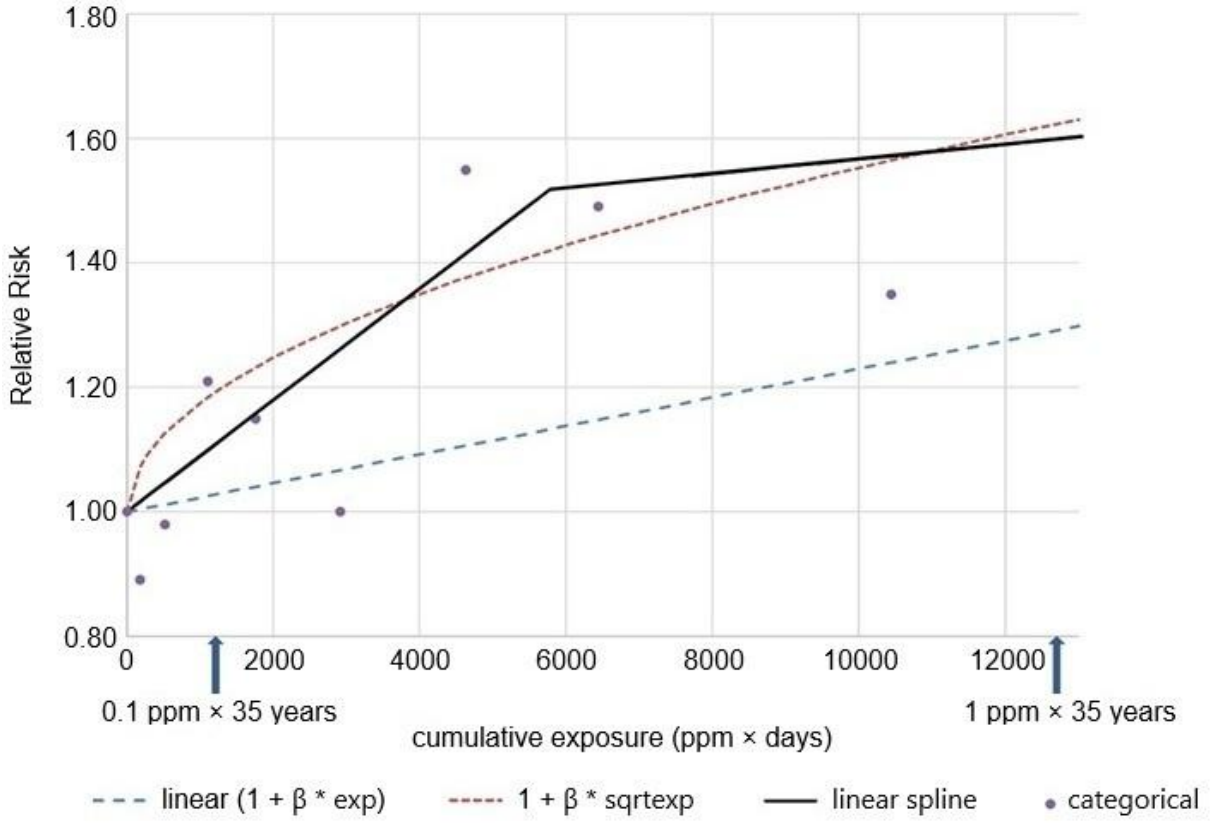


Figure 12. Exposure-response models for breast cancer incidence versus occupational cumulative exposure in the NIOSH cohort, in females, 15-year exposure lag.

This figure was modified from US EPA (2016a) Figure 4-10 by OEHHA to show the key below the graph. Models shown in this figure are linear (1 + β*exp) [relative risk (RR) = 1 + β x exposure]; 1 + β*sqrtexp [RR = 1 + β x sqrt(exposure)]; linear spline [two-piece linear spline model with knot at 5750 ppm-days]; and categorical [RR = $e^{(\beta \times \text{exposure})}$], with categorical exposures (deciles) plotted at the mean cumulative exposure for each category. 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.

This model had a low *p*-value = 0.01 and a good visual fit to the categorical data, especially in the lower exposure region. An advantage of this model is that it involved the use of individual rather than categorical exposure data which likely increased the model precision. The potential advantages of categorical over continuous data models discussed above did not play a major role in model selection for the NIOSH cohort data since there is no evidence that outlying values had an important impact on the two-piece linear spline model, and the two-piece linear spline model provided

a good fit to the NIOSH cohort data. Another advantage of the model selected by US EPA is that its underlying linear form avoids the complexity that some of the non-linear models would introduce into the unit risk calculations (e.g., dependence on the selected point of departure). This model is also biologically plausible, considering EtO is a genotoxic carcinogen and attenuation at higher exposure levels is often seen with occupational carcinogens. While a few of the other models had somewhat lower *p*-values or somewhat lower AIC scores (e.g., models using a 20-year exposure lag), these differences were relatively small and some of the other models did not provide as good of a fit in the lower-exposure region as the selected model (US EPA, 2016a; 2016b). Models using peak and average exposure did not fit the data as well as those involving cumulative exposure. 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." US EPA's and OEHHA's justifications for not selecting several of the other models were similar to those used for lymphoid cancer model selection and are thus not repeated here.

As with lymphoid cancer mortality, OEHHA evaluated several exposure-response models using the published publicly available categorical data, but none of these models resulted in a better visual fit or had lower *p*-values than the two-piece linear regression model. Overall, OEHHA concluded that the lower portion of the two-piece linear spline model with a knot at 5750 ppm-days is the most appropriate exposure-response model for estimating the lower-exposure breast cancer risks of EtO.

Breast Cancer IUR Calculations

The lower slope of the two-piece linear spline model with a knot at 5750 ppm-days selected by US EPA for breast cancer 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}).

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. This LEC_{01} corresponds to an IUR of 1.48 $(ppm)^{-1}$. However, this value was developed under the assumption that relative risk is independent of age and did not account for increased early-life susceptibility to cancer. Thus, US EPA performed alternate analyses to obtain an

"adult-exposure-only" unit risk estimate which was rescaled to a 70-year lifetime to obtain the "adult-based" unit risk estimate of 7.04×10^{-4} $(\mu g/m^3)^{-1}$ or 1.28×10^{-3} $(ppb)^{-1}$ for breast cancer (US EPA, 2016a; 2016b). OEHHA concurs with this approach.

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) based on the following rationale and approach (US EPA, 2016a).

"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 **5.5×10^{-3} $(ppb)^{-1}$** or 3.0×10^{-3} $(\mu g/m^3)^{-1}$ (rounded), with lymphoid cancer contributing about 75–80% of the total risk. Although breast cancer is more common than lymphoid cancer, lymphoid cancer made the largest contribution because the slope of the exposure-response curve in the lower exposure regions (i.e., below the respective knots) was much steeper for lymphoid cancer than for breast cancer (slopes of 7.58×10^{-4} and 8.98×10^{-5} and upper bounds of 2.98×10^{-3} and 1.84×10^{-4} for lymphoid and breast cancer, respectively).

The corresponding combined cancer potency factor, also known as the cancer slope factor (CSF), is 11 $(mg/kg\text{-}day)^{-1}$ and is calculated from the total cancer IUR using the following equation (OEHHA, 2009b), where 70 kg is the reference human body weight, 20 m^3/day is the reference human inspiration rate, and CF is the conversion factor from µg to mg (1000 µg = 1 mg).

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

$$= \frac{3.0 \times 10^{-3}\ (\mu g/m^3)^{-1} \times 70\ kg \times 1000\ \mu g/mg}{20\ m^3/day}$$

$$= 11\ (mg/kg\text{-}day)^{-1}\ (rounded)$$

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 kilogram (kg) of body weight (OEHHA, 2009b). It should be noted that these values are for excess cancer risk, and as such, express the risk above the background risk. Background EtO cancer risk is the cancer risk due to endogenous and ambient background EtO exposures. As mentioned earlier, background levels of EtO in ambient air result from a variety of minor non-point sources such as water-logged soil, combustion of fossil fuels, and release from consumer products (e.g., residues in fumigated food products and skin care products; IARC, 2008; 2012; Kirman et al., 2021). Thus, the EtO IUR and CSF are meant to compute risk levels associated with exogenous EtO exposures above the background levels in the body and environment.

In summary, US EPA (2016a) combined the cancer unit risk estimates for lymphoid cancer in males and females and breast cancer in females to calculate a final cancer IUR of 5.5×10^{-3} $(ppb)^{-1}$ or 3.0×10^{-3} $(\mu g/m^3)^{-1}$ and a CSF of 11 $(mg/kg\text{-}day)^{-1}$. OEHHA agrees with these values and the general approaches used in their development. A summary of the data sources and variables used to calculate these values is provided in Table 13.

Table 13. Summary of the variables used, data sources, and results of US EPA's inhalation unit risk and cancer slope factor calculations for 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 with a knot at 1,600 ppm-days	Two-piece linear spline with a knot at 5,750 ppm-days	NA
β (per ppm-days)[a]	7.58×10^{-4}	8.98×10^{-5}	NA
β 95% CI [a]	2.98×10^{-3}	1.84×10^{-4}	NA
EC_{01} (ppm)[b]	7.48×10^{-3}	1.38×10^{-2}	NA
LEC_{01} (ppm)[b]	1.90×10^{-3}	6.75×10^{-3}	NA
Extrapolation	Linear	Linear	NA
Unit risk[c] $(ppm)^{-1}$	4.78	1.28	5.5
Cancer slope factor $(mg/kg\text{-}day)^{-1}$	NA	NA	11

Abbreviations: β – lower slope of the respective two-piece linear spline 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}; NA – not applicable; NIOSH – National Institute for Occupational Safety and Health.

[a] These values represent the excess relative risk of cancer per ppm-days of cumulative EtO exposure and its one-sided 95% confidence interval upper bound.

[b] As discussed in the text of this document, these values were developed for cancer incidence and were derived by US EPA based on the assumption that EtO-related cancer relative risk is independent of age (US EPA, 2016a)

[c] These unit risks are the "adult-based unit risk estimates" described in the text of this document. The values for each cancer type were used to develop the IUR of 5.5 $(ppm)^{-1}$ [5.5×10^{-3} $(ppb)^{-1}$] for both cancers combined proposed by OEHHA.

Additional Evaluations of Bias

Several quantitative and qualitative evaluations were performed by OEHHA to assess potential biases and errors in the NIOSH study (Kelly-Reif et al., 2025; Steenland et al., 2003; Steenland et al., 2004). Exposure misclassification and the healthy worker effect were of particular interest.

With regards to exposure misclassification, a validated exposure model was used by the NIOSH study researchers, accounting for 85% of the variance in an independent set of EtO sampling data. Accounting for this level of variance is generally considered very good for retrospective exposure models of this type (Hornung et al., 1994). Bogen et al. (2019) suggested that exposures occurring before 1976, the first year that EtO sampling data were available for the NIOSH cohort, may have been under-predicted by the NIOSH exposure model. However, this analysis had several weaknesses. For example, several assumptions were used to make predictions regarding the historical EtO exposures. However, the information used to support these assumptions was either very limited or unclear. In fact, the authors acknowledged that some of their supportive data, “were limited in scope and quantitative detail.” In addition, Bogen et al. (2019) provided very little to no validation data for several of their key model input variables and no validation data for their final exposure estimates. Overall, because of these and other weaknesses, the analyses of Bogen et al. (2019) could not be used to make definitive conclusions regarding the NIOSH exposure model.

An important aspect of the exposure assessment methods used in the NIOSH study was that the same methods and model were used for all study participants, regardless of cancer status. Because of this, any misclassification of exposure that occurred was likely non-differential (i.e., at similar levels in cancer cases as in controls). This is important because this type of non-differential error typically biases relative risk estimates towards the null and not towards the positive associations reported in the NIOSH study (Greenland, 1998a). Crump (2006) has shown statistically that in some circumstances, exposure misclassification, even if non-differential, can cause a truly linear exposure-response relationship to appear to have a more supra-linear shape. However, the analyses presented by Crump (2006) suggest that very large degrees of exposure misclassification would have to occur to cause major changes to the shape of the exposure-response curve (i.e., cause major bias), and there is no indication that this very large degree of misclassification occurred in the NIOSH cohort study.

On the topic of exposure assessment, 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 high-intensity short-duration exposure scenario 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 potential magnitude of this issue in the NIOSH lymphoid cancer findings 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% of workers with high-intensity short-duration exposures) in the middle exposure categories. A range of percentages was assessed since data on the true percentage were not publicly available. To simulate the removal of workers with high-intensity exposures (and therefore possibly higher risks), exclusions were made 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 (e.g., 10% or less) on exposure-response slopes. This suggests that this issue did not have a major effect on the IUR calculations or the generalizability of the NIOSH findings.

Two aspects of the healthy worker effect in the NIOSH cohort, the healthy hire effect and the healthy worker survivor effect (Arrighi and Hertz-Picciotto, 1994), were evaluated by OEHHA and others. The healthy hire effect is based on the finding that people who work tend to be healthier than the general population, which includes people who do not work because of illness. This effect tends to bias relative risk estimates in occupational studies like the NIOSH study towards the null (i.e., towards finding no association) if the general population is used as the “unexposed” comparison group. Importantly, this bias is unlikely to have affected the NIOSH study results used by US EPA (2016a; 2016b) and OEHHA in their IUR calculations 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 work earlier. This effect also tends to bias relative risk estimates downwards and generally affects workers in the higher categories of cumulative exposure. An evaluation of the impact of healthy worker survivor bias in this cohort was published by NIOSH but as described above, used potentially biased methods (Park, 2020). Researchers at the University of California at Berkeley recently performed a more complete assessment of the healthy worker survivor effect in the NIOSH cohort breast cancer and lymphohematopoietic cancer results (Picciotto et al., 2026). Analyses included evaluating associations between cancer risks and employment duration or age at employment termination, and associations between employment termination and EtO exposure in the preceding years. The results from these particular analyses cannot

be used to make definitive conclusions about the degree to which the EtO-cancer findings may be biased. However, these analyses provided fairly strong evidence that at least some healthy worker survivor effect exists in the NIOSH cohort results and that this effect most likely biased relative risk estimates towards the null and not towards creating false associations (Picciotto et al., 2026).

EtO IUR Value Developed by the Texas Commission on Environmental Quality

Description and Comparison to the US EPA and OEHHA IURs

In 2020, TCEQ published a risk assessment document for EtO in which they calculated an IUR by applying the standard CPH model to the NIOSH data for lymphoid cancer mortality. Breast cancer was not included in their IUR calculations (discussed in further detail below). Using the standard CPH model, TCEQ estimated that the EtO concentration associated with a 1 in 100,000 risk of lymphoid cancer death was 9.67×10^{-3} ppm, with a 95% lower bound of 4.07×10^{-3} ppm. These values were then used to calculate an IUR of 1.03×10^{-3} $(\text{ppm})^{-1}$ with an upper bound of 2.46×10^{-3} $(\text{ppm})^{-1}$ (unadjusted for TCEQ's age-dependent adjustment factor).

As seen in Table 14, the TCEQ IUR is markedly lower than the corresponding "adult-based" unit risk estimate of 5.5 $(\text{ppm})^{-1}$ [equivalent to 5.5×10^{-3} $(\text{ppb})^{-1}$] established by US EPA (2016a) and OEHHA. Table 14 also lists the major differences in the methods used by these agencies to develop their IURs. Most of these differences had relatively small impacts on these IURs. For example, US EPA and OEHHA both used lymphoid cancer incidence in the life-table analyses while TCEQ used lymphoid cancer mortality. However, this difference only accounted for a 2.2-fold difference in the IURs. In addition, US EPA's and OEHHA's inclusion of breast cancer only increased their IURs by about 13% (i.e., from 4.78 to 5.5 $(\text{ppm})^{-1}$). TCEQ did not include breast cancer, and their decision to exclude females from their derivation increased their IUR by about 22% (from 1.93×10^{-3} to 2.46×10^{-3} $(\text{ppm})^{-1}$).

By far, the largest factor causing the difference between US EPA's/OEHHA's and TCEQ's IURs was the choice of exposure-response model. This can easily be seen in Figure 11, where the line representing the TCEQ model is far lower on the graph and much less steep in the lower exposure region (e.g., below 1600 ppm-days) than the model selected by US EPA and OEHHA or almost any other model. This very large difference in steepness means that the predicted RRs at any given exposure level in the lower exposure region will be dramatically lower for the TCEQ model than for the US EPA- and OEHHA-selected model, and this major difference in steepness was the primary reason why the TCEQ and US EPA/OEHHA IURs are dramatically different.

TCEQ's Exposure-Response Model

The primary reason why US EPA (2022a; 2022b) and OEHHA rejected TCEQ's 2020 EtO cancer IUR was TCEQ's decision to use the standard CPH model for its IUR calculations. US EPA (2016a; 2016b) evaluated the standard CPH model but found that it provided a very poor fit to the NIOSH cohort data, especially in the lower-exposure region. As explained 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 exposure -response data. EPA rejects TCEQ's model because it is inconsistent with the underlying epidemiological exposure-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 exposure-response model selected by TCEQ dramatically underestimates the EtO risks in the lower-exposure range of the NIOSH study. This can be easily seen in Figure 11, where the predicted relative risks from the TCEQ model in the lower exposure region are much lower than those predicted by the categorical ORs or almost any other model (including several models with better statistical and empirical fits). 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.

In 2025, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a consensus report on their review of TCEQ's risk assessment of EtO, at the request of TCEQ (NASEM, 2025). In their report, the NASEM committee strongly criticized TCEQ's decision to use the standard CPH model. Specific criticisms of this decision included TCEQ's over-reliance on certain statistical considerations (e.g., *p*-values), TCEQ's failure to adequately consider certain empiric data such as the categorical ORs, and TCEQ's failure to "prioritize selecting a model that best fits the lowest end of the exposure-response." NASEM also agreed with US EPA and OEHHA that the lymphoid cancer exposure-response relationship appeared to be "supralinear," which is different than the form exhibited by the standard CPH model (see Figure 11). Overall, NASEM noted that with regard to modeling the NIOSH data, "of the two models [the standard Cox proportional hazards model and the two-piece

linear spline model], the two-piece spline model may better reflect the supra-linear exposure-response shape at the lowest end of the exposure distribution."

TCEQ's decision to use the standard CPH model appears to have been based mostly on purely statistical or mode of action (MOA) considerations. However, a large part of TCEQ's justification for using this model was based on the results of their "reality check" calculations described below. OEHHA, US EPA, and NASEM (NASEM, 2025; US EPA, 2022a; 2022b) have reviewed these "reality checks" and have found them to be problematic. A description of TCEQ's "reality checks" and their important limitations are described below.

Table 14. Differences between TCEQ's and US EPA's IURs and IUR development methods.

Factor	US EPA / OEHHA	TCEQ
IUR[a]	5.5 $(ppm)^{-1}$	2.46×10^{-3} $(ppm)^{-1}$
Sex	Males and females	Males only
Breast cancer	Included	Excluded
Cancer incidence or mortality[b]	Incidence	Mortality
Exposure-response model	Two-piece linear spline model	Standard CPH model

Abbreviations: CPH – Cox Proportional Hazards (model); IUR – inhalation unit risk; TCEQ – Texas Commission on Environmental Quality.

(a) The TCEQ IUR presented here is not adjusted for TCEQ's age-dependent adjustment factors.

(b) This information describes whether the life-table or corresponding analyses were based on cancer incidence or cancer mortality.

TCEQ's "Reality Check"

TCEQ (2020a) provided several "reality check" calculations in an effort to justify their decision to use the standard CPH model. However, these calculations involved major flaws that limited their validity and usefulness. In its main "reality check," TCEQ estimated the numbers of cases expected in the NIOSH cohort using SMR-type procedures and the lymphoid cancer relative risks generated from either their standard CPH model or US EPA's two-piece linear spline model. Based on these

procedures, TCEQ reported that while the standard CPH model resulted in a good approximation of the actual number of cases observed in the NIOSH cohort, the two-piece linear spline model gave a dramatic overestimation of this number. However, since SMR-type methods were used, the baseline cancer rates used by TCEQ in these calculations were those from the general US population, not those from the NIOSH cohort or any other comparable group of unexposed workers. Because of this, 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 exposure response models for their actual risk assessment calculations" (US EPA, 2022b).

OEHHA reviewed TCEQ's "reality check" calculations and agrees with US EPA's conclusions that these calculations were flawed. OEHHA also agrees with US EPA that a major source of bias in TCEQ's "reality check" calculations was the healthy worker effect. As discussed above, the healthy worker effect can include both the healthy hire effect and the healthy worker survivor effect, and TCEQ's "reality check" calculations did not appropriately consider either of these issues. For example, TCEQ performed a sensitivity analysis in which they attempted to account for the healthy hire effect by incorporating an estimated healthy worker effect of 15–16% (i.e., an

assumption that NIOSH workers were 15–16% “healthier” than the general population with regards to cancer mortality). However, this assumption was based on an estimate of the healthy hire effect from a population that was much different than the NIOSH cohort (Kirkeleit et al., 2013). These differences included the country (Norway versus the US), the health care systems (Norway has universal health care coverage while the US does not), follow-up years (1981–2003 versus <1950–1998 in the Norway study and the NIOSH cohort, respectively), occupations (the Norway study included “the whole range of industries and occupations in Norway” while the NIOSH cohort only included sterilization plant workers), and ages (the average age at the end of follow-up was 46.3 years in the Norway study and 56.3 years in the NIOSH cohort). Given these major differences it seems unlikely that TCEQ’s sensitivity analysis provided an accurate accounting for the healthy hire effect. TCEQ’s “reality check” calculations also did not account for the healthy worker survivor effect. As discussed above, recent analyses by researchers suggest that this bias likely had some impact on the NIOSH cohort findings (Picciotto et al., 2026). And like the healthy hire effect, failure to account for this particular bias probably also led to some inaccuracies in TCEQ’s “reality check” calculations. In its recent report, NASEM (2025) also criticized the TCEQ’s use of the Norwegian study in its effort to account for the healthy worker effect and noted several of TCEQ’s misconceptions regarding both the healthy hire and healthy worker survivor effects. For example, in its criticisms, NASEM stated that, “TCEQ inappropriately applied U.S. general population background hazard rates when calculating the model-predicted number of lymphoid cancer deaths. TCEQ justified this decision by incorrectly concluding that there was no evidence of Healthy Worker Effect”. Overall, for the reasons given above, OEHHA considered TCEQ’s “reality check” calculations to be flawed, and as such, not an appropriate justification for TCEQ’s decision to use the standard CPH model. Further details on US EPA’s and NASEM’s evaluations of TCEQ’s “reality checks” and TCEQ’s overall EtO risk assessment can be found elsewhere (NASEM, 2025; US EPA, 2022a; 2022b).

TCEQ’s Exclusion of Breast Cancer

TCEQ’s (2020a), OEHHA’s, and US EPA’s (2016a) IUR calculations were all based on findings from the NIOSH cohort study (Steenland et al., 2003; Steenland et al., 2004), and all included risks of lymphoid cancer. However, while US EPA’s and OEHHA’s IUR calculations also included breast cancer, TCEQ’s did not. TCEQ’s decision not to include breast cancer appears 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. 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."

These two methodological 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 US EPA that the two issues mentioned above are major flaws, and the meta-analyses by Marsh, Vincent, and their respective colleagues should not 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 identified several flaws, including the mischaracterization of an EtO biomarker of exposure (Hb 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 only "a snapshot in time of exposure and health outcome" (US EPA, 2022a). The cross-sectional nature of this study 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 (2020) study and agrees with US EPA's conclusion that because of these flaws, this study cannot be used to support the assertion that EtO is unassociated with breast cancer.

In its review of the literature on EtO and breast cancer, 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 reviewed US EPA's evaluations and agrees with its assessment regarding breast cancer. In its 2025 review of the TCEQ EtO risk assessment, NASEM criticized TCEQ's failure to use typical systematic review procedures in its breast cancer hazard identification evaluations, stating that, "…the committee found that the process for evaluation of prior evidence in TCEQ's hazard assessment fails to provide a credible basis for its hazard conclusions." NASEM (2025) also criticized TCEQ's over-reliance on the

Marsh et al. (2019) and Vincent et al. (2019) meta-analyses and TCEQ's incomplete or incorrect evaluations of the healthy hire and healthy worker survivor effects.

OEHHA's search for literature published after US EPA's 2016 review identified four community-based studies that investigated associations between EtO exposure and breast cancer (Attachment C). As discussed above, although none of these studies reported clear or consistent associations, all had major limitations which likely limited their ability to identify effects. The strongest and clearest information linking EtO to breast cancer comes from the high-quality NIOSH study. This includes the 2003 Steenland et al. publication which reported strong evidence of an association between EtO and breast cancer incidence, and the more recent Kelly-Reif et al. (2025) publication which reported strong evidence of an association between EtO and breast cancer mortality. The study by Mikoczy et al. (2011) also identified evidence of an association between EtO and breast cancer incidence with rate ratios of 1.00 (reference category), 2.76 (95% CI = 1.20–6.33), and 3.55 (95% CI = 1.58–7.93) for cumulative EtO exposure levels of 0–0.13, 0.14–0.21, and ≥0.22 ppm-years, respectively (Mikoczy et al., 2011). Overall, OEHHA agrees with US EPA and NASEM that breast cancer should be included in EtO-cancer unit risk calculations.

Considerations on Ambient Background

The derivation of the IUR was based on workplace EtO exposures above the endogenous and ambient background levels. The RR estimates from the NIOSH study account for the baseline risk in the study population, which reflects the lymphoid and breast cancer risks due to background exposures to EtO and other chemicals, as well as other risk factors. Using the IUR to calculate risk associated with the endogenous or ambient EtO concentrations implies calculations outside the region covered by the IUR analysis. When the IUR is used to compute cancer risk associated with ambient EtO concentrations from areas without a known emission source, such concentrations likely fall below the intercept of the dose-response curve of the occupational cohort, leading to some uncertainty. The scenario is not unique to EtO and covered in US EPA's Guidelines for Carcinogen Risk Assessment (US EPA, 2005a). As US EPA (2016a) states:

> "Although the actual exposure-response relationship at low exposure levels is unknown, the clear evidence of EtO mutagenicity supports the linear low-exposure extrapolation that was used (U.S. EPA, 2005a). The linear low-exposure extrapolation from the 95% lower bound on the exposure level associated with the 1% extra risk level is considered to be a plausible upper bound on the risk at lower exposure levels. Actual low-exposure risks are expected to be lower, to an unknown extent."

Therefore, it is assumed that the IUR developed from above-background exposures also applies in this range. This is consistent with the approach used across the Hot Spots Program in determining the ambient risk associated with air toxic exposures.[13] In this regard, risk estimates based on ambient EtO levels are not inconsistent with the lifetime background rates of lymphoid and breast cancers (3% for lymphoid cancers and 15% for breast cancer) (US EPA, 2016a; 2022b).

Considerations on Endogenous Exposures and HEV adduct studies

Kirman et al. suggested using endogenous levels as a "reality check" of the proposed updated IUR (Kirman et al., 2021; 2025). These analyses rest on the assumption that HEV adducts in non-smokers without occupational exposure can be converted into an equivalent EtO air concentration. However, there are no tenable toxicokinetic models or data to support using the HEV levels to back-calculate endogenous-equivalent air concentrations of EtO. In this regard, ATSDR (2022b) concluded that data are not available to demonstrate that background HEV levels in non-smokers are direct indicators of internal, endogenous EtO exposures.

OEHHA also considers this inappropriate because the contribution of endogenous levels of EtO and other risk factors to the baseline rates of lymphoid and breast cancer is unknown (US EPA, 2016a). No studies have characterized the exposure-response relationship between endogenous EtO and cancer, and there are no data to indicate whether the nature of the dose-response relationship between endogenous EtO and cancer is identical to the exogenous EtO versus cancer relationship derived from the NIOSH study.

In one analysis, 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.

However, tobacco smoke is a complex chemical mixture containing over 70 recognized carcinogens, including EtO (IARC, 2004). EtO exposure levels are much higher in occupationally-exposed populations compared to tobacco smokers, and EtO's contribution to the process of cancer development associated with exposure to

[13] For example, applications in the Multiple Air Toxics Exposure Study V (MATES V) (https://www.aqmd.gov/home/air-quality/air-quality-studies/health-studies/mates-v), and in California Air Toxics Assessment (CATA) (https://california-air-toxics-assessment-californiaarb.hub.arcgis.com)

the complex chemical mixture of tobacco smoke is unknown. It is not appropriate to attribute specific cancer outcomes in smokers, of which there are many (IARC, 2012), to EtO or any other single carcinogenic chemical component of tobacco smoke. Therefore, it should not be expected that studies of tobacco smoking (e.g., Diver et al., 2012; Kroll et al., 2012) would observe positive associations with the same cancer outcomes as those that have been observed in studies of occupational exposure to EtO (e.g., Steenland et al., 2004).

Additionally, IARC (2012), 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 lymphoid cancer risks from exposures to tobacco smoking, which includes relatively low levels of EtO.

These findings do not contradict the findings of the NIOSH mortality study (Steenland et al., 2004), where internal analyses indirectly controlling for tobacco smoking found positive trends for cumulative exposure to EtO and lymphoid tumors (non-Hodgkin's lymphoma, myeloma, lymphocytic leukemia) in men.

Risk Management Issues

As mentioned in 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. Risk assessment is separate and distinct from risk management (NRC 1983), thus OEHHA does not include risk management issues (e.g., identifying, assessing, and mitigating Hot Spots chemical emissions) in its health risk assessments or recommendations. Thus, identifying specific sources of emissions (e.g., specific EtO-utilizing sterilization facilities) and risk management approaches (e.g., EtO emission mitigation measures, and potential impacts on medical device availability) are beyond the scope of

OEHHA's mandate and the present risk assessment document on the proposed updated EtO IUR.

The proposed updated IUR is focused on additional risk due to exogenous exposures (i.e., risk that is above the background risk). As described in the present document, the IUR for EtO was derived from analyses of cancer exposure-response data from the NIOSH occupational cohort. In these analyses, exogenous occupational EtO exposure levels were assessed and used to calculate RRs. Standard practices of evaluating mechanisms of EtO's carcinogenicity were used to determine that a linear low-exposure extrapolation of the CSF would be appropriate for use in characterizing inhalation risk at ambient air concentrations below those encountered in occupational settings.

VIII. 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 for EtO. Specifically, OEHHA's review has identified the NIOSH human epidemiology study (Steenland et al., 2004; Steenland et al., 2003; US EPA, 2016a; 2016b) as the best available study for conducting exposure-response analyses for EtO. The NIOSH human epidemiology study was deemed to be more sensitive than the rodent studies and was used for deriving the IUR in OEHHA's quantitative cancer risk assessment of EtO. The use of human data also avoids the potential uncertainties involved in extrapolating risks from laboratory animal studies. OEHHA agrees with US EPA (2016a) that the two-piece linear spline model (with a knot at 1600 ppm-days for lymphoid cancer and a knot at 5750 ppm-days for breast cancer) is the best model overall for deriving the cancer IUR for EtO from the NIOSH cohort study. In its updated literature search and systematic review, OEHHA did not identify any new scientific information that would necessitate a change to US EPA's basic IUR approach (e.g., study and model evaluation and selection). 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 3.0×10^{-3} $(\mu g/m^3)^{-1}$ or 5.5×10^{-3} $(ppb)^{-1}$ is a scientifically sound and reliable estimate of the cancer risks of EtO.

IX. REFERENCES

Angerer J, Bader M, and Krämer A (1998). Ambient and biochemical effect monitoring of workers exposed to ethylene oxide. *Int Arch Occup Environ Health*. 71(1): 14–18. DOI: 10.1007/s004200050244.

Archer VE, Coons T, Saccomanno G, and Hong DY (2004). Latency and the lung cancer epidemic among united states uranium miners. *Health Phys*. 87(5): 480–489. DOI: 10.1097/01.hp.0000133216.72557.ab.

Arrighi HM and Hertz-Picciotto I (1994). The evolving concept of the healthy worker survivor effect. *Epidemiology*. 5(2): 189–196. 10.1097/00001648-199403000-00009. DOI: 10.1097/00001648-199403000-00009.

ATSDR (2022). *Toxicological Profile for Ethylene Oxide*. United States Department of Health and Human Services. Agency for Toxic Substances and Disease Registry (ATSDR). Last accessed Feb. 05, 2026, from https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf

Axelson O (1978). Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health*. 4:85–89

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

Bolt MH and Thier R (2006). Relevance of the deletion polymorphisms of the glutathione s-transferases GSTT1 and GSTM1 in pharmacology and toxicology. *Curr Drug Metab*. 7(6): 613–628. DOI: 10.2174/138920006778017786.

Boogaard PJ, Rocchi PSJ, and Van Sittert NJ (1999). Biomonitoring of exposure to ethylene oxide and propylene oxide by determination of hemoglobin adducts: Correlations between airborne exposure and adduct levels. *Int Arch Occup Environ Health*. 72(3): 142–150. DOI: 10.1007/s004200050353.

Breslow N and Day N (1987). “The Design and Analysis of Cohort Studies.” In: *International Agency for Research on Cancer (ed) Statistical Methods in Cancer Research* Vol II IARC Scientific Publications no 82.

Brown CD, Asgharian B, Turner MJ, and Fennell TR (1998). Ethylene oxide dosimetry in the mouse. *Toxicol Appl Pharmacol*. 148(2): 215–222. DOI: 10.1006/taap.1997.8349.

Brown CD, Wong BA, and Fennell TR (1996). *In vivo* and *in vitro* kinetics of ethylene oxide metabolism in rats and mice. *Toxicol Appl Pharmacol*. 136(1): 8–19. DOI: 10.1006/taap.1996.0002.

Brugnone F, Perbellini L, Faccini G, and Pasini F (1985). Concentration of ethylene oxide in the alveolar air of occupationally exposed workers. *Am J Ind Med*. 8(1): 67–72. DOI: 10.1002/ajim.4700080109.

Brugnone F, Perbellini L, Faccini GB, Pasini F, Bartolucci GB, and Derosa E (1986). Ethylene oxide exposure: Biological monitoring by analysis of alveolar air and blood. *Int Arch Occup Environ Health*. 58(2): 105–112. DOI: 10.1007/BF00380761.

Buckley JP, Keil AP, McGrath LJ, and Edwards JK (2015). Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology*. 26(2): 204–212. DOI: 10.1097/EDE.0000000000000217.

Bulka C, Nastoupil LJ, Koff JL, Bernal-Mizrachi L, Ward KC, Williams JN, Bayakly AR, Switchenko JM, Waller LA, and Flowers CR (2016). Relations between residential proximity to EPA-designated toxic release sites and diffuse large B-cell lymphoma incidence. *South Med J*. 109(10):606–614. DOI: 10.14423/SMJ.0000000000000545.

CARB (2023a). *Emission Inventory Criteria and Guidelines (EICG). Appendix A (List of Substances)*. California Air Resources Board (CARB). Last accessed Feb. 05, 2026, from https://ww2.arb.ca.gov/sites/default/files/2022-10/Appendix%20A.pdf

CARB (2026). California emissions inventory data analysis and reporting system (CEIDARS). Data received from the California Air Resources Board (CARB) on April 9, 2026.

Carlsson H, Aasa J, Kotova N, Vare D, Sousa PFM, Rydberg P, Abramsson-Zetterberg L, and Törnqvist M (2017). Adductomic screening of hemoglobin adducts and monitoring of micronuclei in school-age children. *Chem Res Toxicol*. 30(5): 1157–1167. DOI: 10.1021/acs.chemrestox.6b00463.

CDHS (1987). *Part B. Health Effects of Ethylene Oxide*. California Department of Health Services (CDHS). Air Toxics Unit, Office of Environmental Health Hazard Assessment. Last accessed Feb. 05, 2026, from https://ww2.arb.ca.gov/sites/default/files/classic/toxics/id/summary/ethylenoxideb.pdf

CDHS (1988). *Proposition 65 Risk-Specific Intake Levels, Ethylene Oxide*. California Department of Health Services (CDHS). Office of Environmental Health Hazard Assessment.

Celentano DD and Szklo M (2019). *Gordis Epidemiology*, 6th edn. Elsevier, Philadelphia, PA.

Chen J, Hart JE, VoPham T, Elliott EG, Birmann BM, and Laden F (2024). Association of residential exposure to hazardous air pollutants with risk of non-Hodgkin lymphoma and multiple myeloma. *Cancer Epidemiol Biomarkers Prev.* 33(7): 961–964. DOI: 10.1158/1055-9965.EPI-23-1598. Last accessed Feb. 26, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC11216852/pdf/nihms-1990883.pdf

Chen X (2018). A temporal analysis of the association between breast cancer and socioeconomic and environmental factors. *GeoJournal*. 83: 1239–1256. DOI: 10.1007/s10708-017-9824-5.

Crump KS (2006). The effect of random error in exposure measurement upon the shape of the exposure response. *Dose Response.* 3(4): 456–464. DOI: 10.2203/dose-response.003.04.002. Last accessed Feb. 26, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC2477201/pdf/hormes-03-456.pdf

Csanády GA, Denk B, Pütz C, Kreuzer PE, Kessler W, Baur C, Gargas ML, and Filser JG (2000). A physiological toxicokinetic model for exogenous and endogenous ethylene and ethylene oxide in rat, mouse, and human: Formation of 2-hydroxyethyl adducts with hemoglobin and DNA. *Toxicol Appl Pharmacol*. 165(1): 1–26. DOI: 10.1006/taap.2000.8918.

Davis JA, Gift JS, and Zhao QJ (2011). Introduction to benchmark dose methods and U.S. EPA's Benchmark Dose Software (BMDS) version 2.1.1. *Toxicol Appl Pharmacol*. 254(2): 181–191. DOI: 10.1016/j.taap.2010.10.016.

Diver WR, Patel AV, Thun MJ, Teras LR, and Gapstur SM (2012). The association between cigarette smoking and non-Hodgkin lymphoid neoplasms in a large US cohort study. *Cancer Causes Control*. 23(8):1231–40. DOI: 10.1007/s10552-012-0001-3.

Dunkelberg H (1982). Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. *Br J Cancer*. 46(6): 924–933. DOI: 10.1038/bjc.1982.303. Last accessed Feb. 05, 2026, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2011226/pdf/brjcancer00435-0085.pdf

Duus U, Osterman-Golkar S, Törnqvist M, Mowrer J, Holm S, and Ehrenberg L (1989). Studies of Determinants of Tissue Dose and Cancer Risk from Ethylene Oxide Exposure. *Proc Symp Management of Risk from Genotoxic Substances in the Environment*: 141–153.

Ehrenberg L, Hiesche KD, Osterman-Golkar S, and Wenneberg I (1974). Evaluation of genetic risks of alkylating agents: Tissue doses in the mouse from air contaminated with ethylene oxide. *Mutat Res*. 24(2): 83–103. DOI: 10.1016/0027-5107(74)90123-7.

Evidence Partners (2025). DistillerSr. Last accessed Feb. 26, 2026, from https://www.distillersr.com/products/distillersr-systematic-review-software

Fennell TR and Brown CD (2001). A physiologically based pharmacokinetic model for ethylene oxide in mouse, rat, and human. *Toxicol Appl Pharmacol*. 173(3): 161–175. DOI: 10.1006/taap.2001.9184.

Filser JG and Bolt HM (1984). Inhalation pharmacokinetics based on gas uptake studies. *Arch Toxicol*. 55, 219–223. DOI: 10.1007/BF00341014.

Filser JG, Denk B, Törnqvist M, Kessler W, and Ehrenberg L (1992). Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene. *Arch Toxicol*. 66(3): 157–163. DOI: 10.1007/BF01974008.

Filser JG, Kessler W, Artati A, Erbach E, Faller T, Kreuzer PE, Li Q, Lichtmannegger J, Numtip W, Klein D, Pütz C, Semder B, and Csanády GA (2013). Ethylene oxide in blood of ethylene-exposed B6C3F1 mice, Fischer 344 rats, and humans. *Toxicol Sci*. 136(2): 344–358. DOI: 10.1093/toxsci/kft218. Last accessed Feb. 05, 2026, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858200/pdf/kft218.pdf

Filser JG and Klein D (2018). A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. *Toxicol Lett*. 286: 54–79. DOI: 10.1016/j.toxlet.2017.07.896.

Garcia E, Hurley S, Nelson DO, Hertz A, and Reynolds P (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health*. 14:14. DOI: 10.1186/1476-069X-14-14.

Garman RH, Snellings WM, and Maronpot RR (1985). Brain tumors in F344 rats associated with chronic inhalation exposure to ethylene oxide. *Neurotoxicology*. 6(1): 117–137.

Gordis L (2014). *Epidemiology*, 5th edn. Elsevier Saunders

Greenberg HL, Ott MG, and Shore RE (1990). Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. *Br J Ind Med*. 47(4): 221–230. DOI: 10.1136/oem.47.4.221.

Greenland S (1998a). "Basic methods of senitivity analysis and external adjustment." In: *Rothman K, Greenland S (eds) Modern Epidemiology*. 2nd edn. Lippincott Raven. Philadelphia, PA. Pages 343–357.

Greenland S (1998b). "Causation and causal inference." In: *Rothman K, Greenland S (eds) Modern Epidemiology*. 2nd edn. Lippincott Raven. Philadelphia, PA. Pages 7–28.

Greenland S and Longnecker MP (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*. 135(11): 1301–1309. DOI: 10.1093/oxfordjournals.aje.a116237.

Hagmar L, Welinder H, Lindén K, Attewell R, Osterman-Golkar S, and Törnqvist M (1991). An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. *Int Arch Occup Environ Health*. 63(4): 271–277. DOI: 10.1007/bf00386377.

Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, VoPham T, Mittleman MR, Tamimi RM, and Laden F (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the Nurses' Health Study II. *Environ Health*. 17(1): 28. DOI: 10.1186/s12940-018-0372-3.

Hattis D (1987). *Pharmacokinetic/mechanism-based analysis of the carcinogenic risk of ethylene oxide*. Research Org. Massachusetts Institute of Technology, Cambridge (USA). Center for Technology, Policy and Industrial Development. Report Number: PB-88-188784/XAB; CTPID-87-1. Last accessed Feb. 05, 2026, from https://www.osti.gov/servlets/purl/7067804

Higgins JPT, Morgan RL, Rooney AA, Taylor KW, Thayer KA, Silva RA, Lemeris C, Akl EA, Bateson TF, Berkman ND, Glenn BS, Hróbjartsson A, LaKind JS, McAleenan A, Meerpohl JJ, Nachman RM, Obbagy JE, O'Connor A, Radke EG, Savović J, Schünemann HJ, Shea B, Tilling K, Verbeek J, Viswanathan M, and Sterne JAC (2024a). A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environ Int*. 186: 108602. DOI: 10.1016/j.envint.2024.108602. Last accessed Feb. 26, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC11098530/pdf/nihms-1985993.pdf

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, and Page MJ (2024b). "Chapter 7: Considering bias and conflicts of interest among included studies." In: *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.5 (updated August 2024). Last accessed Feb. 26, 2026, from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-07

Hill AB (1965). The environment and disease: Association or causation? *Proc R Soc Med*. 58(5): 295–300.

Hornung RW, Greife AL, Stayner LT, Steenland NK, Herrick RF, Elliott LJ, Ringenburg VL, and Morawetz J (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. *Am J Ind Med*. 25(6): 825–836. DOI: 10.1002/ajim.4700250607.

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CI, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, and Cronin KA (2014). *SEER [Surveillance, Epidemiology, and End ResultsProgram] Cancer Statistics Review, 1975–2012*. National Cancer Institute. Last accessed Feb. 05, 2026, from https://seer.cancer.gov/archive/csr/1975_2012/

IARC (1994). "Ethylene Oxide." In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. *Volume 60. Some Industrial Chemicals*. International Agency for Research on Cancer (IARC). Lyon, France. 60: 73–159. Last accessed May 11, 2026, from https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Industrial-Chemicals-1994

IARC (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. Tobacco Smoke and Involuntary Smoking*. International Agency for Research on Cancer (IARC). Lyon, France. Last accessed May 11, 2026, from https://publications.iarc.who.int/Book-And-Report-Series-2004.

IARC (2008). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 97. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide).* International Agency for Research on Cancer (IARC). Lyon, France. 97: 3–471. Last accessed April 13, 2026, from https://www.ncbi.nlm.nih.gov/books/NBK321405/pdf/Bookshelf_NBK321405.pdf

IARC (2012). "Ethylene Oxide." In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100F. Chemical Agents and Related Occupations. A Review of Human Carcinogens.* International Agency for Research

on Cancer (IARC). Lyon, France. Last accessed Feb. 05, 2026, from https://www.ncbi.nlm.nih.gov/books/n/iarcmono100f/a028/

INED (2023). Standardized mortality ratio. Institut National d'Études Démographiques [French Institute for Demographic Studies; INED]. Last accessed Feb. 05, 2026, from https://www.ined.fr/en/glossary/standardized-mortality-rate/#:~:text=The%20standardized%20mortality%20rate%20(SMR,rates%20as%20the%20standard%20population

Ish JL, Madrigal JM, Pearce JL, Keil AP, Fisher JA, Jones RR, Sandler DP, and White AJ (2025). Industrial air emissions and breast cancer incidence in a United States-wide prospective cohort. *Epidemiology*. 36(3): 391–400. DOI: 10.1097/EDE.0000000000001837.

Jain RB (2020). Associations between observed concentrations of ethylene oxide in whole blood and smoking, exposure to environmental tobacco smoke, and cancers including breast cancer: Data for US children, adolescents, and adults. *Environ Sci Pollut Res Int*. 27(17): 20912–20919. DOI: 10.1007/s11356-020-08564-z.

Jones RR, Fisher JA, Medgyesi DN, Buller ID, Liao LM, Gierach G, Ward MH, and Silverman DT (2023). Ethylene oxide emissions and incident breast cancer and non-Hodgkin lymphoma in a U.S. Cohort. *J Natl Cancer Inst*. DOI: 10.1093/jnci/djad004.

Kelly-Reif K, Bertke SJ, Stayner L, and Steenland K (2025). Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort. *Environ Health Perspect*. 133(5): 57013. DOI: 10.1289/EHP15566. Last accessed Feb. 26, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC12097532/pdf/ehp15566.pdf

Kenwood BM, McLoughlin C, Zhang L, Zhu W, Bhandari D, De Jesús VR, and Blount BC (2021). Characterization of the association between cigarette smoking intensity and urinary concentrations of 2-hydroxyethyl mercapturic acid among exclusive cigarette smokers in the National Health and Nutrition Examination Survey (NHANES) 2011–2016. *Biomarkers*. 26(7):656–664. DOI: 10.1080/1354750X.2021.1970809.

Kirkeleit J, Riise T, Bjorge T, and Christiani DC (2013). The healthy worker effect in cancer incidence studies. *Am J Epidemiol*. 177(11): 1218–1224. DOI: 10.1093/aje/kws373.

Kirman CR, Li AA, Sheehan PJ, Bus JS, Lewis RC, and Hays SM (2021). Ethylene oxide review: Characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *J Toxicol Environ Health*, Part B. 24(1): 1–29. DOI: 10.1080/10937404.2020.1852988. Last accessed Feb. 05, 2026, from https://www.tandfonline.com/doi/epdf/10.1080/10937404.2020.1852988?needAccess=true

Kirman CR, Sheehan PJ, Li AA, Bus JS, Su SH, Dopart PJ, Watson HN, Moynihan EE, and Reiss R (2025). Characterization of background exposures to ethylene oxide in the United States: a reality check on theoretical health risks for potentially exposed populations near industrial sources. *Int J Environ Res Public Health*. 22(4):597. DOI: 10.3390/ijerph22040597. Last accessed Feb. 05, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC12026671/pdf/ijerph-22-00597.pdf

Kroll ME, Murphy F, Pirie K, Reeves GK, Green J, Beral V; Million Women Study Collaborators (2012). Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. *Br J Cancer*. 107(5):879–87. DOI: 10.1038/bjc.2012.333.

Langholz B and Richardson DB (2010). Fitting general relative risk models for survival time and matched case-control analysis. *Am J Epidem*. 171(3): 377–383. DOI: 10.1093/aje/kwp403. Last accessed Feb. 05, 2026, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291085/pdf/kwp403.pdf

Lash TL, VanderWeele TJ, Haneause S, and Rothman KJ (2021). *Modern epidemiology* (Fourth). Lippincott Williams & Wilkins.

Lewalter J (1996). N-alkylvaline levels in globin as a new type of biomarker in risk assessment of alkylating agents. *Int Arch Occup Environ Health*. 68: 519–530. DOI: 10.1007/BF00377881.

Lin YS, Thayer KA, White P, Morozov V, and Persad AS (2025). Uncovering the connection: ethylene exposure and endogenous ethylene oxide levels in humans. *J Expo Sci Environ Epidemiol*. 36: 361-374. DOI: 10.1038/s41370-025-00826-7.

Lipfert FW and Wyzga RE (2019). Longitudinal relationships between lung cancer mortality rates, smoking, and ambient air quality: A comprehensive review and analysis. *Crit Rev Toxicol*. 49(9): 790–818. DOI: 10.1080/10408444.2019.1700210.

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Groth DH, Khan A, Ackerman LJ, and Cockrell BY (1984). Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. *Toxicol Appl Pharmacol*. 76(1): 69–84. DOI: 10.1016/0041-008X(84)90030-9.

Manjanatha MG, Shelton SD, Chen Y, Parsons BL, Myers MB, McKim KL, Gollapudi BB, Moore NP, Haber LT, Allen B, and Moore MM (2017). Dose and temporal evaluation of ethylene oxide-induced mutagenicity in the lungs of male Big Blue mice following inhalation exposure to carcinogenic concentrations. *Environ Mol Mutagen*. 58(3): 122–134. DOI: 10.1002/em.22080.

Marsh GM, Keeton KA, Riordan AS, Best EA, and Benson SM (2019). Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: A systematic literature review and meta-analysis. *Int Arch Occup Environ Health*. 92(7): 919–939. DOI: 10.1007/s00420-019-01438-z.

Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, Liaw J, and Smith AH (2007). Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. *J Natl Cancer Inst*. 99(12): 920–928. DOI: 10.1093/jnci/djm004.

McNamee R (2003). Confounding and confounders. *Occup Environ Med*. 60(3): 227. DOI: 10.1136/oem.60.3.227.

Mikoczy Z, Tinnerberg H, Björk J, and Albin M (2011). Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: Updated cohort study findings 1972–2006. *Int J Environ Res Public Health*. 8(6): 2009–2019. DOI: 10.3390/ijerph8062009.

Mráz J, Hanzlíková I, and Brabec M (2024). Toxicokinetic relationship between the adducts in globin and their cleavage products in the urine: Implications for human biomonitoring. *Toxicol Lett*. 398:82–88. DOI: 10.1016/j.toxlet.2024.06.007.

NASEM (2025). *Review of Texas Commission on Environmental Quality's Ethylene Oxide Development Support Document*. National Academies of Sciences, Engineering, and Medicine (NASEM).Washington, DC: The National Academies Press. DOI: 10.17226/28592. Last accessed Feb. 26, 2026, from https://www.nationalacademies.org/read/28592

NCBI (2023). *PubChem Compound Summary for CID 6354, Ethylene Oxide*. National Library of Medicine (NLM), National Center for Biotechnology Information (NCBI). Last accessed Feb. 05, 2026, from https://pubchem.ncbi.nlm.nih.gov/compound/Ethylene-Oxide

NIH (2023a). *NCI Dictionary of Cancer Terms*. Hazard Ratio. National Cancer Institute (NCI) at the National Institutes of Health (NIH). Last accessed Feb. 05, 2026, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hazard-ratio

NIH (2023b). *NCI Dictionary of Cancer Terms*. Odds Ratio. National Cancer Institute (NCI) at the National Institutes of Health (NIH). Last accessed Feb. 05, 2026, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/odds-ratio

NOAA (2023). *CAMEO Chemicals Chemical Data Sheet*. *Ethylene Oxide*. National Oceanic and Atmospheric Administration (NOAA). Last accessed Feb. 05, 2026, from https://cameochemicals.noaa.gov/chemical/694

NRC (1983). Risk Assessment in the Federal Government: Managing the Process. National Research Council Washington, DC: The National Academies Press, from https://www.nationalacademies.org/publications/366

NTP (1987). *Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS no 75-21-8) in B6C3F1 mice (Inhalation Studies)*. National Toxicology Program (NTP) Technical Report Series. 326: 1–114. Last accessed Feb. 05, 2026, from https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr326.pdf

NTP (2019). *Risk of Bias Tool*. National Toxicology Program (NTP). Last updated April 23, 2025. Last accessed Feb. 05, 2026, from https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/riskbias/index.html

NTP (2021). “Ethylene Oxide, CAS No. 75-21-8.” In: *15th Report on Carcinogens*. National Toxicology Program (NTP). Last accessed Feb. 05, 2026, from https://ntp.niehs.nih.gov/ntp/roc/content/profiles/ethyleneoxide.pdf

NTP (2025). *Report of Carcinogens Handbook on Methods for Conducting Cancer Hazard Evaluations*. Last accessed Feb. 26, 2026, from https://ntp.niehs.nih.gov/research/assessments/cancer/handbook

NYDH (2023). *Confidence Intervals - Statistics Teaching Tools*. New York State Department of Health (NYDH). Last accessed Feb. 05, 2026, from https://www.health.ny.gov/diseases/chronic/confint.htm

OEHHA (2009a). Appendix B. Chemical-specific summaries of the information used to derive unit risk and cancer potency values. In *Technical Support Document For Cancer Potency Factors.* Office of Environmental Health Hazard Assessment (OEHHA). Last accessed Feb. 05, 2026, from https://oehha.ca.gov/media/downloads/crnr/appendixb.pdf

OEHHA (2009b).*Technical Support Document for cancer Potency Factors. Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures*. Office of Environmental Health Hazard Assessment (OEHHA). Last accessed Feb. 05, 2026, from https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

OEHHA (2015). *Risk Assessment Guidelines. Guidance Manual for Preparation of Health Risk Assessments.* Office of Environmental Health Hazard Assessment (OEHHA). Last accessed Feb. 05, 2026, fromhttps://oehha.ca.gov/media/downloads/crnr/2015guidancemanual.pdf

OEHHA (2023). *The Proposition 65 List. Chemicals Known to the State to Cause Cancer or Reproductive Toxicity*. Office of Environmental Health Hazard Assessment (OEHHA). Last accessed Feb. 05, 2026, from https://oehha.ca.gov/media/downloads/proposition-65//p65chemicalslistsinglelisttable2021p.pdf

Orsini N, Bellocco R, and Greenland S (2006). Generalized least squares for trend estimation of summarized dose-response data. *Stata J*. 6(1): 40–57. DOI: 10.1177/1536867X0600600103.

Park RM (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *Am J Ind Med*. 63(7): 577–588. DOI: 10.1002/ajim.23115.

Parsons BL, Manjanatha MG, Myers MB, McKim KL, Shelton SD, Wang Y, Gollapudi BB, Moore NP, Haber LT, and Moore MM (2013). Temporal changes in K-ras mutant fraction in lung tissue of Big Blue B6C3F1 mice exposed to ethylene oxide. *Toxicol Sci*. 136(1): 26–38. DOI: 10.1093/toxsci/kft190.

Picciotto S, Hertz-Picciotto I (2015). Commentary: healthy worker survivor bias: a still-evolving concept. *Epidemiology*. 26(2): 213–215. DOI: 10.1097/EDE.0000000000000233.

Picciotto S, Kelly-Reif K, Eisen EA, Stayner LT, Costello S (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *Am J Epidemiol*. Mar 9:kwag052. DOI: 10.1093/aje/kwag052. Epub ahead of print. PMID: 41800785.

Rietjens I, Michael A, Bolt HM, Siméon B, Andrea H, Nils H, Christine K, Angela M, Gloria P, Daniel R, Natalie T, and Gerhard E (2022). The role of endogenous versus exogenous sources in the exposome of putative genotoxins and consequences for risk assessment. *Arch Toxicol*. 96(5): 1297–1352. DOI: 10.1007/s00204-022-03242-0.

Robinson ES and Dhammapala R (2025). Analysis of ambient ethylene oxide mixing ratios in the United States. *Am Chem Soc Environ Sci Technol Air*. 2(11): 2467–2480. DOI: 10.1021/acsestair.5c00186. Last accessed Feb. 05, 2026, from https://pubs.acs.org/doi/pdf/10.1021/acsestair.5c00186?ref=article_openPDF

Ross D (2022). California Grapples with Regulation of Known Carcinogen Ethylene Oxide. *Capital & Main*, Los Angeles, CA. Last accessed Feb. 05, 2026, from https://capitalandmain.com/california-grapples-with-regulation-of-known-carcinogen-ethylene-oxide

Rothman KJ (1986). *Modern Epidemiology*. Little Brown and Co. Boston, MA.

Savitz DA and Wellenius GA (2023). Can cross-sectional studies contribute to causal inference? It depends. *Am J Epidemiol*. 192(4): 514–516. DOI: 10.1093/aje/kwac037. Last accessed May 04, 2026, from https://academic.oup.com/aje/article-pdf/192/4/514/50326634/kwac037.pdf

SCAQMD (2024a). *Sterigenics Emissions Investigation in Ontario*. South Coast Air Quality Management District (SCAQMD). Updated 2026. Last accessed Feb. 05, 2026, from https://www.aqmd.gov/home/news-events/community-investigations/sterigenics-ontario

SCAQMD (2024b). *Sterigenics Emissions Investigation in Vernon*. South Coast Air Quality Management District (SCAQMD). Updated 2026. Last accessed Feb. 05, 2026, from https://www.aqmd.gov/home/news-events/community-investigations/sterigenics

Schlesselman JJ (1978). Assessing effects of confounding variables. *Am J Epidemiol.* 108: 3–8

Selikoff IJ, Hammond EC, and Seidman H (1980). Latency of asbestos disease among insulation workers in the United States and Canada. *Cancer*. 46(12): 2736–2740. DOI: 10.1002/1097-0142(19801215)46:12<2736::aid-cncr2820461233>3.0.co;2-l.

Shy CM, Kleinbaum DG, and Morgenstern H (1978). The effect of misclassification of exposure status in epidemiological studies of air pollution health effects. *Bull N Y Acad Med*. 54(11):1155–1165.

Snellings WM, Weil CS, and Maronpot RR (1981). *Ethylene oxide: Two-year Inhalation Study on Rats* [Final report with cover letter dated October 25, 1991].

Snellings WM, Weil CS, and Maronpot RR (1984). A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. *Toxicol Appl Pharmacol*. 75(1): 105–117. DOI: 10.1016/0041-008x(84)90081-4.

Stayner L, Steenland K, Greife A, Hornung R, Hayes RB, Nowlin S, Morawetz J, Ringenburg V, Elliot L, and Halperin W (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol*. 138(10): 787–798. DOI: 10.1093/oxfordjournals.aje.a116782.

Stayner L, Steenland K, Dosemeci M, and Hertz-Picciotto I (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scand J Work Environ Health*. 29(4): 317–324. DOI: 10.5271/sjweh.737.

Steenland K and Deddens JA (1997). Increased precision using countermatching in nested case-control studies. *Epidemiology*. 8(3): 238–242. DOI: 10.1097/00001648-199705000-00002.

Steenland K, Stayner L, and Deddens J (2004). Mortality analyses in a cohort of 18235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. *Occup Environ Med*. 61(1): 2–7.

Steenland K, Whelan E, Deddens J, Stayner L, and Ward E (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control*. 14(6): 531–539. DOI: 10.1023/a:1024891529592.

Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, and Bodnar CM (2009). Mortality study update of ethylene oxide workers in chemical manufacturing: A 15 year update. *J Occup Environ Med*. 51(6): 714–723. DOI: 10.1097/JOM.0b013e3181a2ca20.

Szwiec E, Friedman L, and Buchanan S (2020). Levels of ethylene oxide biomarker in an exposed residential community. *Int J Environ Res Public Health*. 17:8646. DOI: 10.3390/ijerph17228646. Last accessed April 14, 2026, from https://www.mdpi.com/1660-4601/17/22/8646/pdf?version=1605928849

TCEQ. (2020). *Ethylene Oxide Carcinogenic Dose-Response Assessment, CAS Registry Number: 75-21-8.* Texas Commission on Environmental Quality (TCEQ). Last accessed Feb. 05, 2026, from https://www.tceq.texas.gov/toxicology/ethylene-oxide

Tenny S and Hoffman MR (2022). Relative Risk. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing. Updated March 27, 2023. Last accessed Feb. 05, 2026, from https://www.ncbi.nlm.nih.gov/books/NBK430824/

Teta MJ, Benson LO, and Vitale JN (1993). Mortality study of ethylene oxide workers in chemical manufacturing: A 10 year update. *Br J Ind Med*. 50(8): 704–709. DOI: 10.1136/oem.50.8.704.

UNC (2023). "Risk and Rate Measures in Cohort Studies." In: *Eric Notebook* (Second Edition No. 7). University of North Carolina (UNC) Gillings School of Global Public Health. Last accessed Feb. 05, 2026, from https://sph.unc.edu/wp-content/uploads/sites/112/2015/07/nciph-ERIC7-17-08.pdf

US EPA (2005).*Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens.* EPA/630/R-03/003F. Pages 1–125. United States Environmental Protection Agency (US EPA), Risk Assessment Forum. Washington, DC. Last accessed Feb. 05, 2026, from https://www.epa.gov/sites/default/files/2013-09/documents/childrens_supplement_final.pdf

US EPA (2012). *Benchmark Dose Technical Guidance*. EPA/100/R-12/001. United States Environmental Protection Agency (US EPA), Risk Assessment Forum. Washington, DC. Last accessed Feb. 05, 2026, from https://www.epa.gov/sites/default/files/2015-01/documents/benchmark_dose_guidance.pdf

US EPA (2015). *Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide*. EPA-SAB-15-012. United States Environmental Protection Agency (US EPA). Washington, DC. Last accessed May 11, 2026, from https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100RODV.txt

US EPA (2016a). *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8): In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-16/350Fa. United States Environmental Protection Agency (US EPA), Office of Research and Development, National Center for Environmental Assessment. Washington, DC. Last accessed Feb. 05, 2026, from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf

US EPA (2016b). *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide: Appendices (CASRN 75-21-8). In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-16/350Fb. United States Environmental Protection Agency (US EPA). Last accessed April 11, 2026, from https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=529971

US EPA (2018). *National Air Toxics Assessment*. United States Environmental Protection Agency (US EPA). Last accessed Feb. 05, 2026, from https://www.epa.gov/national-air-toxics-assessment

US EPA (2022a). *Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review*. 87. 40 cfr part 63. [EPA-HQ-OAR-2018-0746; FRL-6494.1-02-OAR]. United States Environmental Protection Agency (US EPA). Federal Register. Last accessed Feb. 05, 2026, from https://www.federalregister.gov/documents/2022/12/21/2022-27522/reconsideration-of-the-2020-national-emission-standards-for-hazardous-air-pollutants-miscellaneous

US EPA (2022b). *Summary of Public Comments and Responses for the Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review*. United States Environmental Protection Agency (US EPA) Office of Air Quality Planning and Standards Sector Policies and Programs Division (E-143-01). Last accessed Feb. 05, 2026, from https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0200

US EPA (2022c). ORD Staff Handbook for Developing IRIS Assessments. U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-22/268, 2022. https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=545991

US EPA (2023a). Toxics Release Inventory (TRI) Program. United States Environmental Protection Agency (US EPA). Updated Jan. 27, 2026. Last accessed Feb. 05, 2026, from https://www.epa.gov/toxics-release-inventory-tri-program

US EPA (2023b). Toxics Release Inventory (TRI) Program. Reporting for TRI Facilities.United States Environmental Protection Agency (US EPA). Updated Jan. 23, 2026. Last accessed Feb. 05, 2026, from https://www.epa.gov/toxics-release-inventory-tri-program/reporting-tri-facilities

US EPA (2023c). Toxics Release Inventory (TRI) Program. Tri-listed Chemicals. United States Environmental Protection Agency (US EPA). Updated Jan. 27, 2026. Last accessed Feb. 05, 2026, from https://www.epa.gov/toxics-release-inventory-tri-program/tri-listed-chemicals

US EPA (2025). Monitor Values Report - Hazardous Air Pollutants. United States Environmental Protection Agency (US EPA). Last accessed Feb. 06, 2026 from https://www.epa.gov/outdoor-air-quality-data/monitor-values-report-hazardous-air-pollutants

Valdez-Flores C, Li AA, Bender TJ, and Teta MJ (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Anal*. 45(9): 2822–2837. DOI: 10.1111/risa.70057. Last accessed Feb. 26, 2026, from https://onlinelibrary.wiley.com/doi/epdf/10.1111/risa.70057

Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, Best EA, and Mundt KA (2019). Ethylene oxide: Cancer evidence integration and dose-response implications. *Dose Response*. 17(4): 1559325819888317. DOI: 10.1177/1559325819888317. Last accessed Feb. 05, 2026, from https://journals.sagepub.com/doi/pdf/10.1177/1559325819888317

Yong LC, Schulte PA, Wiencke JK, Boeniger MF, Connally LB, Walker JT, Whelan EA, and Ward EM (2001). Hemoglobin adducts and sister chromatid exchanges in hospital workers exposed to ethylene oxide: Effects of glutathione S-transferase T1 and M1 genotypes. *Cancer Epidemiol Biomarkers Prev*. 10(5): 539–550.

Zeljezic D, Mladinic M, Kopjar N, and Radulovic AH (2016). Evaluation of genome damage in subjects occupationally exposed to possible carcinogens. *Toxicol Ind Health*. 32(9): 1570–1580. DOI: 10.1177/0748233714568478.

ATTACHMENT A

Information on OEHHA's systematic review of the epidemiologic and animal studies of ethylene oxide and cancer

OEHHA evaluated US EPA's 2016 review on the scientific literature on carcinogenic effects of ethylene oxide (EtO) and found it to be comprehensive in covering the studies published up to that time. OEHHA identified animal and epidemiological studies of EtO and cancer with quantitative exposure estimates in the US EPA assessment. To identify relevant studies published since the 2016 US EPA assessment, OEHHA performed a systematic review. Studies identified from US EPA's 2016 assessment and from OEHHA's updated literature search were evaluated for potential use in the derivation of the cancer inhalation unit risk factor (IUR) for EtO.

Populations, Exposures, Comparators, and Outcomes Criteria

OEHHA used Populations, Exposures, Comparators, and Outcomes (PECO) criteria to identify studies for the hazard identification and exposure-response assessment. The inclusion criteria are shown in the PECO statement provided in Table A1. To meet the PECO criteria, a study should meet all aspects of the PECO statement. Since inhalation is the main route of EtO exposure in humans, exposure in this systematic review was restricted to the inhalation route only. The exposure was also restricted to capture animal studies with longer exposure durations (>1 year) which are more valuable in estimating tumor development. The outcome was restricted to cancer outcomes only. Studies with supplemental information relevant to the aim of this assessment but not meeting the PECO criteria were tracked during the literature screening process (Table A2). These studies may provide relevant information to the assessment but couldn't be used to derive an IUR. Studies categorized as supplemental material included studies in non-mammalian species, *in vitro* studies, *in silico* models, physiologically-based pharmacokinetic/toxicokinetic (PBPK) studies, non-PECO routes of exposure (e.g., intraperitoneal injection, oral administration), exposure assessment or characterization (no health outcome) studies, and human case reports or case series. Some of these studies were summarized in the IUR document (i.e., in the "Toxicokinetics" and "Genotoxicity" sections), and some reviews without original research data were tracked to support the overall assessment.

Table A1. Populations, Exposures, Comparators, and Outcomes (PECO) criteria.

Category	Inclusion Criteria
Populations	**Human:** Studies of any population and life stage (occupational or general population, including children and other sensitive populations). **Animal:** Non-human mammalian animal species of any life stage, including preconception, *in utero*, lactation, peripubertal, and adult stages.
Exposures	Relevant forms: EtO (CAS 75-21-8), synonyms or occupations associated with EtO use (e.g., working in sterilization facilities). **Human:** Any quantitative exposure to EtO via inhalation as determined by controlled exposure, measured concentration of substance in contact medium (i.e., air), biomarkers of exposure (e.g., serum levels), or occupation in a job involving exposure. **Animal:** Any quantitative exposure to EtO via inhalation for at least 1 year. Studies involving exposures to mixtures will be included only if they include animals exposed to EtO alone.
Comparators	**Human:** Studies reporting effect measures (e.g., incidence rate, relative risk, standardized mortality ratio, odds ratio) based on a comparison or referent population with lower exposure levels, no exposure, or exposure below detection limits of EtO; or cases versus controls; or a repeated-measures design. Case series or case reports will be marked as supplemental if relevant. **Animal:** A concurrent group exposed to a vehicle-only treatment (vehicle control) or an untreated control. The control could be a baseline measurement in repeated measure studies.
Outcomes	Cancer outcomes

Table A2. Major categories of "potentially relevant supplemental material".

Category	Evidence	Typical Assessment Use
TK data and PBPK models	Studies describing PBPK models for EtO, studies describing TK data for all animal species, and human studies reporting concentrations in two or more physiological compartments (e.g., serum, organs, urine, breast milk, fetus, but not hair, nails) are tagged as potential relevant supplemental material	These studies are tracked and reviewed for potential inclusion in the "Toxicokinetics" section of the assessment, which includes summarizing ADME data and discussion on PBPK models for cross-species comparison, internal dose predictions, and consideration to support quantitative extrapolations.
Mechanistic studies	Mechanistic studies reporting genotoxicity and other key characteristics of carcinogens are tagged as "potentially relevant supplemental information" (including evidence on electrophilicity or possible metabolic activation to electrophiles, induction of oxidative stress, chronic inflammation, immunosuppression, causing immortalization, modulation of receptor-mediated effects, alteration of cell proliferation, cell death, or nutrient supply)	Mechanistic studies that provide evidence on carcinogenicity are summarized and included in the assessment to support the cancer hazard evaluation.

Abbreviations: ADME – Absorption, distribution, metabolism, and elimination. PBPK – physiologically-based pharmacokinetics, TK – toxicokinetics

Table A2. Major categories of "potentially relevant supplemental material" (continued).

Category	Evidence	Typical Assessment Use
Non-mammalian model systems	Studies in non-mammalian model systems, e.g., fish, birds, *C. elegans*	Studies in non-mammalian models can be summarized to support evaluations of consistency across species or to provide mechanistic information. In the latter case, the studies should be also tagged as "mechanistic studies."
Non-inhalation routes of exposure	Experimental studies utilizing a non-inhalation route of administration	Studies with exposure routes other than inhalation are tracked and summarized if there is limited data on inhalation exposure to support the evaluation of consistency across routes of exposure, or to support the evidence on carcinogenicity.
Shorter exposure time (animal studies)	Animal studies with exposure durations less than a year	Subchronic studies are tracked and may be used in the dose-response assessment when studies with longer exposure durations are lacking. Studies with shorter exposure durations can provide useful information to support the evaluation of consistency across different durations of exposure.

Abbreviations: ADME – Absorption, distribution, metabolism, and elimination. PBPK – physiologically-based pharmacokinetics, TK – toxicokinetics

Table A2. Major categories of "potentially relevant supplemental material" (continued).

Category	Evidence	Typical Assessment Use
Case studies, case series, worker surveillance studies	These human studies include a single individual or small group of subjects who developed health outcomes after being exposed to the chemical of interest, but these studies lack proper control groups and statistical analyses.	These studies are tracked and may support the hazard identification evidence and selection of critical studies.
Ecological studies	Ecological studies can provide useful information for the exposure-response analysis on a population level, but, due to the lack of information on individual exposures, ecological studies can't be used in dose-response analyses.	Ecological studies may provide useful information regarding exposure-dependent health effects. These studies may be summarized to support the hazard identification and selection of critical effects.
Exposure Assessment or risk assessment	Exposure assessment studies that determine the exposure without measuring toxicological outcomes, or risk assessment studies that compare exposure levels to regulatory levels to assess potential risk.	Exposure assessment studies may provide useful information to support developing exposure criteria. A comprehensive summary of potential exposure sources and levels is beyond the scope of this assessment.

Abbreviations: ADME – Absorption, distribution, metabolism, and elimination. PBPK – physiologically-based pharmacokinetics, TK – toxicokinetics

Table A2. Major categories of "potentially relevant supplemental material" (continued).

Category	Evidence	Typical Assessment Use
Comparator other than listed in PECO (Human Studies)	Human studies with a comparison group exposed to EtO for shorter periods of time.	These studies are tracked and may support the exposure-response assessment.
Mixture studies	Mixture studies do not meet the PECO criteria because they do not contain an exposure or treatment group assessing only the chemical of interest.	These mixture studies are relevant for cumulative risk analyses, but these fall outside the scope of this assessment.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.	Studies are tracked for potential use in identifying missing studies and current scientific opinions.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation.	
Non-Cancer Effects	Studies reporting non-cancer outcomes	Studies reporting non-cancer outcomes may provide useful information regarding the carcinogenic mechanisms, mode of action, and identification of target organs.

Abbreviations: ADME – Absorption, distribution, metabolism, and elimination. PBPK – physiologically-based pharmacokinetics, TK – toxicokinetics

Literature search strategy

Two separate literature searches were conducted, one for identifying epidemiological studies and the other for identifying animal cancer studies. The searches were restricted to studies published after January 2016 to October 2025 (human evidence) or November 2025 (animal evidence). Several electronic databases were searched, including PubMed, Web of Science, Embase, and SciFinder. Recent review articles, government reports, and the bibliographies of all included publications were also searched. The literature searches were updated in April 2026 before the release of the assessment.

Search terms were meant to be inclusive and aimed at finding studies of EtO and cancer in human populations (Table A3) and animal models (Tables A4, A5, and A6). The human evidence literature search included using the chemical name and its synonyms, as well as terms to identify epidemiological research. The literature search for animal studies included a combination of EtO, experimental animal, and cancer outcome terms.

Screening process

Records identified in the literature searches were evaluated as to whether they met the PECO criteria. The titles and abstracts of all identified articles were searched to see if the publication or study met the PECO criteria described in Table A1. Screening was performed using structure forms in Excel for human evidence or Distiller SR (Evidence Partners, 2025) for animal evidence. Study screening was performed by two independent primary screeners. Screening conflicts were resolved by discussion between the primary screeners, with consultation by a third reviewer if needed. Screening was performed first at the title and abstract (TIAB) level. During the TIAB screening, records with no abstract were initially evaluated based on title relevance. The eligibility status of non-English studies was assessed using online translation tools or engagement with a native speaker. Studies that had relevant information about the carcinogenicity of EtO but were not suitable for the dose-response assessment were tagged as supplemental information. In full-text screening, the full text for all citations that met the PECO criteria in the title/abstract screening were reviewed. Beyond failing to meet the PECO criteria, studies were excluded during full-text screening due to insufficient reporting of critical information shown below. Detailed logs of the reasons for exclusion and for tagging supplemental material were kept.

Critical reporting information for epidemiologic studies included the following.

- Sample size
- Exposure characterization and/or measurement method
- Outcome ascertainment method
- Study design

Critical reporting information for animal studies included the following.

- Species
- Test article name
- Exposure concentration, duration, and continuity
- Route of exposure

The results of the literature searches and screening can be found in Figures 1 and 2 in the main IUR document.

Table A3. List of search terms used in literature search update.

Database	Query	Total articles included
PubMed	("epidemiol*"[tiab] OR "cohort"[tiab] OR "case control"[tiab] OR "case referent"[tiab] OR "cross sectional"[tiab] OR "follow-up"[tiab] OR "followup"[tiab] OR "standardized mortality rat*"[tiab] OR "standardized incidence rat*"[tiab] OR "proportional mortality"[tiab] OR "proportionate mortality"[tiab] OR "proportional cancer mortality"[tiab] OR "retrospective cohort"[tiab] OR "prospective cohort"[tiab] OR "retrospective stud*"[tiab] OR "prospective stud*"[tiab] OR "prospective mortality"[tiab] OR "longitudinal stud*"[tiab] OR ecological-study[tiab] OR ecological-studies[tiab] OR "case-crossover"[tiab] OR "case-cross over"[tiab] OR case-report*[tiab] OR "case series"[tiab] OR "clinical trial*"[tiab] OR "clinical controlled trial*"[tiab] OR "controlled clinical trial*"[tiab] OR "randomized controlled trial*"[tiab] OR "double blind*"[tiab] OR "intervention stud*"[tiab] OR "crossover design*"[tiab] OR "crossover stud*"[tiab] OR "crossover trial*"[tiab] OR "crossover experiment*"[tiab] OR "cross-over design*"[tiab] OR "cross-over stud*"[tiab] OR "cross-over trial*"[tiab] OR "cross-over experiment*"[tiab] OR "person year*"[tiab] OR "national death index"[tiab] OR "national death rate*"[tiab] OR "vital record*"[tiab] OR "cancer registr*"[tiab] OR "population based"[tiab] OR "general population"[tiab] OR "occupation*"[tiab] OR "worker*"[tiab] OR "workmen"[tiab] OR "employe*"[tiab] OR "employment"[tiab] OR "industr*"[tiab] OR "factory"[tiab] OR "factories"[tiab] OR "workplace"[tiab] OR "company"[tiab] OR "companies"[tiab] OR "job exposure matrix"[tiab] OR "questionnaire"[tiab] OR "interview"[tiab] OR meta-analys*[tiab] OR metaanalys*[tiab] OR "systematic review"[pt]) AND ("ethylene oxide"[tiab] OR "ethylene oxide"[mh] OR 75-21-8[rn])	468

Table A3. List of search terms used in literature search update (continued).

Database	Query	Total articles included
Web of Science	"ethylene oxide" (Topic) and "epidemiol*" OR "cohort" OR "case control" OR "case referent" OR "cross sectional" OR "follow-up" OR "followup" OR "standardized mortality rat*" OR "standardized incidence rat*" OR "proportional mortality" OR "proportionate mortality" OR "proportional cancer mortality" OR "retrospective cohort" OR "prospective cohort" OR "retrospective stud*" OR "prospective stud*" OR "prospective mortality" OR "longitudinal stud*" OR ecological-study OR ecological-studies OR "case-crossover" OR "case-cross over" OR case-report* OR "case series" OR "clinical trial*" OR "clinical controlled trial*" OR "controlled clinical trial*" OR "randomized controlled trial*" OR "double blind*" OR "intervention stud*" OR "crossover design*" OR "crossover stud*" OR "crossover trial*" OR "crossover experiment*" OR "cross-over design*" OR "cross-over stud*" OR "cross-over trial*" OR "cross-over experiment*" OR "person year*" OR "national death index" OR "national death rate*" OR "vital record*" OR "cancer registr*" OR "population based" OR "general population" OR "occupation*" OR "worker*" OR "workmen" OR "employe*" OR "employment" OR "industr*" OR "factory" OR "factories" OR "workplace" OR "company" OR "companies" OR "job exposure matrix" OR "questionnaire" OR "interview" OR meta-analys* OR metaanalys* OR "systematic review" (Topic) and 2016-2025 (Year Published)	1354

Table A3. List of search terms used in literature search update (continued).

Database	Query	Total articles included
Embase	('ethylene oxide'/exp OR 'ethylene oxide' OR 'ethylene oxide':ti,ab OR '75 21 8':rn) AND 'mastocytomas':ti,ab OR 'mastocytosis':ti,ab OR 'mcf-7':ti,ab OR 'medulloblastoma':ti,ab OR 'medulloblastomas':ti,ab OR 'medullocytoma':ti,ab OR 'medullocytomas':ti,ab OR 'medulloepithelioma':ti,ab OR 'medulloepitheliomas':ti,ab OR 'medullomyoblastoma':ti,ab OR 'medullomyoblastomas':ti,ab OR 'melanoacanthoma':ti,ab OR 'melanoacanthomas':ti,ab OR 'melanoameloblastoma':ti,ab OR 'melanocytoma':ti,ab OR 'melanocytomas':ti,ab OR 'melanoma':ti,ab OR 'melanomas':ti,ab OR 'melanomatosis':ti,ab OR 'meningioblastoma':ti,ab OR 'meningioma':ti,ab OR 'meningiomas':ti,ab OR 'meningiomatosis':ti,ab OR 'mesenchymoma':ti,ab OR 'mesenchymomas':ti,ab OR 'mesonephroma':ti,ab OR 'mesonephromas':ti,ab OR 'mesothelioma':ti,ab OR 'mesotheliomas':ti,ab OR 'metaplasia':ti,ab OR 'metastases':ti,ab OR 'metastasis':ti,ab OR 'metastatic':ti,ab OR 'microcarcinoma':ti,ab OR 'microcarcinomas':ti,ab OR 'microglioma':ti,ab OR 'microgliomas':ti,ab OR 'micrometastases':ti,ab OR 'micrometastasis':ti,ab OR 'mucositis':ti,ab OR 'myelodysplasia':ti,ab OR 'myelodysplasias':ti,ab OR 'myelodysplastic':ti,ab OR 'myelofibrosis':ti,ab OR 'myelolipoma':ti,ab OR 'myelolipomas':ti,ab OR 'myeloma':ti,ab OR 'myelomas':ti,ab OR 'myelomatosis':ti,ab OR 'myeloproliferation':ti,ab OR 'myeloproliferations':ti,ab OR 'myeloproliferative':ti,ab OR 'myelosuppression':ti,ab OR 'myoblastoma':ti,ab OR 'myoblastomas':ti,ab OR 'myoepithelioma':ti,ab OR 'myoepitheliomas':ti,ab OR 'myofibroblastoma':ti,ab OR 'myofibroblastomas':ti,ab OR 'myofibroma':ti,ab OR 'myofibromas':ti,ab OR 'myofibromatosis':ti,ab OR 'myofibrosarcoma':ti,ab OR 'myofibrosarcomas':ti,ab OR 'myolipoma':ti,ab OR 'myolipomas':ti,ab OR 'myoma':ti,ab OR 'myomas':ti,ab OR 'myopericytoma':ti,ab OR 'myosarcoma':ti,ab OR 'myosarcomas':ti,ab OR 'myxofibroma':ti,ab OR 'myxofibromas':ti,ab OR 'myxolipoma':ti,ab OR 'myxolipomas':ti,ab OR 'myxoliposarcoma':ti,ab OR 'myxoma':ti,ab OR 'myxomas':ti,ab OR 'naevus':ti,ab OR 'neoplasia':ti,ab OR 'neoplasm':ti,ab OR 'neoplasms':ti,ab OR 'neoplastic':ti,ab OR 'nephroblastoma':ti,ab OR 'nephroblastomas':ti,ab OR 'neurilemmoma':ti,ab OR 'neurilemmomas':ti,ab OR 'neurilemmomatosis':ti,ab OR 'neurilemoma':ti,ab OR	211

2731 **Table A3. List of search terms used in literature search update (continued).**

Database	Query	Total articles included
Embase (continued)	'neurilemomas':ti,ab OR 'neurinoma':ti,ab OR 'neurinomas':ti,ab OR 'neuroblastoma':ti,ab OR 'neuroblastomas':ti,ab OR 'neurocytoma':ti,ab OR 'neurocytomas':ti,ab OR 'neuroepithelioma':ti,ab OR 'neuroepitheliomas':ti,ab OR 'neurofibroma':ti,ab OR 'neurofibromas':ti,ab OR 'neurofibromatosis':ti,ab OR 'neurofibrosarcoma':ti,ab OR 'neurofibrosarcomas':ti,ab OR 'neurolipocytoma':ti,ab OR 'neuroma':ti,ab OR 'neuromas':ti,ab OR 'neuronevus':ti,ab OR 'neurothekeoma':ti,ab OR 'neurothekeomas':ti,ab OR 'nevus':ti,ab OR 'nonhodgkin':ti,ab OR 'nonhodgkins':ti,ab OR 'nonseminoma':ti,ab OR 'nonseminomas':ti,ab OR 'nonseminomatous':ti,ab OR 'odontoameloblastoma':ti,ab OR 'odontoma':ti,ab OR 'oligoastrocytoma':ti,ab OR 'oligoastrocytomas':ti,ab OR 'oligodendroglioma':ti,ab OR 'oligodendrogliomas':ti,ab OR 'oncocytoma':ti,ab OR 'oncocytomas':ti,ab OR 'oncogen':ti,ab OR 'oncogene':ti,ab OR 'oncogenes':ti,ab OR 'oncogenesis':ti,ab OR 'oncogenic':ti,ab OR 'oncogens':ti,ab OR 'oncologic':ti,ab OR 'oncologist':ti,ab OR 'oncologists':ti,ab OR 'oncology':ti,ab OR 'oncoprotein':ti,ab OR 'oncoproteins':ti,ab OR 'opsoclonus-myoclonus':ti,ab OR 'orchioblastoma':ti,ab OR 'orchioblastomas':ti,ab OR 'osteoblastoma':ti,ab OR 'osteoblastomas':ti,ab OR 'osteochondroma':ti,ab OR 'osteochondromas':ti,ab OR 'osteochondrosarcoma':ti,ab OR 'osteochondrosarcomas':ti,ab OR 'osteoclastoma':ti,ab OR 'osteoclastomas':ti,ab OR 'osteofibrosarcoma':ti,ab OR 'osteoma':ti,ab OR 'osteomas':ti,ab OR 'osteosarcoma':ti,ab OR 'osteosarcomas':ti,ab OR 'pancreatoblastoma':ti,ab OR 'pancreatoblastomas':ti,ab OR 'papilloma':ti,ab OR 'papillomas':ti,ab OR 'papillomata':ti,ab OR 'papillomatosis':ti,ab OR 'papillomavirus':ti,ab OR 'papillomaviruses':ti,ab OR 'parachordoma':ti,ab OR 'parachordomas':ti,ab OR 'paraganglioma':ti,ab OR 'paragangliomas':ti,ab OR 'paraneoplastic':ti,ab OR 'perineurioma':ti,ab OR 'perineuriomas':ti,ab OR 'phaeochromocytoma':ti,ab OR 'phaeochromocytomas':ti,ab OR 'pheochromoblastoma':ti,ab OR 'pheochromoblastomas':ti,ab OR 'pheochromocytoma':ti,ab OR 'pheochromocytomas':ti,ab OR 'pilomatricoma':ti,ab OR 'pilomatricomas':ti,ab OR 'pilomatrixoma':ti,ab OR 'pilomatrixomas':ti,ab OR 'pinealblastoma':ti,ab OR 'pinealoblastoma':ti,ab OR 'pinealoblastomas':ti,ab OR	See above.

Table A3. List of search terms used in literature search update (continued).

Database	Query	Total articles included
Embase (continued)	'pinealoma':ti,ab OR 'pinealomas':ti,ab OR 'pineoblastoma':ti,ab OR 'pineoblastomas':ti,ab OR 'pineocytoma':ti,ab OR 'pineocytomas':ti,ab OR 'plasmacytoma':ti,ab OR 'plasmacytomas':ti,ab OR 'pneumoblastoma':ti,ab OR 'pneumoblastomas':ti,ab OR 'pneumocytoma':ti,ab OR 'polyembryoma':ti,ab OR 'polyembryomas':ti,ab OR 'polyhistioma':ti,ab OR 'polyhistiomas':ti,ab OR 'polyp':ti,ab OR 'polyposis':ti,ab OR 'polyps':ti,ab OR 'porocarcinoma':ti,ab OR 'porocarcinomas':ti,ab OR 'poroma':ti,ab OR 'poromas':ti,ab OR 'precancer':ti,ab OR 'precancerous':ti,ab OR 'preleukaemia':ti,ab OR 'preleukaemias':ti,ab OR 'preleukemia':ti,ab OR 'preleukemias':ti,ab OR 'premalignant':ti,ab OR 'preneoplastic':ti,ab OR 'prolactinoma':ti,ab OR 'prolactinomas':ti,ab OR 'protooncogene':ti,ab OR 'protooncogenes':ti,ab OR 'pseudotumor':ti,ab OR 'pseudotumors':ti,ab OR 'radiochemotherapy':ti,ab OR 'radioimmunotherapies':ti,ab OR 'radioimmunotherapy':ti,ab OR 'reninoma':ti,ab OR 'reninomas':ti,ab OR 'reticuloendothelioma':ti,ab OR 'reticuloendotheliomas':ti,ab OR 'reticulohistiocytoma':ti,ab OR 'reticulohistiocytomas':ti,ab OR 'reticulosis':ti,ab OR 'retinoblastoma':ti,ab OR 'retinoblastomas':ti,ab OR 'rhabdomyoma':ti,ab OR 'rhabdomyomas':ti,ab OR 'rhabdomyosarcoma':ti,ab OR 'rhabdomyosarcomas':ti,ab OR 'rhabdosarcoma':ti,ab OR 'rhabdosarcomas':ti,ab OR 'sarcoma':ti,ab OR 'sarcomas':ti,ab OR 'sarcomatosis':ti,ab OR 'schwannoma':ti,ab OR 'schwannomas':ti,ab OR 'schwannomatosis':ti,ab OR 'seminoma':ti,ab OR 'seminomas':ti,ab OR 'seminomatous':ti,ab OR 'somatostatinoma':ti,ab OR 'somatostatinomas':ti,ab OR 'somatotropinoma':ti,ab OR 'somatotropinomas':ti,ab OR 'spermatocytoma':ti,ab OR 'spiradenoma':ti,ab OR 'spiradenomas':ti,ab OR 'spongioblastoma':ti,ab OR 'spongioblastomas':ti,ab OR 'steatocystoma':ti,ab OR 'steatocystomas':ti,ab OR 'subependymoma':ti,ab OR 'subependymomas':ti,ab OR 'syringadenoma':ti,ab OR 'syringadenomas':ti,ab OR 'syringocystadenoma':ti,ab OR 'syringocystadenomas':ti,ab OR 'syringoma':ti,ab OR 'syringomas':ti,ab OR 'teratocarcinoma':ti,ab OR 'teratocarcinomas':ti,ab OR 'teratoma':ti,ab OR 'teratomas':ti,ab OR 'thecoma':ti,ab OR 'thecomas':ti,ab OR 'thymolipoma':ti,ab OR 'thymolipomas':ti,ab OR 'thymoma':ti,ab OR 'thymomas':ti,ab OR 'trichilemmoma':ti,ab OR	See above.

Table A3. List of search terms used in literature search update (continued).

Database	Query	Total articles included
Embase (continued)	'trichilemmomas':ti,ab OR 'trichoadenoma':ti,ab OR 'trichoblastoma':ti,ab OR 'trichoblastomas':ti,ab OR 'trichodiscoma':ti,ab OR 'trichodiscomas':ti,ab OR 'trichoepithelioma':ti,ab OR 'trichoepitheliomas':ti,ab OR 'trichofolliculoma':ti,ab OR 'trichofolliculomas':ti,ab OR 'tricholemmoma':ti,ab OR 'tricholemmomas':ti,ab OR ('tumor':ti,ab OR 'tumors':ti,ab OR 'tumour':ti,ab OR 'tumours':ti,ab) NOT ('tnf':ti,ab OR 'necrosis factor':ti,ab) OR 'tumorgenesis':ti,ab OR 'tumorgenic':ti,ab OR 'tumorigenesis':ti,ab OR 'tumorigenic':ti,ab OR 'tumorogenesis':ti,ab OR 'tumorogenic':ti,ab OR 'vipoma':ti,ab OR 'vipomas':ti,ab OR 'waldenstrom':ti,ab OR 'waldenstroms':ti,ab OR 'xanthoastrocytoma':ti,ab OR 'xanthoastrocytomas':ti,ab OR 'xanthofibroma':ti,ab OR 'xanthofibromas':ti,ab OR 'xanthogranuloma':ti,ab OR 'xanthogranulomas':ti,ab OR 'xanthoma':ti,ab OR 'xanthomas':ti,ab OR 'xanthosarcoma':ti,ab OR 'xanthosarcomas':ti,ab) NOT (('animal model'/exp OR 'animal model' OR 'animal experiment'/exp OR 'animal experiment' OR 'nonhuman'/exp OR 'nonhuman' OR 'animal'/exp OR 'animal') NOT ('human'/exp OR 'human')) AND [2016-2025]/py	See above.
Scifinder	Search References: 75-21-8, Limit to Journal, Limit to database CAPlus, Limit to 2016-2025, Limit to concept: human, humans, homosapiens	326

Table A4. List of search terms used in literature search using PubMed and Web of Science.

Step/Category	Search terms
1. Chemical terms	"ethylene oxide"[mh] OR "ethylene oxide"[tiab] OR OR 75-21-8[rn]
2. PubMed Cancer Strategy	neoplasms OR American Cancer Society OR angiogenesis inducing agents OR antibodies, neoplasm OR antigens, neoplasm OR antineoplastic agents OR antineoplastic protocols OR biomarkers, tumor OR biopsy [mh] OR biopsy [tw] OR bone marrow purging OR bone marrow transplantation OR cancer care facilities OR cancer vaccines OR carcinogenicity tests OR carcinogens OR chemoembolization, therapeutic OR clonal evolution [mh] OR clonal evolution [tw] OR colonography, computed tomographic OR colonoscopy OR colposcopy OR combined modality therapy OR cryosurgery OR cytapheresis OR dna, neoplasm OR drug resistance, neoplasm OR drug screening assays, antitumor OR early detection of cancer OR gene expression regulation, neoplastic OR genes, neoplasm OR graft vs tumor effect OR hematopoietic stem cell transplantation OR hematopoietic stem cell mobilization OR immunotherapy, adoptive OR leukostasis OR lymph node excision OR lymphocytes, tumor-infiltrating OR mammography OR mastectomy OR medical oncology OR metastasectomy OR mohs surgery OR myelodysplastic-myeloproliferative diseases OR neoplasm grading OR neoplasm proteins OR neoplasm staging OR neoplasm transplantation OR neoplastic processes OR neoplastic stem cells OR oncogene fusion OR oncogenic viruses OR oncology nursing OR oncology service, hospital OR oncolytic viruses OR papanicolaou test [mh] OR papillomavirus vaccines OR peripheral blood stem cell transplantation OR polyomavirus OR radiotherapy OR radiotherapy planning, computer assisted OR rna, neoplasm OR second-look surgery OR SEER program OR stem cell transplantation [mh:noexp] OR transplantation conditioning OR tumor cells, cultured OR tumor escape OR tumor lysis syndrome OR tumor necrosis factors OR receptors, tumor necrosis factor OR tumor necrosis factor receptor-associated peptides and proteins OR ultrasonography, mammary OR AACR OR AJCC [tw] OR (ASCO NOT fungi) OR IARC OR "National Cancer Institute (U.S.)" [mh] OR UICC OR aCML [tw] OR AGCUS [tw] OR AILD [tw] OR AML [tw] OR ANLL [tw] OR ASCUS [tw] OR ATLL [tw] OR BRCA [tw] OR BRCA1 [tw] OR BRCA2 [tw] OR CIN [tw] OR CLL [tw] OR CMML [tw] OR CMPD [tw] OR ECCL [tw] OR EGIST [tw] OR FMTC [tw] OR GLNH [tw] OR HNPCC [tw] OR HNSCC

2736 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	[tw] OR HPV [tw] OR HSIL [tw] OR ICD OO [tw] OR JCML [tw] R JMML [tw] OR LGLL [tw] OR MGUS [tw] OR MLH1[tw] OR MPD [tw] OR MSH2[tw] OR NSCLC [tw] OR RAEB [tw] OR RCMD [tw] OR SCLC [tw] OR VOD [tw] OR 5q syndrome [tw] OR BCR ABL [tw] OR c erbB 2 [tw] OR c erbB2 [tw] OR carney complex [tw] OR cone biopsy [tw] OR denys drash [tw] OR essential thrombocythemia [tw] OR estrogen receptor negative [tw] OR estrogen receptor positive [tw] OR li fraumeni [tw] OR meigs syndrome [tw] OR molar pregnancy [tw] OR mycosis fungoides [tw] OR peutz jeghers [tw] OR sentinel lymph node [tw] OR sezary syndrome [tw] OR struma ovarii [tw] OR sturge weber [tw] OR zollinger ellison [tw] OR (aberrant [tw] AND crypt [tw] AND foci [tw]) OR ((anti-n-methyl-d-aspartate [tw] OR anti-nmda) AND encephalitis [tw]) OR (barrett [tw] AND esophagus [tw]) OR (gestational [tw] AND trophoblastic [tw]) OR (microsatellite [tw] AND instability [tw]) OR (paget [tw] AND (breast [tw] OR nipple [tw])) OR (polycythemia [tw] AND vera [tw]) OR (radiation [tw] AND therapy [tw]) OR (WAGR [tw] AND syndrome [tw]) OR (pap [tw] AND (smear [tw] OR smears [tw])) OR cervical smear [tw] OR cervical smears [tw] OR pap test [tw] OR pap tests [tw] OR (PSA [tw] AND prostate) OR PSA test [tw] OR PSA testing [tw] OR (prostate [tw] AND specific [tw] AND antigen [tw]) OR acanthoma [tw] OR acanthomas [tw] OR acrochordon [tw] OR acrochordons [tw] OR acrospiroma [tw] OR acrospiromas [tw] OR adamantinoma [tw] OR adamantinomas [tw] OR adenoacanthoma [tw] OR adenoacanthomas [tw] OR adenoameloblastoma [tw] OR adenoameloblastomas [tw] OR adenocanthoma [tw] OR adenocanthomas [tw] OR adenocarcinoma [tw] OR adenocarcinomas [tw] OR adenofibroma [tw] OR adenofibromas [tw] OR adenolipoma [tw] OR adenolipomas [tw] OR adenolymphoma [tw] OR adenolymphomas [tw] OR adenoma [tw] OR adenomas [tw] OR adenomatosis [tw] OR adenomatous [tw] OR adenomyoepithelioma [tw] OR adenomyoepitheliomas [tw] OR adenomyoma [tw] OR adenomyomas [tw] OR adenosarcoma [tw] OR adenosarcomas [tw] OR adenosis [tw] OR aesthesioneuroblastoma [tw] OR aesthesioneuroblastomas [tw] OR ameloblastoma [tw] OR ameloblastomas [tw] OR amyloidoses [tw] OR amyloidosis [tw] OR anaplasia [tw] OR androblastoma [tw] OR androblastomas [tw] OR angioblastoma [tw] OR angioblastomas [tw] OR angioendothelioma [tw] OR angioendotheliomas [tw] OR angioendotheliomatosis [tw] OR angiofibroma [tw] OR angiofibromas [tw] OR angiofibrosarcoma [tw] OR angiogenesis factor [tw] OR angiokeratoma [tw] OR

2737 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	angiokeratomas [tw] OR angioleiomyoma [tw] OR angioleiomyomas [tw] OR angiolipoma [tw] OR angiolipomas [tw] OR angioma [tw] OR angiomas [tw] OR angiomatosis [tw] OR angiomyolipoma [tw] OR angiomyolipomas [tw] OR angiomyoma [tw] OR angiomyomas [tw] OR angiomyxoma [tw] OR angiomyxomas [tw] OR angioreticuloma [tw] OR angioreticulomas [tw] OR angiosarcoma [tw] OR angiosarcomas [tw] OR anticancer [tw] OR anticarcinogenesis [tw] OR anticarcinogenic [tw] OR antimutagenesis [tw] OR antineoplastic [tw] OR antioncogene [tw] OR antioncogenes [tw] OR antitumor [tw] OR antitumors [tw] OR antitumour [tw] OR antitumours [tw] OR apudoma [tw] OR apudomas [tw] OR argentaffinoma [tw] OR argentaffinomas [tw] OR arrhenoblastoma [tw] OR arrhenoblastomas [tw] OR astroblastoma [tw] OR astroblastomas [tw] OR astrocytoma [tw] OR astrocytomas [tw] OR astroglioma [tw] OR astrogliomas [tw] OR atypia [tw] OR baltoma [tw] OR basiloma [tw] OR basilomas [tw] OR biochemotherapies [tw] OR biochemotherapy [tw] OR bioradiotherapy [tw] OR Birt-Hogg-Dube [tw] OR blastoma [tw] OR blastomas [tw] OR Buschke-Lowenstein [tw] OR cachexia [tw] OR cancer [tw] OR cancerous [tw] OR cancers [tw] OR carcinogen [tw] OR carcinogenesis [tw] OR carcinogenic [tw] OR carcinogens [tw] OR carcinoid [tw] OR carcinoma [tw] OR carcinomas [tw] OR carcinomatosis [tw] OR carcinosarcoma [tw] OR carcinosarcomas [tw] OR cavernoma [tw] OR cavernomas [tw] OR cementoma [tw] OR cementomas [tw] OR cerbB2 [tw] OR ceruminoma [tw] OR ceruminomas [tw] OR chemodectoma [tw] OR chemodectomas [tw] OR chemoimmunoradiotherapy [tw] OR chemoimmunotherapies [tw] OR chemoimmunotherapy [tw] OR chemoprevention [tw] OR chemoradiation [tw] OR chemoradiotherapies [tw] OR chemoradiotherapy [tw] OR cherubism [tw] OR chloroma [tw] OR chloromas [tw] OR cholangiocarcinoma [tw] OR cholangiocarcinomas [tw] OR cholangiohepatoma [tw] OR cholangioma [tw] OR cholangiomas [tw] OR cholangiosarcoma [tw] OR cholesteatoma [tw] OR cholesteatomas [tw] OR chondroblastoma [tw] OR chondroblastomas [tw] OR chondroma [tw] OR chondromas [tw] OR chondrosarcoma [tw] OR chondrosarcomas [tw] OR chordoma [tw] OR chordomas [tw] OR chorioadenoma [tw] OR chorioadenomas [tw] OR chorioangioma [tw] OR chorioangiomas [tw] OR choriocarcinoma [tw] OR choriocarcinomas [tw] OR chorioepithelioma [tw] OR chorioepitheliomas [tw] OR chorionepithelioma [tw] OR chorionepitheliomas [tw] OR choristoma

Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	[tw] OR choristomas [tw] OR chromaffinoma [tw] OR chromaffinomas [tw] OR cocarcinogenesis [tw] OR collagenoma [tw] OR collagenomas [tw] OR colonoscopies [tw] OR coloscopy [tw] OR coloscopies [tw] OR comedocarcinoma [tw] OR comedocarcinomas [tw] OR condyloma [tw] OR condylomas [tw] OR corticotropinoma [tw] OR corticotropinomas [tw] OR craniopharyngioma [tw] OR craniopharyngiomas [tw] OR cylindroma [tw] OR cylindromas [tw] OR cyst [tw] OR cysts [tw] OR cystadenocarcinoma [tw] OR cystadenocarcinomas [tw] OR cystadenofibroma [tw] OR cystadenofibromas [tw] OR cystadenoma [tw] OR cystadenomas [tw] OR cystoma [tw] OR cystomas [tw] OR cystosarcoma [tw] OR cystosarcomas [tw] OR dentinoma [tw] OR dentinomas [tw] OR dermatofibroma [tw] OR dermatofibromas [tw] OR dermatofibrosarcoma [tw] OR dermatofibrosarcomas [tw] OR dermoid [tw] OR desmoid [tw] OR desmoplastic [tw] OR dictyoma [tw] OR dysgerminoma [tw] OR dysgerminomas [tw] OR dyskeratoma [tw] OR dyskeratomas [tw] OR dysmyelopoiesis [tw] OR dysplasia [tw] OR dysplastic [tw] OR ectomesenchymoma [tw] OR ectomesenchymomas [tw] OR elastofibroma [tw] OR elastofibromas [tw] OR enchondroma [tw] OR enchondromas [tw] OR enchondromatosis [tw] OR endothelioma [tw] OR endotheliomas [tw] OR ependymoblastoma [tw] OR ependymoblastomas [tw] OR ependymoma [tw] OR ependymomas [tw] OR epidermoid [tw] OR epithelioma [tw] OR epitheliomas [tw] OR erythroleukaemia [tw] OR erythroleukaemias [tw] OR erythroleukemia [tw] OR erythroleukemias [tw] OR erythroplakia [tw] OR erythroplakias [tw] OR erythroplasia [tw] OR esthesioneuroblastoma [tw] OR esthesioneuroblastomas [tw] OR esthesioneuroepithelioma [tw] OR esthesioneuroepitheliomas [tw] OR exostosis [tw] OR fibroadenoma [tw] OR fibroadenomas [tw] OR fibroadenosarcoma [tw] OR fibroadenosis [tw] OR fibrochondrosarcoma [tw] OR fibroelastoma [tw] OR fibroelastomas [tw] OR fibroepithelioma [tw] OR fibroepitheliomas [tw] OR fibrofolliculoma [tw] OR fibrofolliculomas [tw] OR fibroid [tw] OR fibroids [tw] OR fibrolipoma [tw] OR fibrolipomas [tw] OR fibroliposarcoma [tw] OR fibroma [tw] OR fibromas [tw] OR fibromatosis [tw] OR fibromyoma [tw] OR fibromyomas [tw] OR fibromyxolipoma [tw] OR fibromyxoma [tw] OR fibromyxomas [tw] OR fibroodontoma [tw] OR fibroodontomas [tw] OR fibrosarcoma [tw] OR fibrosarcomas [tw] OR fibrothecoma [tw] OR fibrothecomas [tw] OR fibroxanthoma [tw] OR fibroxanthomas [tw] OR fibroxanthosarcoma [tw] OR fibroxanthosarcomas [tw]

2739 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	OR ganglioblastoma [tw] OR ganglioblastomas [tw] OR gangliocytoma [tw] OR gangliocytomas [tw] OR ganglioglioma [tw] OR gangliogliomas [tw] OR ganglioneuroblastoma [tw] OR ganglioneuroblastomas [tw] OR ganglioneurofibroma [tw] OR ganglioneurofibromas [tw] OR ganglioneuroma [tw] OR ganglioneuromas [tw] OR gastrinoma [tw] OR gastrinomas [tw] OR germinoma [tw] OR germinomas [tw] OR glioblastoma [tw] OR glioblastomas [tw] OR gliofibroma [tw] OR gliofibromas [tw] OR glioma [tw] OR gliomas [tw] OR gliomatosis [tw] OR glioneuroma [tw] OR glioneuromas [tw] OR gliosarcoma [tw] OR gliosarcomas [tw] OR glomangioma [tw] OR glomangiomas [tw] OR glomangiomatosis [tw] OR glomangiomyoma [tw] OR glomangiomyomas [tw] OR glomangiosarcoma [tw] OR glomangiosarcomas [tw] OR glucagonoma [tw] OR glucagonomas [tw] OR gonadoblastoma [tw] OR gonadoblastomas [tw] OR gonocytoma [tw] OR gonocytomas [tw] OR granuloma [tw] OR granulomas [tw] OR granulomatosis [tw] OR gynaecomastia [tw] OR gynandroblastoma [tw] OR gynecomastia [tw] OR haemangioblastoma [tw] OR haemangioblastomas [tw] OR haemangioma [tw] OR haemangiomas [tw] OR haemangiopericytoma [tw] OR haemangiopericytomas [tw] OR haemangiosarcoma [tw] OR haemangiosarcomas [tw] OR hamartoma [tw] OR hamartomas [tw] OR hemangioblastoma [tw] OR hemangioblastomas [tw] OR hemangioendothelioma [tw] OR hemangioendotheliomas [tw] OR hemangioendotheliosarcoma [tw] OR hemangioendotheliosarcomas [tw] OR hemangioma [tw] OR hemangiomas [tw] OR hemangiomatosis [tw] OR hemangiopericytoma [tw] OR hemangiopericytomas [tw] OR hemangioperithelioma [tw] OR hemangiosarcoma [tw] OR hemangiosarcomas [tw] OR hepatoblastoma [tw] OR hepatoblastomas [tw] OR hepatocarcinoma [tw] OR hepatocarcinomas [tw] OR hepatocholangiocarcinoma [tw] OR hepatocholangiocarcinomas [tw] OR hepatoma [tw] OR hepatomas [tw] OR hibernoma [tw] OR hibernomas [tw] OR hidradenoma [tw] OR hidradenomas [tw] OR hidrocystoma [tw] OR hidrocystomas [tw] OR histiocytoma [tw] OR histiocytomas [tw] OR hodgkin [tw] OR hodgkins [tw] OR hydatidiform [tw] OR hydradenoma [tw] OR hydradenomas [tw] OR hypernephroma [tw] OR hypernephromas [tw] OR immunochemoradiotherapy [tw] OR immunochemotherapies [tw] OR immunochemotherapy [tw] OR immunocytoma [tw] OR immunocytoma [tw] OR immunoradiotherapy [tw] OR insulinomas [tw] OR integrative oncology [tw]

Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	OR kasabach-merritt [tw] OR keratoacanthoma [tw] OR keratoacanthomas [tw] OR keratosis [tw] OR leiomyoblastoma [tw] OR leiomyoblastomas [tw] OR leiomyofibroma [tw] OR leiomyofibromas [tw] OR leiomyoma [tw] OR leiomyomas [tw] OR leiomyomatosis [tw] OR leiomyosarcoma [tw] OR leiomyosarcomas [tw] OR leukaemia [tw] OR leukaemias [tw] OR leukemia [tw] OR leukemias [tw] OR leukoplakia [tw] OR leukoplakias [tw] OR lipoadenoma [tw] OR lipoadenomas [tw] OR lipoblastoma [tw] OR lipoblastomas [tw] OR lipoblastomatosis [tw] OR lipoma [tw] OR lipomas [tw] OR lipomatosis [tw] OR liposarcoma [tw] OR liposarcomas [tw] OR luteinoma [tw] OR luteoma [tw] OR luteomas [tw] OR lymphangioendothelioma [tw] OR lymphangioendotheliomas [tw] OR lymphangioleiomyomatosis [tw] OR lymphangioma [tw] OR lymphangiomas [tw] OR lymphangiomatosis [tw] OR lymphangiomyoma [tw] OR lymphangiomyomas [tw] OR lymphangiomyomatosis [tw] OR lymphangiosarcoma [tw] OR lymphangiosarcomas [tw] OR lymphoepithelioma [tw] OR lymphoepitheliomas [tw] OR lymphoma [tw] OR lymphomas [tw] OR lymphoproliferation [tw] OR lymphoproliferations [tw] OR lymphoproliferative [tw] OR lymphoscintigraphic [tw] OR lymphoscintigraphy [tw] OR macroglobulinemia [tw] OR macroglobulinemias [tw] OR macroprolactinoma [tw] OR malignancies [tw] OR malignancy [tw] OR malignant [tw] OR maltoma [tw] OR maltomas [tw] OR mammogram [tw] OR mammograms [tw] OR masculinovoblastoma [tw] OR mastocytoma [tw] OR mastocytomas [tw] OR mastocytosis [tw] OR mcf-7 [tw] OR medulloblastoma [tw] OR medulloblastomas [tw] OR medullocytoma [tw] OR medullocytomas [tw] OR medulloepithelioma [tw] OR medulloepitheliomas [tw] OR medullomyoblastoma [tw] OR medullomyoblastomas [tw] OR melanoacanthoma [tw] OR melanoacanthomas [tw] OR melanoameloblastoma [tw] OR melanocytoma [tw] OR melanocytomas [tw] OR melanoma [tw] OR melanomas [tw] OR melanomatosis [tw] OR meningioblastoma [tw] OR meningioma [tw] OR meningiomas [tw] OR meningiomatosis [tw] OR mesenchymoma [tw] OR mesenchymomas [tw] OR mesonephroma [tw] OR mesonephromas [tw] OR mesothelioma [tw] OR mesotheliomas [tw] OR metaplasia [tw] OR metastases [tw] OR metastasis [tw] OR metastatic [tw] OR microcarcinoma [tw] OR microcarcinomas [tw] OR microglioma [tw] OR microgliomas [tw] OR micrometastases [tw] OR micrometastasis [tw] OR mucositis [tw] OR myelodysplasia [tw] OR myelodysplasias [tw] OR

Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	myelodysplastic [tw] OR myelofibrosis [tw] OR myelolipoma [tw] OR myelolipomas [tw] OR myeloma [tw] OR myelomas [tw] OR myelomatosis [tw] OR myeloproliferation [tw] OR myeloproliferations [tw] OR myeloproliferative [tw] OR myelosuppression [tw] OR myoblastoma [tw] OR myoblastomas [tw] OR myoepithelioma [tw] OR myoepitheliomas [tw] OR myofibroblastoma [tw] OR myofibroblastomas [tw] OR myofibroma [tw] OR myofibromas [tw] OR myofibromatosis [tw] OR myofibrosarcoma [tw] OR myofibrosarcomas [tw] OR myolipoma [tw] OR myolipomas [tw] OR myoma [tw] OR myomas [tw] OR myopericytoma [tw] OR myosarcoma [tw] OR myosarcomas [tw] OR myxofibroma [tw] OR myxofibromas [tw] OR myxolipoma [tw] OR myxolipomas [tw] OR myxoliposarcoma [tw] OR myxoma [tw] OR myxomas [tw] OR naevus [tw] OR neoplasia [tw] OR neoplasia [tw] OR neoplasm [tw] OR neoplasms [tw] OR neoplastic [tw] OR nephroblastoma [tw] OR nephroblastomas [tw] OR neurilemmoma [tw] OR neurilemmomas [tw] OR neurilemmomatosis [tw] OR neurilemoma [tw] OR neurilemomas [tw] OR neurinoma [tw] OR neurinomas [tw] OR neuroblastoma [tw] OR neuroblastomas [tw] OR neurocytoma [tw] OR neurocytomas [tw] OR neuroepithelioma [tw] OR neuroepitheliomas [tw] OR neurofibroma [tw] OR neurofibromas [tw] OR neurofibromatosis [tw] OR neurofibrosarcoma [tw] OR neurofibrosarcomas [tw] OR neurolipocytoma [tw] OR neuroma [tw] OR neuromas [tw] OR neuronevus [tw] OR neurothekeoma [tw] OR neurothekeomas [tw] OR nevus [tw] OR nonhodgkin [tw] OR nonhodgkins [tw] OR nonseminoma [tw] OR nonseminomas [tw] OR nonseminomatous [tw] OR odontoameloblastoma [tw] OR odontoma [tw] OR oligoastrocytoma [tw] OR oligoastrocytomas [tw] OR oligodendroglioma [tw] OR oligodendrogliomas [tw] OR oncocytoma [tw] OR oncocytomas [tw] OR oncogen [tw] OR oncogene [tw] OR oncogenes [tw] OR oncogenesis [tw] OR oncogenic [tw] OR oncogens [tw] OR oncologic [tw] OR oncologist [tw] OR oncologists [tw] OR oncology [tw] OR oncoprotein [tw] OR oncoproteins [tw] OR opsoclonus-myoclonus [tw] OR orchioblastoma [tw] OR orchioblastomas [tw] OR osteoblastoma [tw] OR osteoblastomas [tw] OR osteochondroma [tw] OR osteochondromas [tw] OR osteochondrosarcoma [tw] OR osteochondrosarcomas [tw] OR osteoclastoma [tw] OR osteoclastomas [tw] OR osteofibrosarcoma [tw] OR osteoma [tw] OR osteomas [tw] OR osteosarcoma [tw] OR osteosarcomas [tw] OR pancreatoblastoma [tw] OR pancreatoblastomas [tw] OR papilloma [tw] OR papillomas [tw] OR

2742 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	papillomata [tw] OR papillomatosis [tw] OR papillomavirus [tw] OR papillomaviruses [tw] OR parachordoma [tw] OR parachordomas [tw] OR paraganglioma [tw] OR paragangliomas [tw] OR paraneoplastic [tw] OR perineurioma [tw] OR perineuriomas [tw] OR phaeochromocytoma [tw] OR phaeochromocytomas [tw] OR pheochromoblastoma [tw] OR pheochromoblastomas [tw] OR pheochromocytoma [tw] OR pheochromocytomas [tw] OR pilomatricoma [tw] OR pilomatricomas [tw] OR pilomatrixoma [tw] OR pilomatrixomas [tw] OR pinealblastoma [tw] OR pinealoblastoma [tw] OR pinealoblastomas [tw] OR pinealoma [tw] OR pinealomas [tw] OR pineoblastoma [tw] OR pineoblastomas [tw] OR pineocytoma [tw] OR pineocytomas [tw] OR plasmacytoma [tw] OR plasmacytomas [tw] OR pneumoblastoma [tw] OR pneumoblastomas [tw] OR pneumocytoma [tw] OR polyembryoma [tw] OR polyembryomas [tw] OR polyhistioma [tw] OR polyhistiomas [tw] OR polyp [tw] OR polyposis [tw] OR polyps [tw] OR porocarcinoma [tw] OR porocarcinomas [tw] OR poroma [tw] OR poromas [tw] OR precancer [tw] OR precancerous [tw] OR preleukaemia [tw] OR preleukaemias [tw] OR preleukemia [tw] OR preleukemias [tw] OR premalignant [tw] OR preneoplastic [tw] OR prolactinoma [tw] OR prolactinomas [tw] OR protooncogene [tw] OR protooncogenes [tw] OR pseudotumor [tw] OR pseudotumors [tw] OR radiochemotherapy [tw] OR radioimmunotherapies [tw] OR radioimmunotherapy [tw] OR reninoma [tw] OR reninomas [tw] OR reticuloendothelioma [tw] OR reticuloendotheliomas [tw] OR reticulohistiocytoma [tw] OR reticulohistiocytomas [tw] OR reticulosis [tw] OR retinoblastoma [tw] OR retinoblastomas [tw] OR rhabdomyoma [tw] OR rhabdomyomas [tw] OR rhabdomyosarcoma [tw] OR rhabdomyosarcomas [tw] OR rhabdosarcoma [tw] OR rhabdosarcomas [tw] OR sarcoma [tw] OR sarcomas [tw] OR sarcomatosis [tw] OR schwannoma [tw] OR schwannomas [tw] OR schwannomatosis [tw] OR seminoma [tw] OR seminomas [tw] OR seminomatous [tw] OR somatostatinoma [tw] OR somatostatinomas [tw] OR somatotropinoma [tw] OR somatotropinomas [tw] OR spermatocytoma [tw] OR spiradenoma [tw] OR spiradenomas [tw] OR spongioblastoma [tw] OR spongioblastomas [tw] OR steatocystoma [tw] OR steatocystomas [tw] OR subependymoma [tw] OR subependymomas [tw] OR syringadenoma [tw] OR syringadenomas [tw] OR syringocystadenoma [tw] OR syringocystadenomas [tw] OR syringoma [tw] OR syringomas [tw] OR teratocarcinoma [tw] OR teratocarcinomas [tw] OR teratoma [tw] OR teratomas [tw] OR thecoma

2743 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	[tw] OR thecomas [tw] OR thymolipoma [tw] OR thymolipomas [tw] OR thymoma [tw] OR thymomas [tw] OR trichilemmoma [tw] OR trichilemmomas [tw] OR trichoadenoma [tw] OR trichoblastoma [tw] OR trichoblastomas [tw] OR trichodiscoma [tw] OR trichodiscomas [tw] OR trichoepithelioma [tw] OR trichoepitheliomas [tw] OR trichofolliculoma [tw] OR trichofolliculomas [tw] OR tricholemmoma [tw] OR tricholemmomas [tw] OR tumor [tw] OR tumorgenesis [tw] OR tumorgenic [tw] OR tumorigenesis [tw] OR tumorigenic [tw] OR tumorogenesis [tw] OR tumorogenic [tw] OR tumors [tw] OR tumour [tw] OR tumours [tw] OR vipoma [tw] OR vipomas [tw] OR waldenstrom [tw] OR waldenstroms [tw] OR xanthoastrocytoma [tw] OR xanthoastrocytomas [tw] OR xanthofibroma [tw] OR xanthofibromas [tw] OR xanthogranuloma [tw] OR xanthogranulomas [tw] OR xanthoma [tw] OR xanthomas [tw] OR xanthosarcoma [tw] OR xanthosarcomas [tw] OR Acta Oncol [ta] OR Acta Radiol Oncol Radiat Phys Biol [ta] OR Acta Radiol Oncol [ta] OR Adv Cancer Res [ta] OR Adv Immun Cancer Ther [ta] OR Ai Zheng [ta] OR Am J Cancer [ta] OR Am J Clin Oncol [ta] OR Am Soc Clin Oncol Educ Book [ta] OR Anal Cell Pathol [ta] OR Ann Oncol [ta] OR Ann Surg Oncol [ta] OR Anti cancer Drugs [ta] OR Anticancer Agents Med Chem [ta] OR Anticancer Drug Des [ta] OR Anticancer Res [ta] OR Asia Pac J Clin Oncol [ta] OR BMC Cancer [ta] OR Baillieres Clin Oncol [ta] OR Biochim Biophys Acta [ta] OR Blood Cancer J [ta] OR Br J Cancer Suppl [ta] OR Br J Cancer [ta] OR Brain Tumor Pathol [ta] OR Breast Cancer Res Treat [ta] OR Breast Cancer Res [ta] OR Breast Cancer [ta] OR Breast J [ta] OR Bull Assoc Fr Etud Cancer [ta] OR Bull Cancer Radiother [ta] OR Bull Cancer [ta] OR CA Cancer J Clin [ta] OR Can J Oncol [ta] OR Can Oncol Nurs J [ta] OR Cancer Biochem Biophys [ta] OR Cancer Biol Ther [ta] OR Cancer Biomark [ta] OR Cancer Biother Radiopharm [ta] OR Cancer Biother [ta] OR Cancer Bull [ta] OR Cancer Causes Control [ta] OR Cancer Cell Int [ta] OR Cancer Cell [ta] OR Cancer Cells [ta] OR Cancer Chemother Biol Response Modif [ta] OR Cancer Chemother Pharmacol [ta] OR Cancer Chemother Rep 2 [ta] OR Cancer Chemother Rep 3 [ta] OR Cancer Chemother Rep [ta] OR Cancer Clin Trials [ta] OR Cancer Commun [ta] OR "Cancer Commun (Lond)" [ta] OR Cancer Control [ta] OR Cancer Cytol [ta] OR Cancer Cytopathol [ta] OR Cancer Detect Prev Suppl [ta] OR Cancer Detect Prev [ta] OR Cancer Discov [ta] OR Cancer Drug Deliv [ta] OR Cancer Epidemiol Biomarkers Prev [ta] OR Cancer Epidemiol [ta] OR Cancer Gene Ther [ta] OR Cancer Genet [ta] OR

2744 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	Cancer Genet Cytogenet [ta] OR Cancer Genomics Proteomics [ta] OR Cancer Imaging [ta] OR Cancer Immun [ta] OR Cancer Immunol Immunother [ta] OR Cancer Immunol Res [ta] OR Cancer Inform [ta] OR Cancer Invest [ta] OR Cancer J Sci Am [ta] OR Cancer J [ta] OR Cancer Lett [ta] OR Cancer Med [ta] OR Cancer Metastasis Rev [ta] OR Cancer Microenviron [ta] OR Cancer Nurs [ta] OR Cancer Pract [ta] OR Cancer Prev Control [ta] OR Cancer Prev Res Phila [ta] OR Cancer Radiother [ta] OR Cancer Res Treat [ta] OR Cancer Res [ta] OR Cancer Sci [ta] OR Cancer Surv [ta] OR Cancer Treat Rep [ta] OR Cancer Treat Res [ta] OR Cancer Treat Res Commun [ta] OR Cancer Treat Rev [ta] OR Cancer [ta] OR Carcinogenesis [ta] OR Cell Growth Differ [ta] OR Cell Oncol Dordr [ta] OR Chin Clin Oncol [ta] OR Chin J Cancer [ta] OR Chin J Cancer [ta] OR Clin Breast Cancer [ta] OR Clin Cancer Res [ta] OR Clin Colorectal Cancer [ta] OR Clin Exp Metastasis [ta] OR Clin J Oncol Nurs [ta] OR Clin Lymphoma Myeloma Leuk [ta] OR Clin Lymphoma [ta] OR Clin Oncol R Coll Radiol [ta] OR Clin Oncol [ta] OR Clin Transl Oncol [ta] OR CNS Oncol [ta] OR Contemp Oncol [ta] OR Crit Rev Oncog [ta] OR Crit Rev Oncol Hematol [ta] OR Curr Cancer Drug Targets [ta] OR Curr Oncol Rep [ta] OR Curr Oncol [ta] OR Curr Opin Oncol [ta] OR Curr Probl Cancer [ta] OR Curr Treat Options Oncol [ta] OR Dimens Oncol Nurs [ta] OR Drug Resist Updat [ta] OR Eksp Onkol [ta] OR Endocr Relat Cancer [ta] OR Eur J Cancer B Oral Oncol [ta] OR Eur J Cancer Care Engl [ta] OR Eur J Cancer Clin Oncol [ta] OR Eur J Cancer Prev [ta] OR Eur J Cancer [ta] OR Eur J Gynaecol Oncol [ta] OR Eur J Surg Oncol [ta] OR Front Radiat Ther Oncol [ta] OR Future Oncol [ta] OR Gan No Rinsho [ta] OR Gan To Kagaku Ryoho [ta] OR Gastric Cancer [ta] OR Gastrointest Cancer Res [ta] OR Genes Chromosomes Cancer [ta] OR Gulf J Oncolog [ta] OR Gynecol Oncol [ta] OR Head Neck Oncol [ta] OR Hematol Oncol Clin North Am [ta] OR Hematol Oncol Stem Cell Ther [ta] OR Hematol Oncol [ta] OR Hered Cancer Clin Pract [ta] OR Horm Cancer [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum [ta] OR IARC Monogr Eval Carcinog Risk Chem Man [ta] OR IARC Monogr Eval Carcinog Risks Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risks Hum [ta] OR IARC Sci Publ [ta] OR Important Adv Oncol [ta] OR Indian J Cancer [ta] OR Infect Agent Cancer [ta] OR Innov Oncol Nurs [ta] OR Int Adv Surg Oncol [ta] OR Int J Biol Markers [ta] OR Int J Cancer Suppl [ta] OR Int J Cancer [ta] OR Int J Clin Oncol [ta] OR Int J

2745 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	Gastrointest Cancer [ta] OR Int J Gynecol Cancer [ta] OR Int J Hyperthermia [ta] OR Int J Oncol [ta] OR Int J Radiat Oncol Biol Phys [ta] OR Int J Surg Oncol [ta] OR Integr Cancer Ther [ta] OR Invasion Metastasis [ta] OR Invest New Drugs [ta] OR J Adolesc Young Adult Oncol [ta] OR J Assoc Pediatr Oncol Nurses [ta] OR J Cancer Educ [ta] OR J Cancer Epidemiol Prev [ta] OR J Cancer Res Clin Oncol [ta] OR J Cancer Res [ta] OR J Cancer Surviv [ta] OR J Chemother [ta] OR J Clin Oncol [ta] OR J Community Support Oncol [ta] OR J Dermatol Surg Oncol [ta] OR J Egypt Natl Canc Inst [ta] OR J Environ Pathol Toxicol Oncol [ta] OR J Exp Clin Cancer Res [ta] OR J Exp Ther Oncol [ta] OR J Geriatr Oncol [ta] OR J Gynecol Oncol [ta] OR J Hematol Oncol [ta] OR J Immunother Emphasis Tumor Immunol [ta] OR J Immunother [ta] OR J Mammary Gland Biol Neoplasia [ta] OR J Med Imaging Radiat Oncol [ta] OR J Natl Cancer Inst Monogr [ta] OR J Natl Cancer Inst [ta] OR J Natl Compr Canc Netw [ta] OR J Neurooncol [ta] OR J Oncol Manag [ta] OR J Oncol Pract [ta] OR J Oncol [ta] OR J Pediatr Hematol Oncol [ta] OR J Pediatr Oncol Nurs [ta] OR J Soc Integr Oncol [ta] OR J Support Oncol [ta] OR J Surg Oncol Suppl [ta] OR J Surg Oncol [ta] OR J Thorac Oncol [ta] OR Jaarb Kankeronderz Kankerbestrijd Ned [ta] OR JAMA Oncol [ta] OR JCO Clin Cancer Inform [ta] OR Jpn J Cancer Res [ta] OR Jpn J Clin Oncol [ta] OR Klin Onkol [ta] OR Lancet Oncol [ta] OR Leuk Lymphoma [ta] OR Leuk Res [ta] OR Leukemia [ta] OR Lung Cancer [ta] OR Lutte Cancer [ta] OR Magy Onkol [ta] OR Med Oncol Tumor Pharmacother [ta] OR Med Oncol [ta] OR Med Pediatr Oncol Suppl [ta] OR Med Pediatr Oncol [ta] OR Melanoma Res [ta] OR Mol Cancer Res [ta] OR Mol Cancer Ther [ta] OR Mol Cancer [ta] OR Mol Oncol [ta] OR Monogr Neoplast Dis Var Sites [ta] OR NCI Monogr [ta] OR Nat Rev Cancer [ta] OR Nat Rev Clin Oncol [ta] OR Natl Cancer Inst Monogr [ta] OR Natl Cancer Inst Res Rep [ta] OR Neoplasia [ta] OR Neoplasma [ta] OR Neuro oncol [ta] OR Nippon Gan Chiryo Gakkai Shi [ta] OR Noshuyo Byori [ta] OR Nutr Cancer [ta] OR ONS Connect [ta] OR ONS News [ta] OR Oncogene Res [ta] OR Oncogene [ta] OR Oncol Nurs Forum [ta] OR Oncol Rep [ta] OR Oncol Res [ta] OR Oncol Res Treat [ta] OR Oncologist [ta] OR Oncology Huntingt [ta] OR Oncology [ta] OR Oncotarget [ta] OR Onkologie [ta] OR Open Clin Cancer J [ta] OR Oral Oncol [ta] OR Papillomavirus Res [ta] OR Pathol Oncol Res [ta] OR Pediatr Blood Cancer [ta] OR Pediatr Hematol Oncol [ta] OR Pigment Cell Melanoma Res [ta] OR Pract Radiat Oncol [ta] OR Princess

2746 **Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).**

Step/Category	Search terms
2. PubMed Cancer Strategy (continued)	Takamatsu Symp [ta] OR Proc Am Assoc Cancer Res [ta] OR Proc Can Cancer Conf [ta] OR Proc Natl Cancer Conf [ta] OR Prog Clin Cancer [ta] OR Prog Exp Tumor Res [ta] OR Prog Tumor Res [ta] OR Prostate Cancer Prostatic Dis [ta] OR Psychooncology [ta] OR Radiat Oncol Investig [ta] OR Radiat Oncol [ta] OR Radiol Oncol [ta] OR Radiother Oncol [ta] OR Recent Results Cancer Res [ta] OR Rep Carcinog Backgr Doc [ta] OR Rev Mex Cir Ginecol Cancer [ta] OR S Afr Cancer Bull [ta] OR Sci Rep Res Inst Tohoku Univ Med [ta] OR Sel Cancer Ther [ta] OR Semin Cancer Biol [ta] OR Semin Oncol Nurs [ta] OR Semin Oncol [ta] OR Semin Radiat Oncol [ta] OR Semin Surg Oncol [ta] OR Semin Urol Oncol [ta] OR Strahlenther Onkol [ta] OR Suppl J Med Oncol Tumor Pharmacother [ta] OR Suppl Tumori [ta] OR Support Cancer Ther [ta] OR Support Care Cancer [ta] OR Surg Oncol Clin N Am [ta] OR Surg Oncol [ta] OR Symp Fundam Cancer Res [ta] OR Target Oncol [ta] OR Technol Cancer Res Treat [ta] OR Thorac Cancer [ta] OR Transl Oncol [ta] OR Tumor Res [ta] OR Tumori [ta] OR Tumour Biol [ta] OR Urol Oncol [ta] OR Vet Comp Oncol [ta] OR Vopr Onkol [ta] OR World J Surg Oncol [ta] OR Z Krebsforsch Klin Onkol Cancer Res Clin Oncol [ta] OR Z Krebsforsch [ta] OR Zhongguo Fei Ai Za Zhi [ta] OR Zhonghua Zhong Liu Za Zhi [ta]
Combine Chemical and Cancer Terms	(#1 AND #2) NOT ("poly(ethylene oxide)" OR "poly (ethylene oxide)")
3. Experimental animal terms	("Animals, Genetically Modified"[mh] OR "Animals, Inbred Strains"[mh] OR "Chimera"[mh] OR "Animals, Laboratory"[mh] OR "models, animal"[mh] OR animals[mh:noexp] OR "animal experimentation"[mh] OR "murinae"[mh]) OR ("animal stud*"[tiab] OR ape[tiab] OR apes[tiab] OR balb[tiab] OR bonobo*[tiab] OR bovine[tiab] OR C57[tiab] OR C57bl[tiab] OR callithrix[tiab] OR canis[tiab] OR capra[tiab] OR capuchin*[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cavia[tiab] OR chicken[tiab] OR chickens[tiab] OR chimpanzee*[tiab] OR chinchilla*[tiab] OR cow[tiab] OR cows[tiab] OR cricetinae[tiab] OR "danio rerio"[tiab] OR equus[tiab] OR felis[tiab] OR ferret[tiab] OR ferrets[tiab] OR fish[tiab] OR "flying fox"[tiab] OR "Fruit bat"[tiab] OR gibbon*[tiab] OR goat[tiab] OR

2747

Table A4. List of search terms used in literature search using PubMed and Web of Science (continued).

Step/Category	Search terms
3. Experimental animal terms	goats[tiab] OR guppy[tiab] OR horse[tiab] OR horses[tiab] OR jird[tiab] OR jirds[tiab] OR leontopithecus[tiab] OR "long-evans"[tiab] OR macaque*[tiab] OR marmoset*[tiab] OR medaka[tiab] OR merione[tiab] OR meriones[tiab] OR muridae[tiab] OR murinae[tiab] OR "Mustela putorius"[tiab] OR nomascus[tiab] OR "non human primate*"[tiab] OR orangutan*[tiab] OR "pan paniscus"[tiab] OR "pan troglodytes"[tiab] OR pig[tiab] OR piglet*[tiab] OR pigs[tiab] OR polecat*[tiab] OR quail[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodentia[tiab] OR rodents[tiab] OR saguinus[tiab] OR sheep[tiab] OR sheeps[tiab] OR siamang*[tiab] OR "Sprague-Dawley"[tiab] OR swine[tiab] OR swines[tiab] OR symphalangus[tiab] OR tamarin*[tiab] OR vervet*[tiab] OR wistar[tiab] OR "wood mouse"[tiab] OR zebrafish[tiab]) OR ((boar[tiab] OR boars[tiab] OR dog[tiab] OR dogs[tiab] OR gerbil*[tiab] OR "guinea pig*"[tiab] OR hamster[tiab] OR hamsters[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR "pongo pygmaeus"[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR sow[tiab] OR sows[tiab]) NOT medline[sb]) OR (("in vitro"[tiab] OR "in vitro techniques"[mh] OR "cell line*"[tiab]) AND "animals"[mh:noexp])
4. Combine chemical, cancer, and animals	#3 AND #4

Table A5. List of search terms used for animal studies using Embase.

Step/ Category	Search Terms
1. Chemical terms	ethylene oxide'/de OR 'ethylene oxide':ti,ab OR 75-21-8:rn
PubMed Cancer Strategy	('neoplasm'/exp OR 'american cancer society':ti,ab OR 'angiogenic factor'/exp OR 'cancer antibody'/de OR 'tumor antigen'/exp OR 'antineoplastic agent'/exp OR 'antineoplastic protocol'/de OR 'tumor marker'/exp OR 'biopsy'/exp OR 'biopsy':ti,ab OR 'bone marrow purging'/de OR 'bone marrow transplantation'/exp OR 'cancer center' OR 'cancer vaccine'/exp OR 'carcinogen testing'/de OR 'carcinogen'/exp OR 'chemoembolization'/de OR 'clonal evolution'/de OR 'clonal evolution':ti,ab OR 'computed tomographic colonography'/de OR 'colonoscopy'/de OR 'colposcopy'/de OR 'multimodal cancer therapy'/de OR 'cryosurgery'/exp OR 'cytapheresis'/exp OR 'neoplasm dna':ti,ab OR 'early cancer diagnosis'/de OR 'gene expression regulation'/de OR 'tumor gene'/de OR 'graft versus tumor effect'/exp OR 'hematopoietic stem cell transplantation'/exp OR 'stem cell mobilization'/de OR 'adoptive immunotherapy'/exp OR 'leukostasis'/de OR 'lymph node dissection'/exp OR 'tumor associated leukpcyte' OR 'mammography'/exp OR 'mastectomy'/exp OR 'oncology'/exp OR 'metastasis resection'/de OR 'mohs micrographic surgery' OR 'mixed myelodysplastic myeloproliferative disease'/exp OR 'cancer grading'/exp OR 'tumor protein'/de OR 'cancer staging'/de OR 'cancer transplantation'/de OR 'oncogenesis and malignant transformation'/exp OR 'cancer stem cell'/de OR 'gene fusion'/de OR 'tumor virus'/de OR 'oncology nursing'/exp OR 'oncolytic virus'/exp OR 'papanicolaou test'/de OR 'wart virus vaccine'/de OR 'peripheral blood stem cell transplantation'/de OR 'polyomavirus'/exp OR 'radiotherapy'/exp OR 'radiotherapy planning system'/de OR 'neoplasm rna':ti,ab OR 'second-look surgery'/de OR 'seer program':ti,ab OR 'cancer registry'/de OR 'stem cell transplantation'/de OR 'mesenchymal stem cell transplantation'/de OR 'transplantation conditioning'/exp OR 'tumor cell culture'/exp OR 'tumor escape'/de OR 'tumor lysis syndrome'/de OR 'tumor necrosis factor'/de OR 'tumor necrosis factor receptor'/de OR 'tumor necrosis factor receptor-associated factor'/de OR 'echomammography'/de OR 'aacr':ti,ab OR 'ajcc':ti,ab OR ('asco':ti,ab NOT 'fungi':ti,ab) OR 'iarc':ti,ab OR 'national cancer institute':ti,ab OR 'uicc':ti,ab OR 'acml':ti,ab OR 'agcus':ti,ab OR 'aild':ti,ab OR 'aml':ti,ab OR 'anll':ti,ab OR 'ascus':ti,ab OR 'atll':ti,ab OR 'brca':ti,ab OR 'brca1':ti,ab OR 'brca2':ti,ab OR 'cin':ti,ab OR 'cll':ti,ab OR 'cmml':ti,ab OR 'cmpd':ti,ab OR 'eccl':ti,ab

2751 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	OR 'egist':ti,ab OR 'fmtc':ti,ab OR 'glnh':ti,ab OR 'hnpcc':ti,ab OR 'hnscc':ti,ab OR 'hpv':ti,ab OR 'hsil':ti,ab OR 'icd o':ti,ab OR 'jcml':ti,ab OR 'jmml':ti,ab OR 'lgll':ti,ab OR 'mgus':ti,ab OR 'mlh1':ti,ab OR 'mpd':ti,ab OR 'msh2':ti,ab OR 'nsclc':ti,ab OR 'raeb':ti,ab OR 'rcmd':ti,ab OR 'sclc':ti,ab OR 'vod':ti,ab OR '5q syndrome':ti,ab OR 'bcr abl':ti,ab OR 'c erbb 2':ti,ab OR 'c erbb2':ti,ab OR 'carney complex':ti,ab OR 'cone biopsy':ti,ab OR 'denys drash':ti,ab OR 'essential thrombocythemia':ti,ab OR 'estrogen receptor negative':ti,ab OR 'estrogen receptor positive':ti,ab OR 'li fraumeni':ti,ab OR 'meigs syndrome':ti,ab OR 'molar pregnancy':ti,ab OR 'mycosis fungoides':ti,ab OR 'peutz jeghers':ti,ab OR 'sentinel lymph node':ti,ab OR 'sezary syndrome':ti,ab OR 'struma ovarii':ti,ab OR 'sturge weber':ti,ab OR 'zollinger ellison':ti,ab OR 'aberrant':ti,ab AND 'crypt':ti,ab AND 'foci':ti,ab OR (('anti-n-methyl-d-aspartate':ti,ab OR 'anti-nmda') AND 'encephalitis':ti,ab) OR ('barrett':ti,ab AND 'esophagus':ti,ab) OR ('gestational':ti,ab AND 'trophoblastic':ti,ab) OR ('microsatellite':ti,ab AND 'instability':ti,ab) OR ('paget':ti,ab AND ('breast':ti,ab OR 'nipple':ti,ab)) OR ('polycythemia':ti,ab AND 'vera':ti,ab) OR ('radiation':ti,ab AND 'therapy':ti,ab) OR ('wagr':ti,ab AND 'syndrome':ti,ab) OR ('pap':ti,ab AND ('smear':ti,ab OR 'smears':ti,ab)) OR 'cervical smear':ti,ab OR 'cervical smears':ti,ab OR 'pap test':ti,ab OR 'pap tests':ti,ab OR ('psa':ti,ab AND 'prostate') OR 'psa test':ti,ab OR 'psa testing':ti,ab OR ('prostate':ti,ab AND 'specific':ti,ab AND 'antigen':ti,ab) OR 'acanthoma':ti,ab OR 'acanthomas':ti,ab OR 'acrochordon':ti,ab OR 'acrochordons':ti,ab OR 'acrospiroma':ti,ab OR 'acrospiromas':ti,ab OR 'adamantinoma':ti,ab OR 'adamantinomas':ti,ab OR 'adenoacanthoma':ti,ab OR 'adenoacanthomas':ti,ab OR 'adenoameloblastoma':ti,ab OR 'adenoameloblastomas':ti,ab OR 'adenocanthoma':ti,ab OR 'adenocanthomas':ti,ab OR 'adenocarcinoma':ti,ab OR 'adenocarcinomas':ti,ab OR 'adenofibroma':ti,ab OR 'adenofibromas':ti,ab OR 'adenolipoma':ti,ab OR 'adenolipomas':ti,ab OR 'adenolymphoma':ti,ab OR 'adenolymphomas':ti,ab OR 'adenoma':ti,ab OR 'adenomas':ti,ab OR 'adenomatosis':ti,ab OR 'adenomatous':ti,ab OR 'adenomyoepithelioma':ti,ab OR 'adenomyoepitheliomas':ti,ab OR 'adenomyoma':ti,ab OR 'adenomyomas':ti,ab OR 'adenosarcoma':ti,ab OR 'adenosarcomas':ti,ab OR 'adenosis':ti,ab OR 'aesthesioneuroblastoma':ti,ab

2752

2753

2754 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	OR 'aesthesioneuroblastomas':ti,ab OR 'ameloblastoma':ti,ab OR 'ameloblastomas':ti,ab OR 'amyloidoses':ti,ab OR 'amyloidosis':ti,ab OR 'anaplasia':ti,ab OR 'androblastoma':ti,ab OR 'androblastomas':ti,ab OR 'angioblastoma':ti,ab OR 'angioblastomas':ti,ab OR 'angioendothelioma':ti,ab OR 'angioendotheliomas':ti,ab OR 'angioendotheliomatosis':ti,ab OR 'angiofibroma':ti,ab OR 'angiofibromas':ti,ab OR 'angiofibrosarcoma':ti,ab OR 'angiogenesis factor':ti,ab OR 'angiokeratoma':ti,ab OR 'angiokeratomas':ti,ab OR 'angioleiomyoma':ti,ab OR 'angioleiomyomas':ti,ab OR 'angiolipoma':ti,ab OR 'angiolipomas':ti,ab OR 'angioma':ti,ab OR 'angiomas':ti,ab OR 'angiomatosis':ti,ab OR 'angiomyolipoma':ti,ab OR 'angiomyolipomas':ti,ab OR 'angiomyoma':ti,ab OR 'angiomyomas':ti,ab OR 'angiomyxoma':ti,ab OR 'angiomyxomas':ti,ab OR 'angioreticuloma':ti,ab OR 'angioreticulomas':ti,ab OR 'angiosarcoma':ti,ab OR 'angiosarcomas':ti,ab OR 'anticancer':ti,ab OR 'anticarcinogenesis':ti,ab OR 'anticarcinogenic':ti,ab OR 'antimutagenesis':ti,ab OR 'antineoplastic':ti,ab OR 'antioncogene':ti,ab OR 'antioncogenes':ti,ab OR 'antitumor':ti,ab OR 'antitumors':ti,ab OR 'antitumour':ti,ab OR 'antitumours':ti,ab OR 'apudoma':ti,ab OR 'apudomas':ti,ab OR 'argentaffinoma':ti,ab OR 'argentaffinomas':ti,ab OR 'arrhenoblastoma':ti,ab OR 'arrhenoblastomas':ti,ab OR 'astroblastoma':ti,ab OR 'astroblastomas':ti,ab OR 'astrocytoma':ti,ab OR 'astrocytomas':ti,ab OR 'astroglioma':ti,ab OR 'astrogliomas':ti,ab OR 'atypia':ti,ab OR 'baltoma':ti,ab OR 'basiloma':ti,ab OR 'basilomas':ti,ab OR 'biochemotherapies':ti,ab OR 'biochemotherapy':ti,ab OR 'bioradiotherapy':ti,ab OR 'birt-hogg-dube':ti,ab OR 'blastoma':ti,ab OR 'blastomas':ti,ab OR 'buschke-lowenstein':ti,ab OR 'cachexia':ti,ab OR 'cancer':ti,ab OR 'cancerous':ti,ab OR 'cancers':ti,ab OR 'carcinogen':ti,ab OR 'carcinogenesis':ti,ab OR 'carcinogenic':ti,ab OR 'carcinogens':ti,ab OR 'carcinoid':ti,ab OR 'carcinoma':ti,ab OR 'carcinomas':ti,ab OR 'carcinomatosis':ti,ab OR 'carcinosarcoma':ti,ab OR 'carcinosarcomas':ti,ab OR 'cavernoma':ti,ab OR 'cavernomas':ti,ab OR 'cementoma':ti,ab OR 'cementomas':ti,ab OR 'cerbb2':ti,ab OR 'ceruminoma':ti,ab OR 'ceruminomas':ti,ab OR 'chemodectoma':ti,ab OR 'chemodectomas':ti,ab OR 'chemoimmunoradiotherapy':ti,ab OR 'chemoimmunotherapies':ti,ab OR 'chemoimmunotherapy':ti,ab OR 'chemoprevention':ti,ab OR 'chemoradiation':ti,ab OR 'chemoradiotherapies':ti,ab OR 'chemoradiotherapy':ti,ab OR 'cherubism':ti,ab OR 'chloroma':ti,ab OR

Table A5. List of search terms used for animal studies using Embase (continued).

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'chloromas':ti,ab OR 'cholangiocarcinoma':ti,ab OR 'cholangiocarcinomas':ti,ab OR 'cholangiohepatoma':ti,ab OR 'cholangioma':ti,ab OR 'cholangiomas':ti,ab OR 'cholangiosarcoma':ti,ab OR 'cholesteatoma':ti,ab OR 'cholesteatomas':ti,ab OR 'chondroblastoma':ti,ab OR 'chondroblastomas':ti,ab OR 'chondroma':ti,ab OR 'chondromas':ti,ab OR 'chondrosarcoma':ti,ab OR 'chondrosarcomas':ti,ab OR 'chordoma':ti,ab OR 'chordomas':ti,ab OR 'chorioadenoma':ti,ab OR 'chorioadenomas':ti,ab OR 'chorioangioma':ti,ab OR 'chorioangiomas':ti,ab OR 'choriocarcinoma':ti,ab OR 'choriocarcinomas':ti,ab OR 'chorioepithelioma':ti,ab OR 'chorioepitheliomas':ti,ab OR 'chorionepithelioma':ti,ab OR 'chorionepitheliomas':ti,ab OR 'choristoma':ti,ab OR 'choristomas':ti,ab OR 'chromaffinoma':ti,ab OR 'chromaffinomas':ti,ab OR 'cocarcinogenesis':ti,ab OR 'collagenoma':ti,ab OR 'collagenomas':ti,ab OR 'colonoscopies':ti,ab OR 'coloscopy':ti,ab OR 'coloscopies':ti,ab OR 'comedocarcinoma':ti,ab OR 'comedocarcinomas':ti,ab OR 'condyloma':ti,ab OR 'condylomas':ti,ab OR 'corticotropinoma':ti,ab OR 'corticotropinomas':ti,ab OR 'craniopharyngioma':ti,ab OR 'craniopharyngiomas':ti,ab OR 'cylindroma':ti,ab OR 'cylindromas':ti,ab OR 'cyst':ti,ab OR 'cysts':ti,ab OR 'cystadenocarcinoma':ti,ab OR 'cystadenocarcinomas':ti,ab OR 'cystadenofibroma':ti,ab OR 'cystadenofibromas':ti,ab OR 'cystadenoma':ti,ab OR 'cystadenomas':ti,ab OR 'cystoma':ti,ab OR 'cystomas':ti,ab OR 'cystosarcoma':ti,ab OR 'cystosarcomas':ti,ab OR 'dentinoma':ti,ab OR 'dentinomas':ti,ab OR 'dermatofibroma':ti,ab OR 'dermatofibromas':ti,ab OR 'dermatofibrosarcoma':ti,ab OR 'dermatofibrosarcomas':ti,ab OR 'dermoid':ti,ab OR 'desmoid':ti,ab OR 'desmoplastic':ti,ab OR 'dictyoma':ti,ab OR 'dysgerminoma':ti,ab OR 'dysgerminomas':ti,ab OR 'dyskeratoma':ti,ab OR 'dyskeratomas':ti,ab OR 'dysmyelopoiesis':ti,ab OR 'dysplasia':ti,ab OR 'dysplastic':ti,ab OR 'ectomesenchymoma':ti,ab OR 'ectomesenchymomas':ti,ab OR 'elastofibroma':ti,ab OR 'elastofibromas':ti,ab OR 'enchondroma':ti,ab OR 'enchondromas':ti,ab OR 'enchondromatosis':ti,ab OR 'endothelioma':ti,ab OR 'endotheliomas':ti,ab OR 'ependymoblastoma':ti,ab OR 'ependymoblastomas':ti,ab OR 'ependymoma':ti,ab OR 'ependymomas':ti,ab OR 'epidermoid':ti,ab OR 'epithelioma':ti,ab OR 'epitheliomas':ti,ab OR

2758 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'erythroleukaemia':ti,ab OR 'erythroleukaemias':ti,ab OR 'erythroleukemia':ti,ab OR 'erythroleukemias':ti,ab OR 'erythroplakia':ti,ab OR 'erythroplakias':ti,ab OR 'erythroplasia':ti,ab OR 'esthesioneuroblastoma':ti,ab OR 'esthesioneuroblastomas':ti,ab OR 'esthesioneuroepithelioma':ti,ab OR 'esthesioneuroepitheliomas':ti,ab OR 'exostosis':ti,ab OR 'fibroadenoma':ti,ab OR 'fibroadenomas':ti,ab OR 'fibroadenosarcoma':ti,ab OR 'fibroadenosis':ti,ab OR 'fibrochondrosarcoma':ti,ab OR 'fibroelastoma':ti,ab OR 'fibroelastomas':ti,ab OR 'fibroepithelioma':ti,ab OR 'fibroepitheliomas':ti,ab OR 'fibrofolliculoma':ti,ab OR 'fibrofolliculomas':ti,ab OR 'fibroid':ti,ab OR 'fibroids':ti,ab OR 'fibrolipoma':ti,ab OR 'fibrolipomas':ti,ab OR 'fibroliposarcoma':ti,ab OR 'fibroma':ti,ab OR 'fibromas':ti,ab OR 'fibromatosis':ti,ab OR 'fibromyoma':ti,ab OR 'fibromyomas':ti,ab OR 'fibromyxolipoma':ti,ab OR 'fibromyxoma':ti,ab OR 'fibromyxomas':ti,ab OR 'fibroodontoma':ti,ab OR 'fibroodontomas':ti,ab OR 'fibrosarcoma':ti,ab OR 'fibrosarcomas':ti,ab OR 'fibrothecoma':ti,ab OR 'fibrothecomas':ti,ab OR 'fibroxanthoma':ti,ab OR 'fibroxanthomas':ti,ab OR 'fibroxanthosarcoma':ti,ab OR 'fibroxanthosarcomas':ti,ab OR 'ganglioblastoma':ti,ab OR 'gangioblastomas':ti,ab OR 'gangliocytoma':ti,ab OR 'gangliocytomas':ti,ab OR 'ganglioglioma':ti,ab OR 'gangliogliomas':ti,ab OR 'ganglioneuroblastoma':ti,ab OR 'ganglioneuroblastomas':ti,ab OR 'ganglioneurofibroma':ti,ab OR 'ganglioneurofibromas':ti,ab OR 'ganglioneuroma':ti,ab OR 'ganglioneuromas':ti,ab OR 'gastrinoma':ti,ab OR 'gastrinomas':ti,ab OR 'germinoma':ti,ab OR 'germinomas':ti,ab OR 'glioblastoma':ti,ab OR 'glioblastomas':ti,ab OR 'gliofibroma':ti,ab OR 'gliofibromas':ti,ab OR 'glioma':ti,ab OR 'gliomas':ti,ab OR 'gliomatosis':ti,ab OR 'glioneuroma':ti,ab OR 'glioneuromas':ti,ab OR 'gliosarcoma':ti,ab OR 'gliosarcomas':ti,ab OR 'glomangioma':ti,ab OR 'glomangiomas':ti,ab OR 'glomangiomatosis':ti,ab OR 'glomangiomyoma':ti,ab OR 'glomangiomyomas':ti,ab OR 'glomangiosarcoma':ti,ab OR 'glomangiosarcomas':ti,ab OR 'glucagonoma':ti,ab OR 'glucagonomas':ti,ab OR 'gonadoblastoma':ti,ab OR 'gonadoblastomas':ti,ab OR 'gonocytoma':ti,ab OR 'gonocytomas':ti,ab OR 'granuloma':ti,ab OR 'granulomas':ti,ab OR 'granulomatosis':ti,ab OR 'gynaecomastia':ti,ab OR 'gynandroblastoma':ti,ab OR 'gynecomastia':ti,ab

2759

2760

2761 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	OR 'haemangioblastoma':ti,ab OR 'haemangioblastomas':ti,ab OR 'haemangioma':ti,ab OR 'haemangiomas':ti,ab OR 'haemangiopericytoma':ti,ab OR 'haemangiopericytomas':ti,ab OR 'haemangiosarcoma':ti,ab OR 'haemangiosarcomas':ti,ab OR 'hamartoma':ti,ab OR 'hamartomas':ti,ab OR 'hemangioblastoma':ti,ab OR 'hemangioblastomas':ti,ab OR 'hemangioendothelioma':ti,ab OR 'hemangioendotheliomas':ti,ab OR 'hemangioendotheliosarcoma':ti,ab OR 'hemangioendotheliosarcomas':ti,ab OR 'hemangioma':ti,ab OR 'hemangiomas':ti,ab OR 'hemangiomatosis':ti,ab OR 'hemangiopericytoma':ti,ab OR 'hemangiopericytomas':ti,ab OR 'hemangioperithelioma':ti,ab OR 'hemangiosarcoma':ti,ab OR 'hemangiosarcomas':ti,ab OR 'hepatoblastoma':ti,ab OR 'hepatoblastomas':ti,ab OR 'hepatocarcinoma':ti,ab OR 'hepatocarcinomas':ti,ab OR 'hepatocholangiocarcinoma':ti,ab OR 'hepatocholangiocarcinomas':ti,ab OR 'hepatoma':ti,ab OR 'hepatomas':ti,ab OR 'hibernoma':ti,ab OR 'hibernomas':ti,ab OR 'hidradenoma':ti,ab OR 'hidradenomas':ti,ab OR 'hidrocystoma':ti,ab OR 'hidrocystomas':ti,ab OR 'histiocytoma':ti,ab OR 'histiocytomas':ti,ab OR 'hodgkin':ti,ab OR 'hodgkins':ti,ab OR 'hydatidiform':ti,ab OR 'hydradenoma':ti,ab OR 'hydradenomas':ti,ab OR 'hypernephroma':ti,ab OR 'hypernephromas':ti,ab OR 'immunochemoradiotherapy':ti,ab OR 'immunochemotherapies':ti,ab OR 'immunochemotherapy':ti,ab OR 'immunocytoma':ti,ab OR 'immunoradiotherapy':ti,ab OR 'insulinomas':ti,ab OR 'integrative oncology':ti,ab OR 'kasabach-merritt':ti,ab OR 'keratoacanthoma':ti,ab OR 'keratoacanthomas':ti,ab OR 'keratosis':ti,ab OR 'leiomyoblastoma':ti,ab OR 'leiomyoblastomas':ti,ab OR 'leiomyofibroma':ti,ab OR 'leiomyofibromas':ti,ab OR 'leiomyoma':ti,ab OR 'leiomyomas':ti,ab OR 'leiomyomatosis':ti,ab OR 'leiomyosarcoma':ti,ab OR 'leiomyosarcomas':ti,ab OR 'leukaemia':ti,ab OR 'leukaemias':ti,ab OR 'leukemia':ti,ab OR 'leukemias':ti,ab OR 'leukoplakia':ti,ab OR 'leukoplakias':ti,ab OR 'lipoadenoma':ti,ab OR 'lipoadenomas':ti,ab OR 'lipoblastoma':ti,ab OR 'lipoblastomas':ti,ab OR 'lipoblastomatosis':ti,ab OR 'lipoma':ti,ab OR 'lipomas':ti,ab OR 'lipomatosis':ti,ab OR 'liposarcoma':ti,ab OR 'liposarcomas':ti,ab OR 'luteinoma':ti,ab OR 'luteoma':ti,ab OR 'luteomas':ti,ab OR 'lymphangioendothelioma':ti,ab OR

2762

2763 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'lymphangioendotheliomas':ti,ab OR 'lymphangioleiomyomatosis':ti,ab OR 'lymphangioma':ti,ab OR 'lymphangiomas':ti,ab OR 'lymphangiomatosis':ti,ab OR 'lymphangiomyoma':ti,ab OR 'lymphangiomyomas':ti,ab OR 'lymphangiomyomatosis':ti,ab OR 'lymphangiosarcoma':ti,ab OR 'lymphangiosarcomas':ti,ab OR 'lymphoepithelioma':ti,ab OR 'lymphoepitheliomas':ti,ab OR 'lymphoma':ti,ab OR 'lymphomas':ti,ab OR 'lymphoproliferation':ti,ab OR 'lymphoproliferations':ti,ab OR 'lymphoproliferative':ti,ab OR 'lymphoscintigraphic':ti,ab OR 'lymphoscintigraphy':ti,ab OR 'macroglobulinemia':ti,ab OR 'macroglobulinemias':ti,ab OR 'macroprolactinoma':ti,ab OR 'malignancies':ti,ab OR 'malignancy':ti,ab OR 'malignant':ti,ab OR 'maltoma':ti,ab OR 'maltomas':ti,ab OR 'mammogram':ti,ab OR 'mammograms':ti,ab OR 'masculinovoblastoma':ti,ab OR 'mastocytoma':ti,ab OR 'mastocytomas':ti,ab OR 'mastocytosis':ti,ab OR 'mcf-7':ti,ab OR 'medulloblastoma':ti,ab OR 'medulloblastomas':ti,ab OR 'medullocytoma':ti,ab OR 'medullocytomas':ti,ab OR 'medulloepithelioma':ti,ab OR 'medulloepitheliomas':ti,ab OR 'medullomyoblastoma':ti,ab OR 'medullomyoblastomas':ti,ab OR 'melanoacanthoma':ti,ab OR 'melanoacanthomas':ti,ab OR 'melanoameloblastoma':ti,ab OR 'melanocytoma':ti,ab OR 'melanocytomas':ti,ab OR 'melanoma':ti,ab OR 'melanomas':ti,ab OR 'melanomatosis':ti,ab OR 'meningioblastoma':ti,ab OR 'meningioma':ti,ab OR 'meningiomas':ti,ab OR 'meningiomatosis':ti,ab OR 'mesenchymoma':ti,ab OR 'mesenchymomas':ti,ab OR 'mesonephroma':ti,ab OR 'mesonephromas':ti,ab OR 'mesothelioma':ti,ab OR 'mesotheliomas':ti,ab OR 'metaplasia':ti,ab OR 'metastases':ti,ab OR 'metastasis':ti,ab OR 'metastatic':ti,ab OR 'microcarcinoma':ti,ab OR 'microcarcinomas':ti,ab OR 'microglioma':ti,ab OR 'microgliomas':ti,ab OR 'micrometastases':ti,ab OR 'micrometastasis':ti,ab OR 'mucositis':ti,ab OR 'myelodysplasia':ti,ab OR 'myelodysplasias':ti,ab OR'myelodysplastic':ti,ab OR 'myelofibrosis':ti,ab OR 'myelolipoma':ti,ab OR 'myelolipomas':ti,ab OR 'myeloma':ti,ab OR 'myelomas':ti,ab OR 'myelomatosis':ti,ab OR 'myeloproliferation':ti,ab OR' myoblastoma':ti,ab OR 'myoblastomas':ti,ab OR 'myoepithelioma':ti,ab OR 'myoepitheliomas':ti,ab OR'myeloproliferations':ti,ab OR 'myeloproliferative':ti,ab OR 'myelosuppression':ti,ab OR

2764

2765 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'myofibroblastoma':ti,ab OR 'myofibroblastomas':ti,ab OR 'myofibroma':ti,ab OR 'myofibromas':ti,ab OR 'myofibromatosis':ti,ab OR 'myofibrosarcoma':ti,ab OR 'myofibrosarcomas':ti,ab OR 'myolipoma':ti,ab OR 'myolipomas':ti,ab OR 'myoma':ti,ab OR 'myomas':ti,ab OR 'myopericytoma':ti,ab OR 'myosarcoma':ti,ab OR 'myosarcomas':ti,ab OR 'myxofibroma':ti,ab OR 'myxofibromas':ti,ab OR 'myxolipoma':ti,ab OR 'myxolipomas':ti,ab OR 'myxoliposarcoma':ti,ab OR 'myxoma':ti,ab OR 'myxomas':ti,ab OR 'naevus':ti,ab OR 'neoplasia':ti,ab OR 'neoplasm':ti,ab OR 'neoplasms':ti,ab OR 'neoplastic':ti,ab OR 'nephroblastoma':ti,ab OR 'nephroblastomas':ti,ab OR 'neurilemmoma':ti,ab OR 'neurilemmomas':ti,ab OR 'neurilemmomatosis':ti,ab OR 'neurilemoma':ti,ab OR 'neurilemomas':ti,ab OR 'neurinoma':ti,ab OR 'neurinomas':ti,ab OR 'neuroblastoma':ti,ab OR 'neuroblastomas':ti,ab OR 'neurocytoma':ti,ab OR 'neurocytomas':ti,ab OR 'neuroepithelioma':ti,ab OR 'neuroepitheliomas':ti,ab OR 'neurofibroma':ti,ab OR 'neurofibromas':ti,ab OR 'neurofibromatosis':ti,ab OR 'neurofibrosarcoma':ti,ab OR 'neurofibrosarcomas':ti,ab OR 'neurolipocytoma':ti,ab OR 'neuroma':ti,ab OR 'neuromas':ti,ab OR 'neuronevus':ti,ab OR 'neurothekeoma':ti,ab OR 'neurothekeomas':ti,ab OR 'nevus':ti,ab OR 'nonhodgkin':ti,ab OR 'nonhodgkins':ti,ab OR 'nonseminoma':ti,ab OR 'nonseminomas':ti,ab OR 'nonseminomatous':ti,ab OR 'odontoameloblastoma':ti,ab OR 'odontoma':ti,ab OR 'oligoastrocytoma':ti,ab OR 'oligoastrocytomas':ti,ab OR 'oligodendroglioma':ti,ab OR 'oligodendrogliomas':ti,ab OR 'oncocytoma':ti,ab OR 'oncocytomas':ti,ab OR 'oncogen':ti,ab OR 'oncogene':ti,ab OR 'oncogenes':ti,ab OR 'oncogenesis':ti,ab OR 'oncogenic':ti,ab OR 'oncogens':ti,ab OR 'oncologic':ti,ab OR 'oncologist':ti,ab OR 'oncologists':ti,ab OR 'oncology':ti,ab OR 'oncoprotein':ti,ab OR 'oncoproteins':ti,ab OR 'opsoclonus-myoclonus':ti,ab OR 'orchioblastoma':ti,ab OR 'orchioblastomas':ti,ab OR 'osteoblastoma':ti,ab OR 'osteoblastomas':ti,ab OR 'osteochondroma':ti,ab OR 'osteochondromas':ti,ab OR 'osteochondrosarcoma':ti,ab OR'osteochondrosarcomas':ti,ab OR 'osteoclastoma':ti,ab OR 'osteoclastomas':ti,ab OR 'osteofibrosarcoma':ti,ab OR 'osteoma':ti,ab OR 'osteomas':ti,ab OR 'osteosarcoma':ti,ab OR' osteosarcomas':ti,ab OR 'pancreatoblastoma':ti,ab OR 'pancreatoblastomas':ti,ab OR 'papilloma':ti,ab OR 'papillomas':ti,ab OR 'papillomata':ti,ab OR 'papillomatosis':ti,ab OR 'papillomavirus':ti,ab OR

2766

2767 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'papillomaviruses':ti,ab OR 'parachordoma':ti,ab OR 'parachordomas':ti,ab OR 'paraganglioma':ti,ab OR 'paragangliomas':ti,ab OR 'paraneoplastic':ti,ab OR 'perineurioma':ti,ab OR 'perineuriomas':ti,ab OR 'phaeochromocytoma':ti,ab OR 'phaeochromocytomas':ti,ab OR 'pheochromoblastoma':ti,ab OR 'pheochromoblastomas':ti,ab OR 'pheochromocytoma':ti,ab OR 'pheochromocytomas':ti,ab OR 'pilomatricoma':ti,ab OR 'pilomatricomas':ti,ab OR 'pilomatrixoma':ti,ab OR 'pilomatrixomas':ti,ab OR 'pinealblastoma':ti,ab OR 'pinealoblastoma':ti,ab OR 'pinealoblastomas':ti,ab OR 'pinealoma':ti,ab OR 'pinealomas':ti,ab OR 'pineoblastoma':ti,ab OR 'pineoblastomas':ti,ab OR 'pineocytoma':ti,ab OR 'pineocytomas':ti,ab OR 'plasmacytoma':ti,ab OR 'plasmacytomas':ti,ab OR 'pneumoblastoma':ti,ab OR 'pneumoblastomas':ti,ab OR 'pneumocytoma':ti,ab OR 'polyembryoma':ti,ab OR 'polyembryomas':ti,ab OR 'polyhistioma':ti,ab OR 'polyhistiomas':ti,ab OR 'polyp':ti,ab OR 'polyposis':ti,ab OR 'polyps':ti,ab OR 'porocarcinoma':ti,ab OR 'porocarcinomas':ti,ab OR 'poroma':ti,ab OR 'poromas':ti,ab OR 'precancer':ti,ab OR 'precancerous':ti,ab OR 'preleukaemia':ti,ab OR 'preleukaemias':ti,ab OR 'preleukemia':ti,ab OR 'preleukemias':ti,ab OR 'premalignant':ti,ab OR 'preneoplastic':ti,ab OR 'prolactinoma':ti,ab OR 'prolactinomas':ti,ab OR 'protooncogene':ti,ab OR 'protooncogenes':ti,ab OR 'pseudotumor':ti,ab OR 'pseudotumors':ti,ab OR 'radiochemotherapy':ti,ab OR 'radioimmunotherapies':ti,ab OR 'radioimmunotherapy':ti,ab OR 'reninoma':ti,ab OR 'reninomas':ti,ab OR 'reticuloendothelioma':ti,ab OR 'reticuloendotheliomas':ti,ab OR 'reticulohistiocytoma':ti,ab OR 'reticulohistiocytomas':ti,ab OR 'reticulosis':ti,ab OR 'retinoblastoma':ti,ab OR 'retinoblastomas':ti,ab OR 'rhabdomyoma':ti,ab OR 'rhabdomyomas':ti,ab OR 'rhabdomyosarcoma':ti,ab OR 'rhabdomyosarcomas':ti,ab OR 'rhabdosarcoma':ti,ab OR 'rhabdosarcomas':ti,ab OR 'sarcoma':ti,ab OR 'sarcomas':ti,ab OR 'sarcomatosis':ti,ab OR 'schwannoma':ti,ab OR 'schwannomas':ti,ab OR 'schwannomatosis':ti,ab OR 'seminoma':ti,ab OR 'seminomas':ti,ab OR 'seminomatous':ti,ab OR 'somatostatinoma':ti,ab OR 'somatostatinomas':ti,ab OR 'somatotropinoma':ti,ab OR 'somatotropinomas':ti,ab OR 'spermatocytoma':ti,ab OR 'spiradenoma':ti,ab OR 'spiradenomas':ti,ab OR 'spongioblastoma':ti,ab OR 'spongioblastomas':ti,ab OR 'steatocystoma':ti,ab OR 'steatocystomas':ti,ab OR 'subependymoma':ti,ab OR

2768

2769 **Table A5. List of search terms used for animal studies using Embase (continued).**

Step/ Category	Search Terms
PubMed Cancer Strategy (continued)	'subependymomas':ti,ab OR 'syringadenoma':ti,ab OR 'syringadenomas':ti,ab OR 'syringocystadenoma':ti,ab OR 'syringocystadenomas':ti,ab OR 'syringoma':ti,ab OR 'syringomas':ti,ab OR 'teratocarcinoma':ti,ab OR 'teratocarcinomas':ti,ab OR 'teratoma':ti,ab OR 'teratomas':ti,ab OR 'thecoma':ti,ab OR 'thecomas':ti,ab OR 'thymolipoma':ti,ab OR 'thymolipomas':ti,ab OR 'thymoma':ti,ab OR 'thymomas':ti,ab OR 'trichilemmoma':ti,ab OR 'trichilemmomas':ti,ab OR 'trichoadenoma':ti,ab OR 'trichoblastoma':ti,ab OR 'trichoblastomas':ti,ab OR 'trichodiscoma':ti,ab OR 'trichodiscomas':ti,ab OR 'trichoepithelioma':ti,ab OR 'trichoepitheliomas':ti,ab OR 'trichofolliculoma':ti,ab OR 'trichofolliculomas':ti,ab OR 'tricholemmoma':ti,ab OR 'tricholemmomas':ti,ab OR ('tumor':ti,ab OR 'tumors':ti,ab OR 'tumour':ti,ab OR 'tumours':ti,ab) NOT ('tnf':ti,ab OR 'necrosis factor':ti,ab) OR 'tumorgenesis':ti,ab OR 'tumorgenic':ti,ab OR 'tumorigenesis':ti,ab OR 'tumorigenic':ti,ab OR 'tumorogenesis':ti,ab OR 'tumorogenic':ti,ab OR 'vipoma':ti,ab OR 'vipomas':ti,ab OR 'waldenstrom':ti,ab OR 'waldenstroms':ti,ab OR 'xanthoastrocytoma':ti,ab OR 'xanthoastrocytomas':ti,ab OR 'xanthofibroma':ti,ab OR 'xanthofibromas':ti,ab OR 'xanthogranuloma':ti,ab OR 'xanthogranulomas':ti,ab OR 'xanthoma':ti,ab OR 'xanthomas':ti,ab OR 'xanthosarcoma':ti,ab OR 'xanthosarcomas':ti,ab)
3. Combine chemical and cancer terms	(#1 AND #2) NOT ('poly(ethylene oxide)':ti,ab OR 'poly (ethylene oxide)':ti,ab)
4. Experimental animal terms	('transgenic animal'/exp OR 'inbred strain'/de OR 'Chimera'/de OR 'experimental animal'/exp OR 'animal model'/exp OR 'animal experiment'/de) OR ('animal stud*':ti,ab OR 'wood mouse':ti,ab OR murinae:ti,ab OR muridae:ti,ab OR cricetinae:ti,ab OR rodentia:ti,ab OR rodent:ti,ab OR rodents:ti,ab OR ferrets:ti,ab OR ferret:ti,ab OR polecat*:ti,ab OR 'Mustela putorius':ti,ab OR cavia:ti,ab OR callithrix:ti,ab OR marmoset*:ti,ab OR chinchilla*:ti,ab OR jird:ti,ab OR jirds:ti,ab OR merione:ti,ab OR meriones:ti,ab OR cats:ti,ab OR cat:ti,ab OR felis:ti,ab OR canis:ti,ab OR sheep:ti,ab OR sheeps:ti,ab OR goats:ti,ab OR goat:ti,ab OR capra:ti,ab OR saguinus:ti,ab OR tamarin*:ti,ab OR leontopithecus:ti,ab OR ape:ti,ab OR apes:ti,ab OR 'pan paniscus':ti,ab OR bonobo*:ti,ab OR 'pan

Table A5. List of search terms used for animal studies using Embase (continued).

Step/ Category	Search Terms
4. Experimental animal terms (continued)	troglodytes':ti,ab OR gibbon*:ti,ab OR siamang*:ti,ab OR nomascus:ti,ab OR symphalangus:ti,ab OR chimpanzee*:ti,ab OR orangutan*:ti,ab OR horse:ti,ab OR horses:ti,ab OR equus:ti,ab OR cow:ti,ab OR cows:ti,ab OR chicken:ti,ab OR chickens:ti,ab OR wistar:ti,ab OR balb:ti,ab OR C57:ti,ab OR C57bl:ti,ab OR quail:ti,ab OR 'long-evans':ti,ab OR guppy:ti,ab OR medaka:ti,ab OR zebrafish:ti,ab OR 'danio rerio':ti,ab OR 'fish':ti,ab OR 'flying fox':ti,ab OR 'Fruit bat':ti,ab OR 'non human primate*':ti,ab OR capuchin*:ti,ab OR rhesus:ti,ab OR macaque*:ti,ab OR cattle:ti,ab OR bovine:ti,ab OR porcine:ti,ab OR pigs:ti,ab OR pig:ti,ab OR swine:ti,ab OR swines:ti,ab OR piglet*:ti,ab OR 'Sprague-Dawley':ti,ab OR vervet*:ti,ab) OR 'animal tissue, cells or cell components'/exp
5. Combine chemical, cancer and animals	#3 A9:B10AND #4

2772 **Table A6. Animal studies search structure (SciFinder-N).**

Search step	Search Concepts
1	CAS # 75-21-8
2	Limit to Journal Article
3	Limit to animal concept, animals, rat, rats, mice
4	Limit to Database "CAplus"

2773

2774

ATTACHMENT B

Table B1. Studies tagged as supplemental information during screening performed in April 2026.

Reference	Source (animal/human search)	Supplemental information category
Jo JH, Claudine U, Jang SI, Jung EJ, Lee WJ, Bae JW, Kim D, Moon J, Nam SW, Chung EJ, Yi J, Kwon WS. Ethylene oxide impairs sperm motility through dysregulation of Rab proteins. Reprod Toxicol. 2026 Mar;140:109168. doi: 10.1016/j.reprotox.2026.109168. Epub 2026 Jan 12.	Animal	Non-cancer outcome
Lin YS, Morozov V, Wu KY. Integrating PBPK modeling and tobacco biomarkers to interpret N-(2-hydroxyethyl)valine (HEV) hemoglobin adducts in the U.S. population. Int J Hyg Environ Health. 2026 Mar;272:114721. doi: 10.1016/j.ijheh.2025.114721. Epub 2025 Dec 17. PMID: 41406903.	Animal and Human	TK or PBPK models
Lin YS, Thayer KA, White P, Morozov V, and Persad AS (2025). Uncovering the connection: ethylene exposure and endogenous ethylene oxide levels in humans. *J Expo Sci Environ Epidemiol*. 36: 361-374. DOI: 10.1038/s41370-025-00826-7.	Animal and Human	TK or PBPK models
Picciotto S, Kelly-Reif K, Eisen EA, Stayner LT, Costello S. How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. Am J Epidemiol. 2026 Mar 9:kwag052. doi: 10.1093/aje/kwag052. Epub ahead of print. PMID: 41800785.	Human	No original data

Abbreviations: TK – Toxicokinetics; PBPK models – Physiological based Pharmacokinetics models

2780

ATTACHMENT C

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026[a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	OEHHA's Finding
1	Georgia Comprehensive Cancer Registry	Ecologic	N/A	EPA Toxic Release Inventory	N/A	Diffuse large B-Cell lymphoma incidence	Age, sex, race	Rate ratio = 0.9968 for each 1 mile of increasing distance to an EtO source ($p < 0.001$) Focal clustering around 57% of EtO sites	No	Temporality issues; inadequate exposure assessment; no consideration of confounding
2	Illinois State Cancer Registry	Ecologic	N/A	National Air Toxics Assessment	N/A	Invasive breast cancer incidence	Age	Ratio of $mean_G$ = 1.086 ($p = 0.001$)	No	Temporality issues; inadequate exposure assessment; no consideration of confounding

Abbreviations: EPA – Environmental Protection Agency (US); $mean_G$ – geometric mean; Ref – reference.
References (first author, year): 1 – Bulka (2016); 2 – Chen (2018).
[a] All studies identified were performed in the United States.
[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026 (continued) [a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	Reason for exclusion
3	Nurses' Health Study (NHS) I and II	Cohort	204,788	National Air Toxics Assessment	Median (IQR), ng/m^3 NHS I: 4.70 (2.59–8.10). NHS II: 5.13 (2.87–7.98).	Non-Hodgkin lymphoma, lymphoma subtypes, multiple myeloma incidence	Age, race, BMI, smoking, diet, alcohol, physical activity, marital status, education, occupation, income, region, area-level SES, population density, and others	HR = 1.00 (95% CI = 0.97, 1.03) for all non-Hodgkin's lymphomas. No obvious differences by lymphoma subtype or for multiple myeloma	No	Inadequate exposure assessment; no exposure-response information
4	California Teachers Study	Cohort	112,378	National Air Toxics Assessment	Median (min, max) µg/m^3 approximated from figure: 1E-2 (1E-3, 1E0)	Invasive breast cancer incidence	Age, race	HR = 1.00 (95% CI = 0.92, 1.08) in the upper quintile (not defined)	Yes	Inadequate exposure assessment; potential confounding biases

Abbreviations: BMI – body-mass index; CI – confidence interval; HR – hazard ratio; IQR – inter-quartile range; µg/m^3 – micrograms per cubic meter; ng/m^3 – nanograms per cubic meter; NHS – Nurses' Health Study; SES – socioeconomic status.
References (first author, year): 3 – Chen (2024); 4 – Garcia (2015).
[a] All studies identified were performed in the United States.
[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026 (continued) [a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	Reason for exclusion
5	NHS II	Cohort	109,239	National Air Toxics Assessment	Median (IQR), μg/m^3: 5.25E-03 (2.90E-03, 8.21E-03)	Invasive breast cancer incidence	Age, race, family history, menarche, parity, menopause, hormone use, BMI, smoking, physical activity, diet, alcohol, SES, others	HR = 1.04 (95% CI = 0.94, 1.15) in the upper quartile (not defined). No obvious difference by ER status	Yes	Inadequate exposure assessment
6	Sister Study	Cohort	46,150	EPA Toxic Release Inventory	Prevalence of residential proximity to emissions, n (%) within 3 km: 481 (1.0)	Total breast cancer incidence	Age, year of enrollment, race/ethnicity, educational attainment, census region, area deprivation index	HR=0.8 (95% CI = 0.6, 1.1) comparing those with residential proximity to EtO emissions within 3 km to those without; No obvious difference for ER+ noted	Yes	Inadequate exposure assessment

Abbreviations: BMI – body-mass index; CI – confidence interval; EPA – Environmental Protection Agency (US); ER – estrogen receptor; HR – hazard ratio; IQR – inter-quartile range; NHS – Nurses' Health Study; SES – socioeconomic status.
References (first author, year): 5 – Hart (2018); 6 – Ish (2025).
[a] All studies identified were performed in the United States.
[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026 (continued) [a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	Reason for exclusion
7	National Health and Nutrition Examination Survey	Cross-sectional	5381	Hemoglobin EtO	$Mean_G$ (95% CI), pmol/g-Hb 20+ years: 41.7 (38.7–44.9)	Ever diagnosed with any cancer; ever diagnosed with breast cancer	Gender, race/ethnicity, age, poverty-income ratio, smoking	β = -0.01511 (*p* = 0.34) for any cancer diagnosis; β = 0.02118 (*p* = 0.52) for female breast cancer diagnosis	No	Temporality issues; no exposure response information
8	National Institutes of Health-American Association of Retired Persons Diet and Health Study	Cohort	173,648	EPA Toxic Release Inventory	N/A	Breast cancer and non-Hodgkin lymphoma incidence	State, age, race/ethnicity, smoking	All breast cancer: HR = 1.14 (95% CI = 0.91, 1.45) for highest quartile of AEI ≤3 km. Risk increased for DCIS; non-Hodgkin lymphoma: HR = 0.76 (95% CI = 0.52, 1.13) for highest quartile of AEI ≤3 km	Yes	Inadequate exposure assessment

Abbreviations: AEI – average emission index; β – regression coefficient; CI – confidence interval; DCIS – ductal carcinoma *in situ*; EPA – Environmental Protection Agency (US); HR – hazard ratio; $Mean_G$ – geometric mean; pmol/g-Hb – picomoles per gram of hemoglobin.
References (first author, year): 7 – Jain (2020); 8 – Jones (2023).
[a] All studies identified were performed in the United States.
[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026 (continued) [a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	Reason for exclusion
9	NIOSH cohort, medical supply and spice sterilization facilities	Cohort	7549	Individual exposure samples and validated exposure prediction modeling	Median (IQR), ppm-days 3056 (865, 9712)	Breast cancer mortality	Birth cohort, duration of employment, race, parity, menopause, OCs, mammogram, sex (all female)	Provided in the text of the main document	Yes	Advanced to detailed evaluations
10	NIOSH cohort, medical supply and spice sterilization facilities	Cohort	17,185	Individual exposure samples and validated exposure prediction modeling	Mean ± SD, ppm-years: 25.6 ± 62.1	Lung, breast, and lymphopoietic cancer mortality, nonmalignant respiratory disease	Age, cumulative EtO or employment duration, gender, race, lagged exposure	Focus was on the healthy worker effect	No	Incomplete methods used

Abbreviations: IQR – inter-quartile range; NIOSH – National Institute of Occupational Safety and Health; OC – oral contraceptive; SD – standard deviation.
References (first author, year): 9 – Kelly-Reif (2025); 10 – Park (2020).
[a] All studies identified were performed in the United States.
[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

Table C1. Epidemiologic studies of ethylene oxide and cancer identified in OEHHA's updated literature search: January 1, 2016 to April 2026 (continued) [a,b].

Ref	Participants	Study design	N	Exposure assessment	Average exposure levels	Specific outcomes	Confounders	Summary of results	Dose response assessed	Reason for exclusion
11	Union Carbine Corporation	Cohort	2053	Estimates from literature (1940–1956); 1957–1988 routine monitoring, personal sampling	ppm-years: 67	Lymphoid cancer mortality; all mortality causes	Age, sex (all male)	Provided in the text of the main document	Yes	Advanced to detailed evaluations

References (first author, year): 11 – Valdez-Flores (2025).

[a] All studies identified were performed in the United States.

[b] OEHHA's findings regarding study exclusion or advancement for detailed study evaluations and consideration in exposure-response or IUR calculations are presented in the final column. If a study was excluded, the reason why is provided. These reasons are discussed in further detail in the text of the main document.

2781

ATTACHMENT D

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a].

STUDY	NIOSH	UCC	Sweden
Design			
Design Description	Longitudinal cohort study; 18,235 male and female workers from 13 US sterilization facilities; includes workers who worked at least 3–12 months at one of the facilities; follow-up through 1998 (lymphoid cancer) and 2021 (breast cancer); average or median follow-up of 26.8 years for lymphoid cancer and approximately 44 years for breast cancer	Longitudinal cohort study; 2053 male workers at 2 chemical production facilities in West Virginia; includes workers active or hired from 1940 to 1988; follow-up through 2013	Longitudinal cohort study; 2171 male and female workers employed at least 1 year before 1986; follow-up 1972–2006; two Swedish plants producing medical equipment sterilized with EtO
Design Description	High	High	High
Temporality	High	High	High
Selection			
Selection Methods	All male and female workers working at least 3 or 12 months; exposure-response analyses included 17,530 workers (96%); SMRs and/or SIRs reported by exposure level; important aspects of HWSE assessed but not G-methods; separate analyses by sex; no issues with generalizability	All workers active or hired from 1940 to 1988; 278 chlorohydrin production workers excluded; 10 part time workers excluded; only includes male workers; SMRs reported by exposure level (Swaen et al., 2009); no HWSE assessment but UCB assessment suggests this is moderate; males only but no other generalizability issues	All male and female workers employed at least 1 year prior to 1986; SIRs not SMRs reported by exposure level; no HWSE assessment but UCB assessment suggests this is moderate; separate analyses not done by sex; no generalizability issues

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Participation rates	Low percentage of excluded workers (e.g., without exposure information); 233 (73%) of 319 incident breast cancer cases had interview data; interview rates among cases and controls were 73% and 68%, respectively; likely bias (if short-term workers less likely to be interviewed) is towards the null and relatively small	No obvious bias related to initial participation or follow-up	151 workers (7.0%) without data on cumulative exposure; no obvious bias related to initial participation or follow-up
Susceptible subgroups	None identified	None identified	None identified
Methods	High	High	High
Inclusion rates	High	High	High
HHE	High	High	Adequate
SWSE	Adequate	Low	Low
Both Sexes	High	Critical	Low
Susceptible Groups	High	High	High
Generalizable	High	High	High

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Outcome			
Outcome: Description	Includes both lymphoid cancer (mortality only) and breast cancer (incidence and mortality); information on vital status, cause of death, or breast cancer incidence obtained from National Death Index, Social Security Administration, Internal Revenue Service, Lexus Nexus, cancer registries, medical records, and interviews	Mortality only; information on vital status and cancer obtained from the Social Security Administration, the National Death Index, state vital status records, and genealogical sources; average follow-up is 41 years and the authors acknowledge that "longer postexposure follow-up could potentially make it more difficult to distinguish background disease from exposure-related disease;" results for shorter follow-up previously reported; no female breast cancer cases	Mortality and incidence results although mortality results are limited; information on vital status and cause of death obtained from the Statistics Sweden, the Swedish Cancer Registry, and the Swedish population registry; includes breast cancer and lymphohematopoietic cancers but not the subgroup of lymphoid cancer; average follow-up is unclear although analyses stratified by follow-up years are presented
Power	Good statistical power for both lymphoid (N = 53 deaths) and breast cancer (N = 181 deaths and 233 incident cases) analyses	No breast cancer cases; the number of lymphoid cases (N = 25 total) may be too small for precise categorical analyses involving lag periods	Only 18 lymphohematopoietic cancers; separate analyses of lymphoid cancer not presented; only 33 breast cancer cases with 15-year latency
Methods	High	High	High
Relevant Outcome #1	High	High	Critical
Relevant Outcome #2	High	Critical	High
Power #1	High	Adequate	Low
Power #2	High	Critical	Adequate
Follow-up	High	Adequate	Adequate
Incidence and Mortality	Adequate	Low	Adequate

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Exposure			
Exposure: Description	Modeled exposure based on workplace air measurements, sterilization unit size, engineering controls, timing of sterilization, product type, calendar year, and historical process changes; the workplace air measurements included 2700 individual time-weighted exposure values for workers' personal breathing zones, acquired between 1976 and 1985 from 18 different sterilization facilities; no information on blinding but specific and objective methods used; the R^2 value between model estimated and measured values was 0.85 (Hornung, 1994)	Modeled exposure based on interviews, department dictionaries, process manuals, production records, EtO measurements from 1976–1978, measurements from other facilities, broad job categorizations, non-specific multipliers, and other factors (Swaen, 2009); several details not provided; accuracy of non-specific multipliers is unclear; comparability of other facilities is unclear; information on average exposure not provided; no information on blinding but somewhat specific and objective methods used	Estimates for six job categories based on a small number of EtO measurements available from 1973–1975, major changes in production methods and environmental control, "subjective memories", and fitted time trends; this information was linked to work histories to estimate average daily exposure for each year worked from 1964–1986 (Hagmar, 1991); no information on blinding but somewhat specific and objective methods used; overall, poorly described with few details
Validation	Model validated against 46 average EtO air measurements from the same facilities which were not used in the original model; model results are clear; no data prior to 1976 for validation	Non-specific information about, "Medical records of acute exposures to EtO support the ranking scheme with respect to the frequency of inhalation and dermal exposures." (Greenberg, 1990); no comparison of model estimates to known values	Very broad categories of estimated exposure levels were compared to exposure levels estimated using hydroxyethyl adducts to N-terminal valine in hemoglobin; the validity of this method is unclear; involves only small numbers of study participants (n = 4–16)

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Exposure Range	Cumulative exposure: median = 2044 ppm-days, mean = 9818 ppm-days, 75th percentile = 8486 ppm-days; average exposure intensity = 3–5 ppm; overall: there appears to be a good range in cumulative exposure and exposure intensity	Cumulative exposure: median = 7480 ppm-days, mean = 24,455 ppm-days, 75th percentile = 28,224 ppm-days; information on average exposure intensity not provided; overall: there appears to be a good range in cumulative exposure although details on exposure intensity are lacking	Cumulative exposure: median = 0.13 ppm-years (47.5 ppm-days), mean = 2.92 ppm-years, 75th percentile = 0.21 ppm-years; highest: 40–75 ppm although these may have been rare and short-term; average exposure intensity: no information; overall: exposures appear to be relatively low compared to other studies
Exposure Assessment	Adequate	Low	Low
Validation	Adequate	Critical	Critical
Exposure Range	High	Adequate	Low
Researcher/Recall Bias	Adequate	Adequate	Adequate
Statistics			
Statistics: Description	Multiple models assessed; categorical and continuous results presented; internal analyses presented; some demographic comparisons provided for breast cancer (Steenland, 2003; Table 2), limited demographic data for lymphoid cancer (US EPA, 2016; Tables D-55 to 60); exposure-response fully assessed; no concerns regarding missing data or outlying values	Few individual models assessed; categorical results not provided for lagged analyses; internal analyses presented; demographic comparisons by exposure or case status not provided in Valdez. (2025); no concerns regarding missing data; unclear if lagged analyses could be impacted by outlying values	Few models assessed; no continuous data analyses but impacts likely only minor or moderate; internal analyses performed; limited demographic comparisons by exposure levels provided in their Table 2 (age, gender, employment history); no concerns regarding missing data or outlying values

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Lag Periods	Multiple lag periods assessed for relevant analyses; lag periods applied to categorical and continuous data analyses	Multiple lag periods assessed but results only presented as maximum likelihood estimates and associated statistics	15 year lag assessed but only applied to external comparison results; unclear if there is sufficient statistical power for lagged exposure-response analyses
Statistical Analysis	High	Adequate	Adequate
Categorical or Continuous Data	High	Low	Low
Internal Analyses	High	High	High
Lag Periods	High	Low	Low
Demographic Comparisons	Adequate	Critical	Adequate
Exposure-response	High	High	High
Multiple Comparisons	High	High	High
Clear Results	High	High	High
Missing Data	High	High	High
Outlying Values	High	Low	High
Confounding			
Confounder Control	Age, sex (stratified, restricted), race, date of birth, calendar time	Age, sex (restricted)	Age, sex, calendar period

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Confounding: Other	A major advantage of the study design is that this study took place in facilities without high exposures to other known carcinogens; limited unadjusted results but impact of adjustments likely minor	278 workers in the chlorohydrin unit who were not involved in EtO production were excluded; a variety of other chemical exposures in EtO areas were noted by Greenberg 1990; carcinogenic exposures in the low EtO exposure group could bias EtO RRs towards the null; not adjusted by race since race was unknown in a "substantial number" of participants; limited unadjusted results but impact of adjustments likely minor	A major advantage of the study design is that this study took place in facilities without high exposures to other known carcinogens; limited unadjusted results but impact of adjustments likely minor
Age and Sex	High	High	High
Other Confounder Control	High	Low	High
Adjusted-Unadjusted	Adequate	Adequate	Adequate
Other			
Conflict of Interest	Primarily government funded	Multiple potential conflicts of interest cited	Appears to be university funded (Metalund project at Lund University)
Selective reporting	No obvious missing results	No obvious missing results	No obvious missing results
Conflict of Interest	High	Critical	High
Selective Reporting Score	High	High	High

Table D1. Study quality evaluation of the epidemiologic occupational studies of ethylene oxide and cancer with information on exposure-response[a] (continued).

STUDY	NIOSH	UCC	Sweden
Overall rating: description	A few weaknesses were identified (modeled exposure, limited demographic comparisons, no lymphoid cancer incidence data) but these were all minor and not expected to have more than minimal impacts on hazard identification or exposure-response assessments	Several moderate and important weaknesses identified including questionable exposure assessment and validation, limited statistical power for lagged analyses, and lack of information on breast cancer	Several moderate and important weaknesses identified including non-specific exposure assessment, limited exposure validation, small sample sizes and low statistical power, and limited range of exposure
Overall rating	**High**	**Low**	**Low**

[a] Rows with text colored in black are used to enter the information that support or justify the rating given to each criterion. Rows with text colored in red are the final quality ratings for each criterion and are to be coded only as “High”, “Adequate”, “Low”, or “Critical” or left blank (if they are not relevant). Study Quality Rating Instructions and Guidance are provided in Attachment E.

Abbreviations: EtO – ethylene oxide; HHE – healthy hire effect; HWSE – healthy worker survivor effect; NIOSH – National Institute for Occupational Safety and Health; RR – relative risk estimate; SIR – standardized incidence ratios; SMR – standardized mortality ratio; U CB – University of California Berkeley; UCC – Union Carbide Corporation

REFERENCES

NIOSH cohort studies

Hornung RW, Greife AL, Stayner LT, Steenland NK, Herrick RF, Elliott LJ, Ringenburg VL, and Morawetz J (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. Am J Ind Med. 25(6): 825–836. DOI: 10.1002/ajim.4700250607

Steenland K, Whelan E, Deddens J, Stayner L, and Ward E (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control*. 14(6): 531–539. DOI: 10.1023/a:1024891529592

Steenland K, Stayner L, and Deddens J (2004). Mortality analyses in a cohort of 18235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. *Occup Environ Med*. 61(1): 2–7

Kelly-Reif K, Bertke SJ, Stayner L, and Steenland K (2025). Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort. Environ Health Perspect. 133(5): 57013. DOI: 10.1289/EHP15566. Last accessed Feb. 26, 2026, from https://pmc.ncbi.nlm.nih.gov/articles/PMC12097532/pdf/ehp15566.pdf

UCC Studies

Greenberg HL, Ott MG, and Shore RE (1990). Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. *Br J Ind Med*. 47(4): 221–230. DOI: 10.1136/oem.47.4.221

Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, and Bodnar CM (2009). Mortality study update of ethylene oxide workers in chemical manufacturing: A 15 year update. *J Occup Environ Med*. 51(6): 714–723. DOI: 10.1097/JOM.0b013e3181a2ca20

Valdez-Flores C, Li AA, Bender TJ, and Teta MJ (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Anal*. 45(9): 2822–2837. DOI: 10.1111/risa.70057. Last accessed Feb. 26, 2026, from https://onlinelibrary.wiley.com/doi/epdf/10.1111/risa.70057

Sweden Studies

Mikoczy Z, Tinnerberg H, Björk J, and Albin M (2011). Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: Updated cohort study findings 1972–2006. Int J Environ Res Public Health. 8(6): 2009–2019. DOI: 10.3390/ijerph8062009

Hagmar L, Welinder H, Lindén K, Attewell R, Osterman-Golkar S, and Törnqvist M (1991). An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. *Int Arch Occup Environ Health*. 63(4): 271–277. DOI: 10.1007/bf00386377

ATTACHMENT E

Study Quality Ratings Instructions and Guidance

Introduction

The goal of this rating system is to judge study quality. It was not designed to judge the overall strength of an association. As such, criteria such as statistical significance, the magnitude of the association, or the presence of consistency across outcomes or studies are not specifically rated here. These criteria are evaluated elsewhere. Bias is evaluated here in the context of study quality since a high likelihood of bias or a high uncertainty regarding bias will generally be associated with low study quality.

Sources

The criteria and ratings included here are based on the following sources:

- The Austin Bradford Hill criteria for causal inference (Hill, 1965)
- Modern Epidemiology II (Greenland, 1998)
- National Toxicology Program's Office of Health Assessment and Translation's (OHAT) 2015 Risk of Bias Rating Tool for Human and Animal Studies (NTP, 2015)
- National Toxicology Program's 2019 Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (NTP, 2019)
- Cochran Collaborations Risk of Bias in Non-randomized Studies – of exposure (ROBINS-E) (Higgins et al., 2024)
- US EPA's Health Assessment Workspace Collaborative (HAWC) Risk of Bias criteria (US EPA, 2025)
- US EPA's 2021 Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments (US EPA, 2021)
- OEHHA's 2025 PFHpA draft Public Health Goal (unpublished)

Instructions

The actual ratings are entered into the accompanying Excel spreadsheet. The document presented here provides instructions and guidance for entering the information and ratings into the Excel spreadsheet. This document as well as the Excel spreadsheet list major criteria headings (e.g., “DESIGN”) as well as subheadings within each major criteria (e.g., “Temporality”, “Design”). There are two general types of rows in the Excel spreadsheet:

- Rows with text colored in black: These are used to enter the information that support or justify the rating given to each criterion

- Rows with text colored in red: These are the final quality ratings for each criterion and are to be coded only as “High”, “Adequate”, “Low”, or “Critical” or left blank (if they are not relevant)

The goal of this document is to list of some of the more common issues or scenarios that should be considered for each criteria rating, and to provide some general guidance or examples for when a criterion should be rated as “High”, “Adequate”, “Low”, or “Critical”. The lists of examples are not exhaustive and may change depending on the exposure and outcome under consideration. In other words, they are meant to provide general guidance rather than to be strict rules. Exceptions may apply and these exceptions can be justified in the appropriate cell in the Excel spreadsheet. This document was primarily written to apply to human studies of EtO and cancer and may not apply to other topics. Reviewers are expected to use their expert judgement when making these ratings.

Notes

- Avoid rating any single weakness twice (i.e., avoid “double counting” a weakness). For example, failure to blind the researchers should be rated in the “Reviewer/recall bias” criteria and not in the “Exposure” or “Outcome” criteria.

- Some ratings of “critical” will represent serious flaws (i.e., the study has essentially no validity and is not used for hazard identification or exposure-response assessment) while others may not (i.e. the study may be considered for some purposes but would be given relatively little weight in the evidence integration or exposure-response stages).

- Some of the criteria used here will involve risk of bias evaluations since studies that have design elements or procedures that cause a high risk of bias are generally deemed to be of low study quality. Importantly though, this quality scoring table is not limited to risk of bias evaluations since the risk of bias for

some study quality factors may be difficult to judge. For example, some of the criteria in this assessment involve judgements about the level of detail or clarity of key study information. Failure of authors to provide some of this critical information does not necessarily indicate a high risk of bias, but it can lessen the interpretability of the study and therefore can indicate low study quality.

- Evaluations of bias should take into account the likelihood, magnitude, and the direction of the bias. Quantitative evaluations of bias are preferred over qualitative evaluations when possible, and information on these quantitative evaluations should be included in the criteria descriptions (e.g., rows with black colored text in the Excel spreadsheet).

- Ratings may differ if the primary goal is hazard identification, exposure-response analyses or both. For EtO, both are important, so ratings should relate to biases that are likely to have minor, major, or important effects on either.

Calculation of final inclusion (or overall participation) rates

Expert judgement should be used when evaluating and rating recruitment, participation, follow-up, and overall final inclusion rates. It is acknowledged that calculating the final inclusion rates can be difficult, and many studies will not report all the necessary information for these calculations. Some general guidelines are provided below for rating the “Participation” criteria as “High” under the assumption that there are likely to be many exceptions. These guidelines can be used as a starting point, with the final rating also taking into account other considerations (e.g., differences between cases and controls, lack of complete information).

- Case-control studies: (final n) / (eligible) ≥70% for both cases and controls

- Cohort or nested case-control studies (NCC): (final n) / (eligible at start of follow-up) ≥70%

- Convenience samples: (final n) / (eligible) ≥80%

- Ecologic: (final n) / (eligible) ≥70%

Here, the word “eligible” is defined as the number of people that were initially attempted to be recruited taking into account reasonable or valid exclusion criteria.

Levels of bias or weaknesses

The words “minor”, “moderate”, “major” and “serious” as used throughout the following ratings descriptions. Their general meanings are provided below although there may be exceptions.

Minor: A weakness or degree of bias that is unlikely to have an impact on effect sizes and/or statistical significance. These will generally have almost no discernable effect on overall hazard identification and exposure response conclusions.

Moderate: A weakness or degree of bias that is likely to have an impact on effect sizes or statistical significance that lessens the study’s utility for hazard identification and/or exposure-response conclusions. However, the weakness or bias is at a level that the study may still be used to help support the findings of stronger studies.

Important: A weakness or degree of bias that significantly impacts the overall conclusions of the study and raises significant concerns about the validity of the study results. The study is likely to receive very little or no weight in the evidence integration or exposure-response stages.

Serious: A weakness or degree of bias that significantly impacts the overall conclusions of the study such that the study is judged to have no validity, or its validity cannot be determined. This should be considered a “fatal flaw”, and the study will not be used in evidence integration or exposure-response stages.

Final overall ratings

There are no pre-defined weights for each criterion and reviewers should use their expert judgment in making these determinations.

Table E1. Study quality rating guidance.

Criteria	Factors to consider	High	Adequate	Low	Critical
DESIGN:					
Design: description	Include information on: • Overall study design • Type of facility, population, cohort name, demographic group (ages, sex, other) • Location • Sample sizes for the most relevant outcomes/analyses • Follow-up period • Study years • Issues related to temporality				
Design	• Are all the key aspects of the underlying or basic study design well explained? • Weaknesses specifically related to participant selection, exposure and outcome assessment, and statistics are rated elsewhere	The overall study design is clearly explained including the underlying design, major hypotheses, location, population, sample sizes, years, and follow-up	• A few relatively minor aspects are difficult to understand but none involve factors that are likely to lead to moderate bias	• Some aspects of the study design are unclear, and these could potentially lead to moderate bias	• Some key aspects of the study design are unclear, and it is likely that this could lead to important bias
Temporality	• Is there good evidence that the exposure came before the outcome?	The design essentially assures that the exposure preceded the outcome. In general, this can include the following designs:	• Study designs listed under high with some minor concern about temporality • Cross-sectional studies where there is	• A significant fraction of the measured exposure may have occurred at the time or after the outcome was assessed, and moderate concern	• Cancer case-control studies based on exposure at or near the time of cancer diagnosis

Criteria	Factors to consider	High	Adequate	Low	Critical
	• Consider any available information on latency • Is there evidence that reverse causality is a concern? • The focus of this criterion is on whether the under-lying study design is one in which it can reasonably be assured that the exposure occurred before the outcome. Weaknesses specifically related to the follow-up periods and lag periods are rated elsewhere	• Prospective cohort • Retrospective cohort • Nested case-control • Case-control studies with retrospective exposure data	strong mechanistic evidence that the exposure causes the outcome but no evidence that the outcome causes the exposure (e.g., perchlorate and thyroid effects) • Exposure measured at the time of outcome ascertainment, but the exposure metric represents long term exposure, and no evidence that outcome has a significant impact on exposure	that the outcome affects the exposure • Cross-sectional studies where there is some moderate empiric or theoretical concern that the outcome may impact exposure levels	• Cross-sectional studies where there is good evidence that the outcome can impact exposure levels • There are concerns and fairly strong evidence that reverse causality explains the observed association
SELECTION:					
Selection methods: description	• How were participants initially defined, identified, and recruited? • Describe sex, life stage, and other major demographic characteristics • What are the major exclusions and are there valid reasons for these exclusions? • Are the participants likely generalizable to a broader population? • Did selection methods likely lead to the Healthy Worker Effect?				

Criteria	Factors to consider	High	Adequate	Low	Critical
Recruitment, participation, exclusion, and final inclusion rates	Include information on: • Initial number of participants recruited • Participation rates (i.e., the number agreeing to participate) • The numbers excluded under each major exclusion criteria • Follow-up rates for cohort studies • Final inclusion rates				
Susceptible subgroups	• Are there data to suggest that some groups may be more susceptible than others? • Describe this evidence and these groups				
Selection methods	• Were the selection methods clearly and thoroughly described? • Were the methods used to select study participants appropriate (e.g., independent of exposure and outcome)? • Were the reasons for exclusions valid? • In a case-control study, were controls representative of the population from which the cases were ascertained?	• Selection methods are clearly and thoroughly described • Final inclusion was independent of exposure and outcome • Selection methods are unlikely to lead to discernable bias (e.g., random selection, all employees • Exclusions are appropriate and independent of exposure and outcome	• Some minor information is missing from the description of the selection methods • Participant selection was not completely independent of exposure and outcome, but this is likely to only lead to minor bias • In case-control studies, there were some minor differences between the populations from which the cases and controls were ascertained	• Some important but not critical information is missing from the description of the selection methods • Participant selection was not completely independent of exposure and outcome, and this may lead to moderate bias • In case-control studies, there were some moderate differences between the populations from which the cases and controls were ascertained	• Critical information is missing from the description of the selection methods • Selection methods are strongly related to exposure or outcome and likely to lead to important bias • In case-control studies, the controls were not representative of the population from which the cases were ascertained • Some exclusions could have led to important bias

Criteria	Factors to consider	High	Adequate	Low	Critical
	• This criterion focuses specifically on the selection methods outside of the HWE. Weaknesses specifically related to the HWE are rated under the "HHE" and "HWSE". Weaknesses specifically related to low or biased inclusion rates are rated under "Inclusion rates"	• Selection issues were appropriately controlled in the statistical analyses (e.g., inverse probability weights) • In case-control studies, the controls represent the population from which the cases were ascertained	• Some exclusions are not fully justified but moderate bias is unlikely	• Some exclusions could have led to moderate bias	
Inclusion rates	• Were recruitment, participation, follow-up, and final inclusion rates adequate? • Are there differences in recruitment, participation, follow-up or final inclusion rates between those with and without the outcome, or between those with higher and lower exposure?	• Final inclusion rates are generally high (e.g., >80%) • Final inclusion rates are somewhat high (e.g., >60%) but are similar across exposure and outcome groups (e.g., within 10%)	• These rates are moderate (e.g., 50-60%) but did not differ by exposure and outcome • Recruitment rates are moderate but other evidence is provided that this is unlikely to lead to moderate or important bias • Some relatively minor information on these rates is not provided • Convenience sampling was used but this is unlikely to	• These rates are moderate (e.g., 50-60%) and there were moderate differences between exposure and outcome groups (e.g., >10-20%) • These rates were moderate and there was limited information on differences between exposure and outcome groups • These rates are relatively low, but effect sizes are large enough that they are unlikely to be fully due	• These rates are low (e.g., <50%) and there were large differences between exposure and outcome groups (e.g., >20%) • Critical information on these rates was not provided • These rates were low, and data showed that there were important differences between participants and non-participants

Criteria	Factors to consider	High	Adequate	Low	Critical
			lead to moderate or important bias • These rates were moderate, but data showed that the differences between participants and non-participants was minor or was fully accounted for (e.g., in the statistical analyses)	to moderate or important bias • These rates were relatively low, and data showed that there were moderate differences between participants and non-participants that were not accounted for	
Healthy hire effect (HHE)	• Were the appropriate results provided to evaluate this potential bias? • Did this potential bias have an impact on study findings? • This criterion applies to occupational studies that use the general population as the "unexposed" comparison group	• SMRs or SIRs for all causes, all cancers, or another common outcome (e.g., cardiovascular disease) are provided for all or most relevant non-reference exposure categories • No evidence of the HHE is seen or it is small enough that it is unlikely to have a discernable impact on results	• These SMRs or SIRs are provided but not by all relevant exposure categories (i.e., they are only provided for all non-reference exposure categories combined) • No information on the HHE is provided but effect sizes are large enough (e.g., >2.0) that moderate or important bias from the HHE is unlikely • Information on the HHE is not directly provided for the most relevant group but it is provided for a group	• The HHE appears large enough and/or the effect sizes are small enough that the HHE may account for the majority of the effect size but some increase in the effect size is still present • Important bias is unlikely for the study cohort as a whole but it is unclear whether this finding applies to a relevant subgroup	• Effect sizes for the analyses of interest are close to or below the null (e.g., RRs near or below 1.0) and there is evidence of a strong HHE (e.g., all cause or common disease SMRs or SIRs well below 0.90) • Effect sizes are near or below the null and there is no information on the HHE

Criteria	Factors to consider	High	Adequate	Low	Critical
			where the HHE is likely to be similar		
Healthy worker survivor effect (HWSE)	• Was the appropriate evidence provided to evaluate this potential bias? • Did this potential bias have an impact on study findings? • This criterion applies to occupational studies that use the general population as the "unexposed" comparison group	• A full assessment was done, and it was found that the HWSE is unlikely to have an impact on study conclusions • A full assessment was not done but there is some evidence that the HWSE did not impact study results	• A full assessment was done, and it was found that the HWSE likely had only a minor impact on study results • Evidence suggests that there was no discernable HWSE, but the assessment had some minor methodological weaknesses	• A full assessment was done, and it was found that the HWSE likely had a moderate impact on study results • An incomplete or no assessment but some other evidence (e.g., results from similar cohorts) that the HWSE had a moderate impact on study results • There were some moderate methodological weaknesses in the assessment	• Incomplete or no assessment but some other evidence that the HWSE had an important impact on study conclusions
Both sexes	• Are both sexes included in the analyses? • Are separate analyses done by sex?	• Both sexes were included and full results by sex are provided	• Separate analyses not provided by sex but there is evidence (empiric, mechanistic, or strong theoretical) that sex differences are unlikely to have an important impact	• Separate analyses not provided by sex and there is some evidence or theoretical concern that sex differences may have had a moderate impact on	• There is some evidence that failure to include or fully evaluate both sexes likely had an important effect on study findings, relevancy, or interpretation

Criteria	Factors to consider	High	Adequate	Low	Critical
	• This criterion does not apply to sex specific outcomes		on findings or relevancy • Analyses by sex are provided although with some minor limitations	study findings or relevancy • Analyses by sex are provided although with some moderate limitations	(Steenland et al., 2004)
Susceptible groups	• Are there likely to be certain groups that are more susceptible to the exposure than others? • Were separate and complete analyses and results for these groups provided?	• Susceptible groups were included in the study and fully and appropriately evaluated in the statistical analyses • There are no susceptibility groups identified	• Susceptible groups were included but there were some minor limitations in the statistical analyses	• Susceptible groups were included but there were some moderate limitations in the statistical analyses • Important susceptibility groups were not included but results from other groups may be useful for evaluating risks overall	• Important susceptibility groups were not included and results from other groups cannot be used to evaluate their risks
Generalizable	• Did the study take place in a group that is likely to represent the target group? • This criterion differs from “susceptibility” in that it is aimed at judging whether study results are more broadly, versus more narrowly, applicable	• Results have direct applicability to the target group	• Results have some applicability to the target group	• Results may have some applicability to the target group, but this is limited or unclear	• Results have very little to no applicability to the target group

Criteria	Factors to consider	High	Adequate	Low	Critical
OUTCOME:					
Outcome: description	• Describe how the outcome was assessed or measured or how cases with the outcome were defined • Describe any information on the sensitivity and specificity of the outcome metric • Describe the timing, frequency, detection rates, and duration of exposure assessment • Is the outcome likely to be reasonably consistent or is it highly variable over time (e.g., long or short half-life)? • Was outcome assessed similarly in people with and without the exposure of interest? • Were all relevant outcomes included? • For cancer, were both cancer incidence and mortality assessed? • Was the appropriate follow-up period included?				
Power	• Is there adequate statistical power to evaluate the relevant outcomes?				
Outcome methods	• Was there a complete and clear description of how the outcome was assessed? • Is this a well described, widely accepted, commonly used, or well validated outcome metric? • Does the outcome metric reliably distinguish between people with and without the outcome of interest (consider the sensitivity and	• A direct, well-described, widely accepted and commonly used method was used • The outcome metric had good sensitivity and specificity compared to a "gold standard" • Not a widely accepted or commonly used outcome but the metric has appropriate validation data	• Meets the criteria for "high" but with some minor weaknesses • Some gaps in the description of the outcome assessment but these are minor • Some minor decrements in sensitivity or specificity • Outcome misclassification likely has only minor impacts on study	• The outcome metric has only moderate sensitivity and specificity • Outcome assessment methods are somewhat unclear • Not a widely accepted method and validation results are modest • Validation data show moderate differences in the validity or accuracy of the outcome assessment	• The outcome metric has very poor specificity or sensitivity • Critical information about outcome assessment is not provided • Not a widely accepted method and no or poor validation data • Important outcome misclassification is likely

Criteria	Factors to consider	High	Adequate	Low	Critical
	specificity of the outcome metric)? • Was the outcome measured independently of exposure? • Did post-exposure interventions affect the outcome (highly exposed asbestos workers receiving CT scans)? • Was the outcome assessed in the most relevant period? • Weaknesses specifically related to blinding, researcher, interviewer, or recall bias are rated under "Researcher/Recall bias"	showing good correlations • The outcome was measured using the same methods in all study participants (i.e., independent of exposure) • Outcome misclassification is likely to be minimal if present	results and conclusions • Minor differences in the validity or accuracy of the outcome assessment across exposure groups	across exposure groups • Outcome misclassification is likely to lead to moderate bias • Some concern that the outcome was not fully independent of exposure	• The outcome was not assessed independently of the exposure status • Critical information on the outcome assessment is not provided • There are important differences in the validity or accuracy of the outcome assessment across exposure groups
Relevant outcome #1	• Did the study include the primary outcome of interest?	• Includes the primary outcome of interest	• Does not include the primary outcome of interest but includes an outcome that is strongly related to or correlated with the primary outcome of interest	• Does not include the primary outcome of interest but may include a metric with some moderate correlation with the primary outcome of interest	• Does not include the primary outcome of interest or a related outcome • Not in the causal chain

Criteria	Factors to consider	High	Adequate	Low	Critical
			• Not the primary outcome but the outcome assessed is in the direct causal chain		
Relevant outcome #2	• Same as above • Only used if there is more than one primary outcome of interest	• Same as above	• Same as above	• Same as above	• Same as above
Power #1	• Did the study have adequate statistical power for the primary analyses of interest? • Review the precision of the main effects and any important subgroup or stratified analyses	• The study had good statistical power (generally ≥80%) for the primary analyses of interest (e.g., lag periods, sex specific analyses)	• The study had good statistical power for the primary analyses of interest but with some minor weaknesses (e.g., the findings were borderline precise) • Good statistical power but with some minor weaknesses in evaluating power	• The study had only moderate statistical power (e.g., <60-70%) • The study had adequate statistical power for some related analyses but not for the primary analysis of interest • The study had good statistical power for the study population overall but not for important subgroups or other key analyses • Limited information leads to moderate difficulties in evaluating power	• The study had inadequate statistical power for all important analyses • No or very limited information is available for evaluating statistical power

Criteria	Factors to consider	High	Adequate	Low	Critical
Power #2	• Same as above • Only used if there is more than one primary outcome of interest	• Same as above	• Same as above	• Same as above	• Same as above
Follow-up	• Was the period between exposure assessment and outcome measurement adequate? • For cancer studies this is generally several years or more • This criterion rates whether the underlying study design included an appropriate follow-up period. Bias due to low or differential follow-up rates is rated in the "Participation" criterion. Failure to evaluate appropriate lag periods in the statistical analysis is rated in the "Lag period" criterion	• There is good evidence or reason to believe that the follow-up period was appropriate	• There is evidence or reason to believe that the follow-up period was not too long or too short, but the weaknesses or concerns are minor • Some minor gaps in the description of the follow-up period • The follow-up period likely covers most of the appropriate follow-up period	• There is evidence or reason to believe that the follow-up period was not too long or too short and this led to moderate weaknesses or concerns • Some moderate gaps in the description of the follow-up period • The follow-up period likely covers some but not most of the appropriate follow-up period	• There is evidence that the follow-up period was likely too long or too short and this led to important bias • Critical elements are missing from the description of the follow-up period
Incidence and mortality	• Did the study examine cancer mortality and cancer incidence?	• The study thoroughly examined both incidence and mortality	• The study only included cancer incidence or only cancer mortality but there is a low	• The study examined cancer incidence and there is evidence or reason to believe the exposure has a	• The study only included cancer incidence and there is strong evidence that the exposure affects

Criteria	Factors to consider	High	Adequate	Low	Critical
	• How well does mortality for the cancer in question reflect cancer incidence? • Are there reasons to believe that mortality may be impacted to a greater extent than incidence?	• The study examined cancer incidence and there is no evidence or reason to believe that the exposure has a greater impact on mortality than incidence • Only mortality was examined but the outcome has a very high mortality rate (e.g., lung cancer)	likelihood that this led to moderate or important bias • The study examined cancer incidence and there is only minor concern that the exposure has a greater impact on mortality than incidence • Only mortality was examined but the outcome has a somewhat high mortality rate	moderately greater impact on mortality than on incidence • The study only examined mortality, and the cancer of interest has a low mortality rate	mortality to a much greater extent than incidence
EXPOSURE:					
Exposure: description	• Describe how the exposure was assessed • Describe the timing, frequency, number of measurements, detection rates, and duration of the exposure assessment • Is the exposure likely to be reasonably consistent or is it highly variable over time (e.g., long or short half-life)? • Was exposure assessed similarly in people with and without the outcome of interest and in people with high and low exposure levels? • Were the researchers blinded, or was exposure measured in a way that researcher, interviewer, or subject recall bias was unlikely? • Was exposure assessed in the most relevant period? • Was any exposure misclassification likely to be differential or non-differential? • What was the possibility of significant exposure outside the time periods that exposure was assessed?				

Criteria	Factors to consider	High	Adequate	Low	Critical
Validation	• Was the exposure assessment process validated? • If so, describe the validation process and its results				
Exposure range	• Provide information on exposure means, medians, and percentiles • Describe how the study exposures differ from general population exposures				
Exposure assessment	• Was there a complete and clear description of how the exposure was assessed? • Is this a well-established, widely accepted or well validated exposure metric? • Does the exposure metric reliably distinguish between people with higher and lower exposure levels considering intensity, frequency and duration of exposure (consider the sensitivity and specify of the exposure metric)? • Was the exposure measured independently of the outcome? • Was exposure assessed in the most	• A direct, well-described, well-established, widely accepted and common method was used • Modeled exposure with appropriate validation data showing good correlations • Exposure measured using the same methods in all participants (i.e., independent of the outcome) • Exposure misclassification is likely to be minimal or not discernable if present • Exposure was assessed in the most relevant period	• Modeled exposure without validation data but using direct, clear, thorough, and well justified and sound methods • Some gaps in the description of the exposure assessment but these are minor • Exposure misclassification is likely to be relatively minor • Minor differences in the validity or accuracy of exposure assessment across outcome groups • Somewhat less direct exposure measurements used (e.g., wide area measurements rather than personal	• Evidence suggests the method used to measure exposure is only moderately related to the relevant exposure • Exposure assessment methods are somewhat unclear or incomplete • Exposure misclassification likely to lead to moderate bias • Moderate differences in the validity or accuracy of exposure assessment across outcome groups • Some moderate concerns about whether exposure was assessed in the most relevant period	• Evidence shows that the method used to measure exposure is not related to the exposure of interest • Exposure misclassification is likely to lead to important bias • Large differences in the validity or accuracy of exposure assessment across outcome groups • Modeled exposure with unclear or poorly rationalized methods and no or poor validation data • Exposure was assessed in a period that is likely not related to exposure in the most relevant period

Criteria	Factors to consider	High	Adequate	Low	Critical
	relevant period (consider life stage and half-life)? • Does the degree of exposure misclassification vary by the level of the outcome? • Weaknesses specifically related to blinding, researcher, interviewer, or recall bias are rated under "Researcher/Recall bias"		sampling or biologic matrices) • The exposure covers a significant part but not all of the relevant exposure period • Occupational studies with some minor missing information on work histories	• The exposure covers only a portion of the relevant exposure period • Some concern that exposure measurement was not fully independent of outcome status • Occupational studies with some moderate gaps in work histories	• Critical information about exposure assessment is not provided • Exposure measurement was not independent of outcome status • Occupational studies with important gaps in work histories
Validation	• What is the quality and thoroughness of the validation procedures? • This criterion focuses on the quality of the validation procedures. Ratings related to actual validation results are considered in the "Exposure assessment method" criteria • This criterion is only used when exposure	• Clear and complete description of validation procedures and results • Sound validation procedures • Thorough and clear validation results • Validation took place in a random subgroup of the study population • Validation took place in a population that is	• Minor weaknesses in the validation procedures • Missing some validation results but these are minor • Minor lack of clarity in the description of the validation procedures or results • Minor differences between the study population and the	• Moderate weaknesses in the validation procedures • Missing some but not all relatively important validation results • Moderate lack of clarity in the description of the validation procedures or results • Moderate differences between the study population and the	• Unusual exposure assessment method with no validation results or clear underlying rationale • Important weaknesses in the validation procedures • Key elements are missing from the description of the validation procedures • The study population and the validation study population are

Criteria	Factors to consider	High	Adequate	Low	Critical
	models or similar procedures are used	directly comparable to the study population	validation study population	validation study population	not comparable on some critical elements
Exposure range	• Did the study have a wide range of exposure and include some people with high exposures? • Considerations of statistical power here should be primarily based on the exposure levels taking into account sample size, confounding control, and the expected effect size at these exposures	• The study involves a very broad range or good contrast of exposure • Examples might include median levels >5-fold higher than NHANES, an occupational study, or an area with known high exposures • There is good evidence that the potency of the agent is such or the study is large enough that detectable effects are expected despite a limited exposure range	• Moderate exposure range although statistical power to detect an effect is likely to be adequate • Some details on the exposure range are lacking but these are minor • There is some less strong evidence that the potency of the agent is such or the study is large enough that detectable effects are expected despite a limited exposure range	• Exposure range is only somewhat higher than general population levels and this is likely to lead to a moderate deficiency in study power • The potency of the agent is such or the study is large enough that borderline detectable effects may be seen despite a limited exposure range • Only a very small proportion of the participants are highly exposed • A few but not all key details on the exposure range are lacking	• Study exposures were likely too low to detect an effect even given a large sample size • Critical information on exposure levels is lacking

Researcher/recall bias	• Were the researchers assessing the exposure blinded to the study outcome? • Were objective or subjective methods used to measure outcome and exposure? • What is the probability of researcher, interviewer or subject recall bias? • Weaknesses specifically related to financial conflicts of interest should be rated under the "Conflict of interest" criterion	• The researchers were appropriately blinded, and this is clearly described • No information on blinding is provided although exposure or outcome were measured in a way that is unlikely to be affected by researcher or recall bias	• Information on blinding is indirect or unclear. Outcome or exposure metrics could be susceptible to researcher or recall bias, but only minor bias is likely • No information on blinding but fairly objective methods were used to assess exposure and outcome • Exposure or outcome metrics are subjective but recall or interviewer bias is likely to be minor • Subjects self-reporting exposures and outcomes were likely not aware of possible links between the exposure and the outcome	• Information on blinding is indirect or unclear. Outcome or exposure metrics could be susceptible to researcher or recall bias and moderate bias is likely • Exposure metric is subjective and researcher or recall bias is likely to be moderate • Subjects self-reporting outcomes might have some indirect awareness of possible links between the exposure and outcome	• No information on blinding is provided, and the outcome and exposure are measured in a way such that the study is highly susceptible to important researcher or recall bias • There is evidence of important recall bias or interviewer bias • Subjects self-reporting outcomes are likely very aware of possible links between the exposure and outcome

Criteria	Factors to consider	High	Adequate	Low	Critical
STATISTICS:					
Statistics: description	• Describe the major aspects of the statistical analysis with a major focus on the analyses involving the most relevant results • Were these clearly presented? • Were demographic comparisons made across exposure and outcome groups? • How were exposure-response, confounders, effect modifiers, mediators, outliers, multiple comparisons, and missing data addressed? • Was there over-matching on exposure? • How were the exposure categories appropriately defined? • Were data distributions considered appropriately and are all statistical assumptions reasonable? • Were outlying values, missing data, and multiple comparisons issues evaluated and controlled for?				
Lag periods	• Describe any known information about the possible latency period • Was this latency addressed appropriately and thoroughly in the statistical analyses and results?				
Statistical analysis	• Were the methods used in the statistical analyses clearly explained, appropriately applied, thorough, and unlikely to introduce bias? • Were data distributions appropriately addressed (e.g., log transformations)? • Appropriate and justifiable category cut-off points	• Appropriate and thorough statistical analyses without significant weaknesses	• Appropriate statistical analyses but with some minor missing elements, minor lack of clarity, or minor weaknesses unlikely to have a moderate or important impact on study conclusions • Minor weaknesses or limitations in the consideration of data distributions	• Moderately important missing or unclear elements or weaknesses that are unlikely to impact the direction of the effect but may moderately impact the effect size • Moderate weaknesses in the consideration of data distributions	• Major weaknesses or missing elements that are likely to cause important bias or to severely limit the interpretability of study findings • Incorrect analyses in the consideration of data distributions likely led to important bias

Criteria	Factors to consider	High	Adequate	Low	Critical
	• Consider the possibility of over-adjustment or co-variance				
Categorical or continuous data	• Were results presented using both categorical and continuous data analyses?	• Thorough categorical and continuous analyses were presented for all important results • One type of analysis is not appropriate for the type of data or associations being assessed	• Both categorical and continuous analyses were presented although with some minor weaknesses or minor missing elements (e.g., only two exposure categories were used; continuous analyses were somewhat unclear or limited; both were not presented for a few relevant results) • Only one type was reported but this led to only minor weaknesses regarding study interpretation, validity, or completeness	• Both categorical and continuous analyses were presented although with a moderate weakness in one type (e.g., the continuous data model may have been a poor fit to the data; incomplete results in one type of analysis; category cut-offs poorly rationalized) • Only one type was reported and this led to moderate weaknesses regarding study interpretation, validity, or completeness	• Only one type of analysis was presented and this had important impacts on study interpretation, validity, or completeness

Criteria	Factors to consider	High	Adequate	Low	Critical
Internal analyses	• Were study results presented using an internal reference group? • This criterion applies mostly to occupational studies • Weaknesses directly related to the analyses and control of the HHE and HWSE should be rated separately	• Study results were presented using a comparable internal reference group	• An internal reference group was used for some but not all relevant outcomes • An internal reference group was used although there are some minor concerns about comparability • An internal reference group was not used but there is strong evidence the results were not impacted by the HHE	• An internal reference group was used although there are some moderate concerns regarding comparability or other factors	• An internal reference group was not used and there is evidence to suggest a strong HHE or other related bias
Lag periods	• Were the likely latency and lag periods appropriately addressed in the statistical analyses? • This criterion rates the incorporation of latency in the statistical analyses. Weaknesses related to the inclusion of an appropriate follow-up period in the underlying study design is rated under the “Follow-up period” criterion	• Lag periods were considered in the statistical analyses, multiple lag periods were evaluated as needed, and the results for all relevant outcomes included appropriate lag periods	• Lag periods were considered in the statistical analyses although with some relatively minor weaknesses (e.g., only a limited number of potential lag periods assessed)	• Lag periods were considered in the statistical analyses although with some moderate weaknesses	• There is good evidence that an important lag period exists, but this was not addressed in the statistical analysis

Criteria	Factors to consider	High	Adequate	Low	Critical
Demographic comparisons	• Does the study provide information comparing groups with different levels of exposure or outcome? • Are these comparisons complete enough to evaluate whether demographic differences are likely to cause bias? • Study design and statistical analyses (e.g., adjustments) should be considered in these ratings	• Full demographic comparisons are made based on exposure or outcome • The study design was such that these demographic comparisons are not needed	• Demographic comparisons are somewhat limited although complete enough to evaluate whether moderate or important bias is possible	• Demographic comparisons are not provided or are limited to an extent that moderate bias is possible	• Demographic comparisons are not provided and there is a reasonable likelihood that demographic differences across exposure or outcome could lead to important bias
Exposure-response	• Were results provided in a manner in which the steepness and the shape of the exposure-response curve can be evaluated?	• Full exposure-response analyses were presented • There was a thorough consideration and evaluation of non-linear exposure-response patterns • Categorical analyses with a sufficient number of individual categories	• Exposure-response analyses were presented although with some minor weaknesses • Examples: limited information on the exposure-response shape, limited number of exposure categories, limited number of models assessed, case or control counts not provided, limited	• Exposure-response analyses were presented although with some moderate weaknesses • Examples: relative risks or means without variance estimates, only p-values provided, unclear or limited modeling procedures, very limited number of model types, no model fit information	• Exposure-response was not assessed • Important weaknesses in the exposure-response analyses • Important data models not used or presented

Criteria	Factors to consider	High	Adequate	Low	Critical
		• Continuous data analyses with assessment of multiple models	information on model fit statistics		
Multiple comparisons	• How many different outcomes and exposures were assessed and how many different results were provided? • Includes multiple different evaluations of subgroups or effect modification, especially without clear *a priori* hypotheses • Reviewers are expected to use their judgement when defining an individual "comparison". For example, testing multiple standard models or lag periods to identify the best fit, highly related exposure or outcome variables, or demographic comparisons may not be considered separate comparisons	• The study had a clear *a priori* hypotheses directly related to the relevant association under consideration • Fewer than 20 unrelated comparisons were made	• The study had a clear *a priori* hypotheses that were indirectly related to the relevant association under consideration • 20-40 unrelated comparisons were made	• The study did not have an *a priori* hypothesis related to the relevant association under consideration • More than 40 unrelated comparisons were made but statistical adjustments were made for multiple comparisons testing	• Many different and unrelated exposures and outcomes were tested and there was no data to support an *a priori* hypothesis for the exposure of interest

Criteria	Factors to consider	High	Adequate	Low	Critical
Clear results	• Are the relevant study results presented clearly and completely? • This criterion rates the clarity of the results that are provided. Situations in which the results for some associations are not reported are rated under "Selective reporting". Weaknesses in the statistical analysis are reported in the "Statistical analysis" criterion	• The results provided are clear and complete	• Some minor weaknesses or omissions in the presentation or reporting of the relevant study results	• Some moderate weaknesses or omissions in the presentation or reporting of the relevant study results • Only p-values, descriptive results (e.g., "statistically significant"), effect sizes without variance estimates, or unadjusted correlation coefficients are reported • Effect estimate units are not provided or are unclear	• Important results are unclear or incomplete to the degree that their validity cannot be assessed
Missing data	• Were there large amounts of missing data? • Was the missing data related to exposure and outcome? • Were the methods used to control for missing data adequate (e.g., adequate imputation procedures)?	• The amount of missing data was so small that it is unlikely to have a discernable impact on study results • There were small to moderate amounts of missing data, but this was not related to exposure or outcome • There were small to moderate amounts of	• Minor concern about whether the methods used to account for missing data were adequate • Missing data was related to exposure or outcome, but this is expected to only lead to minor bias	• There were moderate amounts of missing data with no or limited control procedures • Missing data was somewhat related to exposure or outcome, and the bias from this is likely to be moderate	• There were large amounts of missing data and data was missing in a way that could cause important bias • No analyses or procedures were done to control for or evaluate this bias • No information was provided on the

Criteria	Factors to consider	High	Adequate	Low	Critical
		missing data, but valid imputation or other methods were used to control for this • Sensitivity analyses show that missing values are unlikely to have caused discernable bias		• Information on the amount of missing data was limited	amount of missing data
Outlying values	• Did the researchers evaluate whether outlying values may have impacted their findings? • Were appropriate methods used to control for outlying values?	• Thorough and accurate methods were used to evaluate and control for the presence of outlying values • Categorical data analyses are clear and complete and indicate that bias from outlying values is unlikely • Individual data are provided and show no outlying values	• Categorical analyses with some minor weaknesses • Some minor concerns about the methods or procedures used to identify and control for outlying values • Some indirect data suggesting that outlying values had relatively little impact on study results (e.g., comparable results from other more complete studies) • Individual data are provided and show no strongly influential outlying values	• Categorical analyses with some moderate weaknesses (e.g., limited number of categories) • Moderate concerns about the methods or procedures used to identify and control for outlying values • Individual data are provided and suggests that outlying values may cause moderate bias	• No analyses were done to control for or evaluate this bias and there is some likelihood that a few outlying values could invalidate study conclusions • Individual data show strongly influential outlying values and no methods were used to control for this

Criteria	Factors to consider	High	Adequate	Low	Critical
CONFOUNDING:					
Confounder control	• List the factors that were controlled for in the study • Include factors controlled through statistical analyses, restriction, matching, stratification, and other methods • Include factors that were shown by the authors not to affect results				
Confounding: other	• Describe the most likely other potential confounders (i.e., those factors relatively strongly associated with both exposure and outcome but not in the causal chain) • Were the confounding variables measured reliably and consistently? • What is the likelihood of residual confounding? • Was there a large change in the effect measure after statistical adjustment?				
Age and sex	• Were the study results adequately controlled for age and sex? • Age and sex are related to many exposures (e.g., age and cumulative exposure) and many cancer or disease outcomes	• It was shown that there is not a strong association between the age or sex and the exposure or outcome of interest • Both age and sex were adequately controlled for and the methods used were presented clearly	• These factors were not controlled for but their association with the exposure or outcome is only strong enough to cause minor bias • Weaknesses in the measurement or control of these factors may have led to minor bias • Minor concerns about residual confounding (e.g., some change after adjustments)	• These factors were not controlled for and their association with the exposure or outcome is strong enough to cause moderate bias • Weaknesses in the measurement or control of these factors may have led to moderate bias • Moderate concerns about residual confounding (e.g., large change after statistical adjustments)	• These factors were not controlled for and their association with the exposure or outcome is strong enough to cause important bias • Weaknesses in the measurement or control of one or both of these factors may have led to important bias • Important residual confounding is likely • Critical information needed to assess confounding is missing

Criteria	Factors to consider	High	Adequate	Low	Critical
			• Minor lack of clarity in the methods or results related to confounding by these factors	• Moderate lack of clarity in the methods or results related to confounding by these factors	
Other confounders	• Are there any other major potential confounders and were they adequately controlled? • Was the confounder measured thoroughly and accurately? • How strongly is the potential confounder related to the outcome and exposure? • Is the prevalence of the confounder high enough to cause confounding? • What is the likelihood of residual confounding? • Were time varying confounders considered?	• Same as above plus: • The prevalence of the factor is too low to cause discernable bias • Colliders or intermediates in the causal pathway are treated appropriately	• Same as above plus: • The prevalence of the factor is such that it could cause minor bias • Situations in which an important confounder was not controlled for but this factor is strongly correlated with one that was controlled for • There are relatively minor concerns regarding colliders or intermediates	• Same as above plus: • The prevalence of the factor is such that it could cause moderate bias • Situations in which an important confounder was not controlled for but this factor is moderately correlated with one that was controlled for • There are moderate concerns regarding colliders or intermediates	• Same as above plus: • The prevalence of the factor is such that it could cause important bias • The potential confounder is not related to another factor that was controlled for • There are important concerns regarding colliders or intermediates

Criteria	Factors to consider	High	Adequate	Low	Critical
	• Note: more columns can be added here if there are several known major potential confounders				
Adjusted-unadjusted	• Were both adjusted and unadjusted results reported? • This criterion only rates whether both adjusted and unadjusted results were reported. The likelihood of residual confounding should be rated using the other confounding criteria	• Both were reported • Only one is reported but the authors provide strong justification and evidence that confounding is unlikely	• Only one is reported and there is indirect evidence that confounding did not occur • Both are reported for a related outcome metric	• Only one is reported and there is evidence that moderate confounding could have occurred	• Only one was reported and there is evidence or a large degree of uncertainty that important confounding or residual confounding occurred
OTHER:					
Conflict of interest	• Who funded the study? • Did a study author, funder, or other important entity have a financial interest in the exposure? • Were there other potential conflicts of interest?				
Selective reporting	• Are results provided for all relevant hypotheses and outcome metrics mentioned in the methods or analysis plans? • Describe the completeness of the results for these hypotheses				
Conflict of interest	• Did a study author, funder, or other important entity have a financial interest in the study results?	• Study funding and conflict of interest information is clear and no study author, funder, or other important entity had	• Study authors appear to have some minor financial or other related interest in the exposure or outcome	• Study authors appear to have some moderate financial or other related interest	• A study funder, author or other related entity had a strong financial interest in the study results

Criteria	Factors to consider	High	Adequate	Low	Critical
		an obvious financial or other related interest in the exposure or outcome • The exposure and outcome are such that a financial or other conflict is unlikely	• Study funding and conflict of interest information is limited or somewhat unclear but there is only minor or indirect concern that study funding or conflict of interest affected the results or reporting • A study funder, author, or other important entity may have had some financial interest in the exposure, but methods were in place or other procedures were used that likely limited this bias	in the exposure or outcome • Study funding and conflict of interest information is limited or somewhat unclear raising moderate concern that study funding or conflict of interest affected the results or reporting	• No information on study funding or conflict of interest is provided
Selective reporting	• Are there relevant pre-specified hypotheses in the protocols, methods section, or elsewhere in which findings are not reported that would change the interpretation of the study?	• Findings for all relevant pre-specified hypotheses and outcome/exposure metrics or analyses are fully reported	• Some missing or incomplete findings on relevant pre-specified outcomes or outcome/exposure metrics or analyses but these are minor and do not affect the overall interpretability of the study	• Missing or incomplete findings on relevant pre-specified outcomes or outcome/exposure metrics or analyses that may have some moderate effect on the overall interpretability of the study	• Findings for relevant pre-specified hypotheses or outcome/exposure metrics or analyses are not reported • Reporting outcomes based only on a composite score and the exposure in question is a minor or

Criteria	Factors to consider	High	Adequate	Low	Critical
	• Avoid overlap with the ratings given in the Statistical Analysis and Outcome sections		• Findings for some unplanned hypotheses are presented	• Only statistically significant results are reported • Reporting outcomes based only on a composite score but the exposure in question is a relatively potent part of the composite	less potent part of the composite
OVERALL:					
Overall rating description	• Using all criteria, provide a brief description of the important strengths and weaknesses of each study • List those factors that were the primary drivers of the overall study rating • Identify any critical flaws that are “serious” flaws (i.e., those that make the study findings not valid or uninterpretable)				
Overall rating	• Provide an overall rating for the study taking into account all or the criteria and ratings above	• The study was conducted appropriately, and methods and results are clearly presented. Any minor weaknesses would not be expected to have a discernable effect on study results • The large majority of ratings are classified as Good or Adequate	• May have several low ratings. These may be associated with minor or moderate bias but are unlikely to be associated with important bias • May still be useful as a critical study for hazard identification. May be used for exposure-response analyses but estimates of bias should be quantified (if possible) and	• One or more critical weaknesses but these are not serious flaws • Large number of low ratings in areas likely to be associated with moderate bias or some general overall concern about validity • Not expected to be a critical study for hazard identification or exposure-response assessment but may	• One or more serious flaws • Serious flaws that make the study results uninterpretable • Not useful for either hazard identification or exposure-response assessment • Cannot be used to support stronger studies

Criteria	Factors to consider	High	Adequate	Low	Critical
		• May have one or two low ratings but these are unlikely to be associated with important bias	concerns should be well documented	be used to support stronger studies	

Abbreviations: EtO, ethylene oxide; HHE, healthy hire effect; HWE, healthy worker effect; HWSE, healthy worker survivor effect; NCC, nested case-control; RR, relative risk estimate

References

Greenland S (1998) Causation and causal inference. In: Rothman K, Greenland S (eds) Modern Epidemiology. 2nd edn. Lippincott Raven, Philadelphia, p 7-28

Higgins JPT, Morgan RL, Rooney AA, et al. (2024). A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ Int 186:108602

Hill BA (1965). The environment and disease: association or causation? Proc R Soc Med 58:295-300

NTP (2015). Risk of Bias Tool. National Toxicology Program. Last accessed May 06, 2026 from https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/riskbias/index.html.

NTP (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Toxicology Program. Last accessed May 06, 2026 from https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf?__cf_chl_tk=4W7VTSjDKuyi29Pwlm76JIvJ5OykM4dtifrw9QVdRfE-1778196908-1.0.1.1-OR4LVsnUJ_9U3cWYyc.70OmvqBL4m1F9r4bH4lF1ikU.

Steenland K, Stayner L, Deddens J (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 61(1):2-7

US EPA (2021). Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments. Supplemental Information-Appendix A. US Environmental Protection Agency. Last accessed June 05, 2025 from https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=542033.

US EPA (2025). Health Assessment Workspace Collaborative (HAWC). US Environmental Protection Agency. Last accessed June 06, 2025 from https://hawc.epa.gov/assessment/100500074/