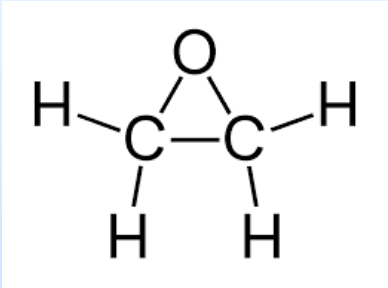
Air Toxics Hot Spots Program

Cancer Inhalation Unit Risk (IUR)

Ethylene oxide (EtO)



Office of Environmental Health Hazard Assessment

Public Workshop

May 5, 2023

Ethylene oxide
Physicochemical Properties

- **Description:** colorless gas at room temperature; sweet ether-like odor. Odor threshold = 430 ppm (782 mg/m^3)
- **Solubility:** soluble in organic solvents; miscible with water: 1 × 10^6 mg/L @ 20°C
- **Boiling point:** 10.7°C (51.3°F) at 760 mm Hg
- **Vapor pressure:** 1095 mm Hg @ 20°C

Ethylene oxide
Listings and Uses

- **Listings**
  - **California Proposition 65:** known to cause cancer
  - **United States Environmental Protection Agency (US EPA):** carcinogenic to humans
  - **International Agency for Research on Cancer (IARC):** Group 1 carcinogen (carcinogenic to humans)
- **Uses**
  - Chemical intermediate in producing other chemicals
  - Sterilizer for medical and laboratory equipment/supplies
  - Fumigant for agricultural products (e.g., herbs and spices)

Ethylene Oxide Emissions California facilities

- **Limited data on EtO emissions:**
  - Reportable under the Hot Spots Program
  - CARB reported a total of 556 pounds of EtO emissions statewide for 2020
- **Non-occupational EtO exposure**
  - Resulting from cigarette smoke and ambient air
  - EtO levels in ambient air due to fossil fuel combustion and release from residues in consumer products
- **SCAQMD EtO air monitoring**
  - Concentration range of 0.02 – 0.17 ppb in South Coast Air Basin for 2022-2023 period
  - EtO concentrations near two medical sterilizer facilities ranged from undetectable to as high as 139 and 103 parts per billion by volume (ppbv)

Ethylene oxide Toxicokinetics

- **Physiologically-based pharmacokinetic models** show comparable blood concentrations across humans, rats and mice over a limited exposure range (≤100 ppm;182 mg/m^3).
- **Absorption:** influenced primarily by ventilation rate and EtO air concentration due to solubility in blood
- **Distribution:** rapid with EtO binding readily to proteins and DNA in tissues throughout the body
- **Metabolism:** two major pathways (detoxifying)

  1) **Hydrolysis –** enzymatic and non-enzymatic; primary pathway in humans
  2) **Glutathione (GSH) conjugation –** via glutathione-S-transferase enzyme; primary pathway in rodents

Ethylene oxide
Toxicokinetics (continued)

- **Elimination:** primarily via urine and exhalation
  - Percentage of radioactivity recovered from rats inhaling ^{14}C-EtO:
    59% – urine
    13% – exhaled air (12% as $^{14}CO_2$, 1% unchanged ^{14}C-EtO)
    4.5% – feces
  - Approximate EtO elimination half-lives ($t_{1/2's}$) in blood:
    humans – 40 min at 1-ppm (1.8 mg/m^3)
    rats – 10 to 19 min at 4-hr 100-ppm (182 mg/m^3)
    mice – 9 minutes at 1-hr 1-ppm (1.8 mg/m^3) or 4-hr 100 ppm (182 mg/m^3)

Ethylene oxide
Endogenous Production

- **Endogenous EtO production:**
  - Cytochrome P450-mediated conversion of ethylene
  - Contributes to adduct levels, such as N-2-hydroxyethylvaline in humans and other species
- **Endogenous ethylene production:**
  - Oxidation of methionine and hemoglobin
  - Lipid peroxidation of fatty acids
  - Metabolism of intestinal bacteria
- **Percentage of ethylene converted to EtO:**
  - Unknown for endogenous ethylene
  - ~3% for exogenous ethylene

Ethylene Oxide Genotoxicity

- **EtO genotoxicity has been extensively reviewed**
  - **US EPA (2016)**
    - clear evidence of genotoxicity
    - sufficient weight of evidence to support a mutagenic mode of action
  - **IARC (1994, 2008, 2012)**
    - strong evidence for a genotoxic mechanism
    - consistently acts as a mutagen and clastogen
  - **ATSDR (2022)**
    - demonstrated to be genotoxic
- **3 additional studies since US EPA review in 2016**
  - Consistent with the overall evidence

Evidence for Ethylene Oxide-Induced Genetic and Related Damage in Humans, Human Cells, and Animals (IARC 2012)

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

- [a] Possibly due to a lack of adequate studies
- [b] Positive responses were seen only at exposure concentrations above those used in the rodent-cancer bioassays
- NR, not reported

Ethylene oxide
Cancer Hazard Evaluation

- **IARC (2012)** – "carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals supported by strong evidence of a genotoxic mechanism.
- **NTP (2021)** – "known to be a human carcinogen."
- **US EPA (2016)** – "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.
- **OEHHA** – agrees with the conclusions of these three agencies regarding the carcinogenicity.

Ethylene oxide
Quantitative Cancer Risk Assessment

- **OEHHA's update of EtO IUR is based on US EPA's 2016 analysis of the exposure-response relationship**
  - Human epidemiological studies are more relevant and sensitive than animal studies
  - NIOSH study (Steenland et al., 2003; Steenland et al., 2004) is of high quality and is the best available study for conducting exposure-response analyses
  - Two-piece linear spline model is the best fitting and most accurate model for assessing the cancer risks of EtO
  - No new scientific information necessitating a change to the US EPA's IUR

Ethylene oxide
Epidemiological Study in Humans
(Steenland et al. 2003, 2004)

- **The National Institute for Occupational Safety and Health (NIOSH) performed a retrospective cohort study, including 17,530 workers from 13 US sterilization facilities in their exposure-response analyses**
- **High quality study**
  - Quality of exposure estimates
  - Cohort size
  - Inclusion of women
  - Multiple study locations
  - Absence of co-exposures
- **OEHHA review**
  - Bradford-Hill guidelines
  - NTP's risk of bias tool

Ethylene oxide
Epidemiological Study in Humans
(Steenland et al. 2003, 2004)

- **EtO-exposed group:** sterilizing medical supplies, treating spices, and/or manufacturing/testing medical sterilizers
- **Endpoints:**
  - lymphohematopoietic cancer mortality and in particular for lymphoid cancer [i.e., non-Hodgkin lymphoma (NHL), myeloma, and lymphocytic leukemia]
  - breast cancer incidence in females
- **Cancer/mortality:** follow-up through Dec. 31, 1998, the date of death or breast cancer diagnosis, or the date of loss to follow-up, whichever was earlier

Ethylene oxide
Epidemiological Study in Humans
(Steenland et al. 2003, 2004)

- **Measured workplace EtO concentrations**
  - Measurements during 1976–1985
  - 2700 individual time-weighted exposure values
- **Estimated individual EtO exposures using a regression model**
  - Facility
  - Exposure category
  - Time period

Ethylene oxide
US EPA – Modeling Considerations

- **Extra risk = $(R_x - R_o)/(1 - R_o)$**
  - R_x is the lifetime risk in the exposed population
  - R_o is the lifetime risk in an unexposed population (i.e., the background risk)
- **Risk estimates were calculated using the β regression coefficients and a life-table analysis that accounts for competing causes of death**
  - Life table analysis
  - 85 years
  - Occupational vs environmental

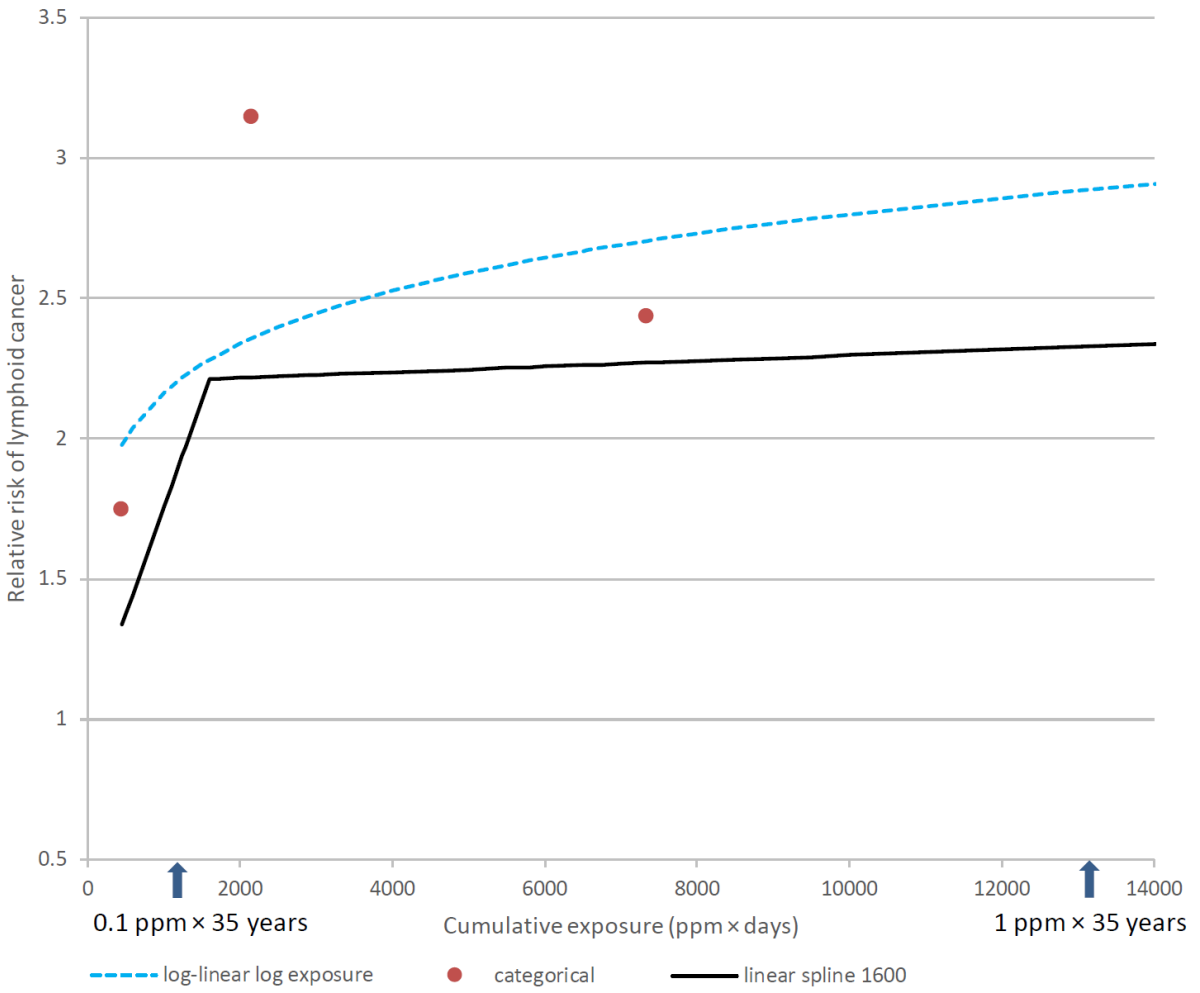
Ethylene oxide Lymphoid Cancer Exposure-Response and IUR Calculations

- Various exposure-response models, different lag periods and different mathematical transformations of the exposure variable

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

- OEHHA found that none of the models evaluated fit the underlying NIOSH study data better than the two-piece linear spline model selected by US EPA

Relative risk estimates for lymphoid cancer from occupational ethylene oxide (US EPA, 2016)



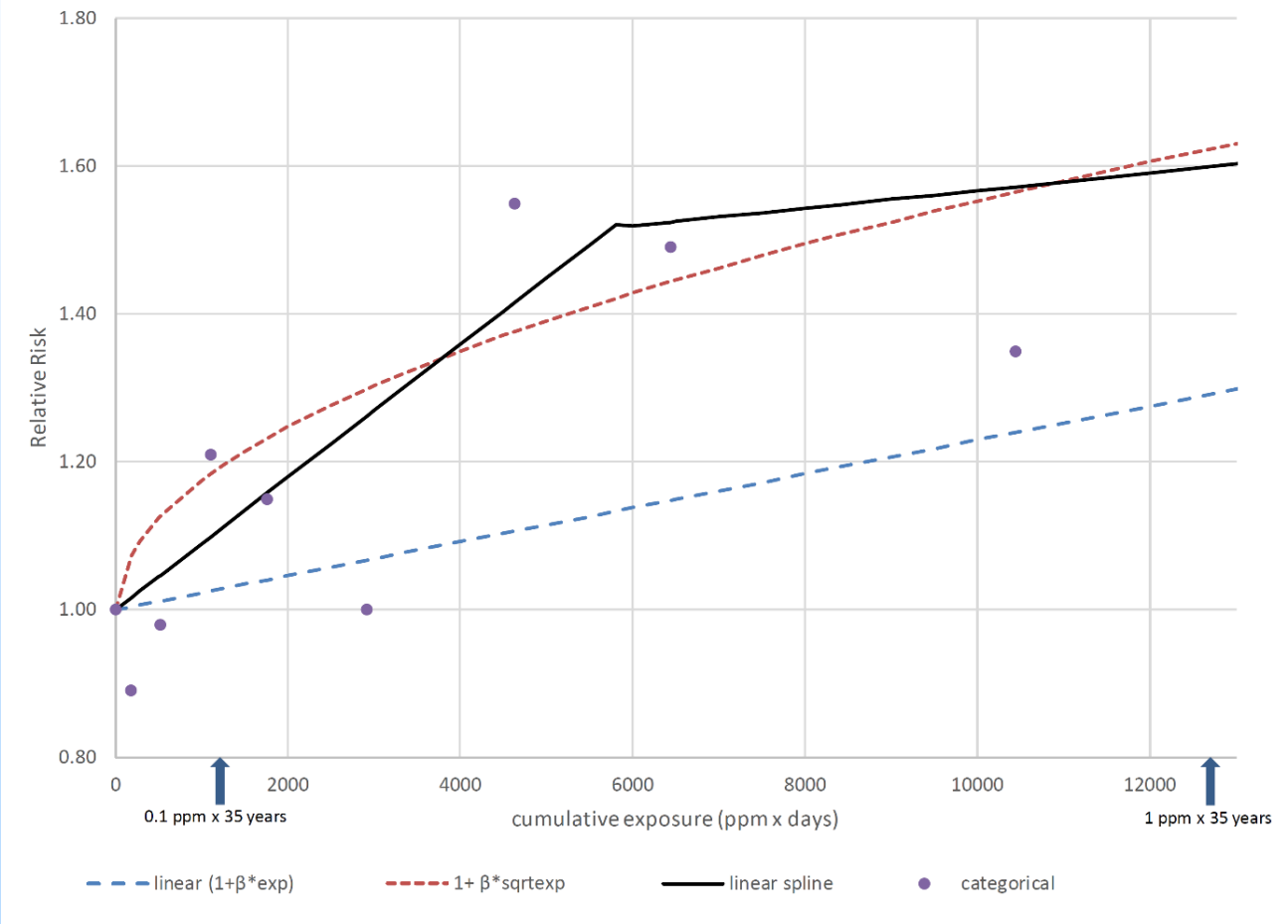
Ethylene oxide
Lymphoid Cancer IUR

- **LEC_{01} (lower 95% confidence limit on the EC_{01}, the estimated effective concentration associated with 1% extra risk) for excess lymphoid cancer mortality**
  - Using a life-table analysis and the lower spline segment from a two-piece linear spline model
  - Linear low-dose extrapolation from the LEC_{01}
- **IUR for lymphoid cancer incidence of 5.26 $(ppm)^{-1}$**
- **OEHHA replicated US EPA's above calculations and obtained the same result**

Ethylene oxide
Breast Cancer Exposure-Response and IUR Calculations

- Model selection (US EPA): Two-piece linear spline regression model
- OEHHA evaluated several other exposure-response models and none of the models resulted in a better visual fit or had lower *p*-values than the two-piece linear spline regression model selected by US EPA.
- OEHHA concluded that US EPA's two-piece linear spline model is the most appropriate exposure-response model for estimating the lower-exposure breast cancer risks of EtO

Relative risk estimates for breast cancer from occupational ethylene oxide (US EPA, 2016)



Ethylene oxide
Breast Cancer IUR

- **Breast cancer risk estimates:** from breast cancer incidence in the same occupational cohort
  - Used the same life-table approach as with lymphoid cancer, the lower spline segment from the two-piece linear spline model for breast cancer, and linear low-dose extrapolation
  - Risks at lower exposures estimated by linear extrapolation from the LEC_{01}
- **IUR for Breast cancer incidence = 1.48 $(ppm)^{-1}$**

Ethylene oxide
Draft Updated IUR

- **Adult-exposure-based EtO Cancer IUR:**
  - 3.3×10^{-3} per µg/m^3 (6.1×10^{-3} per ppb)
  - Combining lymphoid cancer in males and females and breast cancer in females

- **The IUR describes the excess cancer risk (i.e., risk over and above background risk) associated with inhalation exposure to an EtO concentration of 1 µg/m^3.**

Ethylene oxide
Cancer Slope Factor

- **Cancer Slope Factor (CSF) calculation:**

$$\mathrm{CSF} = \frac{\mathrm{IUR} \times 70\ \mathrm{kg} \times \mathrm{CF}}{20\ \mathrm{m^3}} = 12\ \mathrm{per\ mg/kg\text{-}day}$$

Given

70 kg = reference human body weight

20 m^3 = reference human inspiration rate per day

CF = conversion factor from mg to µg (1 mg = 1000 µg)

Ethylene oxide
Using the IUR and CSF for Risk Assessments

- The IUR and CSF describe excess cancer risk (i.e., risk over and above background) associated with exposure to 1 µg EtO/m^3 air or 1 mg of EtO per kg bodyweight per day, respectively.
- The background risk includes cancer risk due to endogenous EtO exposures.
- The EtO IUR and CSF are meant for use in computing risk levels associated with non-zero exogenous exposures (i.e., exposures >0 ppm or 0 mg/kg-day).

Ethylene oxide
Inhalation Unit Risk Comments

- **Written comments can be submitted online**

  https://oehha.ca.gov/comments

- **Comments can also be submitted via email to Kannan Krishnan (Kannan.Krishnan@oehha.ca.gov)**