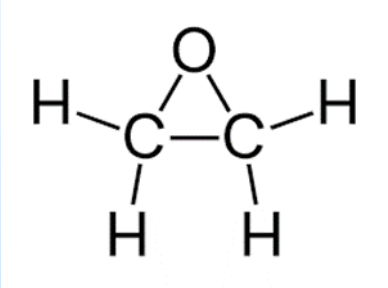
# Informational Item

# Draft Updated Cancer Inhalation Unit Risk Factor for Ethylene Oxide




***Office of Environmental Health Hazard Assessment***

***Presentation to the***

***Scientific Review Panel on Toxic Air Contaminants***

***February 2, 2024***

# Development of Inhalation Unit Risk Factor for Ethylene Oxide

# Public Workshops on Draft Updated IUR for EtO

- Public comment period commenced on April 7, 2023
- Public comment period ended on June 14, 2023
- Two public workshops conducted:
  - Northern California (May 5, 2023)
    - In-person
    - Webcast
  - Southern California (May 16, 2023)
    - In-person

# Outline

- Use of Inhalation Unit Risk Factors (IURs) in the Hot Spots program
- Summary of OEHHA's updated IUR public comment draft for Ethylene Oxide (EtO)
- Topics in public comments
  - Discussion of issues raised
- Next steps
- Points for Panel discussion and input

# The use of IURs in California's Air Toxics Hot Spots Program

- **OEHHA develops Health Guidance Values (HGVs) for high priority Hot Spots chemicals**
  - Derive HGVs based on scientific evidence and following OEHHA's methodology
  - Apply to **emissions** from stationary sources (facilities) required to submit emissions inventory reports to CARB

- **Carcinogens: Inhalation Unit Risk Factors (IURs)**
  - Used to estimate lifetime cancer risks associated with inhalation exposure to a concentration of 1 microgram (µg) per cubic meter in air
  - Used to determine additional cancer risk due to exposures to **emissions** from stationary sources

# EtO - Inhalation Unit Risk Factor (IUR)

- IUR of $8.8 \times 10^{-5}$ $(\mu g/m^3)^{-1}$ [$1.6 \times 10^{-3}$ $(ppb)^{-1}$] developed in 1987 by California Department of Health Services as part of the Toxic Air Contaminant (TAC) program

- New relevant human epidemiological studies were published since adoption of Hot Spots value in 1987

- US EPA's (2016) updated cancer IUR for EtO was based on new human epidemiological data after a comprehensive evaluation of its carcinogenicity

# Summary of OEHHA's Draft IUR Update for EtO

- Leverage work from other health agencies
- Build upon authoritative review conducted by other agencies (following evaluation)

- **Starting point:**
  - US EPA (2016) assessment – studies published since TAC IUR development (1987)

- **OEHHA Effort:**
  - Focused on literature search since US EPA's 2016 assessment
  - Evaluated US EPA's dose-response model selection

# Ethylene oxide: Uses and Emissions

- **Uses**
  - Chemical intermediate in producing other chemicals
  - Sterilizer for medical and laboratory equipment/supplies
  - Fumigant for dried herbs and spices
- **Emissions in California**
  - CARB reported a total of 556 pounds of EtO emissions statewide for 2020
  - Concentrations near two medical sterilizer facilities in the South Coast Air Basin ranged from undetectable to as high as 103 and 139 ppb (parts per billion)
  - Detected in ambient air
  - Component of cigarette smoke
  - Release from residues in consumer products

# EtO Cancer Hazard Identification

- **OEHHA (1987)** – "known to the state to cause cancer" for the purposes of Proposition 65
- **IARC (2012)** – "carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals supported by strong evidence of a genotoxic mechanism.
- **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.
- **NTP (2021)** – "known to be a human carcinogen"

# EtO Toxicokinetics

- **Physiologically-based pharmacokinetic models** show comparable blood concentrations across humans, rats and mice over a limited exposure range (≤100 ppm or ≤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
- **Elimination:** primarily via urine and exhalation

# EtO Endogenous Production

- **Endogenous EtO production:**
  - Produced by Cytochrome P450-mediated conversion of ethylene
  - Contributes to adduct levels, such as hemoglobin adduct N-2-hydroxyethylvaline (HEV), in humans and other species
- **Endogenous ethylene production results from:**
  - 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

# 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
    - Consistent mutagenic and clastogenic action
  - **ATSDR (2022)**
    - Demonstrated genotoxicity
- **3 additional studies since US EPA (2016) review**
  - Consistent with the overall evidence

# Quantitative Cancer Risk Assessment

- **OEHHA's draft updated EtO IUR is based on US EPA's 2016 analysis of the exposure-response relationship**
  - Human epidemiological studies are preferred over animal studies due to direct relevance (i.e., no need for extrapolation)
  - NIOSH study (reported in Steenland et al., 2003; 2004) is of high quality and is the best available study for exposure-response analyses
  - Two-piece linear spline model is the most appropriate for assessing the EtO cancer risks
  - No new scientific information necessitating a change to the US EPA IUR

# Epidemiological Study in Humans
# NIOSH (Steenland et al., 2003, 2004)

- **The National Institute for Occupational Safety and Health (NIOSH) retrospective cohort study**
  - Included 17,530 workers from 13 US sterilization facilities in exposure-response analyses
- **High quality study**
  - Quantitative exposure estimates for individual workers
  - Large cohort size
  - Inclusion of women
  - Multiple study locations
  - Absence of important co-exposures
- **OEHHA's review**
  - Updated Hill criteria for causation
  - NTP's risk of bias tool

# Epidemiological Study in Humans NIOSH (Steenland et al. 2003, 2004)

- **EtO-exposed group:** sterilizing medical supplies, treating spices, and/or manufacturing/testing medical sterilizers
- **Endpoints:**
  - Lymphoid cancer [i.e., non-Hodgkin lymphoma (NHL), myeloma, and lymphocytic leukemia]
  - Breast cancer 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

# Epidemiological Study in Humans NIOSH (Steenland et al. 2003, 2004)

- **Measured workplace EtO concentrations**
  - Workplace air measurements from 1976–1985
  - 2,700 individual time-weighted exposure values
- **Estimated individual EtO exposures using a validated regression model**
  - Facility
  - Exposure category
  - Time period

# 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

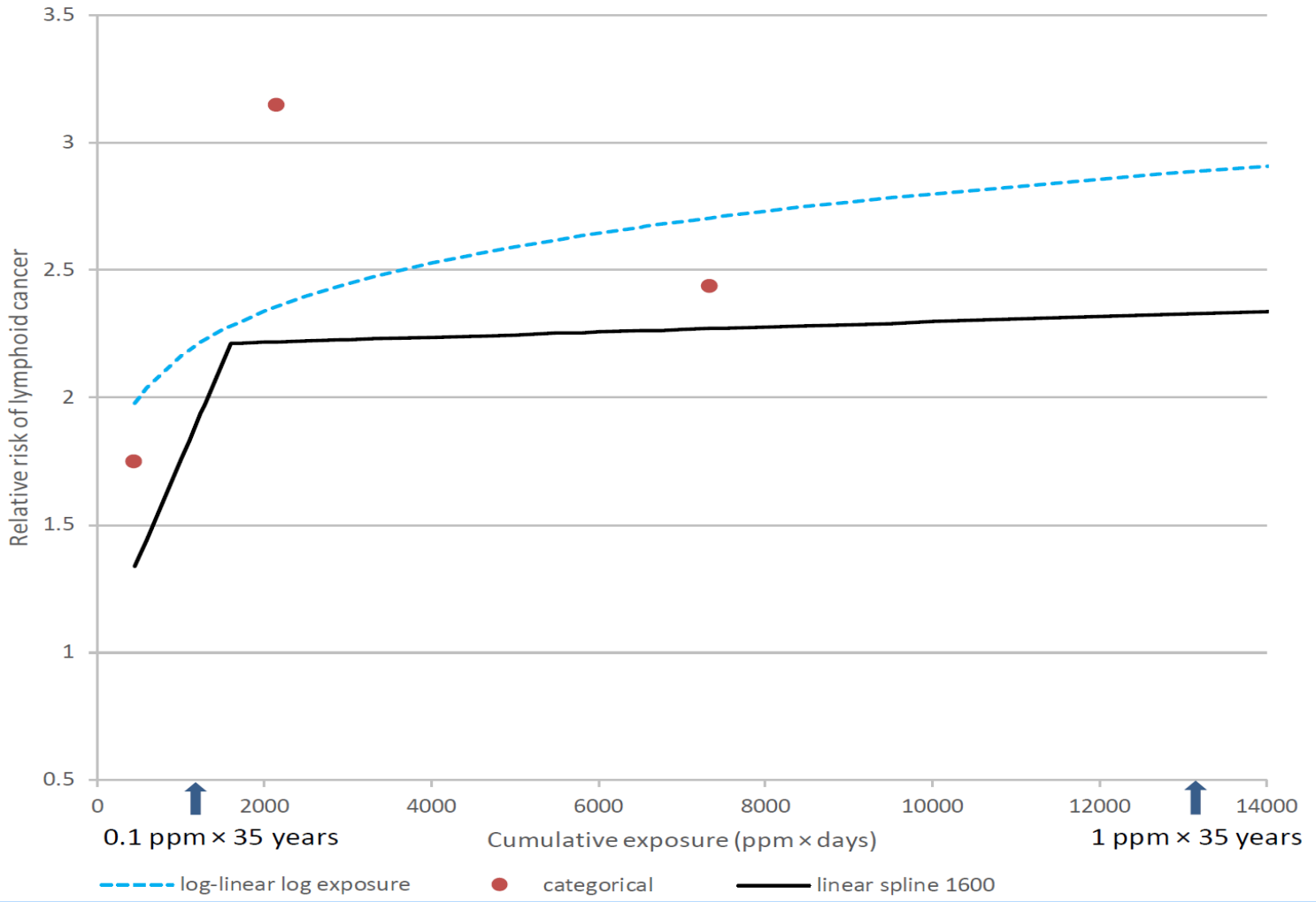
# Lymphoid Cancer Exposure-Response

- Assessment included various exposure-response models, lag periods, and mathematical transformations of the exposure variable

- US EPA (2016) concluded the two-piece linear regression spline model with a knot at 1,600 ppm-days provided the best biologically plausible fit to the data, especially in the lower exposure region

- OEHHA found that none of the other models evaluated fit the study data better than the two-piece linear spline model

# Relative risk estimates for lymphoid cancer from occupational EtO exposure (US EPA, 2016)



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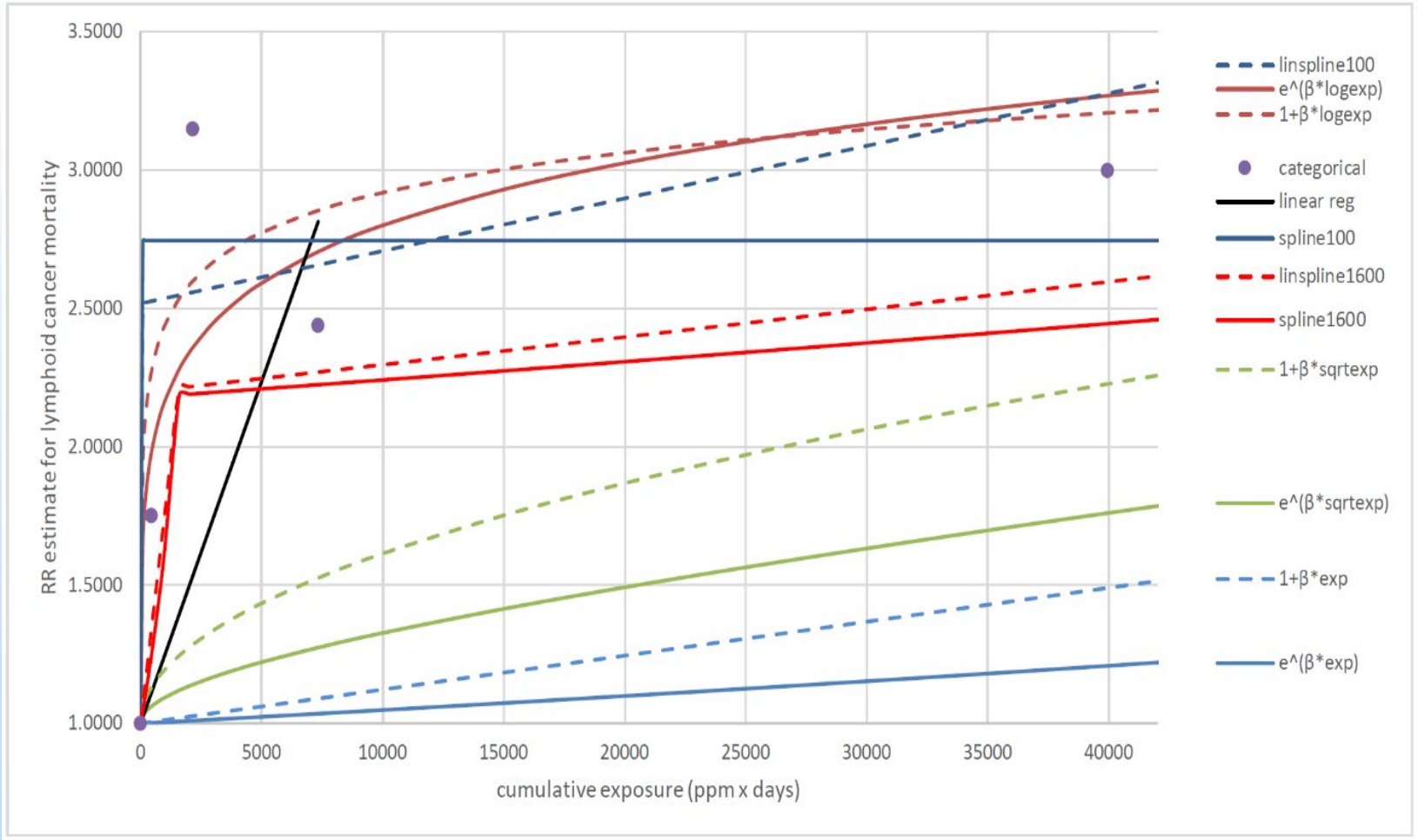


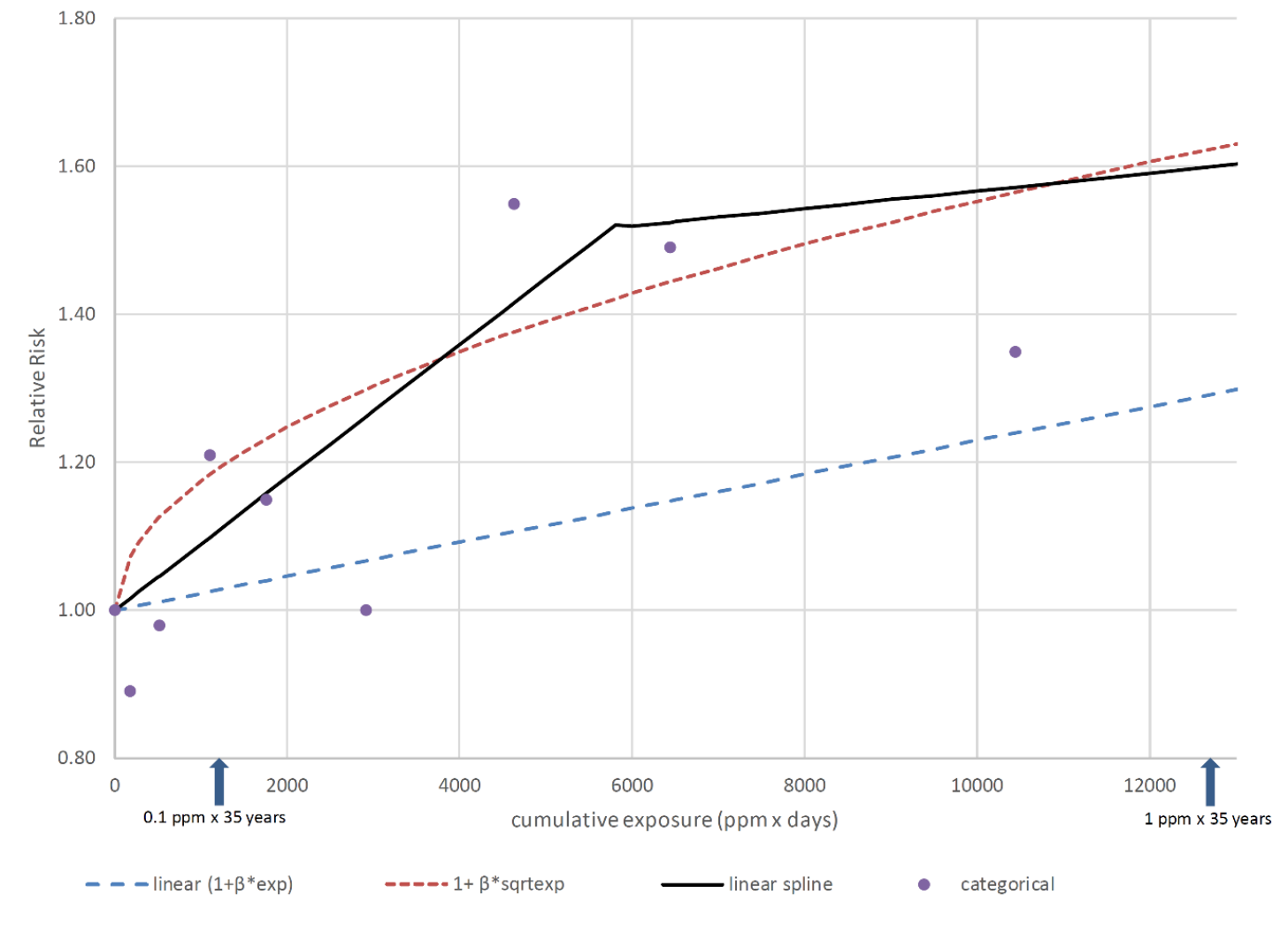
# Lymphoid Cancer IUR

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

# Breast Cancer Exposure-Response

- **Model selection (US EPA): Two-piece linear spline regression model**
- **OEHHA's evaluation:**
  - Included several other exposure-response models
  - Determined none of the models had a better visual fit or lower *p*-values than the two-piece linear spline regression model
  - 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 EtO exposure (US EPA, 2016)



# Breast Cancer IUR

- **Breast cancer risk estimates:** from breast cancer incidence in the same occupational cohort and used:
  - Same life-table approach as with lymphoid cancer
  - 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 $(ppm)^{-1}$**

# Updated EtO IUR
# Public Review Draft

- **Adult-exposure-based EtO Cancer IUR:**
  - $3.3 \times 10^{-3}$ $(\mu g/m^3)^{-1}$ [$6.1 \times 10^{-3}$ $(ppb)^{-1}$]
  - Combined lymphoid cancer in males and females and breast cancer in females

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

# EtO Cancer Slope Factor

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

$$CSF = \frac{IUR \times 70\ kg \times CF}{20\ m^3} = 12\ (mg/kg\text{-}day)^{-1}$$

Given that:

70 kg = reference human body weight

20 $m^3$ = reference human inspiration rate per day

CF = conversion factor from mg to µg (1 mg = 1,000 µg)

# Using the IUR and CSF for Risk Assessment

- The IUR and CSF describe excess cancer risk (i.e., risk above background) associated with EtO exposure at 1 μg/$m^3$ air or 1 mg per kg bodyweight per day, respectively.
- The EtO IUR is meant for use in computing risk levels associated with exposure to EtO emitted by facilities under the Hot Spots program, above the endogenous and ambient background.

# Questions and Initial Input on the Draft Document

# Public comments received on draft updated EtO IUR

- **Received comments from 8 stakeholders**
  - American Chemistry Council
  - EtO Sterilization Association
  - Jeffrey Chuang
  - Life Sciences Coalition
  - Lucy Frasier Toxicology Consulting, on behalf of Life Sciences Coalition
  - South Coast Air Quality Management District
  - Sterigenics
  - UCSF Program on Reproductive Health and Environment
- **Full text of the comments received can be viewed at www.oehha.ca.gov/comments**

# Comment topics

1. Background exposures
2. Study selection for dose-response assessment
3. Dose-response modeling
4. IUR development and application

Topic 1

# BACKGROUND EXPOSURES

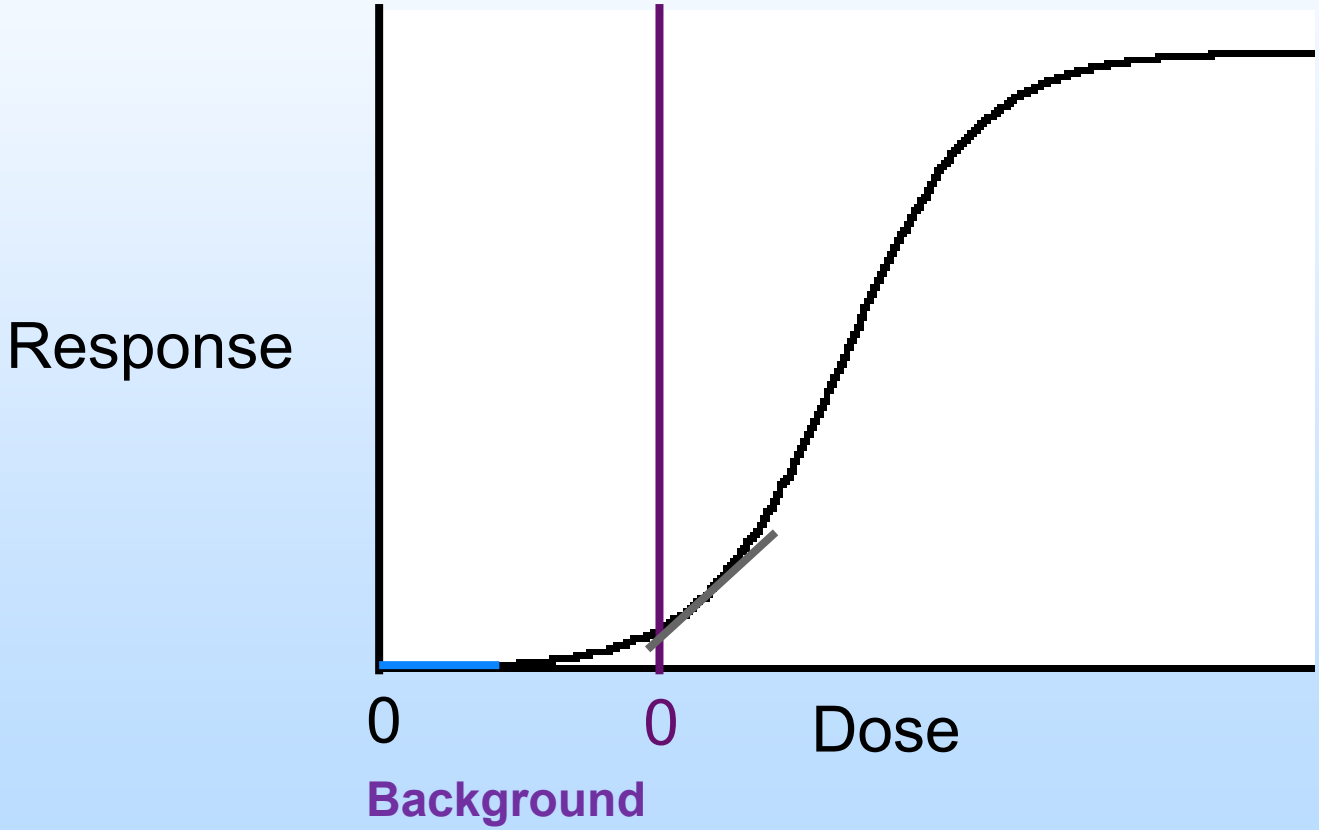
# Background exposures

## Issues raised

**1.1** Accounting for ambient and endogenous background EtO levels in IUR development

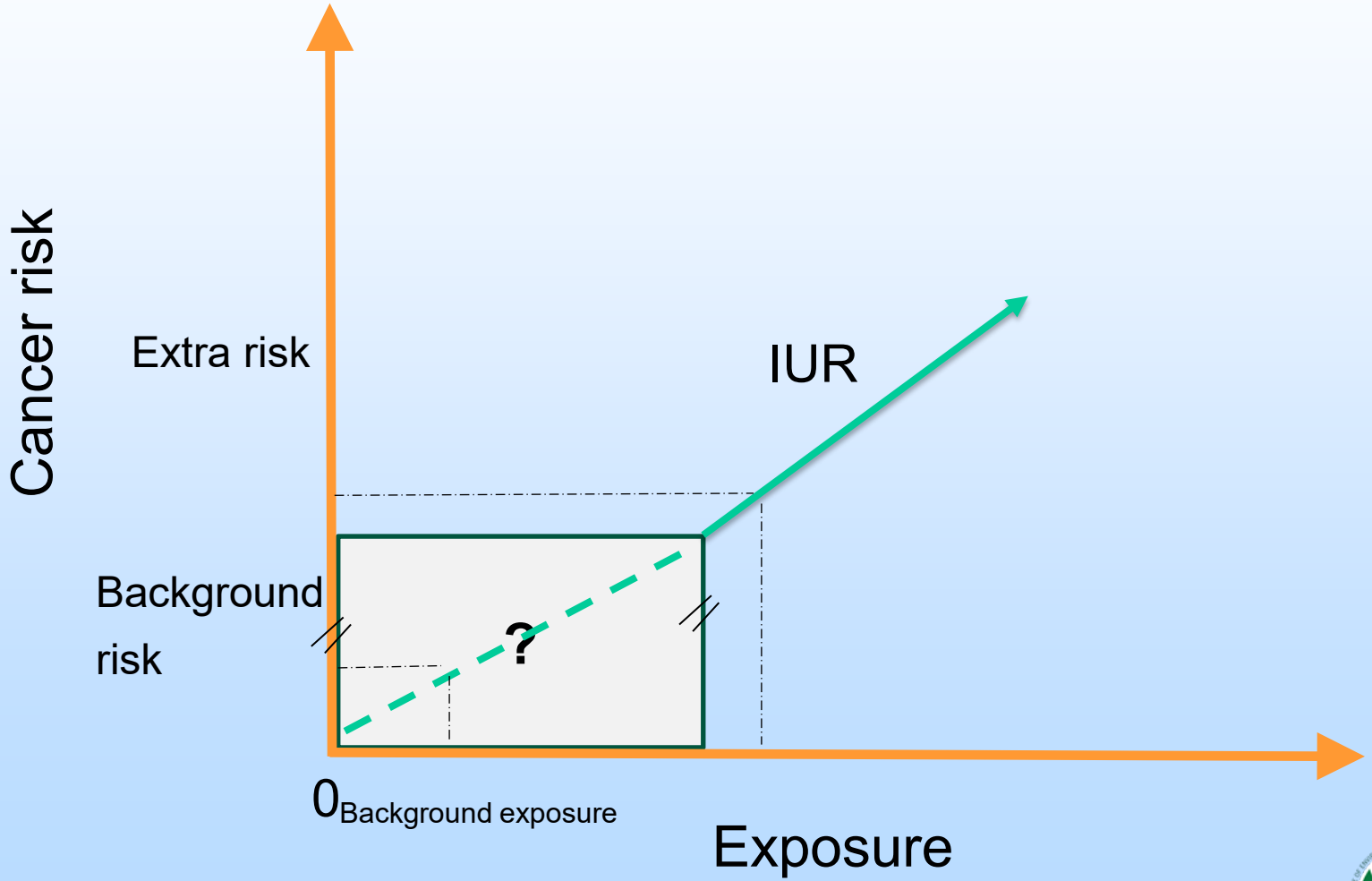
**1.2** Implication of updated IUR in terms of background risk levels

# Background: Implications for Dose-Response



# IUR for EtO

## For computing extra risk above background



# IUR derivation from NIOSH study:
## Risk and exposure are above the background

**Occupational exposure and extra risk of cancer**

**Background Exposure**

- Endogenous
- Ambient

**Background risk**

- Lymphoid Cancer
- Breast Cancer

# Background exposures

## Initial considerations

- Updated IUR is based on the cancer risk **above** background
- IUR is not for interpreting endogenous levels of EtO but concentrations **above** background resulting from a facility's emissions

# Clarifying Questions and Panel Input

- Consideration of background exposure
- Clarification of the use of IUR under Hot Spots program

Topic 2

# STUDY SELECTION FOR DOSE-RESPONSE ASSESSMENT

# Study selection for dose-response assessment

## Issues raised

**2.1** Consideration of studies other than NIOSH study

**2.2** Validity of NIOSH exposure model

# Study selection for dose-response assessment

## Initial considerations

- Limitations of other studies e.g., Union Carbide Corp. cohort study
  - Smaller sample size
  - Unclear accuracy of exposure assessment
  - Potential for co-exposures
  - Failure to include women
  - No use of appropriate exposure lags
- NIOSH exposure regression model
  - Based on many measurements
  - Excellent model validation ($r^2 = 0.85$)
  - Exposures prior to 1978 informed by several factors

Topic 3

# DOSE-RESPONSE MODELING

# Dose-response modeling

## Issues raised

**3.1** Individual NIOSH study data unavailable to conduct an independent evaluation

**3.2** Used categorical data to assess the model fit

**3.3.** Two-piece spline statistical methods:

- Calculation of variance
- Small differences in *p*-values

# Dose-response modeling

## Initial considerations

- Key information available to evaluate the quality of NIOSH cohort study and the dose-response relationship
- Categorical data/results were calculated using long standing, widely accepted methods & considered to be valid by US EPA and OEHHA

# Dose-response modeling

## Initial considerations (contd.)

- Statistical approach is widely accepted and appropriate methods were used
- Model selection is based on several considerations:
  - Evaluations of bias and causal inference
  - Parsimony
  - Biological plausibility
  - Differences between higher and lower dose effects
  - *p* value and other statistical considerations

# Dose-response modeling

## Issues and considerations

## 3.4 TCEQ dose-response modeling

- IUR is 2,000 times lower than the US EPA value
- Cox Proportional Hazards model inconsistent with the underlying epidemiological data
- Reality checks did not account for healthy worker effect and related effects

# Dose-response modeling

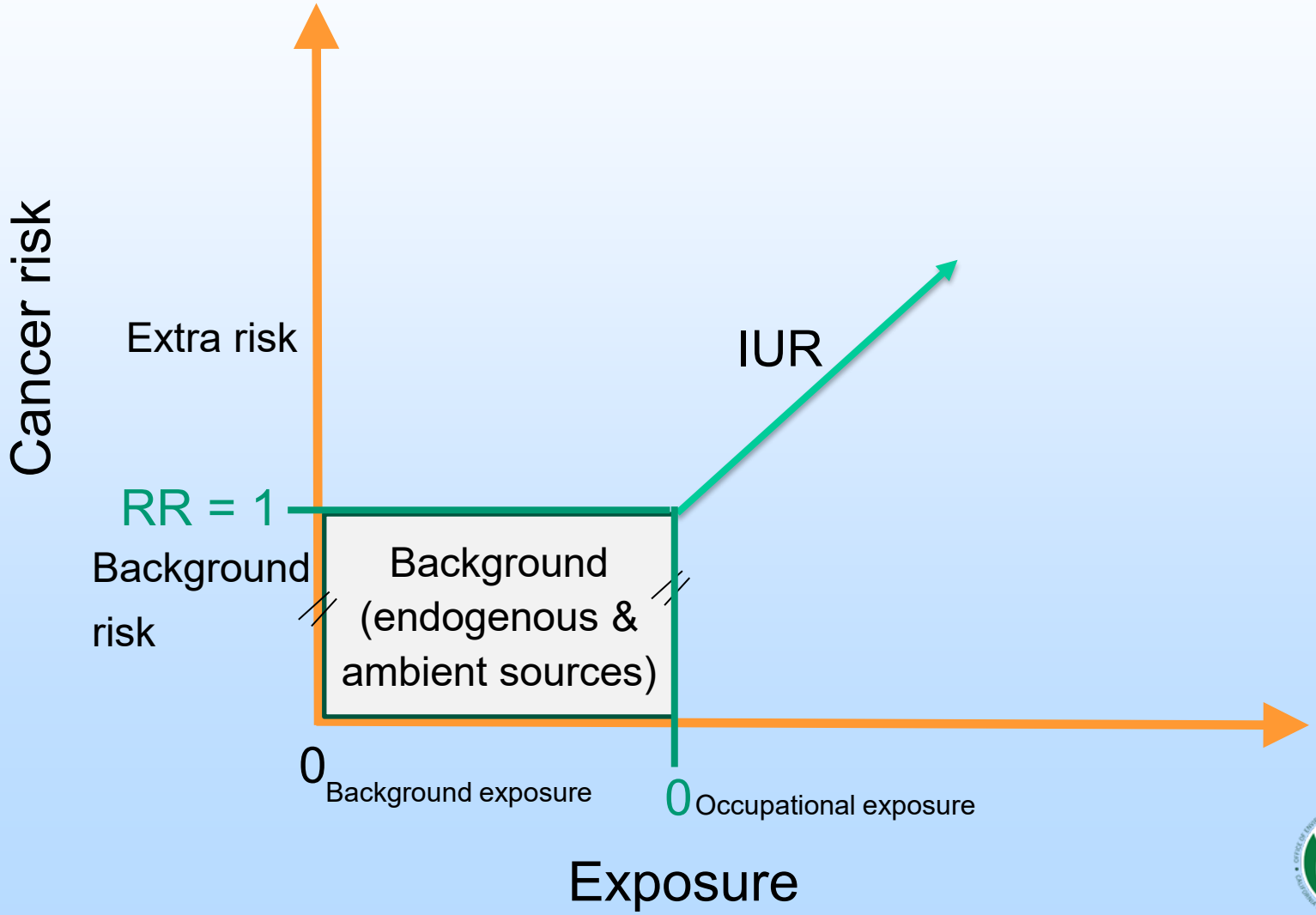
## Issues raised (contd.)

**3.5** Reality check based on background (endogenous and ambient) levels of EtO

**3.6** Use of EtO hemoglobin adducts (HEV) for managing and communicating EtO-related risks

# IUR for EtO

## Derivation from the Occupational Exposures



# Dose-response modeling

## Initial considerations (contd.)

- Unreasonable to use endogenous levels for "reality check" because of unknown contribution of endogenous levels of EtO and other factors to the baseline risk
- IUR is for calculating cancer risk above the baseline, and for EtO exposures above the background
- EtO hemoglobin adducts useful as biomarkers of exposure but not for dose-response assessment

# Dose-response modeling

## Issues raised (contd.)

**3.7** Lack of other supportive evidence for two-piece linear spline model (e.g., animal cancer bioassays, genotoxicity data)

**3.8** Mode of action for EtO carcinogenicity

# Dose-response modeling

## Initial considerations (contd.)

- US EPA's two-piece linear spline model fit the data well and is consistent with OEHHA's default low dose linearity assumption

- Sufficient weight of evidence to support a mutagenic mode of action (US EPA 2016)
  - IUR for EtO derived from human cancer epidemiological data
  - Knowing the mechanism is not a prerequisite for using human data to derive an IUR

# Clarifying Questions and Panel Input

- Selection of NIOSH study
- Model selection (Two-piece linear spline model of US EPA)

Topic 4

# IUR DEVELOPMENT AND APPLICATION

# 4.1. IUR Selection

**Issue raised and Initial Considerations**

- US EPA analyses provided two IURs

1. Adult-exposure based value
   - **IUR = $3.3 \times 10^{-3}$ $(\mu g/m^3)^{-1}$**
   - In OEHHA's public review draft
   - Assumes risk is independent of age

2. Value for application of Age Susceptibility Factors (ASFs):
   - **IUR = $3.0 \times 10^{-3}$ $(\mu g/m^3)^{-1}$**
   - Compatible with application of ASFs

# 4.2. IUR Application

## Issue raised and Initial Considerations

**Issue raised:**

- Difference in cancer risk estimates using Air Toxics “Hot Spots” methodology compared to US EPA’s risk estimate

**Considerations:**

- Not unique to EtO
- Methodological: Difference in cancer risk calculation while using concentration *vs* dose

# Points for Panel Discussion and Input

- Consideration of background exposure
- Selection of NIOSH study
- Model selection (Two-piece linear spline model of US EPA)
- Adopting US EPA's final value
- Clarification of the use of IUR under Hot Spots program

# Next Steps

- Develop written responses to public comments
- Revise the draft in consideration of public comments and SRP input at this meeting
- Bring revised draft to SRP for review at future meeting