



# Overview of the Draft Carcinogenicity Assessment of Ethylene Oxide (EtO)

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Ethylene Oxide Augmented Chemical Assessment Advisory Committee of  
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This presentation will cover:

- Overview of background information from September presentation
- Hazard characterization conclusion
- Mode of action conclusion
- Modeling of the exposure-response data from the NIOSH epidemiology study

- The current (2014) External Review Draft addresses:
  - major SAB (2007) and public comments on the 2006 External Review Draft (Appendix H).
  - most of the shorter-term 2011 NRC recommendations (Appendix K).
  - major public comments on the 2013 public comment draft (Appendix L).
- In response to SAB (2007) recommendations, EPA conducted extensive additional exposure-response modeling of the epidemiologic data, and EPA is seeking SAB review of this new modeling work (Chapter 4 and Appendix D).
- The assessment has been updated to June 2010 with respect to new literature and into 2013 with respect to major new studies (Appendix J) – none of the new studies identified since 2010 were found to impact the final conclusions of the assessment.

- Ethylene Oxide is a gas at room temperature.
- Uses of EtO:
  - The greatest amount of EtO is used as a chemical intermediate.
  - EtO is also used as a sterilizing agent.
- Exposures:
  - Occupational exposures occur as a result of the production and use of ethylene oxide.
  - Environmental exposures occur primarily from emissions from facilities that produce and use EtO.
- EPA has an interest in:
  - Risks from environmental air concentrations of EtO.
  - Occupational risks occurring from the sterilization uses of EtO.

- Inhalation exposure only
- Carcinogenicity only
  - Cancer hazard characterization
  - Mode of action analysis
  - Unit risk estimates (for environmental exposure scenarios)
  - Extra risk estimates for occupational exposure scenarios



## Cancer Hazard Characterization

Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, the total weight of evidence supports the characterization of “**carcinogenic to humans**” (by the inhalation route of exposure), consistent with EPA’s 2005 *Guidelines for Carcinogen Risk Assessment*.

- (1) strong evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers,
  - (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice,
  - (3) clear evidence that EtO is genotoxic/mutagenic, and
  - (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors.
- Majority of 2007 SAB panel agreed with hazard characterization conclusion of “carcinogenic to humans”.
  - More recent studies support the conclusion of “carcinogenic to humans”.
  - This conclusion is consistent with the conclusions of the International Agency for Research on Cancer and the National Toxicology Program.



## Two Inadvertently Omitted Epidemiology Studies

- Morgan et al. (1981)
  - Mortality study of 767 male workers potentially exposed to EtO in EtO production facility
- Ambroise et al. (2005)
  - Mortality study of 181 male pest-control workers; 140 exposed to EtO
- Both studies have small numbers of total cancer deaths (11 and 21, respectively) and are essentially uninformative regarding risks for specific cancer types from EtO exposure.
- EPA determined that inclusion of these studies would not alter the cancer hazard characterization.
- Additional details and HERO links to the studies were provided to the SAB as supplemental information.
- These studies will be included in the final assessment.

- EtO is a direct-acting alkylating agent.
- EtO has been shown to be genotoxic/mutagenic in a wide variety of in vitro and in vivo tests.
- No compelling evidence for alternative or additional modes of action.
  - EPA considered other modes of action proposed in public comments and determined that they have inadequate support and do not provide a basis for alternative conclusions in the assessment (Section J.3.2 of Appendix J and comment #6 of Appendix L).

- **CONCLUSION of Drafts:** Weight of evidence supports a **mutagenic mode of action** for EtO carcinogenicity.
- 2007 SAB panel agreed with conclusion of a mutagenic mode of action.
- More recent information does not alter this finding.
- **IMPLICATIONS of mutagenic mode of action:**
  - Support for linear low-dose extrapolation.
  - Support for assumption of increased early-life susceptibility and application of age-dependent adjustment factors (ADAFs), in accordance with EPA's 2005 *Supplemental Guidance*.



## Derivation of Unit Risk Estimates Based on Human Data: Datasets

- NIOSH study of sterilization workers selected for exposure-response modeling
  - based on multiple considerations: quality of exposure estimates, cohort size, absence of co-exposures, inclusion of women.
  - 2007 SAB panel concurred that NIOSH study was best single study for derivation of risk estimates.
  - In response to other 2007 SAB panel recommendations, EPA re-evaluated the Union Carbide study but determined that this study had many limitations compared to the NIOSH study, particularly in the exposure assessment, so it was not used for modeling (Appendices A and H).
- NIOSH datasets that were modeled:
  - Lymphoid cancer mortality in males and females
  - Breast cancer incidence in subcohort of females with interviews
    - Also breast cancer mortality and breast cancer incidence in the full breast cancer incidence cohort



# NIOSH Exposure Assessment

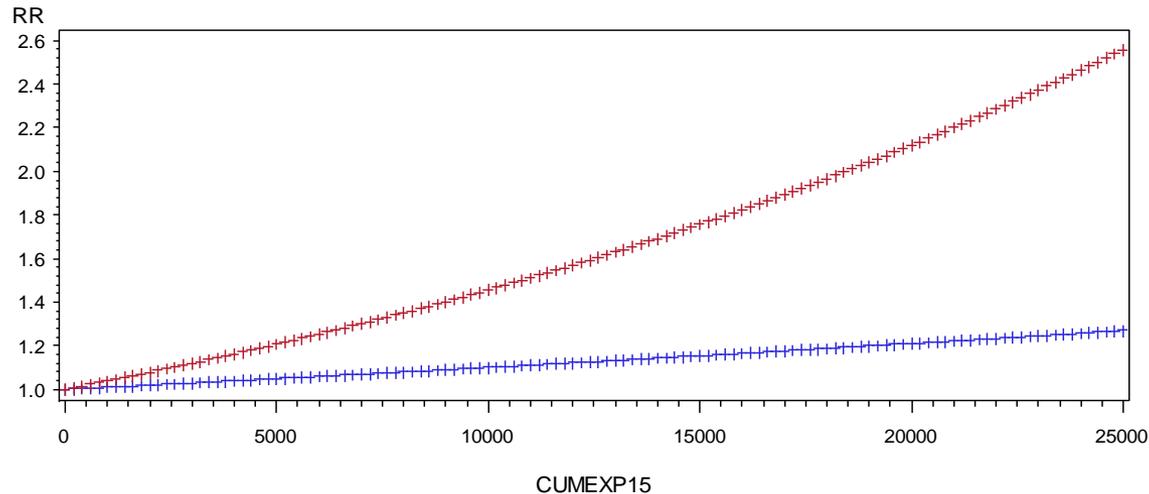
- NIOSH study has quantitative exposure estimates for 17,530 workers from 13 sterilizing facilities.
- Worker exposure estimates were based on work histories and job/location/year-associated exposure levels obtained from a regression model.
- Exposure model development and evaluation described in detail in Hornung et al. (1994)
- Data for regression model were from personal samples from 18 different sterilization facilities (12 for model development; 6 for evaluation) from 1976 – 1985.
- Of > 20 variables investigated, 7 exposure factors included in the final model were: exposure category, product type, size of sterilizer, engineering controls (rear exhaust, aeration procedure), days after sterilization, and calendar year.
- Regression model accounted for 85% of the variation in average exposure levels from the independent test data.



## Derivation of Unit Risk Estimates Based on Human Data: Models

- EPA investigated a number of exposure-response models, including additional continuous exposure models, as recommended by the 2007 SAB panel.
- Many of the models had limitations, primarily due to the supralinear exposure-response relationships (illustrated in following graphics).
  - As suggested by SAB (2007), EPA also investigated use of “errors in variables” modeling to adjust for exposure misclassification; however, the data used to develop the NIOSH exposure model were no longer available.
- For lymphoid cancer, EPA did not find a suitable continuous exposure model and thus used a linear regression of categorical results.
- For breast cancer incidence, EPA selected the best-fitting continuous exposure model (2-piece linear spline model).

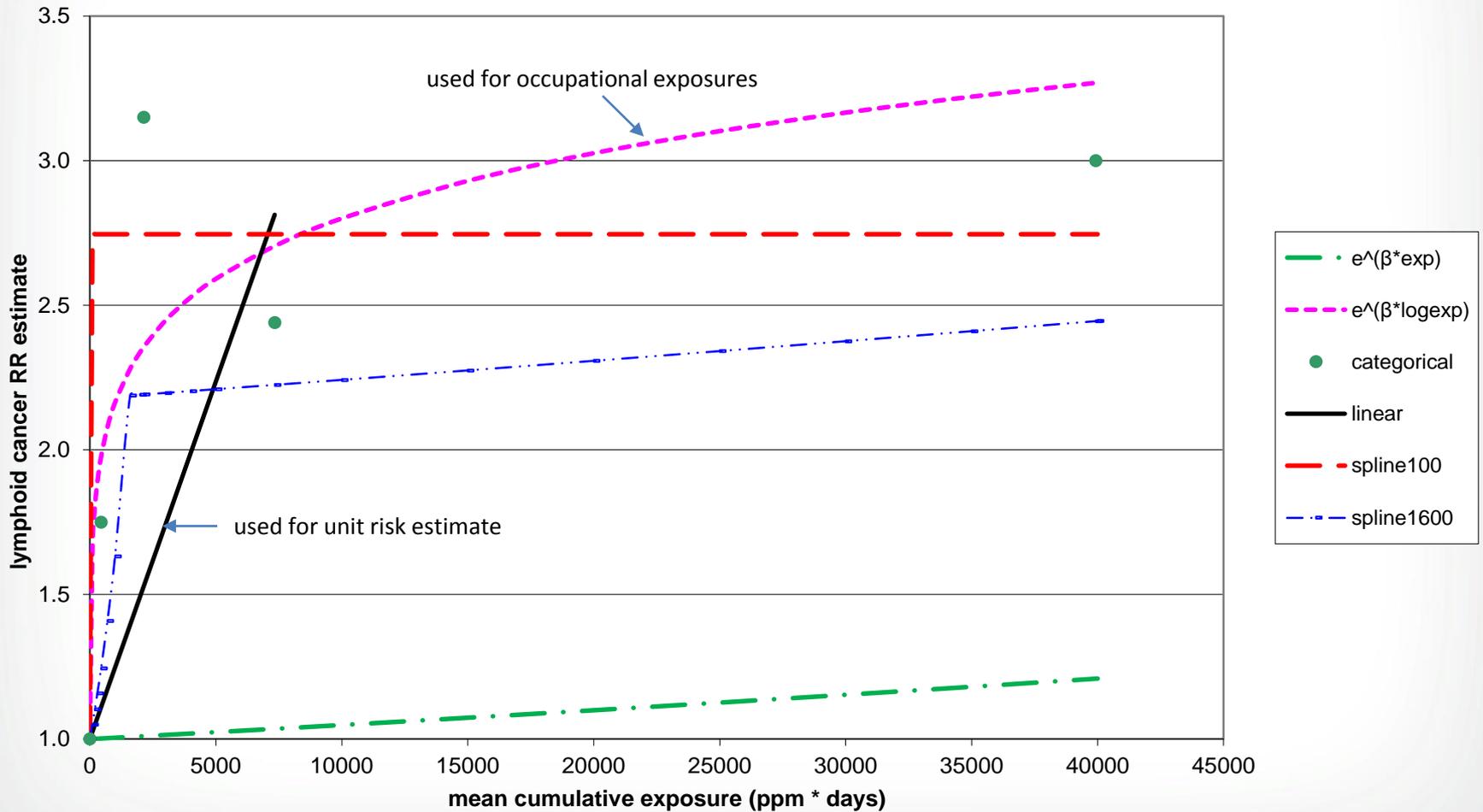
Figure demonstrating that the data for the top 5% of exposures attenuate the slope of log-linear (and, similarly, linear) models



**Figure. Breast cancer incidence.** Comparison of log-linear curve ( $RR = e^{(\beta \times \text{cumexp})}$ ) with all the data (blue line with lower slope) and the log-linear curve after excluding data in the top 5% of exposure (>27,500 ppm-days) (red line with higher slope).

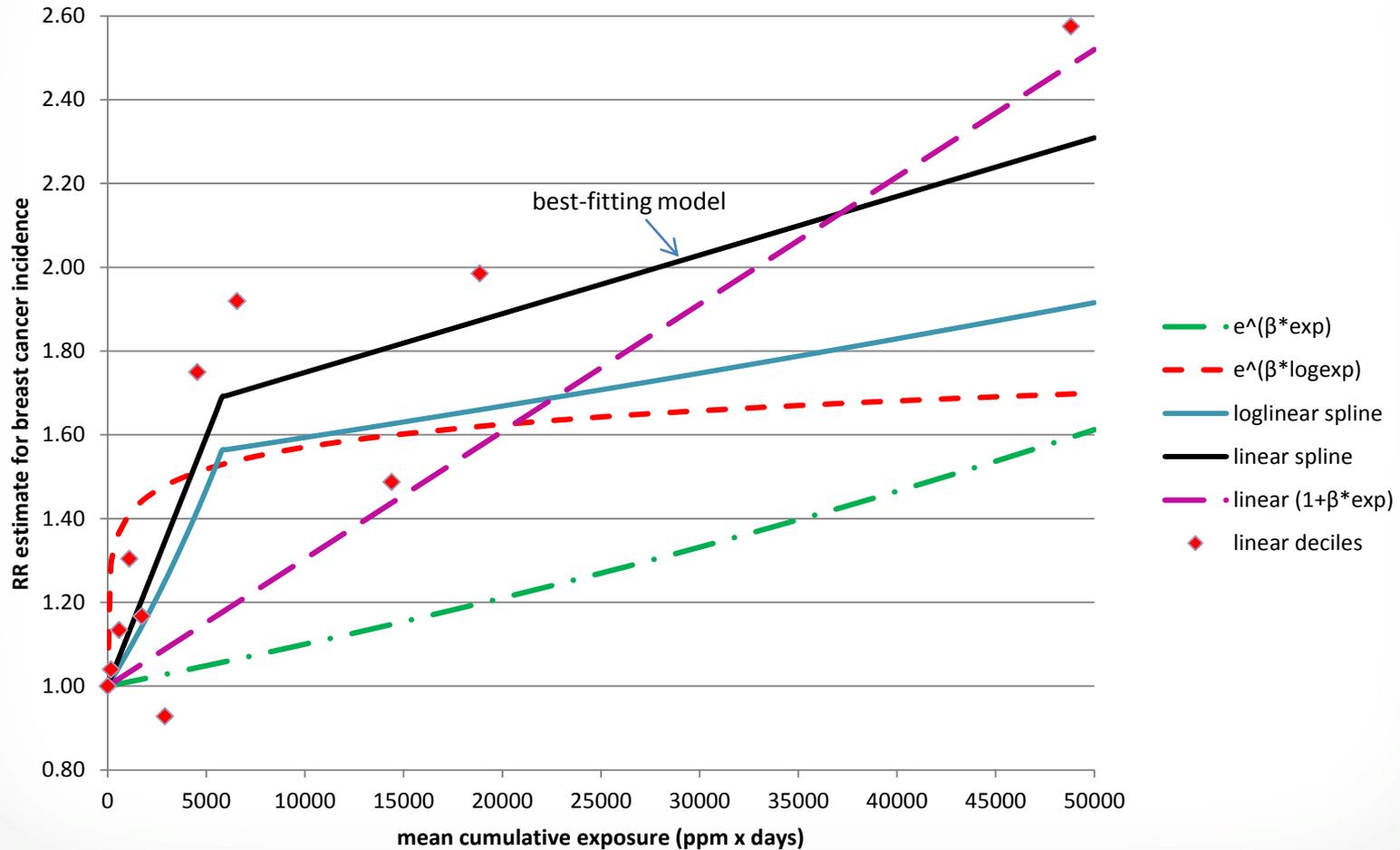


# Exposure-Response Models for Lymphoid Cancer





# Exposure-Response Models for Breast Cancer Incidence





## Derivation of Unit Risk Estimates Based on Human Data : Development of unit risk estimates

- Exposure-response models were incorporated into life-table analyses.
  - Incidence rates used for background disease-specific rates.
  - Life-table analysis used to estimate the 95% lower bound on the exposure level associated with 1% extra risk ( $LEC_{01}$ ).
- $LEC_{01}$  used as point of departure for linear low-dose extrapolation.
- Unit risk estimates for breast cancer and lymphoid cancer combined to develop total cancer unit risk estimate.
- First, these analyses were done to develop preliminary unit risk estimates under the standard assumption the relative risk is independent of age (Section 4.1).
- Then, final human-based unit risk estimates for application of age-dependent adjustment factors were derived under an assumption of increased early-life susceptibility (Section 4.4).

- Unit risk estimate is intended for environmental exposure levels and is not applicable to higher-level exposures that may be encountered in occupational settings.
- Thus, the EtO assessment also presents estimates of extra risk for range of exposure scenarios of interest to OPP (Section 4.7).
- For lymphoid cancer, used the best-fitting continuous exposure model from the published NIOSH study (Cox regression model with log exposure).
- For breast cancer, recommend the same best-fitting continuous exposure model as was used for the derivation of the breast cancer unit risk estimate (2-piece linear spline model).

	Unit risk estimates for environmental exposures	Extra risk estimates for occupational exposures
Lymphoid Cancer	Linear regression of categorical results	Cox regression model with log cumulative exposures
Breast Cancer	2-piece linear spline model	2-piece linear spline model

## **The 2014 draft EtO assessment:**

- Presents extensive new exposure-response modeling.
- Updates the 2006 draft.
- Addresses previous SAB and public comments.
- Is consistent with the short-term recommendations of the NRC.

- One goal is to obtain review of the accuracy, objectivity, and transparency of the revised draft, with an emphasis on sections of the draft that are new or substantially revised:
  1. The genotoxicity sections (Section 3.3.3 and Appendix C).
  2. Appendices H and L (EPA's responses to the 2007 SAB and the 2007 and 2013 public comments).
  3. Appendix J (summary of major new studies).

- EPA's primary goal is to obtain review of sections that deal with:
  1. the new exposure-response modeling of the NIOSH data.
  2. the development of the unit risk estimates and of the estimates of risk associated with occupational exposures.