Overview of the Draft Carcinogenicity Assessment of Ethylene Oxide

Presentation for the
Ethylene Oxide Augmented Chemical Assessment Advisory Committee of the Science Advisory Board
30 September 2014

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Outline of Presentation

This presentation will cover:

- Recent history of Ethylene Oxide (EtO) assessment
- General information on EtO
- Overview of the carcinogenicity assessment
- Major SAB (2007) and public (2013) comments and EPA's responses

Recent History of EtO Assessment

- External Review Draft released in 2006 for public comment and for review by EPA's Science Advisory Board (SAB).
  - EPA has addressed the major SAB and public comments (Appendix H).
- In response to SAB recommendations, EPA conducted extensive additional exposure-response modeling work on the epidemiologic data.
- EPA has chosen to seek SAB review of this new modeling work.
- Revised draft assessment released for public comment in July 2013; also discussed at IRIS bimonthly public meeting in December 2013.
- EPA has made further revisions and addressed the major public comments (Appendix L), resulting in the current draft.

Implementation of 2011 NRC Recommendations

The EtO assessment was near the end of its development at the time of the 2011 NRC recommendations. (Extent of implementation of the recommendations is summarized in Appendix K.)

- Assessment does not include preamble or standardized evidence tables.
- Assessment does include:
  - An executive summary that concisely summarizes major conclusions and analyses
  - An updated literature search using a systematic literature search strategy
  - Use of the HERO database
  - Distinct sections on hazard identification and dose-response assessment
  - Enhanced use of tables, figures, and appendices to streamline the assessment and increase transparency and clarity
  - Expanded discussion on the rationales for study evaluation and selection as well as for other key assessment decisions

General Information

Ethylene Oxide is a gas at room temperature.

Uses of EtO

- The greatest amount of EtO is used as a chemical intermediate in the manufacture of ethylene glycol and other chemicals.
- EtO is also used as a sterilizing agent for medical equipment and as a fumigating agent for spices and certain other materials.

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 Interest in EtO

- EPA's Office of Air and Radiation has an interest in environmental air concentrations of EtO.
  - EtO is on the 1990 Clean Air Act Amendments list of Hazardous Air Pollutants.
- EPA's Office of Pesticide Programs (OPP) has an interest in occupational risks occurring from the use of EtO as a sterilizing agent or fumigant, as well as residues and environmental exposures resulting from the sterilization uses of EtO.
  - EtO is a pesticide registered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Scope of the Assessment

- 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

Overview of Literature Searches

- EPA did not formally record the details of literature search strategies employed in the development of the 2006 External Review Draft.
- There were no critical studies identified as missing during public comment and peer review in 2006-2007.
- EPA incorporated new studies identified through June 2010 into the revised assessment.
- In May 2013, in order to ensure that no critical studies had been missed that would warrant major revisions to the assessment, EPA conducted a well-documented systematic literature search of literature published from January 2006 through May 2013 (Appendix J).
- Two studies published after June 2010 merited in-depth discussion (Section J.2).
- Two additional studies of potential importance to the assessment, both published after the May 2013 search, were noted in public comments in October 2013 and are also reviewed in Appendix J (Section J.3).
- None of the new studies that were identified were found to impact the final conclusions of the assessment.

EtO Inhalation Carcinogenicity Database

- >10 independent occupational epidemiology studies
- 1 cancer bioassay in mice
- 2 cancer bioassays in rats
- Numerous genotoxicity/mutagenicity studies, with data from a wide range of assay systems and species

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, including evidence of chromosome damage in humans exposed to EtO.

- Majority of 2007 SAB panel agreed with hazard characterization conclusion of "carcinogenic to humans".
- More recent studies support the conclusion of "carcinogenic to humans", and EPA has strengthened the hazard discussion in this review draft.

Mode of Action

- 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.
- 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.
- IMPLICATIONS:
  - 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 Guidelines*.

Derivation of Unit Risk Estimates: Summary of Approach

1. Exposure-response analysis of epidemiologic data and model selection (Section 4.1)
   - Includes derivation of preliminary unit risk estimates under standard assumption that relative risk (RR) is independent of age.
2. Exposure-response analysis of rodent data (Section 4.2)
3. Selection of modeling of human data as basis for unit risk estimate (Section 4.3)
4. Derivation of final (proposed) human-based unit risk estimates for application of ADAFs (Section 4.4)
   - Under assumption of increased early-life susceptibility.

Derivation of Unit Risk Estimates Based on Human Data

Study Selection:

- NIOSH study of sterilization workers selected
  - 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.
- 2007 SAB panel also recommended that EPA consider inclusion of Union Carbide data.
  - EPA re-evaluated the UC 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).

Exposure-Response Modeling :

- EPA investigated a number of 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).
- 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).

Risk Attenuates at Highest Exposures

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

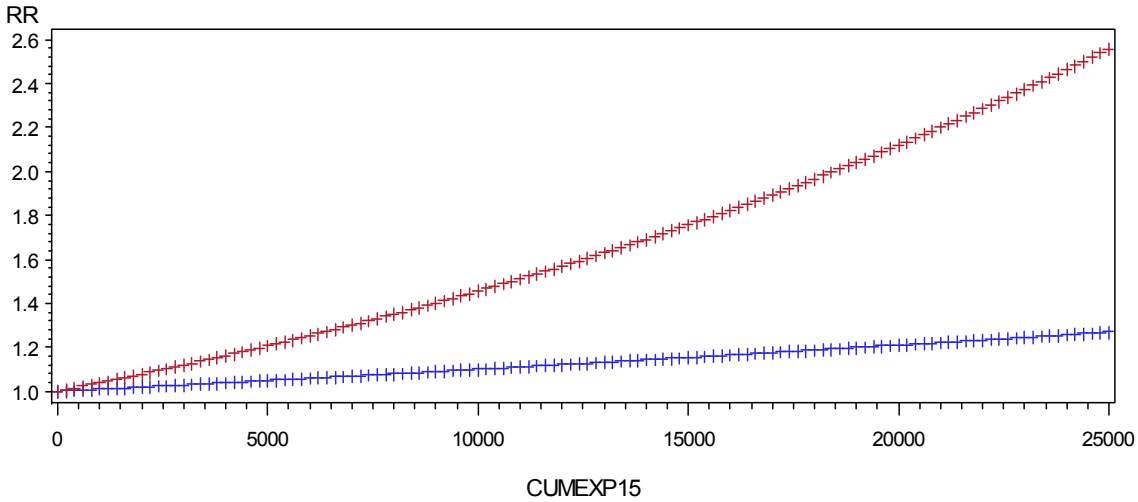
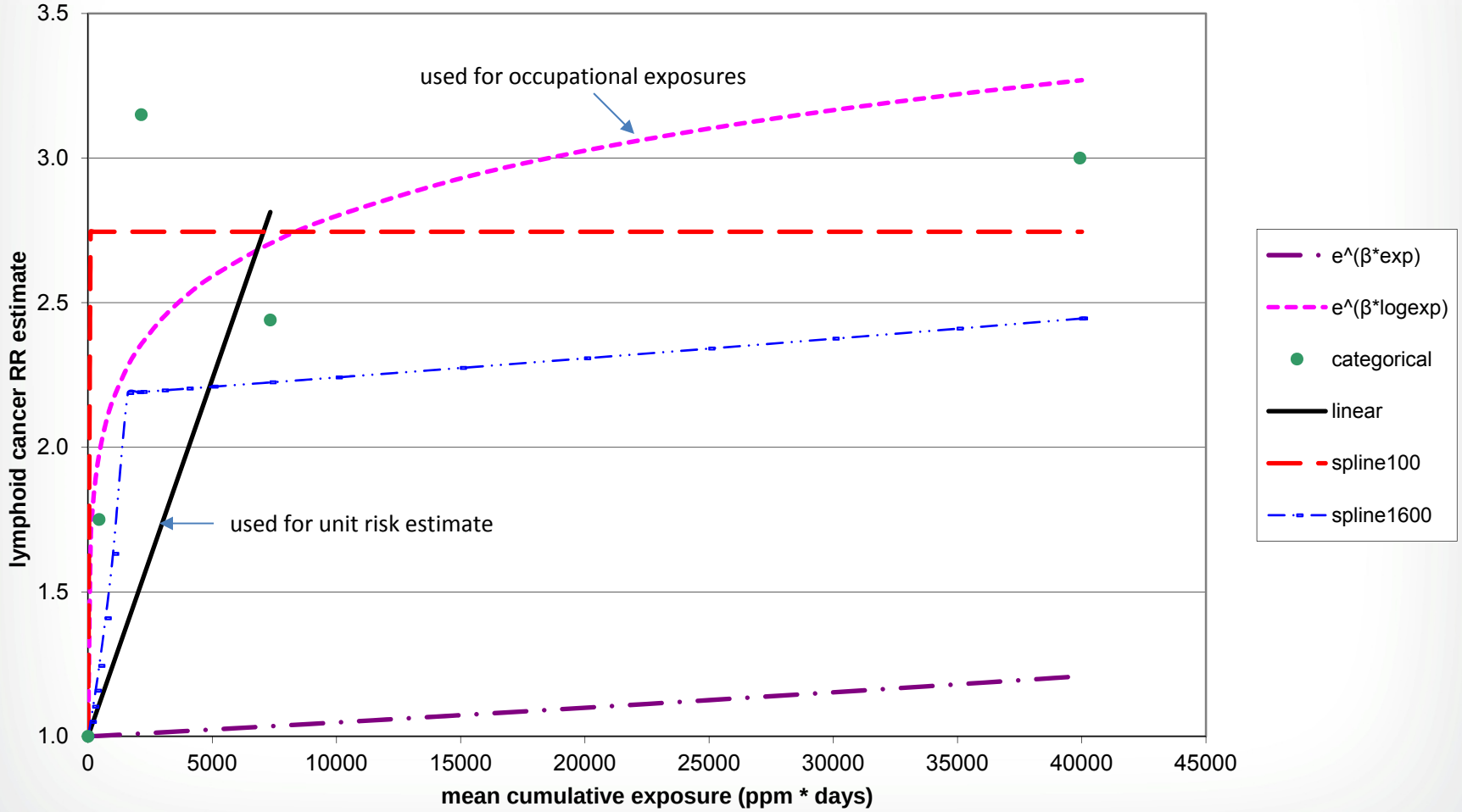
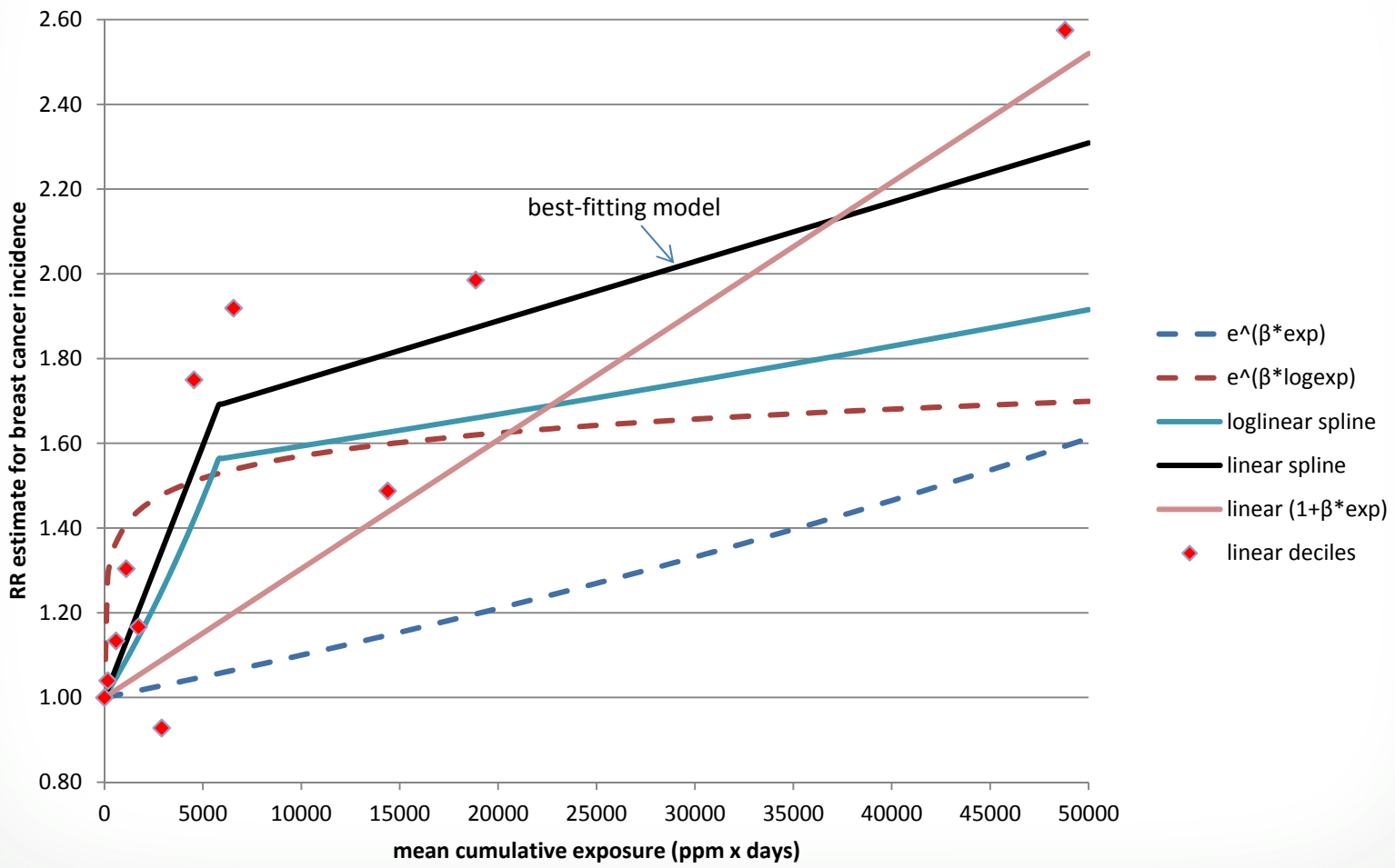


Figure. Breast cancer incidence. Comparison of log-linear curve ($RR = e^{(\beta \times cumexp)}$) with all the data (blue line with lower slope) and the log-linear curve after excluding data in the top 5% of exposure (>27,500 ppm-days) (red line with higher slope).

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.

Application of Age-dependent adjustment factors (ADAFs)

- Because of mutagenic mode of action, increased early-life susceptibility is assumed (EPA's 2005 *Supplemental Guidance*).
- Assumption of increased early-life susceptibility requires a different assumption about age-dependence of the RR for the life-table analysis.
- EPA did alternate life-table analyses under assumption that RR is independent of age *for adults only* to derive the final unit risk estimates (Section 4.4).
  - Included exposure only for ages ≥16 years ("adult-exposure-only" estimates).
  - Re-scaled the estimates to 70-year lifespan for purposes of ADAF calculations ("adult-based" estimates).
- Adult-based unit risk estimates used in conjunction with ADAFs to generate (extra) risk estimates for specific exposure scenarios.
  - Absence of age-specific susceptibility data for EtO; thus, standard ADAFs applied.

Derivation of Extra Risk Estimates for Occupational Exposure Scenarios

- 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 presents extra risk estimates 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).

Major 2007 SAB Comments and EPA's Responses

Comment: Model the continuous exposure data rather than use categorical results for the derivation of unit risk estimates.

EPA's Response:

- EPA made a substantial effort to develop continuous exposure models (Section 4.1).
- Obtained suitable models for breast cancer incidence.
- Obtained no suitable continuous exposure models for lymphoid cancer.
  - Therefore, continued to use linear regression of categorical results for derivation of the lymphoid cancer unit risk estimate.

Major 2007 SAB Comments and EPA's Responses

Comment: Several SAB panel members recommended that EPA also present a nonlinear extrapolation approach.

- Some EtO mutagenicity data were presented in an appendix in support of a nonlinear approach.

EPA's Response:

- EPA performed analyses of the EtO data presented in the appendix and found that these datasets are consistent with low-dose linearity (Appendix H).
- Other considerations also supported the judgment not to include a non-linear approach.
- More recent studies (Appendix J) do not alter that judgment.

Major 2013 Public Comments and EPA's Responses

Comment: EPA should reexamine its risk determination given background and endogenous levels of EtO.

EPA's Response:

- EPA's unit risk estimates are for extra risk (i.e., above background risk).
- Given the high background rates of lymphoid (~3%) and breast (~15%) cancers, EPA does not consider the risk estimates for (known sources of) exogenous exposure to be inconsistent with the data on background and endogenous levels.
  - e.g., based on EPA data for the U.S., upper-bound estimates of risk resulting from a lifetime exposure to the average exposure concentration of EtO from known sources (above background) are between 10^{-6} and 10^{-5}.

Major 2013 Public Comments and EPA's Responses

Comment: A mutagenic mode of action is not supported by the most recent scientific evidence; other modes of action should be considered.

EPA's Response:

- The 2007 SAB panel concurred with EPA's conclusion at that time that a mutagenic mode of action was operative in EtO carcinogenicity.
- In the 2013 public review draft, EPA reviewed more recent information and found this information to be supportive of the earlier conclusion of a mutagenic mode of action.
- EPA reviewed new information presented in public comments (Appendices J and L) and concluded that it did not alter the original finding.
- Other modes of action proposed in public comments are speculative and do not provide a basis for alternative conclusions in the assessment.

Summary

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.

EPA's Goals for this SAB Review

- 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.

EPA's Goals (cont.)

- A secondary 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).

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Acknowledgments

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