Comments to the
Chemical Assessment Advisory Committee (CAAC)
for the IRIS Evaluation of Ethylene Oxide:
Charge Questions #2 & 3 Modeling

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On behalf of the American Chemistry Council (ACC)

November 18-20, 2014
1. Despite the 2007 SAB’s recommendation for EPA to focus on individual data, EPA’s modeling continues to focus on a few categorical rate ratios.

2. The NIOSH breast cancer incidence data are not publicly available; therefore, EPA’s analyses of these “unavailable data” and this endpoint cannot be verified.
3. The NIOSH cancer exposure-response data for breast and lymphoid cancers are not supralinear.

The false impression of supralinearity disappears as the number of categorical rate ratios (RRs) for non-zero exposure increases above the 4 presented by EPA.
Breast Cancer Mortality

Top:
4
Categories

Bottom:
61
Categories
Lymphoid Mortality: Categorical RRs for 4 Non-Zero Exposures Categories

Top:
4 Categories

Lymphoid Mortality: Categorical RRs for 44 Non-Zero Exposures Categories

Bottom:
44 Categories
4. EPA’s method of evaluating different exposure-response models is statistically incorrect, is based only on a summary of the available data and not the individual data themselves, and erroneously rejects more appropriate models and SAB recommendations.

5. The evaluation of selected exposure-response models should not ignore the uncertainty in the cancer response rate in the non-exposed category, should adjust for different estimated baseline risks, and should not restrict the fitted model to have an RR intercept equal to one.

6. We believe that the log-linear model provides the best fits to the individual data for breast cancer mortality and lymphoid cancer mortality, and that these fitted models compare well to the categorical RRss when the comparison adjusts for the difference in estimated baseline risks.
Log-Linear Model Fit to Individual Data for Breast Cancer Mortality Compared to 4 Categorial RRs when Adjusted for the Difference between Estimated Baseline Risks

Top: 4 Categories

Log-Linear Model Fit to Individual Data for Breast Cancer Mortality Compared to 61 Categorial RRs when Adjusted for the Difference between Estimated Baseline Risks

Bottom: 61 Categories
Log-Linear Model Fit to Individual Data for Lymphoid Cancer Mortality Compared to 4 Categorical RRs when Adjusted for the Difference between Estimated Baseline Risks

Log-linear Model fit to Individual Data
Log-linear Model fit to Individual Data; RRs adjusted for the difference between baselines

Adjusted

Log-Linear Model Fit to Individual Data for Lymphoid Cancer Mortality Compared to 44 Categorical RRs when Adjusted for the Difference between Estimated Baseline Risks

Adjusted

Sielken & Associates Consulting, Inc.
The best exposure-response model for all endpoints (including breast cancer) is a continuous log-linear Cox proportional hazards model based on cumulative exposure (not log cumulative exposure) and fit to the individual data.
Additional details:

Web:

Meeting Materials:

Public comment submitted to the SAB Staff Office:

Comments from the American Chemistry Council’s Ethylene Oxide Panel – 10/20/14
(PDF, 127 pp., 2,956,211 bytes)
Extra Slides
8. Contrary to SAB recommendations, EPA uses a non-peer-reviewed supralinear, two-piece spline model for breast cancer incidence.

9. Likelihood-ratio tests show that the two-piece linear spline does not make a statistically significant improvement in the model fits for breast cancer or lymphoid cancer at the 5% significance level.
<table>
<thead>
<tr>
<th>Model</th>
<th>RR</th>
<th>-2 × Log-Likelihood</th>
<th>Reference (page)</th>
<th>Chi-Square Statistic</th>
<th>p-value</th>
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</thead>
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<tr>
<td><strong>Breast Cancer Incidence</strong></td>
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<td>Log-Linear Models</td>
<td></td>
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</tr>
<tr>
<td>Log-Linear – 1 piece</td>
<td>( \exp(\beta \times \text{cumulative exposure}) )</td>
<td>1944.675</td>
<td>D-15</td>
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<td>( \exp(2\text{-piece spline function of cumulative exposure}) )</td>
<td>1940.485</td>
<td>D-14</td>
<td>4.19</td>
<td>0.1231</td>
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<td><strong>Breast Cancer Incidence</strong></td>
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<td></td>
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<td>Linear Models</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Linear – 1 piece</td>
<td>( 1 + \beta \times \text{cumulative exposure} )</td>
<td>1940.260</td>
<td>D-20</td>
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<td>Linear – 2 pieces</td>
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<td>3.325</td>
<td>0.1897</td>
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<td><strong>Breast Cancer Mortality</strong></td>
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<td>Log-Linear Models</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-Linear – 1 piece</td>
<td>( \exp(\beta \times \text{cumulative exposure}) )</td>
<td>920.647</td>
<td>D-37</td>
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<td></td>
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<tr>
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<td>( \exp(2\text{-piece spline function of cumulative exposure}) )</td>
<td>918.037</td>
<td>D-36</td>
<td>2.61</td>
<td>0.2712</td>
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<tr>
<td>Lymphoid Cancer Mortality</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Model</td>
<td>RR</td>
<td>-2 × Log-Likelihood</td>
<td>Reference (page)</td>
<td>Chi-Square Statistic</td>
<td>p-value</td>
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<tr>
<td>Log-Linear Models</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>457.847</td>
<td>D-47</td>
<td>4.566</td>
<td>0.1020</td>
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</table>
10. Inclusion of the UCC data would add substantially to the power of the dose-response analyses.

10.1. EPA failed to incorporate the recently updated Union Carbide Corporation (UCC) epidemiology data. The exposure assessment of the NIOSH studies suffered from several limitations including the absence of data prior to 1976 and a regression model that fixed the calendar year effect to 1978. The exclusion of UCC data on the basis of exposure assessment limitations is, therefore, not justified. Had EPA followed the NAS (2011) recommendations, and used a transparent, standardized and systematic approach to review the strengths and weaknesses of individual studies, EPA likely would not have been able to rely upon the NIOSH studies while rejecting the UCC studies.

10.2. EPA inappropriately ignores the uncertainties in the NIOSH retrospective exposure assessment while emphasizing those of the UCC study. The NIOSH exposure assessment suffered from limitations.

10.2.a. The limitations in NIOSH’s exposure assessment largely invalidate EPA’s reliance solely on the NIOSH epidemiology study and the exclusion of the UCC epidemiology study.

10.2.b. The power of the dose-response assessment would be increased by adding in the data from the UCC study.

10.3. EPA’s dose-response modeling methodology exaggerates the risks and limits the power of the risk assessment by using only data from one epidemiology study (NIOSH).
11. EPA’s exposure-response modeling techniques over predict the number of cancer mortalities actually observed in the NIOSH cohort study.

12. EPA’s exposure-response modeling methodology and choices for the component factors in the calculation of points of departure (PODs) exaggerates the risk by as much as 1500 fold.
13. EPA should present both linear and nonlinear extrapolation approaches.

14. EPA’s proposed direct, DNA-reactive mutagenic MOA is not supported by the most recent scientific evidence and, therefore, does not justify the use of only a linear, non-threshold approach.

15. Several SAB Panel members recommended that both linear and nonlinear extrapolation models be considered in the EO assessment. However, EPA did not include a nonlinear approach.
Charge Question 6

16. EPA’s modeling approach for lymphoid and breast cancer remains incorrect.

The methodological problems identified in Valdez-Flores and Sielken (2013) are relevant despite EPA’s dismissal in Appendix J.3.1.

As part of the public docket we submitted “Comments from Robert L. Sielken, Sielkin [sic] & Associates Consulting - Appendix J (PDF, 10 pp., 289,311 bytes)”. That submission contains the text of EPA’s Appendix J.3.1 with Sielken & Associates Consulting, Inc.’s comments inserted in italics and numbered. This submission is relevant to the portion of Charge Question 6 dealing with Appendix J. We urge the CAAC to carefully review our submission when they review Appendix J.3.1.
17. Combining breast cancer and lymphoid cancer unit risk estimates is **not scientifically justified.** EPA did not discuss **competing risks**, **different background populations**, **incidence vs. mortality**, and the **use of different exposure-response models**.

18. In addition to the inappropriate combining of lymphoid and breast cancer risks, **there are several statistical problems with the way EPA performed this combination.**
References


ADDITIONAL Comments to the Chemical Assessment Advisory Committee (CAAC) for the IRIS Evaluation of Ethylene Oxide: Charge Questions #2 & 3 Modeling

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On behalf of the American Chemistry Council (ACC)

November 18-20, 2014
Table 1 – EO Workplace Exposure Limits

<table>
<thead>
<tr>
<th>Date</th>
<th>Group</th>
<th>Workplace exposure limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946-1947</td>
<td>ACGIH MAC-TWA</td>
<td>100 ppm</td>
</tr>
<tr>
<td>1948-1956</td>
<td>ACGIH TLV-TWA</td>
<td>100 ppm</td>
</tr>
<tr>
<td>1957</td>
<td>ACGIH TLV-TWA</td>
<td>100 ppm to 50 ppm</td>
</tr>
<tr>
<td>1971</td>
<td>OSHA</td>
<td>50 ppm</td>
</tr>
<tr>
<td>1981</td>
<td>ACGIH TLV-TWA</td>
<td>50 ppm to 10 ppm</td>
</tr>
<tr>
<td>1984</td>
<td>ACGIH TLV-TWA</td>
<td>10 ppm to 1 ppm</td>
</tr>
<tr>
<td>1984</td>
<td>OSHA</td>
<td>50 ppm to 1 ppm</td>
</tr>
</tbody>
</table>
No matter how exposure is characterized (% of person years, % of ppm-years, or % of a worker’s total cumulative ppm-years),

a large proportion of the exposure occurred during the period (before 1978) when NIOSH assumed that exposures were fixed equal to their 1978 level.

Similarly, a large proportion of the exposure occurred during the period (before 1976) when NIOSH had NO exposure data.

Going back to the individual worker exposure histories that Sielken & Associates have from NIOSH, we can determine the following:
<table>
<thead>
<tr>
<th>Data Set</th>
<th>% of person years before January 1, 1960</th>
<th>% of ppm-years ETO exposure before January 1, 1960</th>
<th>Average % of individual’s cumulative exposure (accounting for any lag) before January 1, 1960</th>
<th>% of person years before January 1, 1976</th>
<th>% of ppm-years ETO exposure before January 1, 1976</th>
<th>Average % of individual’s cumulative exposure (accounting for any lag) before January 1, 1976</th>
<th>% of person years before January 1, 1978</th>
<th>% of ppm-years ETO exposure before January 1, 1978</th>
<th>Average % of individual’s cumulative exposure (accounting for any lag) before January 1, 1978</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH, M&amp;F, Lag=0</td>
<td>5%</td>
<td>10%</td>
<td>3%</td>
<td>46%</td>
<td>64%</td>
<td>65%</td>
<td>54%</td>
<td>76%</td>
<td>74%</td>
</tr>
<tr>
<td>NIOSH, M&amp;F, Lag=15</td>
<td>5%</td>
<td>11%</td>
<td>3%</td>
<td>46%</td>
<td>65%</td>
<td>62%</td>
<td>54%</td>
<td>77%</td>
<td>70%</td>
</tr>
<tr>
<td>NIOSH, M&amp;F, Lag=20</td>
<td>5%</td>
<td>13%</td>
<td>3%</td>
<td>46%</td>
<td>78%</td>
<td>63%</td>
<td>54%</td>
<td>92%</td>
<td>73%</td>
</tr>
<tr>
<td>NIOSH, M, Lag=0</td>
<td>6%</td>
<td>12%</td>
<td>4%</td>
<td>46%</td>
<td>66%</td>
<td>62%</td>
<td>54%</td>
<td>77%</td>
<td>71%</td>
</tr>
<tr>
<td>NIOSH, M, Lag=15</td>
<td>6%</td>
<td>13%</td>
<td>4%</td>
<td>46%</td>
<td>67%</td>
<td>58%</td>
<td>54%</td>
<td>78%</td>
<td>66%</td>
</tr>
<tr>
<td>NIOSH, M, Lag=20</td>
<td>6%</td>
<td>15%</td>
<td>3%</td>
<td>46%</td>
<td>79%</td>
<td>58%</td>
<td>54%</td>
<td>93%</td>
<td>68%</td>
</tr>
<tr>
<td>NIOSH, F, Lag=0</td>
<td>5%</td>
<td>8%</td>
<td>3%</td>
<td>47%</td>
<td>61%</td>
<td>67%</td>
<td>55%</td>
<td>73%</td>
<td>76%</td>
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<tr>
<td>NIOSH, F, Lag=15</td>
<td>5%</td>
<td>8%</td>
<td>3%</td>
<td>47%</td>
<td>62%</td>
<td>65%</td>
<td>55%</td>
<td>74%</td>
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</tr>
<tr>
<td>NIOSH, F, Lag=20</td>
<td>5%</td>
<td>11%</td>
<td>3%</td>
<td>47%</td>
<td>76%</td>
<td>66%</td>
<td>55%</td>
<td>92%</td>
<td>77%</td>
</tr>
</tbody>
</table>

The important point in the above table is that most of the worker exposure in the NIOSH cohort was before the period when NIOSH had exposure observations.
Impact of Calendar Year Component in Regression Model for ETO:
Fixed at 1978 Level before 1978

ET0 vs Calendar Year

- Model
- 1978
As noted in Sielken-Valdez Flores (2013):

In addition, any apparent supra-linear behavior of the categorical RRs is not surprising and actually is expected in epidemiological studies that usually include exposure errors.

Crump (2005) has investigated this behavior and concluded that “Because of these potential distortions of the exposure–response shape, one should be cautious in drawing conclusions about the shape of the exposure response from epidemiological data. Since even random, unbiased errors in exposure measurement will convert a linear exposure response, and can convert sub-linear response, into a seemingly supralinear shape, one should be particular[ly] cautious about concluding an exposure–response is truly supra-linear. In particular, it could be inadvisable to extrapolate an observed supra-linear exposure response to low exposures to predict human risk.”