

**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

Charge Questions 2 & 3

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.**

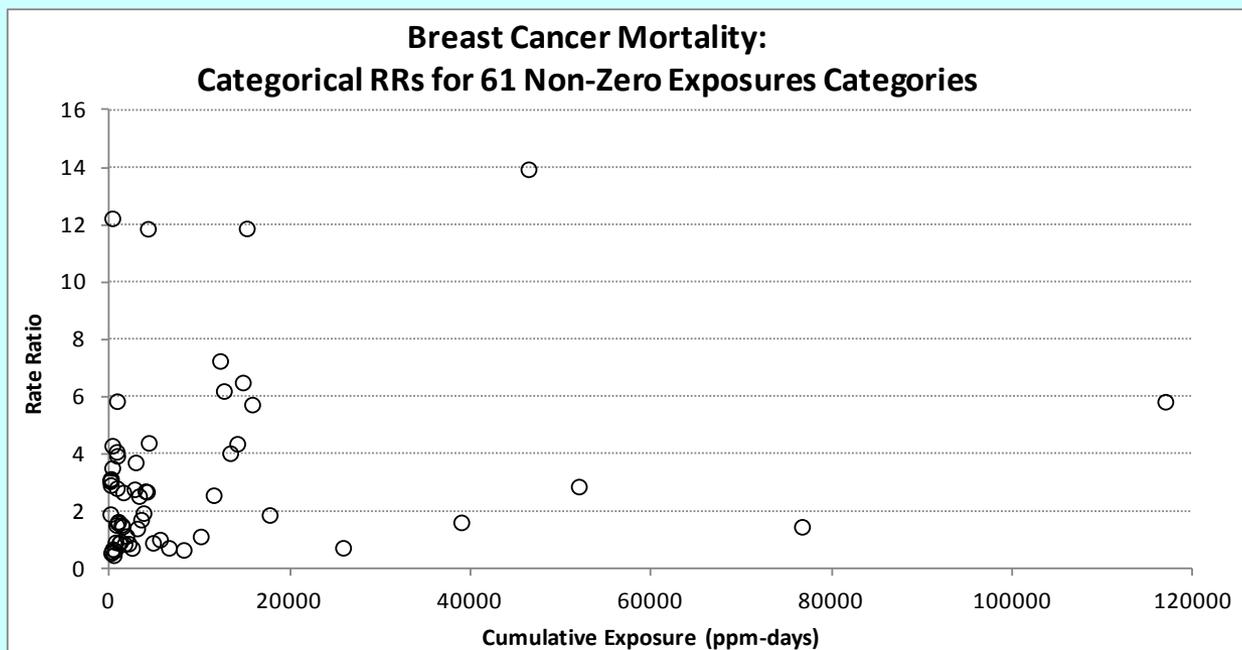
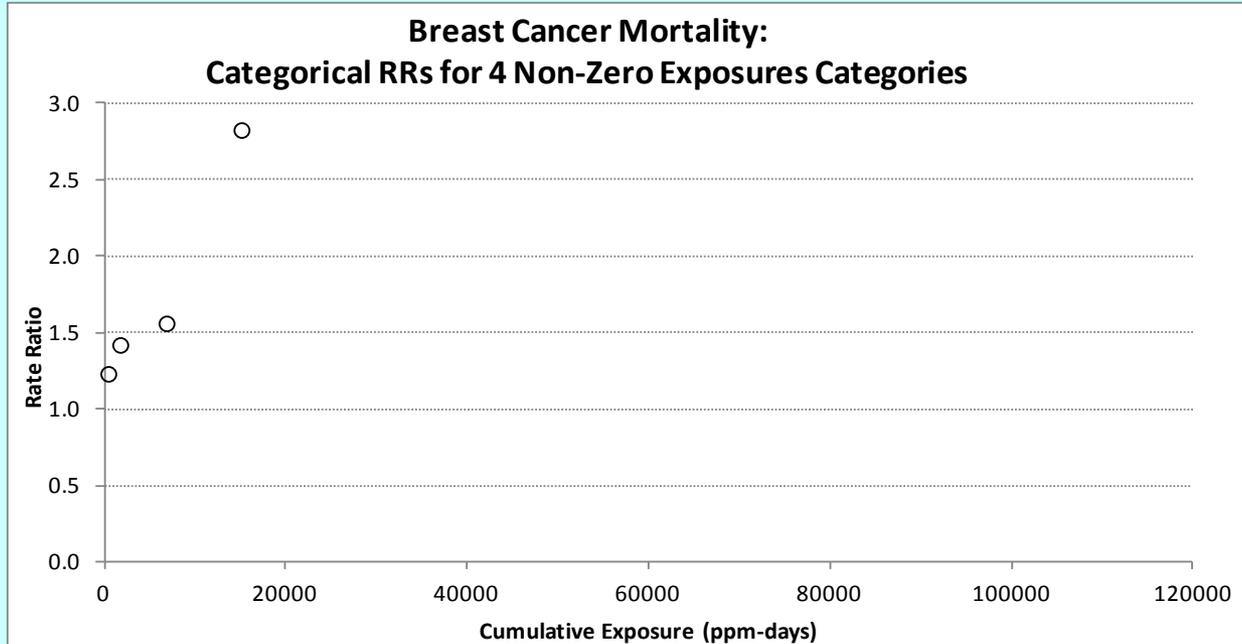
2. The NIOSH breast cancer incidence data are not publicly available; therefore, EPA's analyses of these **“unavailable data”** and this endpoint cannot be verified.

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

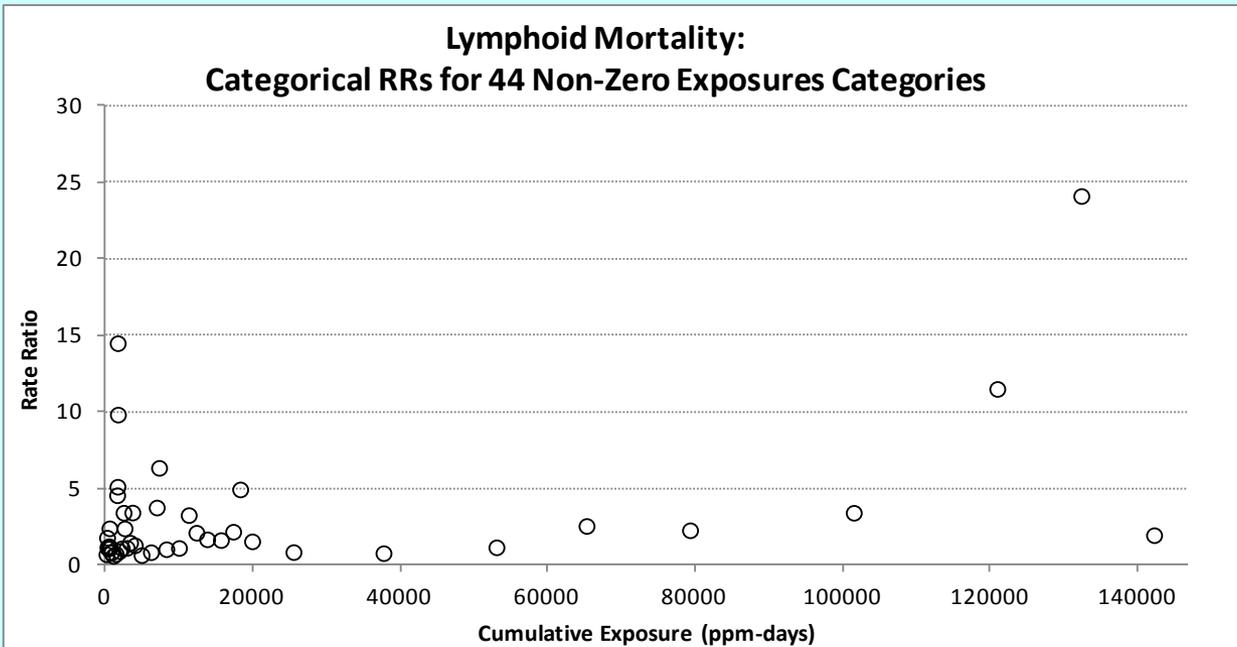
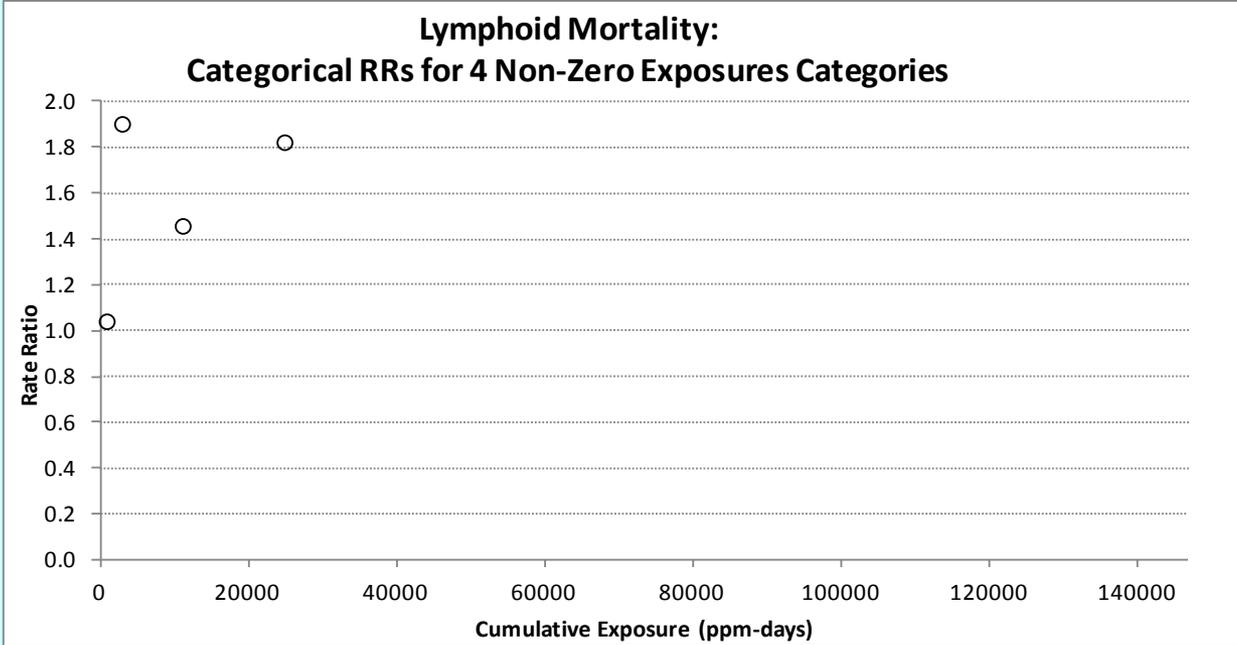
Top:
4
Categories



Bottom:
61
Categories

Lymphoid Cancer Mortality

Top:
4
Categories



Bottom:
44
Categories

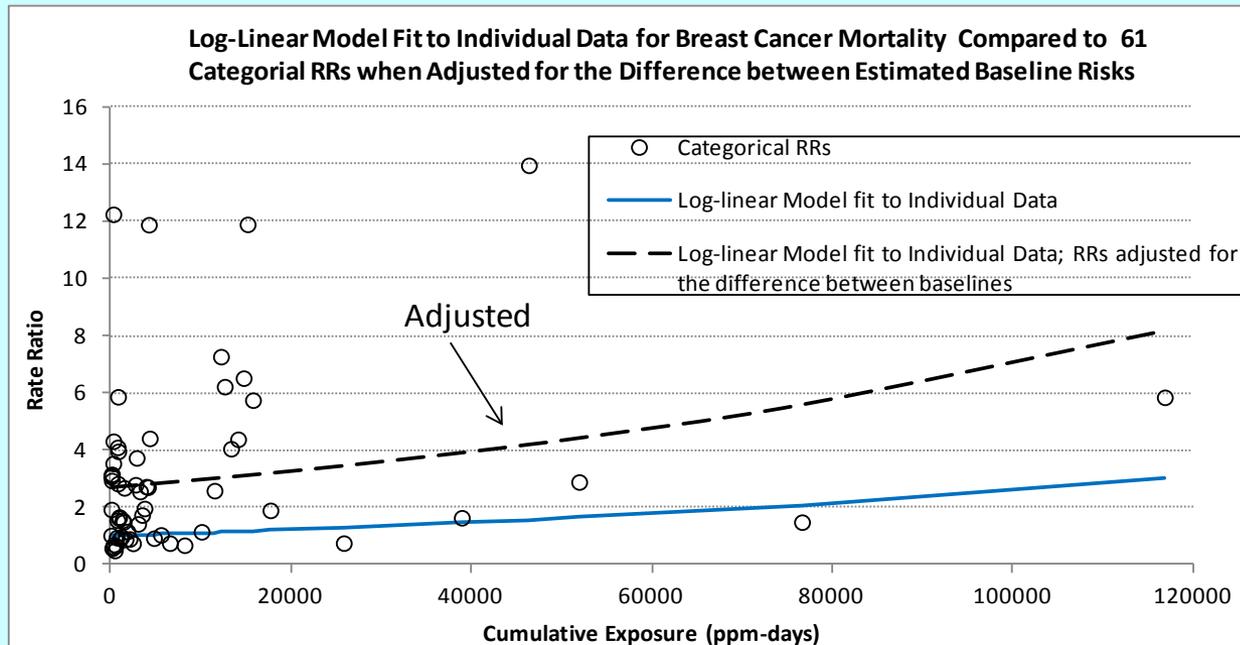
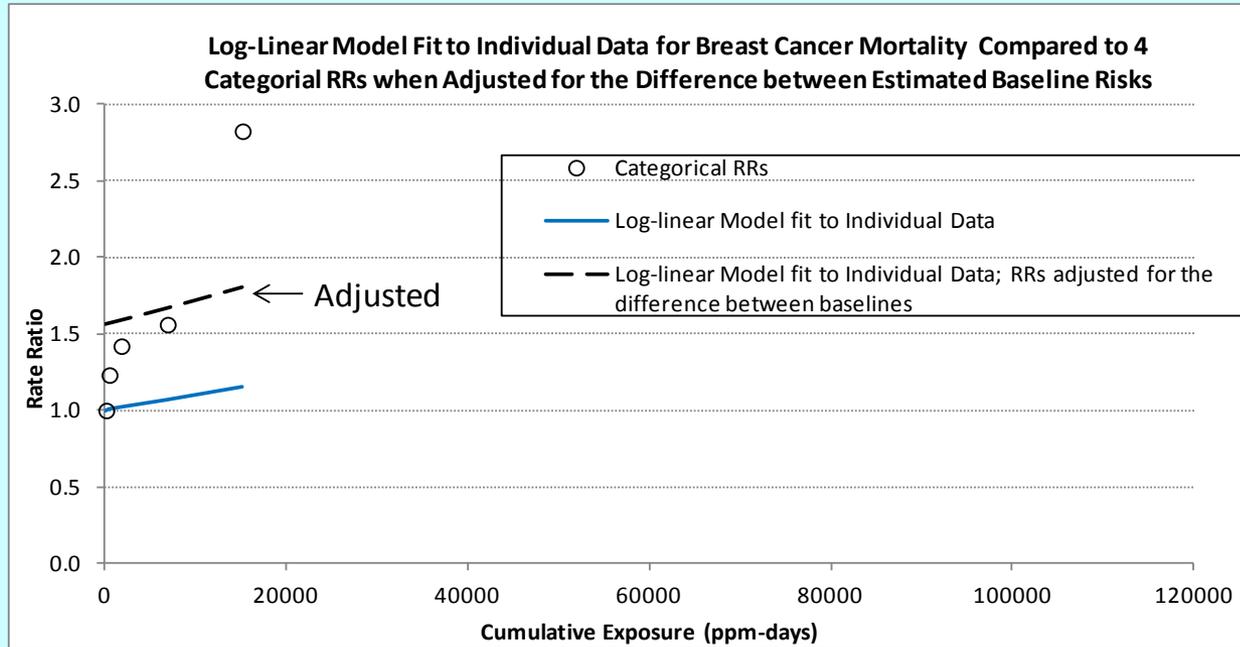
4. EPA's method of evaluating different exposure-response models is statistically incorrect, is based only on a summary of the available data and not the individual data themselves, and erroneously rejects more appropriate models and SAB recommendations.

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 RRs when the comparison adjusts for the difference in estimated baseline risks.

Breast Cancer Mortality

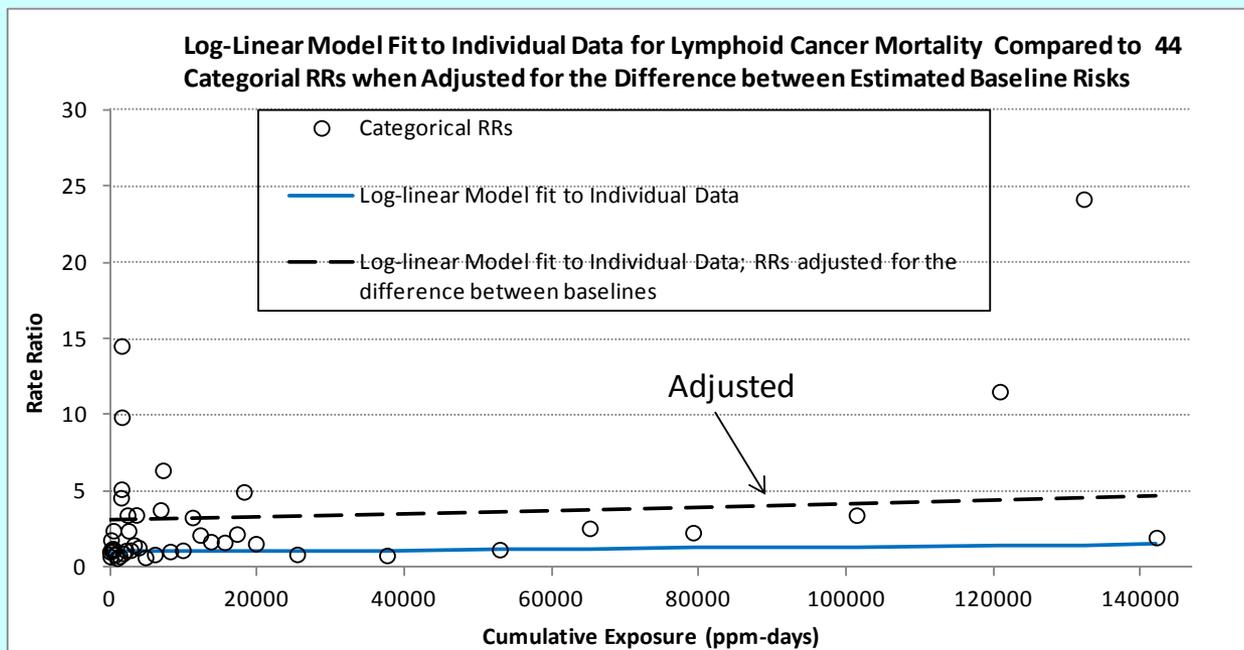
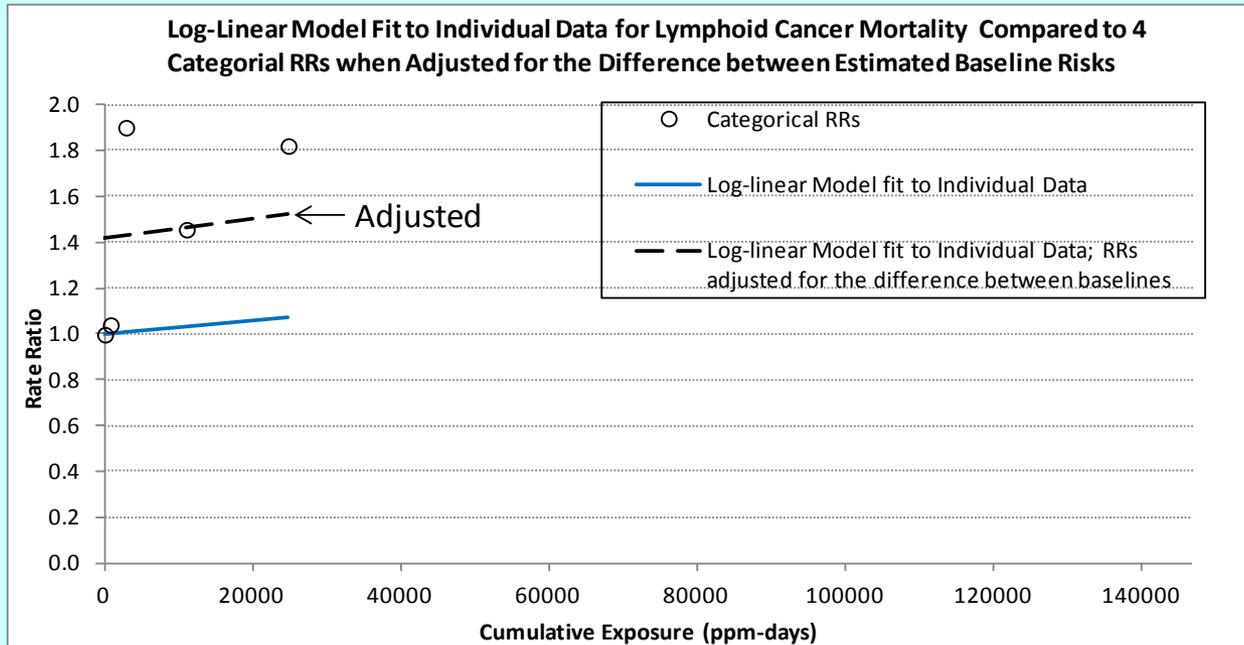
Top:
4
Categories



Bottom:
61
Categories

Lymphoid Cancer Mortality

Top:
4
Categories



Bottom:
44
Categories

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

Charge Questions 2 & 3

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.

Breast Cancer Incidence					
Model	RR	-2 × Log-Likelihood	Reference (page)*	Chi-Square Statistic	p-value
Log-Linear Models					
Log-Linear – 1 piece	exp(Beta × cumulative exposure)	1944.675	D-15		
Log-Linear – 2 pieces	exp(2-piece spline function of cumulative exposure)	1940.485	D-14	4.19	0.1231
Breast Cancer Incidence					
Model	RR	-2 × Log-Likelihood	Reference (page)	Chi-Square Statistic	p-value
Linear Models					
Linear – 1 piece	1 + Beta × cumulative exposure)	1940.260	D-20		
Linear – 2 pieces	1 + 2-piece spline function of cumulative exposure	1936.935	D-20	3.325	0.1897
Breast Cancer Mortality					
Model	RR	-2 × Log-Likelihood	Reference (page)	Chi-Square Statistic	p-value
Log-Linear Models					
Log-Linear – 1 piece	exp(Beta × cumulative exposure)	920.647	D-37		
Log-Linear – 2 pieces	exp(2-piece spline function of cumulative exposure)	918.037	D-36	2.61	0.2712

Lymphoid Cancer Mortality					
Model	RR	-2 × Log-Likelihood	Reference (page)	Chi-Square Statistic	p-value
Log-Linear Models					
Log-Linear – 1 piece	exp(Beta × cumulative exposure)	462.413	D-48		
Log-Linear – 2 pieces	exp(2-piece spline function of cumulative exposure)	457.847	D-47	4.566	0.1020

Charge Question 4

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).

Charge Question 4

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.

Charge Question 5

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.

Charge Question 7

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

Valdez-Flores, Ciriaco, and Robert L. Sielken Jr. Misinterpretation of categorical rate ratios and inappropriate exposure–response model fitting can lead to biased estimates of risk: Ethylene oxide case study. *Regulatory Toxicology and Pharmacology* 67 (2013) 206-214.

Valdez-Flores, Ciriaco, Robert L. Sielken Jr., M. Jane Teta, “Quantitative cancer risk assessment for ethylene oxide inhalation in occupational settings,” *Arch Toxicol* (2011) 85: 1189-1193

Valdez-Flores, Ciriaco, Robert L. Sielken Jr., M. Jane Teta, Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. *Regulatory Toxicology and Pharmacology* 56 (2010) 312–320.

Sielken, Robert L. and Ciriaco Valdez Flores. Life-table calculations of excess risk for incidence versus mortality: Ethylene oxide case study. *Regulatory Toxicology and Pharmacology* 55 (2009) 82–89

Sielken, Robert L. and Ciriaco Valdez Flores. Calculating excess risk with age-dependent adjustment factors and cumulative doses: Ethylene oxide case study. *Regulatory Toxicology and Pharmacology* 55 (2009) 76–81.

**ADDITIONAL Comments to the
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Table 1 – EO Workplace Exposure Limits

<u>Date</u>	<u>Group</u>	<u>Workplace exposure limit</u>
1946-1947	ACGIH MAC-TWA	100 ppm
1948-1956	ACGIH TLV-TWA	100 ppm
1957	ACGIH TLV-TWA	100 ppm to 50 ppm
1971	OSHA	50 ppm
1981	ACGIH TLV-TWA	50 ppm to 10 ppm
1984	ACGIH TLV-TWA	10 ppm to 1 ppm
1984	OSHA	50 ppm to 1 ppm

No matter how exposure is characterized (% of person years, % of ppm-years, or % of a worker's total cumulative ppm-years),

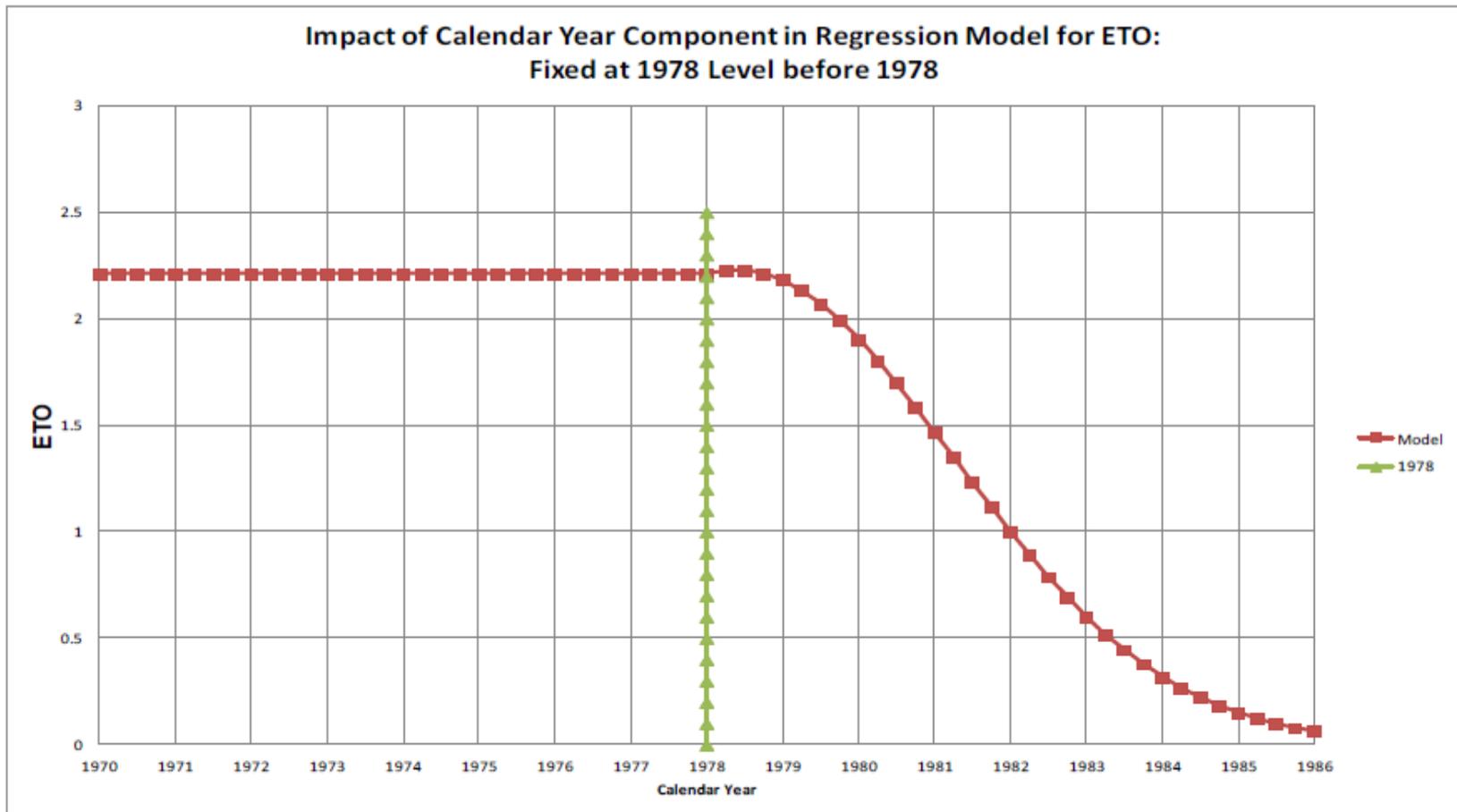
a large proportion of the exposure occurred during the period (before 1978) when NIOSH assumed that exposures were fixed equal to their 1978 level.

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

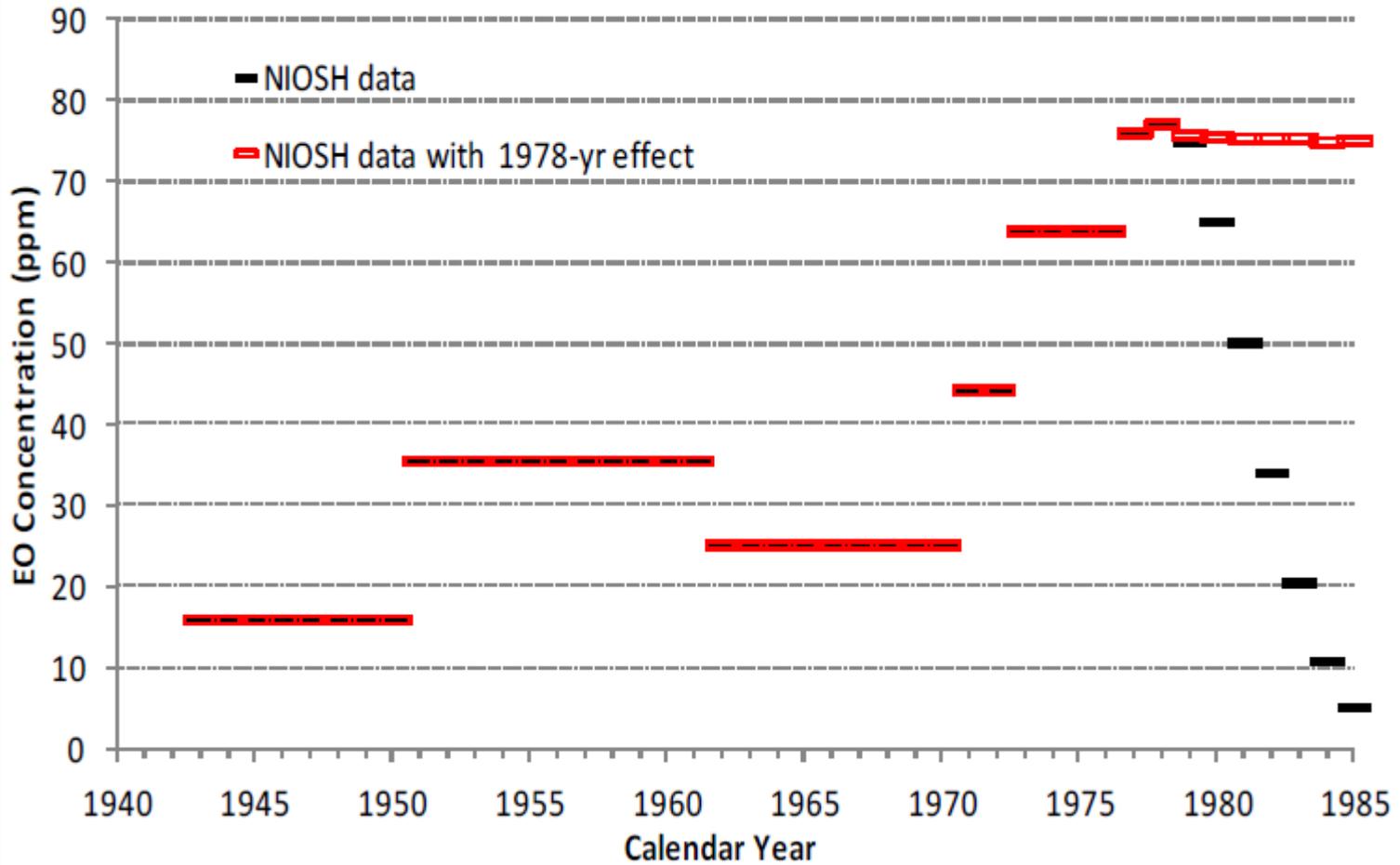
Going back to the individual worker exposure histories that Sielken & Associates have from NIOSH, we can determine the following:

Data Set (Lag in Years)	% of person years before January 1, 1960	% of ppm-years ETO exposure before January 1, 1960	Average % of individual's cumulative exposure (accounting for any lag) before January 1, 1960	% of person years before January 1, 1976	% of ppm-years ETO exposure before January 1, 1976	Average % of individual's cumulative exposure (accounting for any lag) before January 1, 1976	% of person years before January 1, 1978	% of ppm-years ETO exposure before January 1, 1978	Average % of individual's cumulative exposure (accounting for any lag) before January 1, 1978
NIOSH, M&F, Lag=0	5%	10%	3%	46%	64%	65%	54%	76%	74%
NIOSH, M&F, Lag=15	5%	11%	3%	46%	65%	62%	54%	77%	70%
NIOSH, M&F, Lag=20	5%	13%	3%	46%	78%	63%	54%	92%	73%
NIOSH, M, Lag=0	6%	12%	4%	46%	66%	62%	54%	77%	71%
NIOSH, M, Lag=15	6%	13%	4%	46%	67%	58%	54%	78%	66%
NIOSH, M, Lag=20	6%	15%	3%	46%	79%	58%	54%	93%	68%
NIOSH, F, Lag=0	5%	8%	3%	47%	61%	67%	55%	73%	76%
NIOSH, F, Lag=15	5%	8%	3%	47%	62%	65%	55%	74%	74%
NIOSH, F, Lag=20	5%	11%	3%	47%	76%	66%	55%	92%	77%

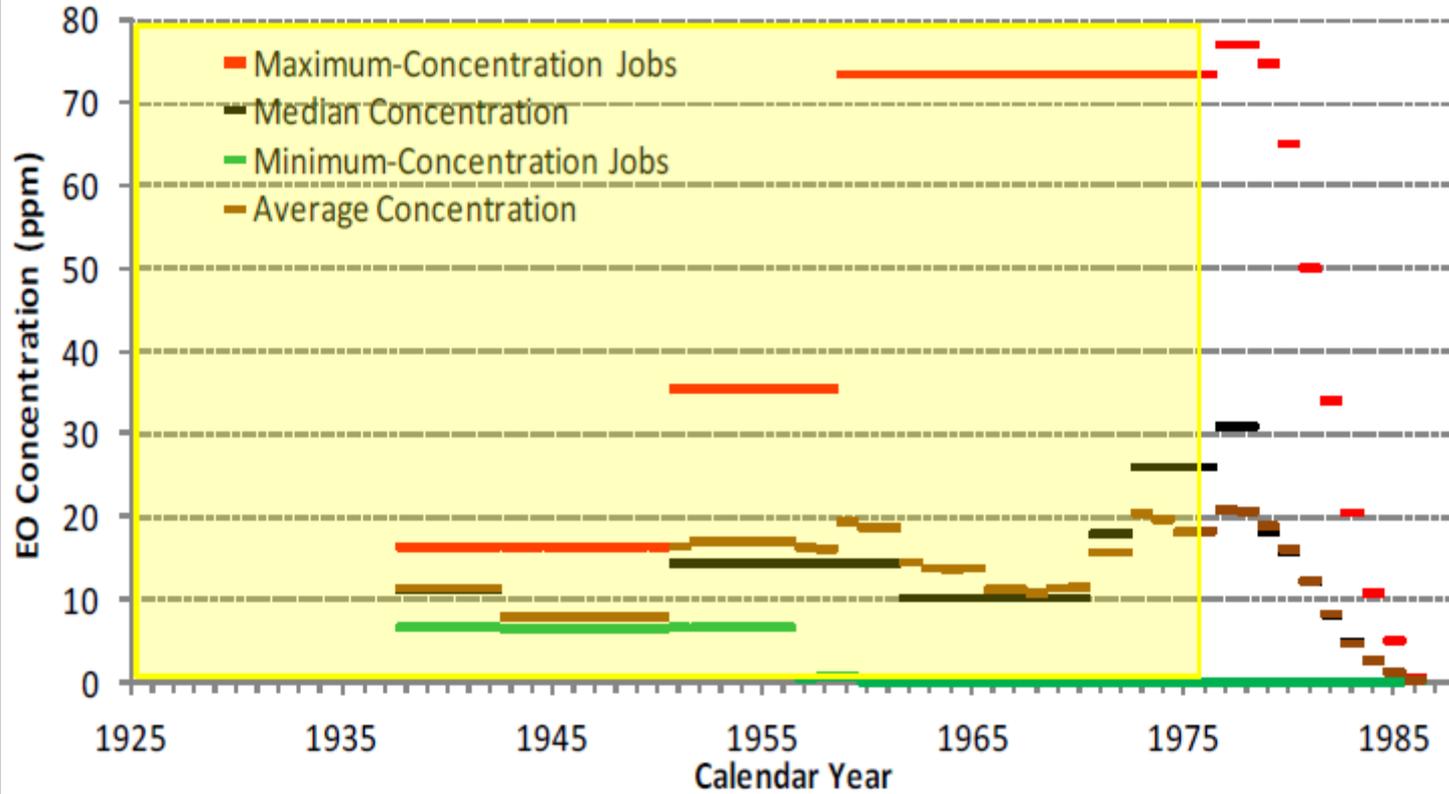
The important point in the above table is that most of the worker exposure in the NIOSH cohort was before the period when NIOSH had exposure observations.



Plant 5, Dept 01, Oper 82



NIOSH Study -- Exposure Concentrations



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.”