Points of Clarification:

Chemical Assessment Advisory Committee (CAAC)
for the IRIS Evaluation of Ethylene Oxide

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On Behalf of the American Chemistry Council

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1. There is a false impression that the breast cancer mortality and lymphoid cancer mortality data are supralinear.

a. One source of this false impression is that the fit of the individual data using the log-linear Cox proportional hazards model with log cumulative exposure as the exposure variable is supralinear. However, the exposure scale being log cumulative exposure (as opposed to cumulative exposure) forces the fitted model to be supralinear when the response frequency is plotted versus the cumulative exposure. (Mathematically, the fitted model with log cumulative exposure can not be anything but supralinear.)

b. A second source of the false impression of supralinearity occurs when the shape of the exposure-response relationship is judged soley on the basis of only 5 categorical rate ratios (RRs). The individual data are more than just the summary represented by only 5 categorical RRs. Slides 4 and 5 from my November 18, 2014, presentation demonstrate the disappearance of “supralinearity” when 20 or more categorical RRs are considered. Slides 7 and 8 from my November 18, 2014, presentation show that the log-linear Cox proportional hazards model (with cumulative exposure as the exposure variable) when fit to all of the individual data (not just 5 categorical RRs) is not supralinear.

c. 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.’’

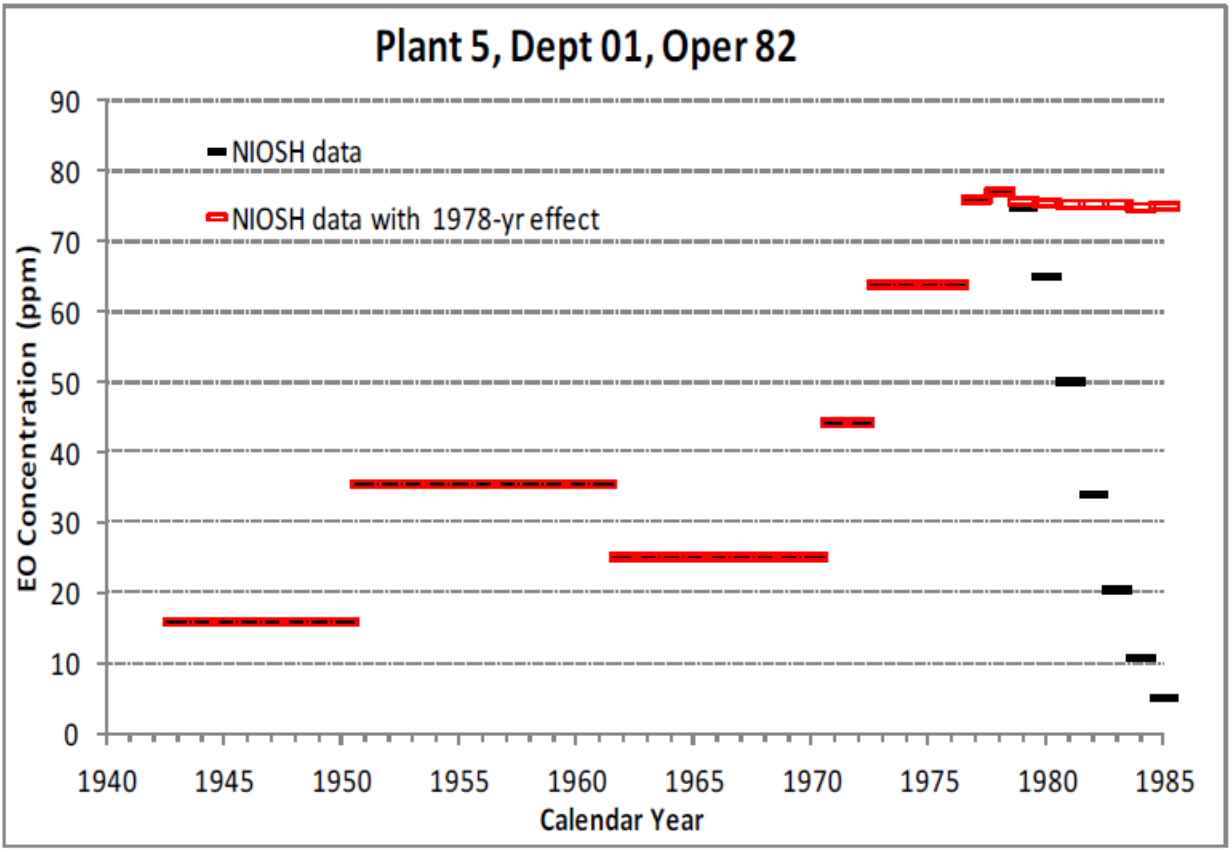
Crump, K.S., 2005. The effect of random error in exposure measurement upon the shape of the exposure response. Dose-Response 3, 456–464 (Formerly Nonlinearity in Biology, Toxicology, and Medicine.).

2. Several CAAC members seem to say that breast cancer mortality and lymphoid cancer mortality data must be supralinear because the log-linear Cox proportional hazards model fit to the individual data using <u>log cumulative exposure</u> is supralinear. However, the exposure scale being <u>log cumulative exposure</u> (as opposed to cumulative exposures) forces the fitted model to be supralinear when response is plotted versus cumulative exposure. (The fitted model with log cumulative exposure can not be anything but supralinear.)

3. The value of fitting the individual data using a log-linear Cox proportional hazards exposure-response model (using cumulative exposure as the exposure variable as opposed to log cumulative exposure) is <u>lost</u> when the resulting fitted model is dismissed because it does not compare well to 5 categorical RRs. The model fit to the individual data is fit to a lot more data than is represented by the 5 categorical RR’s. The exposure-response relationship is not necessarily identified well by 5 categorical RRs (e.g., see Crump (2005)).

4. There was a request from the CAAC for an example of what EPA’s potency estimates would mean in terms of numbers of mortalities. In ACC’s 2013 comments, it was noted in one of the multiple reality checks therein that, in EPA’s words (p. H-38, in EPA’s Appendix H) “The Draft Cancer Assessment grossly over predicts the observed number of cancer mortalities in the study upon which it is based by more than 60 fold.

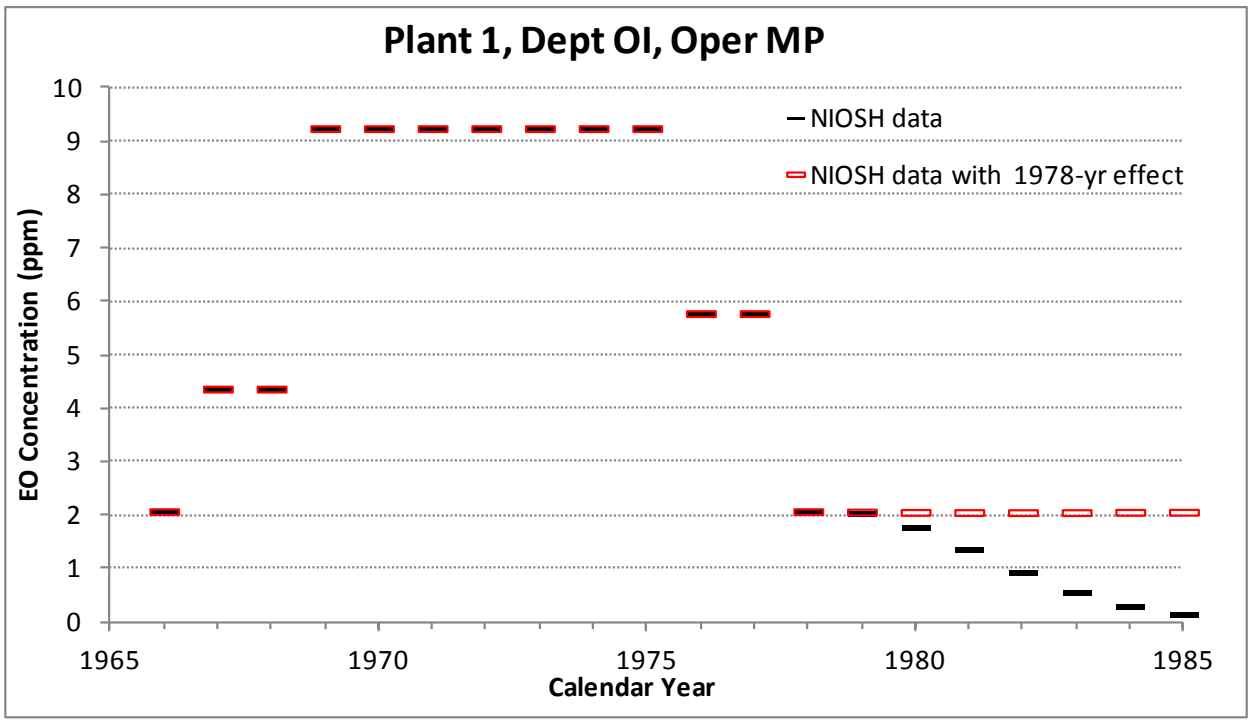
5. In my slide presentation on November 18, 2014, I showed an example in which NIOSH's exposure regression equation estimates before 1978 (when the observed exposure data became sparse or non-existent) showed decreasing exposure levels as you went back in time despite the expectation that exposure levels would increase as you went back in time. The example I showed was as follows:

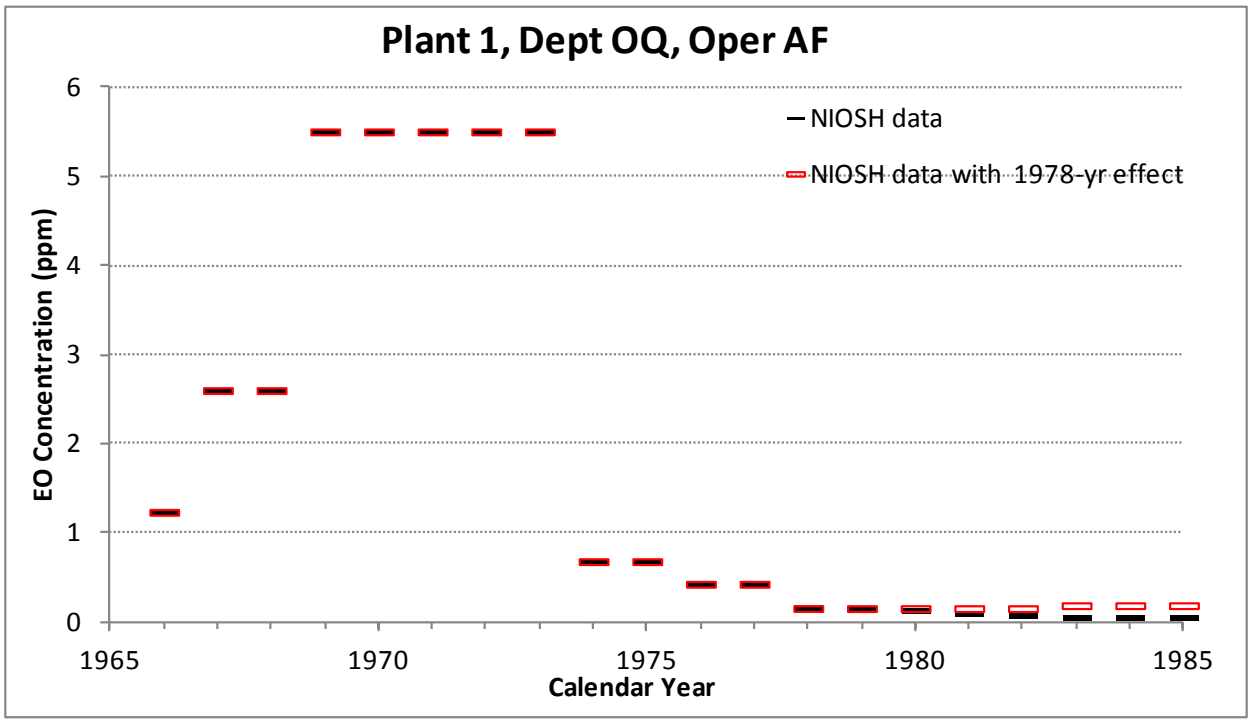


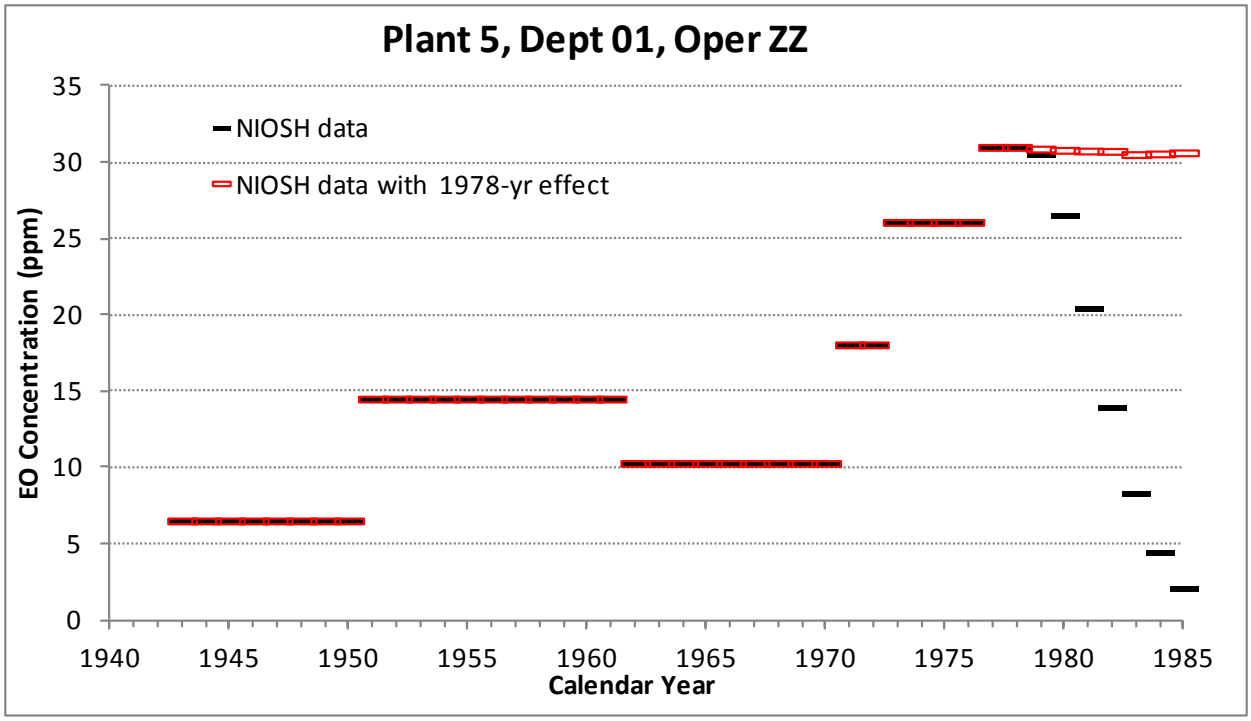
In my oral comments I was unclear as to where this example came from. I did not create this example – I did not have the necessary inputs to NIOSH's regression equation. Instead, the example came directly from NIOSH as part of NIOSH's response to a FOIA request. Such examples are presented on pages 38 to 50 (although the pages are not explicitly numbered, only implicitly numbered in Adobe Acrobat) in ACC's submission "ACC–EtO-Comments–102014.pdf". On page 45, ACC's Comments indicate that

> "Through a Freedom of Information Act request to NIOSH, we received numerical values for the exposure concentrations **(**calculated by NIOSH from their regression model with the Calendar Year effect fixed at its 1978 value before 1978**)** for different plants, departments, and operations over time. Four examples follow."

The 3 examples (other than the one I showed in my November 18, 2014, slides) are as follows:


Plant 1, Dept OI, Oper MP
EO Concentration (ppm)
10
9
8
7
6
5
4
3
2
1
0
1965
1970
1975
1980
1985
Calendar Year
NIOSH data
NIOSH data with 1978-yr effect


Plant 1, Dept OQ, Oper AF
EO Concentration (ppm)
6
5
4
3
2
1
0
1965
1970
1975
1980
1985
Calendar Year
NIOSH data
NIOSH data with 1978-yr effect


Plant 5, Dept 01, Oper ZZ
NIOSH data
NIOSH data with 1978-yr effect
EO Concentration (ppm)
35
30
25
20
15
10
5
0
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
Calendar Year

6. Slides 13 & 14 in the extra slides that I distributed on November 18, 2014 (but did not have the time to present) show that the two-piece spline model did not make a statistically significant improvement in the fit (likelihood) compared to the relevant one-piece model.

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

7. A CAAC member wanted to know if we (ACC) had examples of specific constructive responses to instances where EPA simply dismissed or summarily disagreed with ACC comments.

One example is as follows: In Appendix J.3.1, EPA dismissed the methodological problems identified in Valdez-Flores and Sielken (2013):

> 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.

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.

8. Just to clarify, the "Life Table Method" is a specific method of calculating <u>extra risk</u> by incorporating background age-specific cancer rates, background age-specific survival rates, and the exposure-response-model specific multipliers of these background rates. Life table methods do not refer to comparisons between observed and expected numbers of cancer responses.