



October 20, 2014

SUBMITTED VIA E-MAIL (yeow.aaron@epa.gov)

Mr. Aaron Yeow
Designated Federal Officer
SAB Staff Office
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460-4164

Re: Comments of the American Chemistry Council's Ethylene Oxide Panel (ACC) to the Chemical Assessment Advisory Committee (CAAC) for the IRIS Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft – August 2014)

Dear Mr. Yeow:

The American Chemistry Council (ACC)¹ Ethylene Oxide Panel appreciates the opportunity to submit additional information to the CAAC to review in responding to the draft charge questions for the revised draft IRIS assessment for ethylene oxide (EO). This information is submitted in the following sections which should be considered as attachments to this letter:

- Charge Question #1- Prepared by Dr. Chris Kirman

Precedents represented in the IRIS assessments of other chemicals do not support the selection of a single 15-year lag period. A no lag period should be presented or a range of lag periods including a no lag alternative should be considered in this assessment.

- Charge Question #2- Prepared by Dr. Robert Sielken and Associates

The NIOSH individual exposure data are not available for review. The NIOSH exposure response data for breast and lymphoid cancers that are available are not supralinear.

- Charge Question #3- Prepared by Dr. Richard Irons and Dr. Robert Sielken and Associates

The classification of lymphohematopoietic cancers as a single entity for purposes of risk modeling is not supported by current biology (mode of action) nor is the application of a

¹ The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a \$812 billion enterprise and a key element of the nation's economy. It is the nation's largest exporters, accounting for twelve percent of all U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.



single linear regression model for lymphoid neoplasms consistent with epidemiologic or biologic evidence. 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.

- Charge Question #4- Prepared by Dr. Jane Teta and Dr. Robert Sielken and Associates

The uncertainties associated with the breast cancer incidence study are worthy of greater consideration. The power of the dose-response assessment would be increased by adding in the data from the Union Carbide Corp. (UCC) study. 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 #5- Prepared by Dr. Richard Albertini and Dr. Robert Sielken and Associates

Alternative biologically plausible modes of action (MOAs) have been suggested for at least of some of the tumors attributed to ethylene oxide. 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.

- Charge Question #6- Additional Papers Provided by Dr. Robert Sielken
- Charge Question #7- Prepared by Dr. Robert Sielken and Associates

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.

We urge the CAAC to review this information as it develops draft responses to the charge questions. We also look forward to having comprehensive discussions of these scientific issues at the CAAC meeting on November 18-20, 2014. ACC appreciates your consideration of these comments. If you have any questions or would like additional information, please contact me by phone at 202-249-6714 or by e-mail at bill_gulledge@americanchemistry.com.

Sincerely,

Bill Gulledge

Bill Gulledge
Senior Director, Ethylene Oxide Panel



American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #1
October 2014

Charge Question #1. Exposure lagging. Exposure-response modeling was conducted separately for lymphohematopoietic cancer mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox proportional hazards models, a lag period was used to represent an interval before cancer death (or diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was disregarded because it was not considered relevant for the development of the cancer outcome observed. The lag period for each of the different cancer types was selected empirically based on statistical fit. These exposure lag periods were included in EPA's exposure-response analyses using other model forms for the derivation of cancer risk estimates. Please comment on whether the use of lagged exposure estimates in the derivation of cancer risk estimates and the selection of the lag periods used are clearly described and scientifically appropriate.

ACC recommended on September 23, 2014 the following addition to this charge question:

Please comment on the appropriateness of applying a single, long lag value for this diverse group of cancers.

EPA's assumption of a single, long lag term (15 years) for ethylene oxide (EO) exposures and lymphoid cancers is not well supported (based solely on empirical support). The CAAC should consider the following:

1. Underlying biology:

- Latencies differ for individual leukemias/lymphomas – *Does the adoption of a single value for latency make sense? Should cancer types be evaluated separately?*
 - Latencies for some individual cancer types can be much shorter than 15 years (some lymphomas as little as 2 years; some leukemias as little as 1.5 years) – *Should shorter latency values be considered?*
 - These latencies are taken from the U.S. Centers for Disease Control and Prevention's (CDC) white paper on Minimum Latency & Types or Categories of Cancer (2013) (attached). CDC's review does include consideration of chemically induced leukemias, as benzene and formaldehyde are indicated specifically on page 5. The white paper states "there is substantial overlap in the estimates of latency periods for lymphomas, which range from 2 to 10 years, and leukemias, which range from 1.5 to 15 years" (page 6). The reference list, specifically items 21-27, may be consulted for additional information.
- Assuming a 15-year latency ignores any potential role for EO in affecting late stages of disease (progression) – *Are the lag assumptions consistent with the proposed mode(s) of action?*

2. Precedents from existing IRIS assessments:

- Unfortunately, ACC is not aware of any EPA guidelines for how epidemiology data should be used in a dose-response assessment. Because of this gap, it is important to consider existing IRIS assessments to ensure consistency in the approach used for EO.

- In the existing IRIS assessments for benzene, 1,3-butadiene, and trichloroethylene, the inhalation unit risk is based upon epidemiology data for specific leukemias/lymphomas using cumulative exposure (no exposure lag included). *Should a lag of zero be assumed to be consistent with other IRIS assessments?*
 - The IRIS assessment for coke ovens emissions appears to be the only assessment in which lagging exposure was explicitly considered when estimating cancer potency. The inhalation unit risk was calculated as the geometric mean of 4 different lag assumptions (0, 5, 10, 15 years) since “it is not known which of the lag times is most representative of reality.” *Should a geometric mean of multiple lag assumptions be adopted in recognition of the uncertainty associated with lag?*
3. **Potential policy implications of using a non-zero lag:** There is a potential for inequitable treatment of exposure for toxicity and exposure assessment components of risk assessment. *Are the lag assumptions consistently carried through in the lifetable calculations? In applying the derived unit risk, should a lag term be included when estimating risk to human populations?*

Based upon these considerations, ACC recommends that the lag term should be set to zero when estimating the cancer potency of EO. This will ensure consistency with the vast majority of assessments in the IRIS database, as well as consistency with the published assessment of Valdez-Flores et al. (2010). If, however, a non-zero lag value is assumed for EO, then separate values should be adopted for each cancer type based upon current understanding of their latencies. Inclusion of multiple lag assumptions will permit an evaluation of the uncertainty associated with this step, and will permit the use of geometric mean across multiple assumptions in recognition of this uncertainty.

Christopher R. Kirman
Summit Toxicology

American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Questions #2 and #3
October 2014

Charge Question #2. Breast cancer incidence – model selection. As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

Charge Question #3. Lymphoid cancer – model selection. EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

1. The NIOSH breast cancer incidence data are not publicly available; therefore, EPA's analysis of this endpoint cannot be verified.
2. EPA's method of evaluating different exposure-response models is mathematically incorrect. It is based only on a summary of the available data and not the individual data points and erroneously rejects more appropriate models and SAB recommendations.

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. EPA's method results in a poor basis for model selection and is based on a misinterpretation of categorical rate ratios which leads to inappropriate exposure-response model fitting and biased estimates of risk.

3. Contrary to SAB recommendations, EPA uses a non-peer-reviewed supralinear, two-piece spline model for breast cancer incidence.
4. 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.

Expanding a model from one-piece linear to a two-piece linear model with a knot does not result in a statistically significantly improved fit for

- a) breast cancer incidence,

- b) breast cancer mortality, or
- c) lymphoid cancer mortality.

The following table compares the log-likelihoods for a one-piece model to a two-piece model with one selected knot. The likelihood ratio statistic is compared to a chi-squared distribution with two degrees of freedom (one degree for the selected knot and one for the second linear piece).

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

* Reference is to Appendix D in EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide.

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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Questions 2.a and 3.a
October 2014

Charge Question #2 and 2.a: Breast cancer incidence – model selection. As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

2.a. Please comment on whether the considerations used for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence for the purposes of estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

Charge Question #3 and 3.a: Lymphoid cancer – model selection. EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

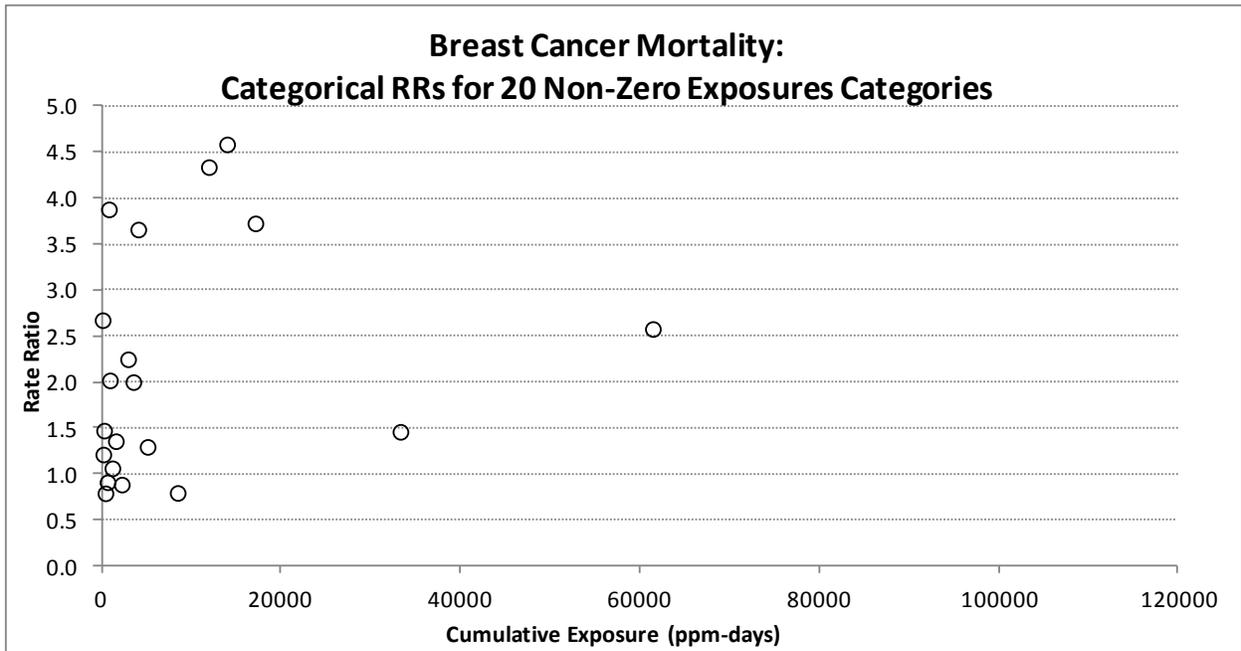
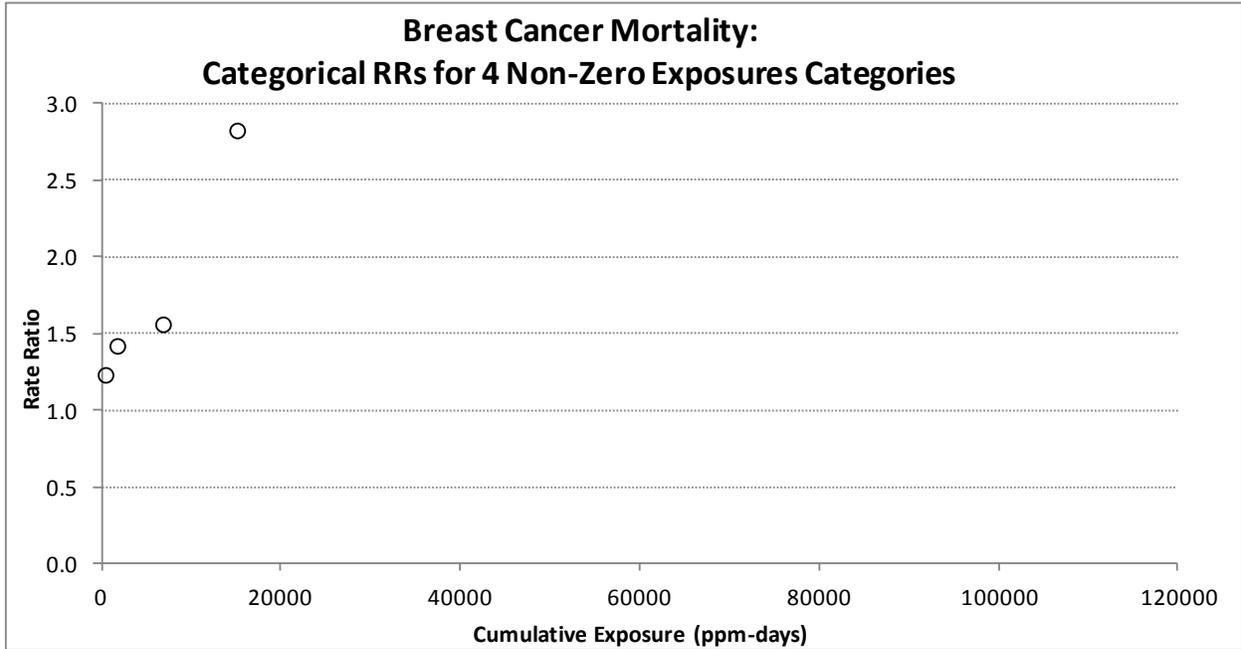
3.a. Please comment on EPA's rationale for its use of the linear regression of the categorical results as the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer (Section 4.1.1.2).

EPA's model selection (addressed in Charge Questions 2 and 3, especially 2.a and 3.a) is fundamentally flawed due to their misinterpretation of categorical ratios.

The NIOSH cancer exposure-response data for breast and lymphoid cancers is not supralinear.

The false impression of supralinearity disappears as the number of categorical rate ratios (RRs) for non-zero exposure increases above the four presented by EPA. Valdez-Flores and Sielken (2013) and its associated Supplemental Material present figures for 4, 20, and 61 categorical RRs for breast cancer mortality and 4, 20, and 44 categorical RRs for lymphoid cancer mortality. (The individual data for breast cancer incidence is not publicly available.) Figure 1 is a simplified figure showing the 4, 20, and 61 categorical RRs for breast cancer mortality. Figure 2 is a simplified figure showing the 4, 20, and 44 categorical RRs for lymphoid cancer mortality. Figure 3 shows the 5 and 10 categorical RRs for breast cancer incidence indicated by Dr. Steenland in his Appendix D. (The NIOSH breast cancer incidence data are not publicly available; therefore, EPA's analyses of this endpoint cannot be verified.)

Figure 1. 4, 20, and 61 categorical RRs for breast cancer mortality



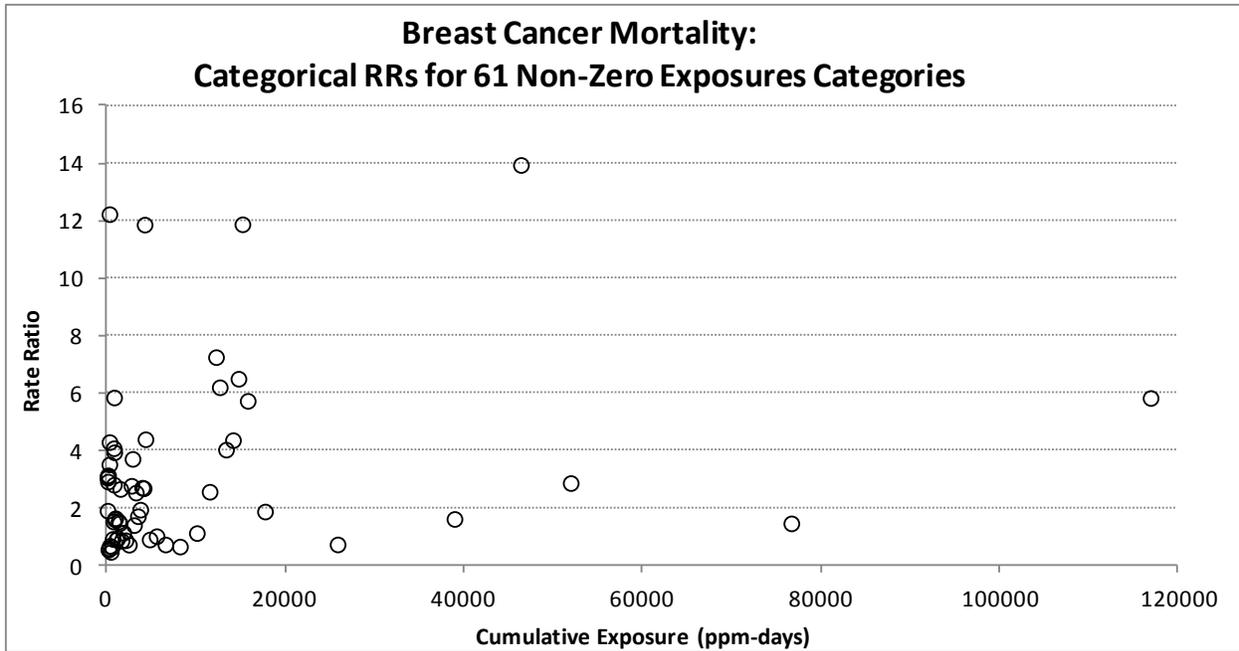
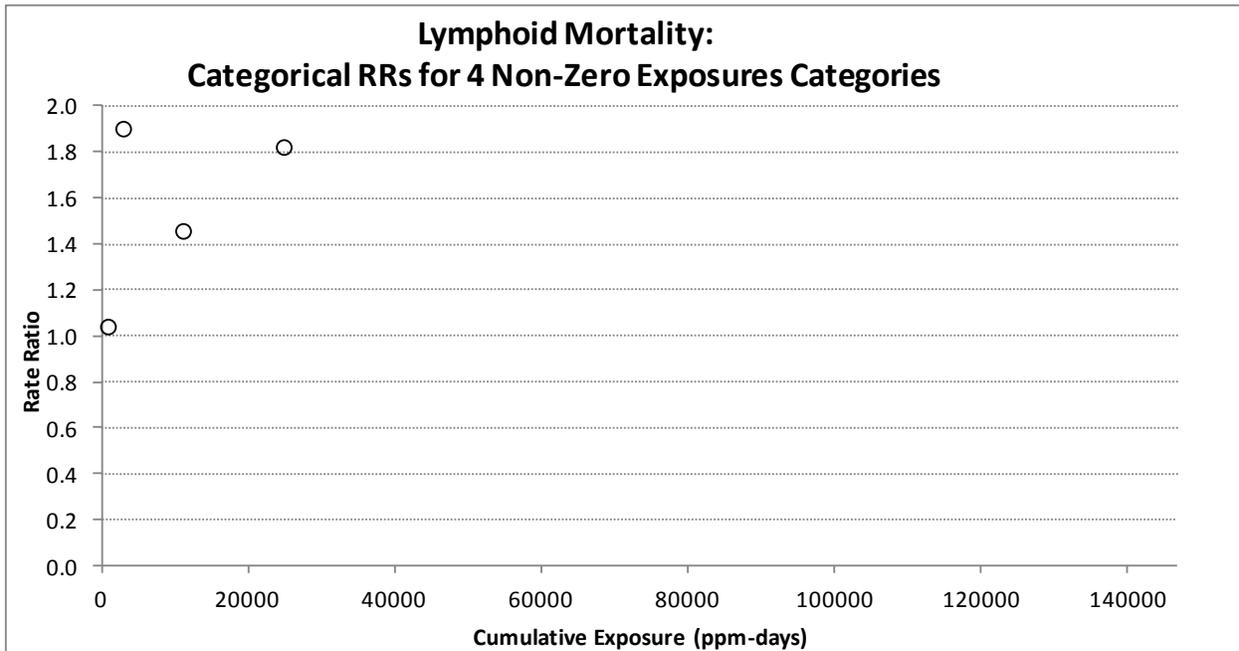


Figure 2. 4, 20, and 44 categorical RRs for lymphoid cancer mortality



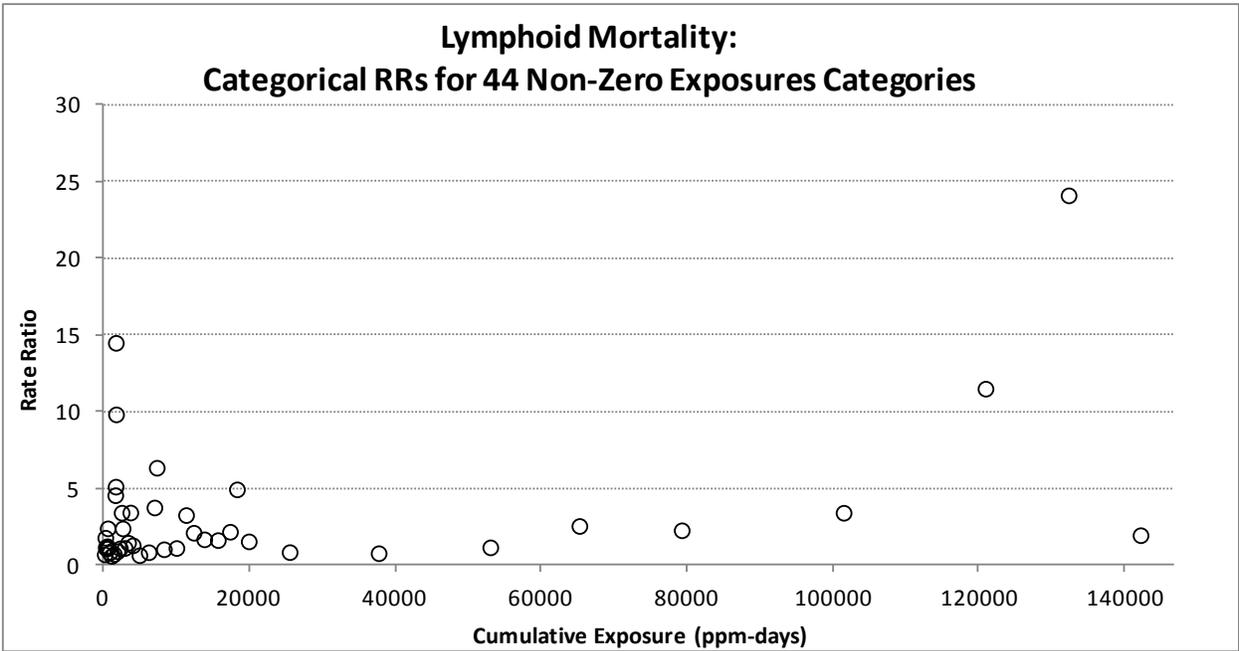
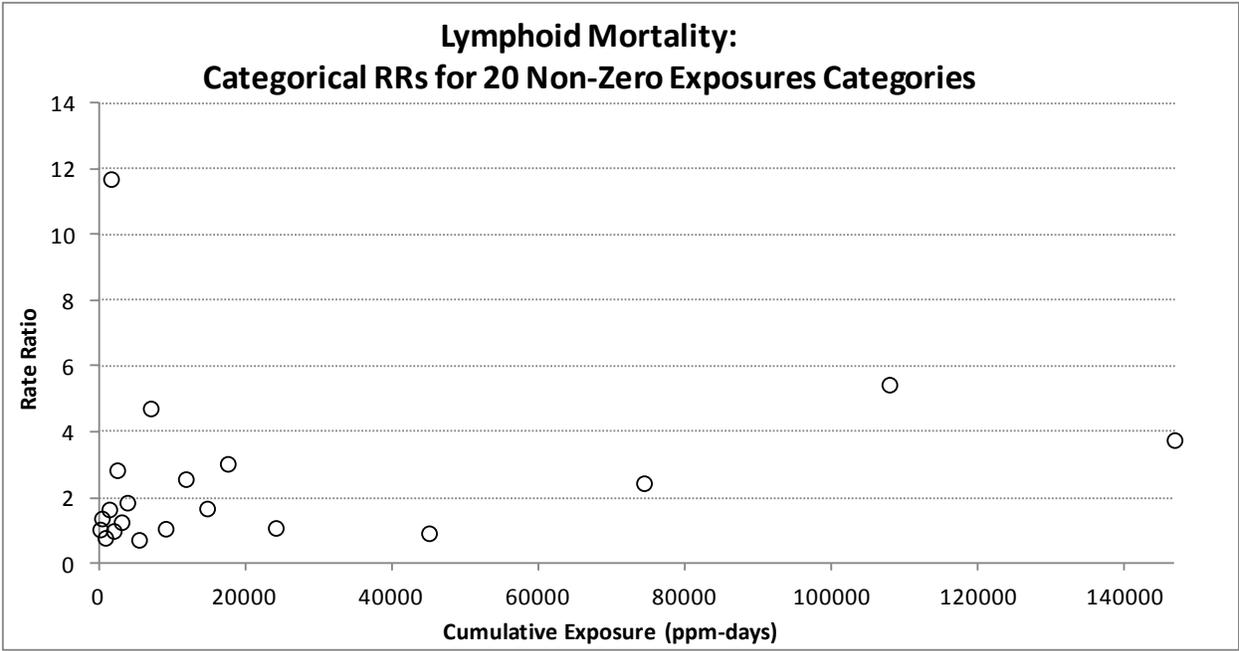
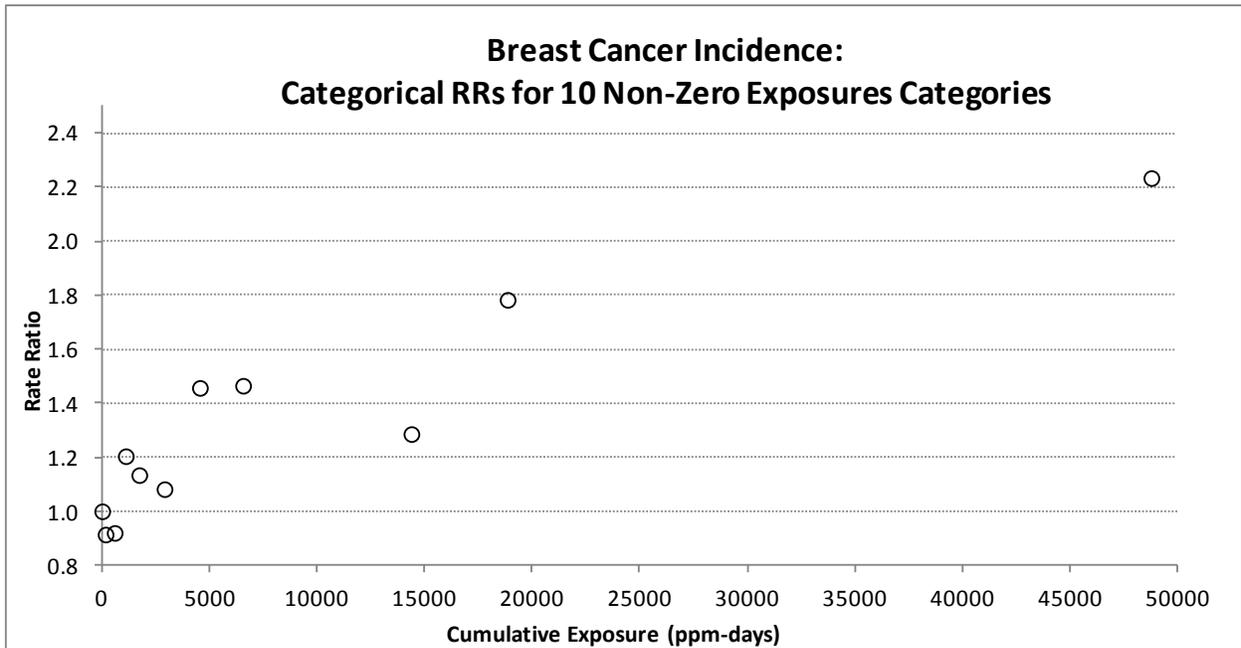
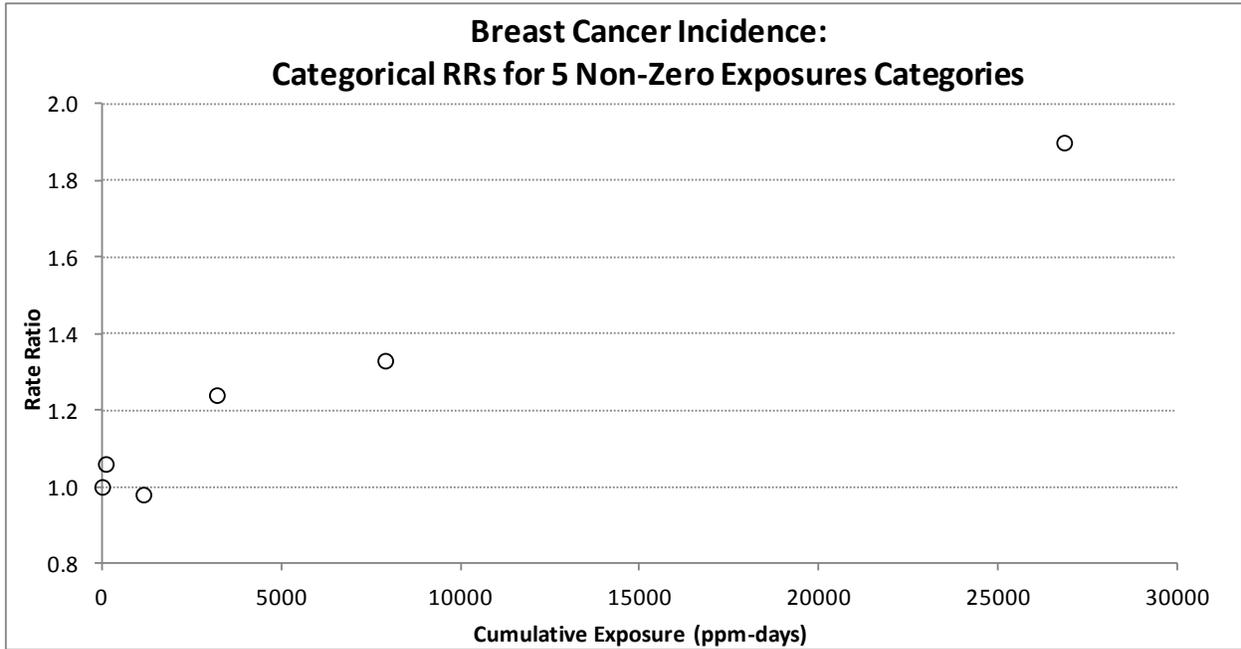


Figure 3. 5 and 10 categorical RRs for breast cancer incidence indicated by Dr. Steenland in his Appendix D

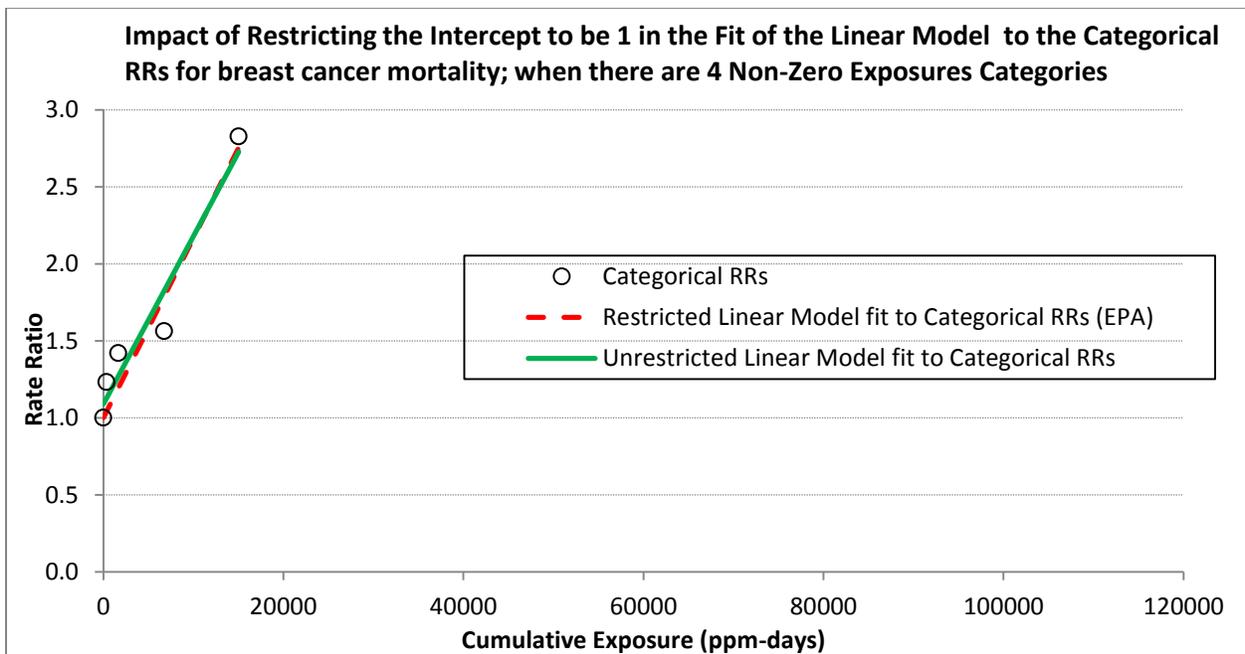


An unrestricted linear model fits the data better than a linear model restricted to have an RR intercept equal to one.

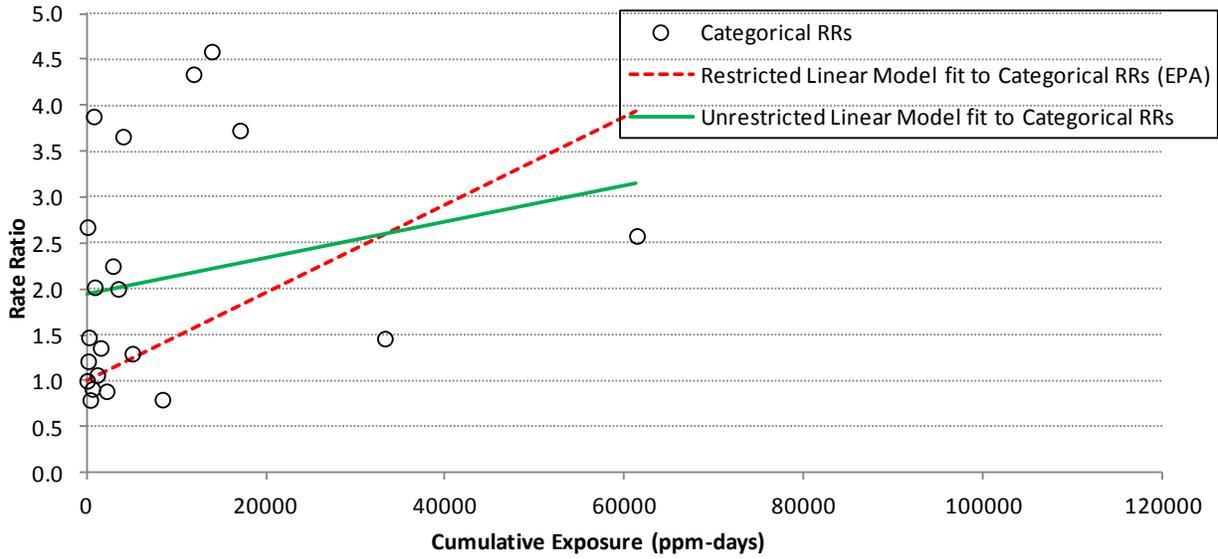
The evaluation of selected exposure-response models should not ignore the uncertainty in the cancer response rate in the non-exposed category, should adjust for different estimated baseline risks, and should not restrict the fitted model to have an RR intercept equal to one.

Figure 4 is for breast cancer mortality. Figure 5 is for lymphoid cancer mortality. Figure 6 is for breast cancer incidence. Figure 6 is based on the 5 and 10 categorical RRs for breast cancer incidence indicated by Dr. Steenland in his Appendix D. (The NIOSH breast cancer incidence data are not publicly available; therefore, EPA's analyses of this endpoint cannot be verified.)

Figure 4. Impact of restricting the intercept to be 1 in the fit of the linear model to the categorical RRs for breast cancer mortality



Impact of Restricting the Intercept to be 1 in the Fit of the Linear Model to the Categorical RRs for breast cancer mortality; when there are 20 Non-Zero Exposures Categories



Impact of Restricting the Intercept to be 1 in the Fit of the Linear Model to the Categorical RRs for breast cancer mortality; when there are 61 Non-Zero Exposures Categories

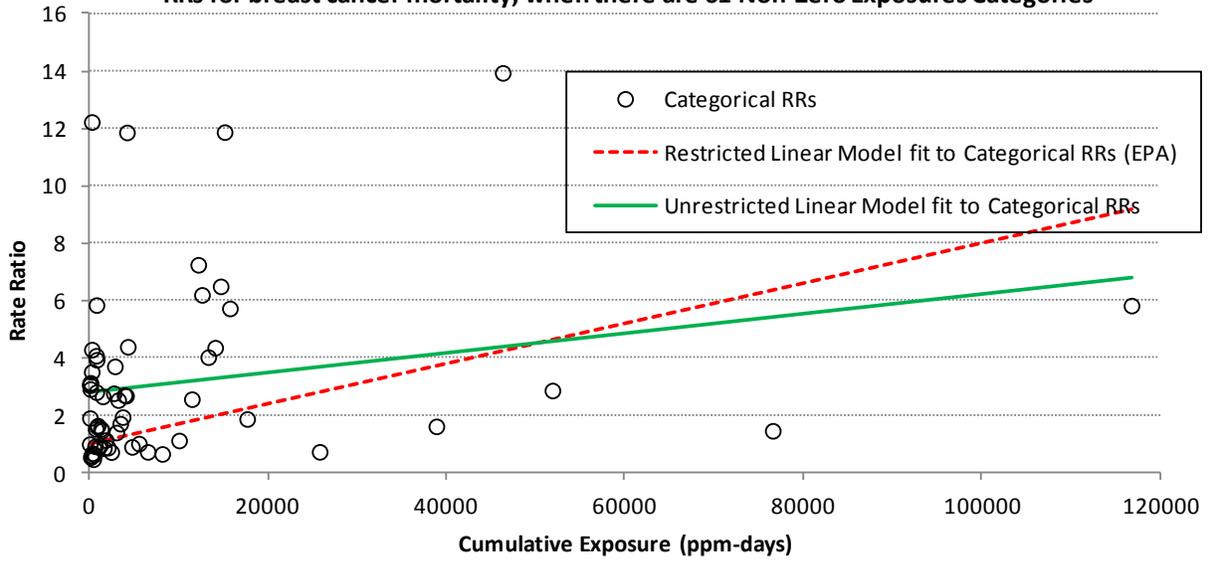
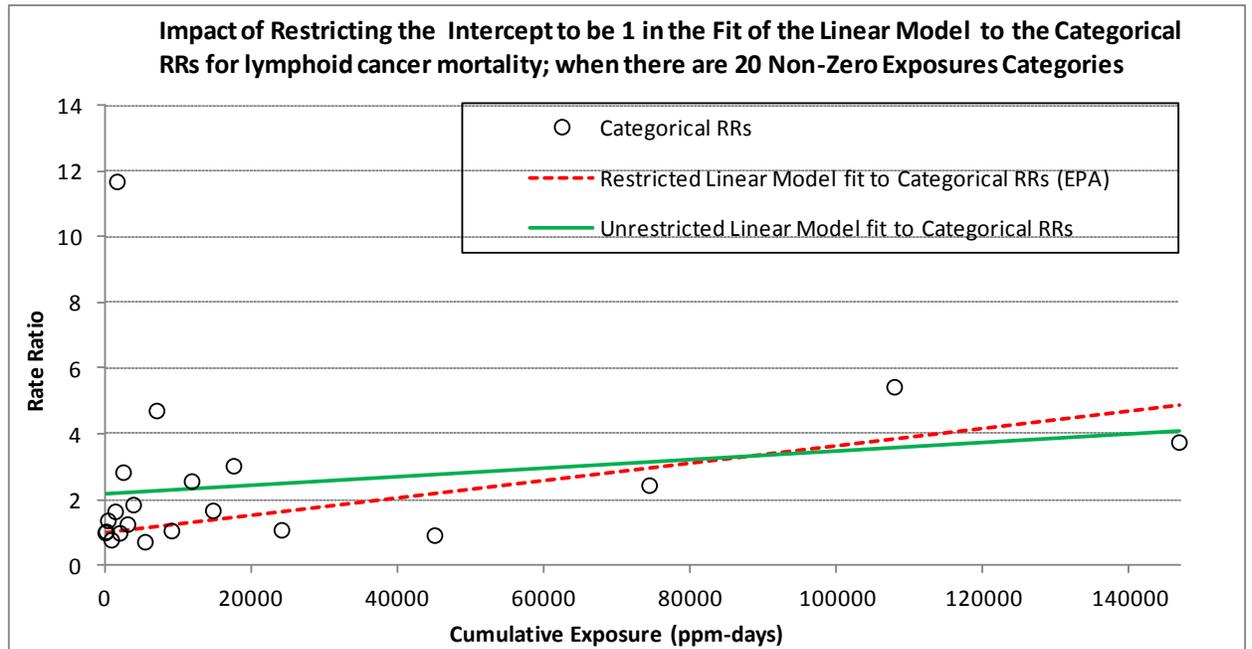
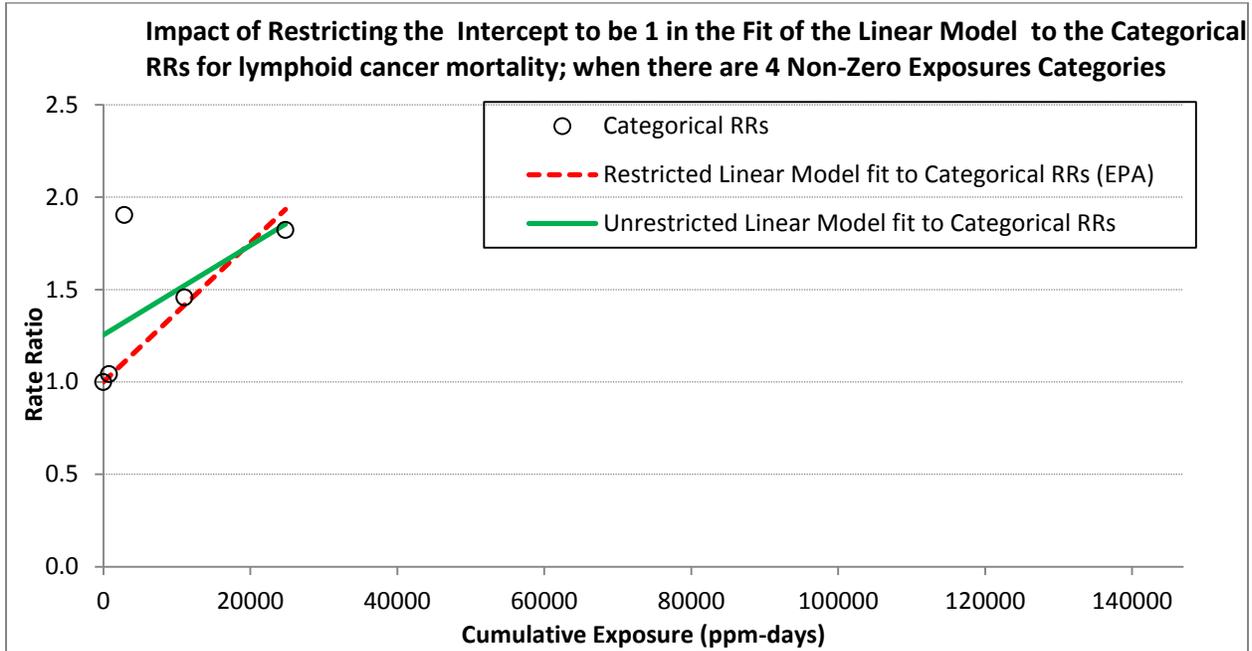


Figure 5. Impact of restricting the intercept to be 1 in the fit of the linear model to the categorical RRs for lymphoid cancer mortality



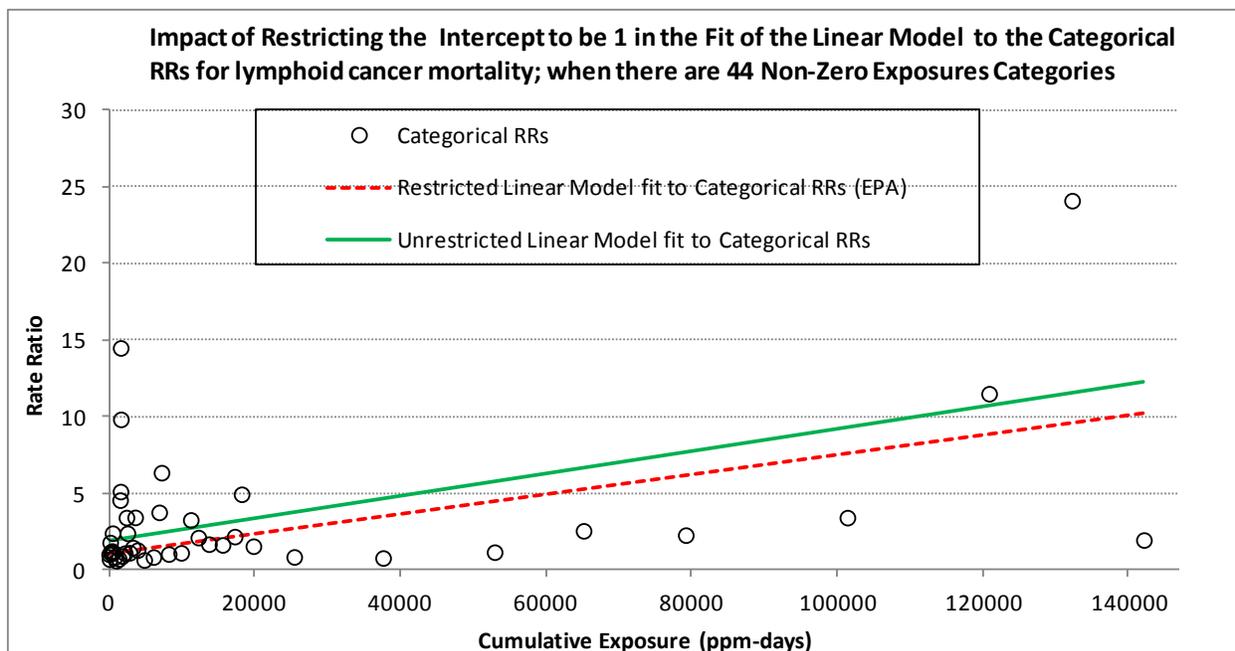
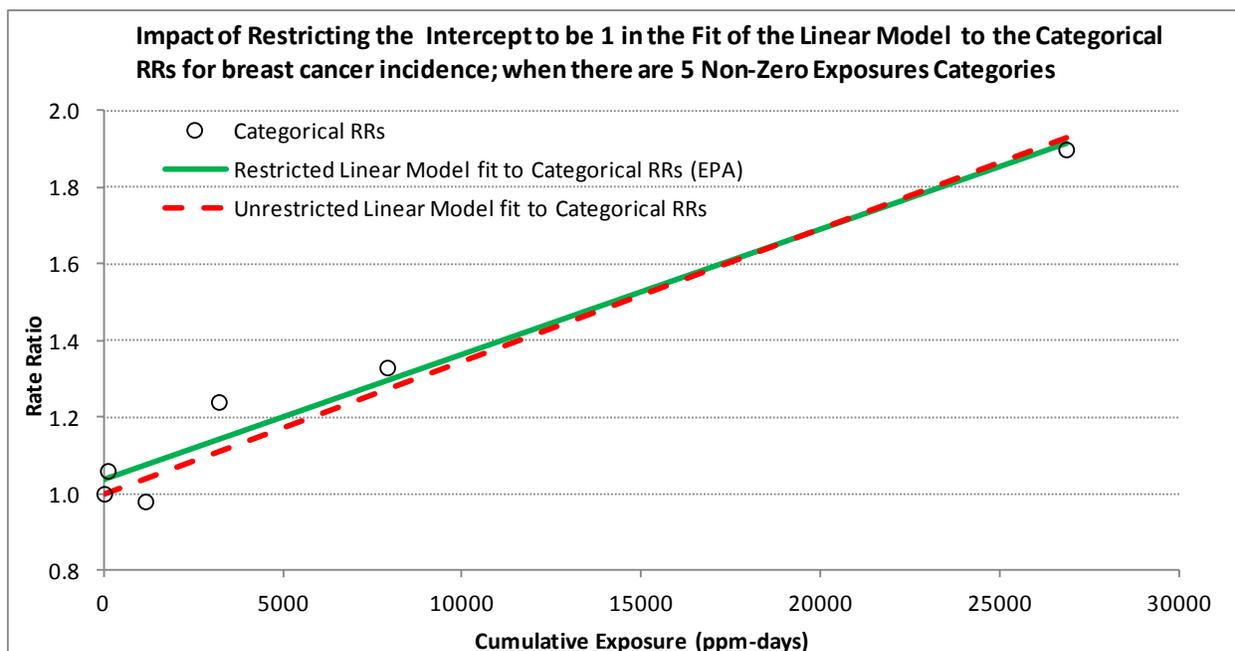
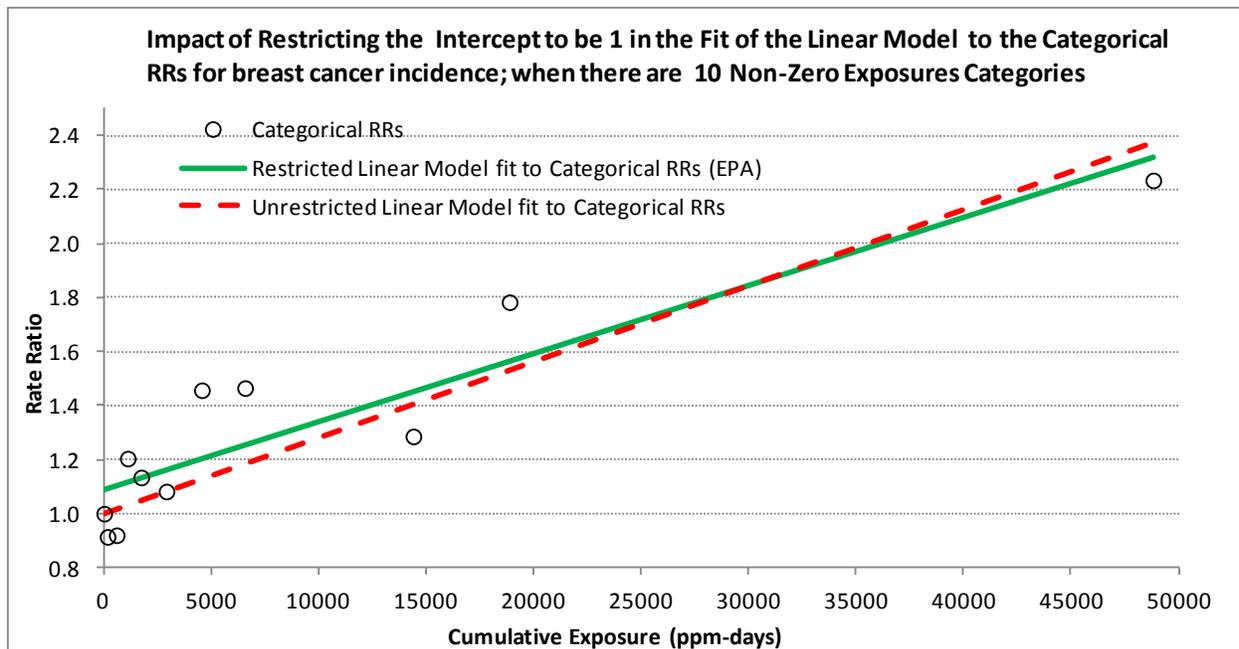


Figure 6. Impact of restricting the intercept to be 1 in the fit of the linear model to the categorical RRs for breast cancer incidence





The log-linear model fit to individual data for lymphoid cancer mortality compares well to the categorical RRs when the comparison adjusts for the difference in estimated baseline risks.

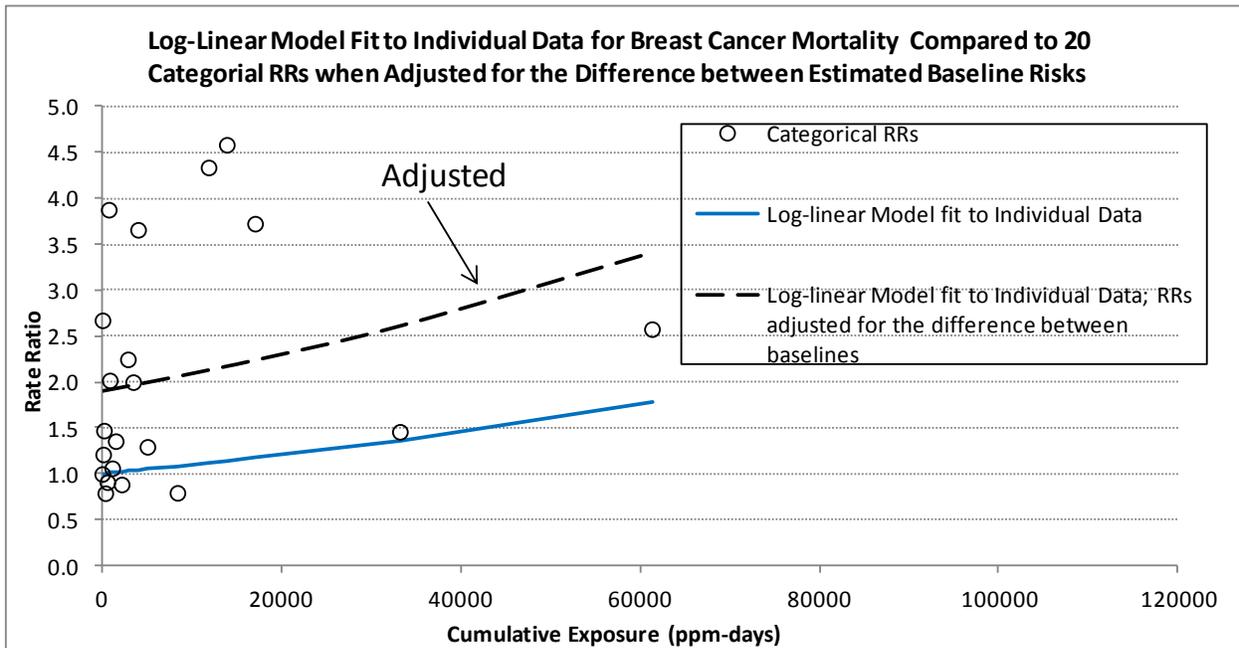
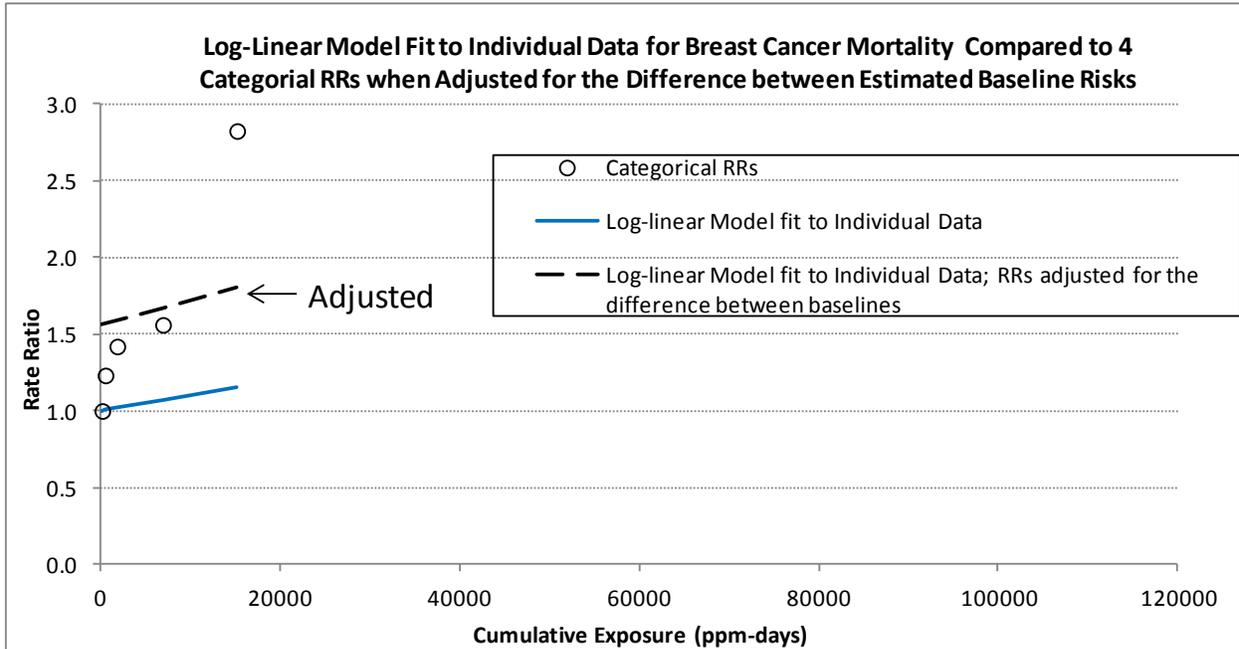
EPA rejects the log-linear model fit to individual data for breast cancer mortality and lymphoid cancer mortality because of a “poor visual fit”. Although not in the 2013 Revised External Peer Review Draft, all of the figures in Chapter 4 of the 2014 draft contain a footnote noting that “the various models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values...” However, if the comparison between the log-linear models fit to the individual data is adjusted for different estimated baseline risks, then the log-linear model is a good fit. This is especially true if the number of categorical RRs is increased.

Figure 7 is for breast cancer mortality. Figure 7 shows the good fit of the log-linear model for 4, 20, and 61 categories (61 categories is one category for each breast cancer mortality among exposed individuals).

Figure 8 is for lymphoid cancer mortality. Figure 8 shows the good fit of the log-linear model for 4, 20, and 44 categories (44 categories is one category for each lymphoid cancer mortality among exposed individuals).

Figure 9 is for breast cancer incidence. Figure 9 is based on the 5 and 10 categorical RRs for breast cancer incidence indicated by Dr. Steenland in his Appendix D.

Figure 7. The log-linear model fit to individual data for breast cancer mortality compares well to the categorical RRs when the comparison adjusts for different estimated baseline risks



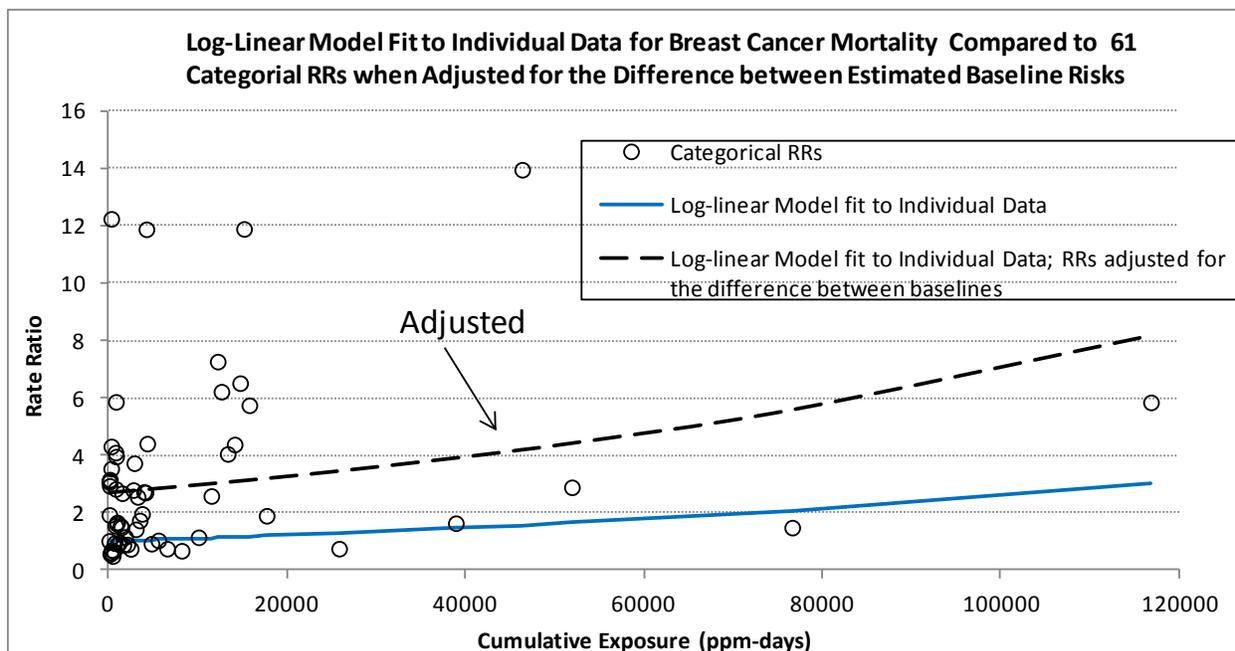
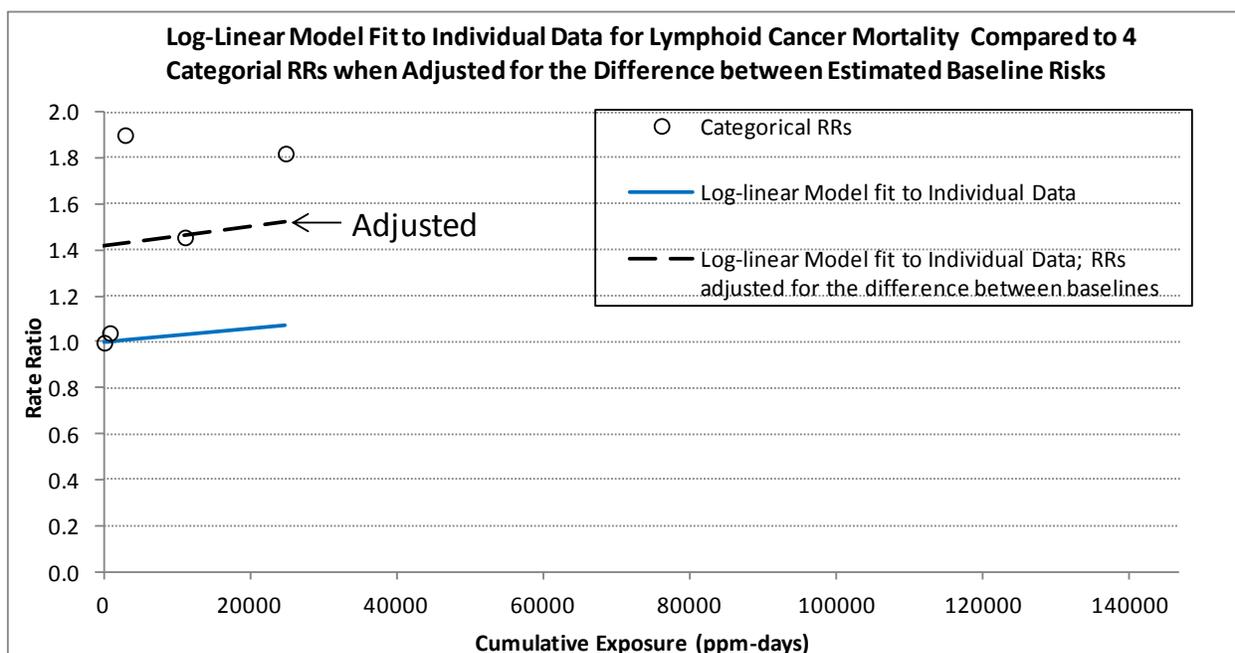


Figure 8. The log-linear model fit to individual data for lymphoid cancer mortality compares well to the categorical RRs when the comparison adjusts for different estimated baseline risks



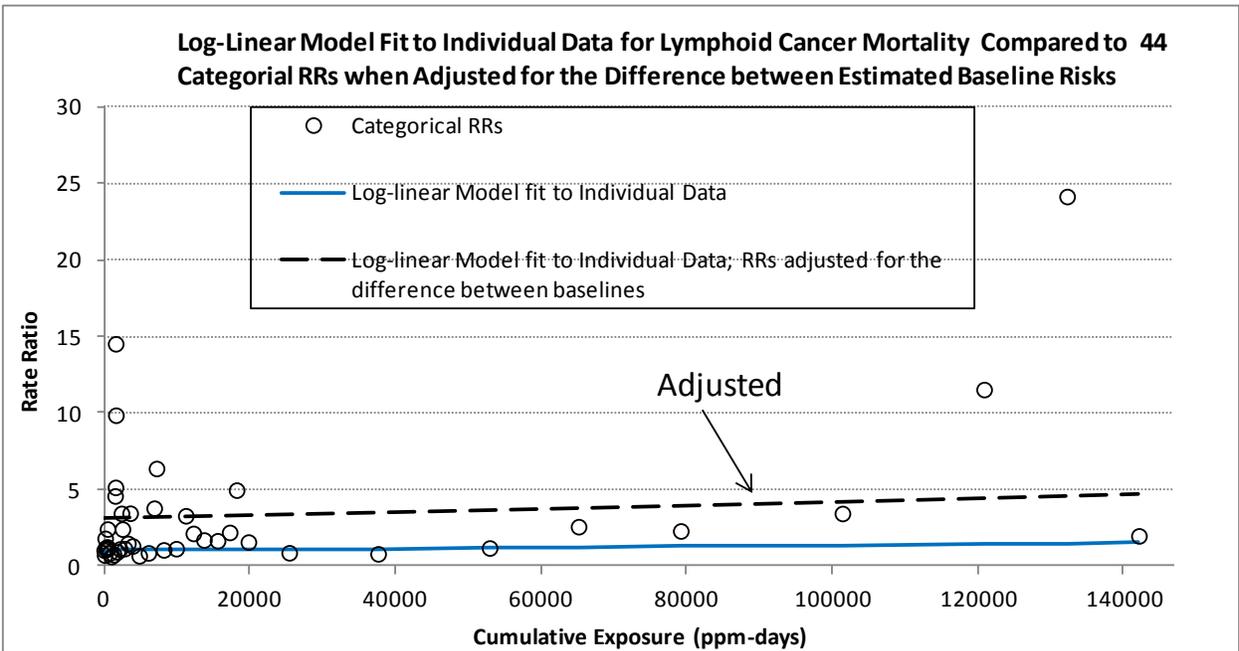
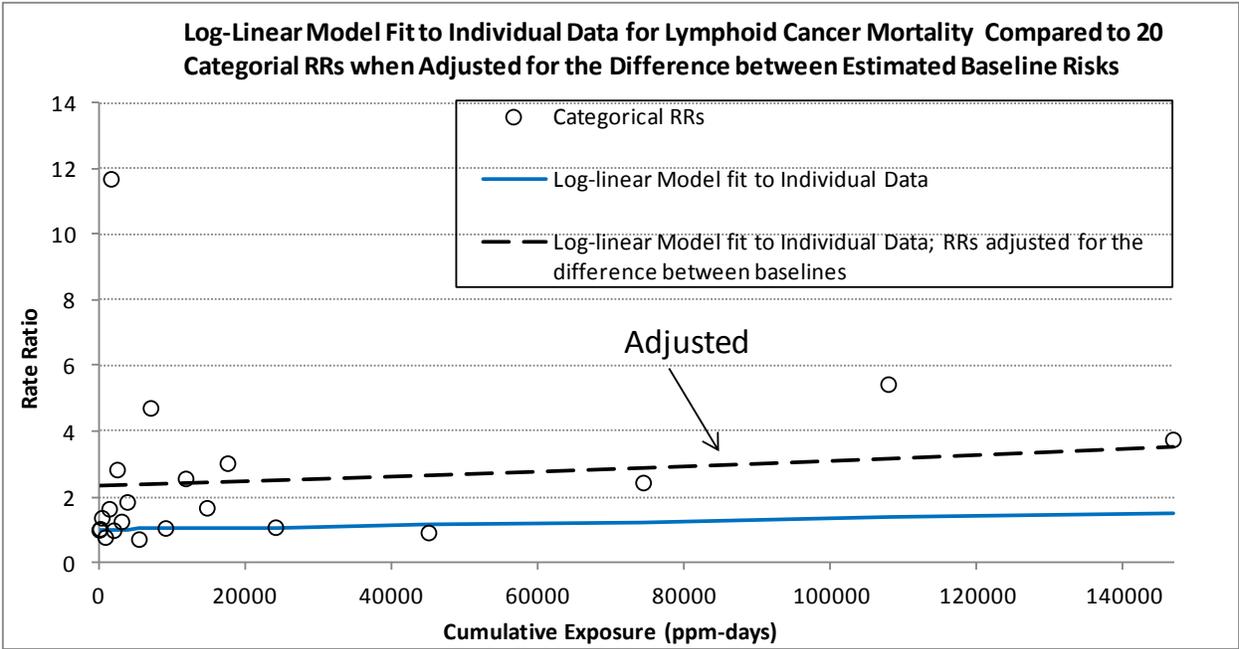
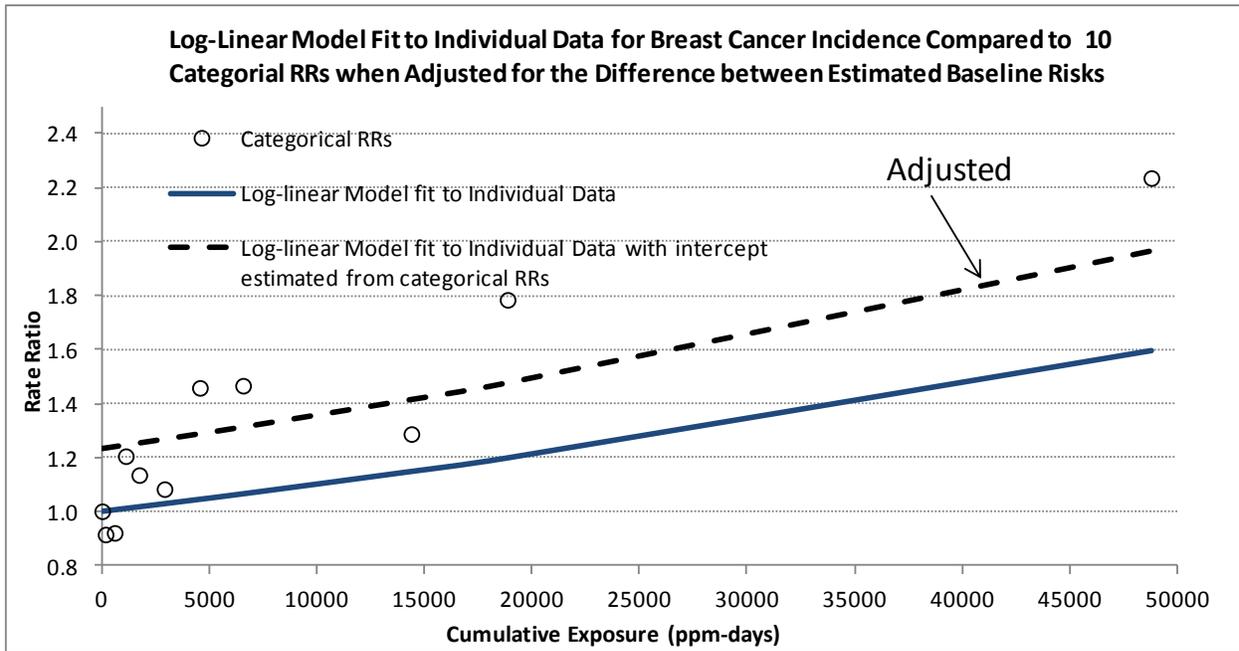
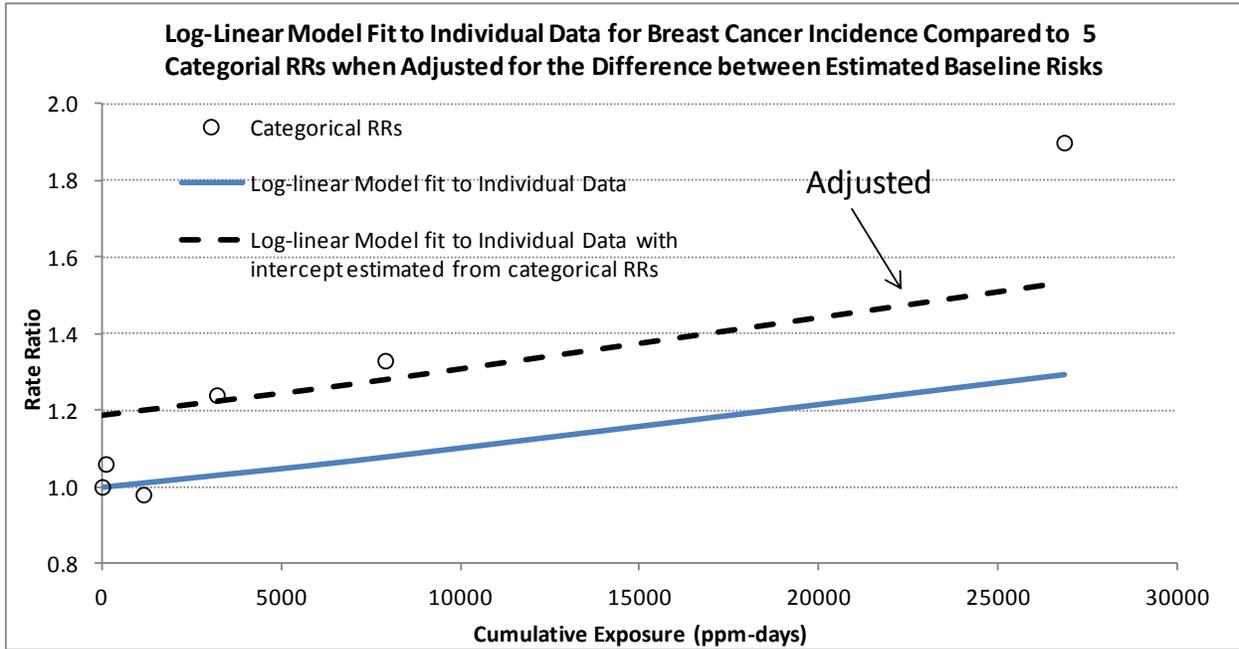


Figure 9. The log-linear model fit to individual data for breast cancer incidence compares well to the categorical RRs when the comparison adjusts for different estimated baseline risks



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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Questions #2.a and #3.b
October 2014

Charge Question #2 and 2.a: Breast cancer incidence – model selection. As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

2.a. Please comment on whether the considerations used for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence for the purposes of estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

Charge Question #3 and 3.b: Lymphoid cancer – model selection. EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

3.b. Please comment on whether the considerations used for model selection and their application in the selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

The following publication is relevant to quantitative cancer risk assessment for ethylene oxide inhalation in occupational settings:

Valdez-Flores, Ciriaco, Robert L. Sielken Jr., M. Jane Teta. (2011). Quantitative cancer risk assessment for ethylene oxide inhalation in occupational settings. *Arch Toxicol*, 85: 1189-93.

Abstract

The estimated occupational ethylene oxide (EO) exposure concentrations corresponding to specified extra risks are calculated for lymphoid mortality as the most appropriate endpoint, despite the lack of a statistically significant exposure-response relationship. These estimated concentrations are for occupational exposures 40 years of occupational inhalation exposure to EO from age 20 to age 60 years. The estimated occupational inhalation exposure concentrations (ppm) corresponding to specified extra risks of

lymphoid mortality to age 70 years in a population of male and female EO workers are based on Cox proportional hazards models of the most recent updated epidemiology cohort mortality studies of EO workers and a standard life-table calculation. An occupational exposure at an inhalation concentration of 2.77 ppm EO is estimated to result in an extra risk of lymphoid mortality of 4 in 10,000 (0.0004) in the combined worker population of men and women from the two studies. The corresponding estimated concentration decreases slightly to 2.27 ppm when based on only the men in the updated cohorts combined. The difference in these estimates reflects the difference between combining all of the available data or focusing on only the men and excluding the women who did not show an increase in lymphoid mortality with EO inhalation exposure. The results of sensitivity analyses using other mortality endpoints (all lymphohematopoietic tissue cancers, leukemia) support the choice of lymphoid tumor mortality for estimation of extra risk.

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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #3
October 2014

Charge Question #3. Lymphoid cancer – model selection.

3.c. EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).

ACC recommended on September 23, 2014 the following addition to this charge question:

The preferred approach to selecting relevant mode of action (MOA) is to employ current understanding of the molecular mechanisms involved in the pathogenesis of specific lymphoid cancers of interest as the basis for selection. Does the current hazard assessment, which assumes a mutagenic MOA for ethylene oxide in developing a preferred model for deriving risk estimates for lymphoid cancers, adequately address science that supports different MOAs that are independent of mutagenesis for specific lymphoid cancers?

The Classification of Lymphohematopoietic Cancers

The classification of lymphohematopoietic cancers as a single entity for purposes of risk modeling is not supported by current biology (mode of action) nor is the application of a single linear regression model for lymphoid neoplasms consistent with epidemiologic or biologic evidence.

International World Health Organization (WHO) criteria for the classification/diagnosis of all hematopoietic and lymphoid neoplasms is based on 1) cell of origin, (i.e. the target cell for transformation in carcinogenesis) and 2) pathogenesis, (i.e. mechanism of transformation) (1, 2).

Recent epidemiology studies have confirmed striking differences in the etiology of different lymphoid neoplasms (3).

The Cells of Origin for Lymphoid Neoplasms

The cells of origin for over 90% of lymphoid cancers are mature B lymphocytes (4) located in peripheral lymphoid tissues; not hematopoietic stem cells (HSC) in the bone marrow (4).

Mature T lymphocytes account for approximately another 7% of lymphoid tumors and arise in peripheral lymph nodes or peripheral extranodal lymphoid tissue; not HSC in the bone marrow (4).

Immature progenitor B- and T- lymphoid cancers, that theoretically (but not likely) * could be derived from a mutagenic event in a HSC, comprise < 3.0% of lymphoid neoplasms (5, 6).

Mature Lymphoid Neoplasms

Together, diffuse large B cell lymphomas (DLBCL) and follicular Lymphomas (FL) comprise approximately 65% of mature lymphoid neoplasms and arise in mature B lymphocytes in peripheral lymphocyte tissue during immune response. These are antigen-dependent tumors, the majority of which have no known etiology. Identified risk factors including chronic inflammation, immunodeficiency diseases and drug- or steroid- induced immunosuppression, the latter of which often exhibit strong associations with Epstein-Barr Virus (EBV) (9).

Chronic lymphocytic leukemia (CLL) and its solid tissue counterpart, small lymphocytic lymphoma (SLL) account for about 10-15% of mature B cell lymphomas (10). These neoplasms originate in a subset of activated B lymphocytes that worldwide appear to be stimulated by a restricted set of auto-antigens (i.e. autoimmune) (11, 12). There is no convincing evidence linking CLL to any external etiology, including ionizing radiation, infections or chemical exposures (13).

Plasma cell myelomas (i.e. multiple myeloma) comprise 10-15% of mature lymphoid neoplasms and originate in mature antigen-committed B lymphocytes that have undergone antigenic stimulation in a peripheral lymph node (14, 15). Consequently plasma cell myeloma can only arise during adaptive immune response and does not originate in bone marrow (14). Research on these tumors has been extensive, often conflicting and complex, reflecting etiologies that are almost certainly multifactorial. However, chronic antigenic stimulation in a peripheral lymph node is an obligatory event. Major risk factors include genetic susceptibility, agriculture (pesticides and farm work are almost always confounding), chronic antigen stimulation, immunodeficiency and autoimmune diseases. Ionizing radiation is also known to be a co-factor in some cases. A recent large European study failed to confirm a risk for organic solvents (16).

Peripheral T/NK cell lymphomas comprise less than 8% of mature lymphoid neoplasms, have no known etiology except for viruses, e.g. EBV (4, 17) and originate in lymph nodes, peripheral extranodal lymphoid tissue but not the bone marrow (2, 17).

Conclusion

As further discussed in Attachment 1, EPA has grouped organs that are derived from different cells of origin. Hematopoietic and lymphoid neoplasms represent many different diseases that can be distinguished on the basis of cell of origin, genetic characteristics, pathogenesis and etiology. For example, non-Hodgkin's lymphoma (NHL) represents over 20 distinct diseases that can be distinguished from each other according to these criteria. In contrast to lymphoid neoplasms, myeloid neoplasms originate either in a pluripotent stem cell or myeloid progenitor cells, with genetic abnormalities used to distinguish these diseases.

* Recent studies reveal that the embryonic origins of hematopoietic and lymphoid lineages are heterogeneous. The majority of T-lymphocyte populations and approximately half of B lymphocyte populations appear to be derived prior to- and independent of- the emergence of hematopoietic stem cells (HSC) (7, 8). These have no known etiologies beyond genetic predisposition.

In the draft IRIS assessment of formaldehyde, EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of lymphohematopoietic (LHP) cancers—“all LHP cancers,” “all leukemias,” and “myeloid leukemias.” The NAS committee that reviewed the draft assessment did not support the grouping of “all LHP cancers” because it combines many diverse cancers that are not closely related in etiology, cells of origin, and other characteristics (NAS 2011). The committee recommended that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.

Consistent with the NAS (2011) recommendations, in the draft assessment of EO, EPA should not combine all tumors of lymphoid and myeloid together, but instead rely on the biological classifications now in routine use by hematologists. The Agency should consider the three categories in the lymphoid group individually. The three cancers in the “lymphoid” category have been examined for males and females, and the NIOSH and UCC studies reviewed these cancers separately and combined using Cox proportional hazard models with cumulative exposure.

No endpoint shows a statistically significant positive slope. The slopes for lymphocytic leukemia and NHL are negative for UCC males and NIOSH females and the slope for multiple myeloma is negative for all gender and study groupings. While there is no clear choice for a target organ, if NHL were selected, the exposure concentration corresponding to a 1-in-a-million added environmental cancer risk could be between 270 to 3,000 fold greater than EPA’s proposed value of 0.3 ppt. Consistent with the state of the science, including the WHO classification (Swerdlow et al. 2008) and NAS (2011), EPA must evaluate each LHP cancer separately, rather than combining them before conducting modeling.

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Attachment 1

TUMOR CLASSIFICATION

1. Hematopoietic and lymphoid neoplasms are diverse in cell of origin and etiology

Lymphohematopoietic (LHP) neoplasms (i.e., hematopoietic and lymphatic) represent many different diseases that can be distinguished on the basis of cell of origin, genetic characteristics, pathogenesis and etiology. The World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues (WHO 2001; 2008) is considered the gold standard for classification of hematopoietic neoplasms. WHO 2001 divides lymphoid neoplasms primarily on the basis of cell of origin. These are further stratified into individually recognized disease subtypes that are defined by level of cell maturation, as well as morphology, molecular and clinical characteristics, including etiology and response to therapy. About 23 subtypes of lymphoid neoplasms were previously lumped under non-Hodgkin lymphoma (NHL), but in WHO are classified under precursor B and T cell neoplasms, mature B neoplasms (e.g., multiple myeloma or chronic lymphocytic leukemia) and mature T and NK cell neoplasms. Each represent one or more subtypes under WHO with individual cells of origin, ranging from precursor B, precursor T to mature B and T cells. NHL cannot be defined in terms of a single cell of origin.

Morton et al. 2006 examined the incidence patterns of lymphoid neoplasms classified using WHO 2001, including NHL, multiple myeloma and acute and chronic lymphocytic leukemia. They concluded, "...the striking differences in incidence patterns by histologic subtype strongly suggest that there is etiologic heterogeneity among lymphoid neoplasms and support the pursuit of epidemiologic analysis by subtype." A similar recommendation was made by the National Academy of Sciences (NAS) in its review of the draft IRIS assessment of formaldehyde, where the NAS stated "The committee does not support consideration of the grouping "all LHP cancers" because this grouping combines diverse cancers that are not closely related in cells of origin and in other characteristics."

The conclusions of the experts in this field conflict with the decision of the NIOSH study authors to group, for statistical analyses, three types of lymphoid neoplasms and all LHP neoplasms, which do not arise from the same cell of origin and which are likely to be etiologically diverse. Similarly, EPA's use of these same categorizations (i.e., grouping three types of cancers as a lymphoid tumor subset and grouping all LHP cancers) is not scientifically supportable. The NIOSH database is limited by cause of death information coming from death certificates, thereby limiting analyses by very specific subtypes. However, analyses using more specific classifications than these large groupings are feasible and should be conducted to provide more scientifically defensible cancer risk values.

2. Absence of a relationship between breast cancer and "lymphoid" neoplasms and lymphoma

No cogent biological rationale exists to conclude that lymphoid neoplasms, comprised of either B or T lymphocytes at any level of maturity, share common origins with carcinoma of the breast in any somatic cell. The extra-embryonic derivation of T lymphocytes is endothelium in the yolk sac that precedes the branching of hematopoietic stem cells (HSC) during the third week of gestation. Only a subset of B lymphocytes are derived from HSC (Tavian & Peault, 2005).

Therefore, both endothelial and lymphohematopoietic cells are derived from common cells in the mesoderm. In contrast, mammary cells which form the ductal network of the breast are of epithelial origin (Watson & Khaled, 2008). The morphogenesis of mammary glands occurs later in gestation. Although mammary epithelial cells commit to differentiation using the same signaling pathways as T cells, these events occur in cells of different origin (embryonic vs extraembryonic) at different stages in embryogenesis.

3. Classification of Hematopoietic and Lymphoid Neoplasms

The world consensus for the classification (and diagnosis) of hematopoietic and lymphoid tissues is promulgated in the WHO publications of 2001 and 2008. Unlike previous ICD classifications which were based solely on morphologic classification (e.g. lymphoma or leukemia), WHO 2001 and 2008 distinguish hematopoietic and lymphoid neoplasms as separate major categories, primarily on the basis of lineage (i.e. myeloid, lymphoid, histiocytic/dendritic and mast cell) and define distinct diseases within each lineage on the basis of morphology, cell of origin, immunophenotype, genetic features, etiology and/or pathogenesis and clinical characteristics including response to therapy.

Lymphoid neoplasms do not represent a single disease but are extremely heterogeneous and include many different discrete individual diseases. For example, non-Hodgkin lymphoma/leukemias represent over 20 distinct diseases that can be distinguished according to the criteria listed above. Lymphoid neoplasms are classified primarily on the level of differentiation (maturation) of the neoplastic cells or their cells of origin, and in many cases can be described as “immature” or “mature” on that basis. Because the same distinct lymphoid neoplasm can possess both leukemic and solid tissue phases, the terms, “leukemia” and “lymphoma” may be used interchangeably to describe the same disease. Consequently, the use of these specific terms is arbitrary and conveys no meaning with respect to the origin of the individual neoplasm.

In contrast to lymphoid neoplasms, hematopoietic (i.e. myeloid) neoplasms originate either in a pluripotent stem cell or myeloid progenitor cells, and structural genetic abnormalities, e.g. gene rearrangements or mutations, are often used to distinguish these diseases.

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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #4
October 2014

Charge Question #4. Uncertainty in the cancer risk estimates. Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

ACC recommended on September 23, 2014 the following additions to this charge question:

- Have uncertainties of the NIOSH exposure assessment been adequately discussed given the absence of data prior to 1979?
- Have uncertainties of the NIOSH breast cancer incidence study been adequately considered?

National Institute for Occupational Safety and Health (NIOSH) Exposure Assessment Uncertainties

The NIOSH exposure assessment is a key element in modeling the epidemiology data and in the ultimate unit risk estimates for both breast cancer and lymphoid tumors. Primarily based on the uncertainties of the Union Carbide Corporation (UCC) exposure assessment, the Agency dismisses the UCC study for dose-response assessment:

Because the exposure assessment conducted for the UCC cohort is much cruder, especially for the highest exposures, than the NIOSH exposure assessment (see above and Appendix A.2.20), especially for the highest exposures, than the NIOSH exposure assessment (which was based on a validated regression model; see Appendix A.2.8), EPA considers the results of the exposure-response analyses of the combined cohort data to have greater uncertainty than those from analyses of the NIOSH cohort alone, despite the additional cases contributed by the UCC cohort.... (p. 3-8).

The uncertainty section (Section 4-47) in the draft IRIS assessment discusses the NIOSH exposure assessment with a long list of positive attributes. The only uncertainty noted is the absence of exposure data during the extended follow up period, a rather unimportant issue in our view. Several other critical limitations, similar to those of the UCC exposure assessment, are not mentioned, the most important of which is the absence of exposure data prior to 1975 and very little data from 1976 to 1978, when most of the worker exposures occurred (Greife et al. 1988). This is clearly noted by Dr. Steenland in Appendix H of the draft IRIS assessment:

There is obviously more uncertainty about the estimation of exposures prior to 1975 when there was no sampling data. This uncertainty is of some concern in the sense that the majority of cumulative exposure metric for most workers is probably contributed by earlier, higher exposures.

In addition, the draft IRIS assessment fails to note that the validation procedure was limited to post-1978 data. In fact, it was limited to 46 arithmetic means from six plants between the years 1979 and 1985. This sheds no light on the accuracy of the pre-1975 estimates. Furthermore, the

effect of calendar year in the regression model was fixed at 1978; that is, “we set each predicted ETO [ethylene oxide] level prior to 1978 equal to the predicted level in 1978. Variation in exposure levels prior to 1978 were modeled as a function of the remaining terms in the model with calendar year effect fixed at 1978” (Horning et al. 1994). As a result, the estimates of maximum ETO concentrations for years before 1978 implausibly decrease as one goes back in time. Therefore, in addition to assuming no effect of calendar year prior to 1978, it was assumed that all the other variables in the model had the same effect before 1978, with calendar year not allowed to vary, as they did after 1978, with calendar year allowed to vary. EPA ignores the above described uncertainties in the NIOSH retrospective exposure assessment while emphasizing those of the UCC study, thereby justifying not using the UCC study, whose exposure estimates do not decrease as one goes back in time. Clearly both exposure assessments suffer from the absence of data in the early years, prior to 1975 for the NIOSH studies and prior to 1957 for the UCC studies.

EPA also dismisses the value of increasing the power of its analyses for males especially with inclusion of the UCC data. The number of male deaths due to “lymphoid” cancers in the NIOSH study is similar to the number of males deaths in this category in the UCC study. UCC would add 12 deaths to the 18 male non-Hodgkin’s lymphoma deaths in the NIOSH study, three more to the four deaths due to multiple myeloma, and two more deaths to the five deaths due to lymphocytic leukemia. These are increases of 67%, 75%, and 40%, or over 60% overall. The UCC contribution to the male data is substantial, despite the much larger NIOSH population, for two reasons: 1) UCC workers have longer average follow up (37 vs. 25 years) and 2) UCC workers have substantially more deceased study subjects (51% vs. 19%).

Both studies suffer from uncertainties in exposure estimation in the early years and both have reasonably good estimates based on industrial hygiene data post-1978 for NIOSH and post-1956 for UCC. At the very least, results should be presented both with and without the UCC data.

Breast Cancer Incidence Study Uncertainties

Another uncertainty issue relates to participation in the breast cancer interview in the breast cancer incidence study (Steenland et al. 2003). The draft IRIS assessment relies on the interview data from this study for derivation of a breast cancer unit risk estimate. One of the recognized uncertainties noted by the study authors is that 32% (2,437 women) were missing interviews, predominately due to inability to locate them. The potential for participation selection bias is noted in the uncertainty section of the IRIS document, but it is quickly dismissed concluding that non-participation in an interview would not be associated with breast cancer or ETO exposure. We do not agree with this approach.

The NIOSH authors of this study note the stronger relationship between duration of exposure than with cumulative exposure and conclude that a causal association with breast cancer is weakened by “possible biases due to non-response.” Non-participants who could not be located would be expected to be shorter-term workers with less cumulative exposure and for whom breast cancer diagnoses could not be identified. Those with stable residence (and likely higher cumulative exposures) are more likely to be interviewed and their breast cancer diagnoses identified.

Steenland et al. (2003) also note their difficulty in reaching a causal interpretation due to inconsistencies in the exposure-response trends. This is reflected in the numerous failed attempts by EPA to model odds ratios from the published results (see Table 5 of Steenland et al. (2003) and Table 4-12 of the draft IRIS assessment), leading ultimately to the selection of a two-piece linear spline model. The NIOSH authors interpret the data only as “*suggestive*” for those with higher cumulative exposures to ETO. The uncertainties associated with the breast cancer incidence study are worthy of greater consideration in the context of the statement in the draft IRIS assessment that “Confidence in the unit risk estimate is particularly high for the breast cancer component.” (p. 4-76)

By strongly urging EPA to revise its IRIS assessment to incorporate these and other considerations, the CAAC will contribute to a much more scientifically credible regulation of ETO exposures.

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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #4
October 2014

Charge Question #4: Uncertainty in the cancer risk estimates. Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

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.

EPA failed to incorporate the 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.

As discussed in Appendix A, NIOSH had no exposure data prior to 1976 and very little from 1976-1978, when most of the worker exposures occurred. The NIOSH validation procedure was limited to post-1978 data. NIOSH's final exposure model did not include all of the available data. In developing its exposure regression, NIOSH used data from 36 different companies including several plants not in the NIOSH study. In addition to assuming no effect of calendar year prior to 1978, it was assumed that all other variables in the regression model estimated using post-1978 data had the same effect before 1978 when calendar year was not allowed to vary. Workplace exposure limits were substantially higher prior to 1978. Fixing the effect in the regression model of calendar year at 1978 for approximately 35 prior years for the most important workers (including the longest and highest exposed) in the exposure assessment created bias.

NIOSH's estimated exposure values before 1978 are unrealistic. Because of the effects of the terms in the regression model, other than "Calendar Year," the maximum estimated EO concentrations for years before 1978 decrease as you go back in time to earlier years. (This is the opposite of what is expected and the findings of the UCC study). The NIOSH study included workers who started working with EO as early as 1943. Even though the workplace exposure limit was set at 100 ppm in the mid-1940s, the average exposure concentrations prior to 1978, estimated by the NIOSH exposure model, are less than the average exposure concentrations in 1978 (see Table 1). However, the workplace time-weighted average exposure limits (ACGIH TLVs) were as high as 100 ppm up to 1957. Moreover, EO is a gas at room temperature or has a very high vapor pressure (1095 mmHg at 20 Celsius) and workers complained about the odor of EO. (Note: odor detection threshold for ethylene oxide has been reported to be 260 ppm and 700 ppm in different references and the level of distinct odor awareness for ethylene oxide has been calculated to be 1,625 ppm.)

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

In addition, with respect to the uncertainty in fixing the calendar effect to 1978, Stayner et al. (1993) stated “[i]t is not possible to test the influence of short-term exposure peaks experienced during the course of a day” and “[t]he mean and median exposure estimates differed substantially, indication that the distributions of these measures were highly skewed. The range of the exposure measures spanned several orders of magnitude.”

Inclusion of the UCC data would add substantially to the power of the dose-response analyses.

The number of deaths due to the three cancers included in NIOSH’s “lymphoid” category indicates that the number of observed responses for males is similar in the UCC study to those for males in the NIOSH study (Valdez-Flores et al., 2010).¹

The UCC data would add 12 deaths to the 18 male non-Hodgkin lymphoma deaths in the NIOSH study; 3 deaths to the 4 deaths due to multiple myeloma and 2 deaths to the 5 deaths due to lymphocytic leukemia. These are increases of 67%; 75% and 40% or over 60 % overall. The UCC contribution to the male data is substantial, despite the much larger NIOSH population, for two reasons. First, UCC workers have much longer average follow up (37 yr. vs. 25 yr.). Second, UCC workers have substantially more deceased study subjects (51% vs. 19%). Both studies

¹ Valdez-Flores, Ciriaco, Robert L. Sielken Jr., M. Jane Teta. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. *Regulatory Toxicology and Pharmacology*, 56: 312-20.

suffer from uncertainties in exposure estimation in the pre-1978 period and both have reasonably good estimates based on industrial hygiene data post- 1978.

Valdez-Flores et al. (2010) reported that when the most recent epidemiological data on individual workers in the NIOSH and updated UCC occupational studies are used to characterize the potential excess cancer risks of environmental exposure to EO, the risk value determined is three orders of magnitude different. In their study, no evidence of a positive cumulative exposure-response relationship was found. In addition, fitted Cox proportional hazards models with cumulative EO exposure do not have statistically significant positive slopes. The lack of increasing trends was corroborated by categorical analyses.

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Appendix A

Comments on NIOSH Exposure Papers: Greife et al. (1988) and Hornung et al. (1994)

Analysis of the exposure values NIOSH developed for the epidemiology study that EPA relied on for its exposure-response modeling reveals several issues. The issues in NIOSH's exposure assessment largely invalidate EPA's reliance solely on the NIOSH epidemiology study and the exclusion of the Union Carbide Corporation (UCC) epidemiology study. No matter how exposure is characterized (either as % of person years, % of ppm-years, or % of a worker's total cumulative ppm-years), a large proportion of the exposure in the NIOSH epidemiology study occurred during the period before 1978 when NIOSH assumed that all exposures were fixed equal to their 1978 level.

Issues with the statistical methods NIOSH used to develop its final regression model for exposure include:

- a. Estimated exposure values before 1978. NIOSH fixed the value for the term for Calendar Year effect in its final regression model but estimated exposures using a regression model assuming that was estimated with a (non-fixed) Calendar Year Effect in the model.
- b. Other than the term "Calendar Year Effect", the maximum estimated EO concentrations for years before 1978 decrease as you go back in time to earlier years. (This is the opposite of what you would expect and opposite to what is indicated in the UCC study).
- c. Attempts to validate the exposure regression were based only on post 1978 predictions. NIOSH did not validate the exposure estimates for years before 1978.
- d. To develop the exposure regression, NIOSH used data from 36 different companies including several plants not in the NIOSH study.
- e. The exposure regression model was developed using one subset of the available data and a second (non-overlapping) subset in the validation exercise. NIOSH's final regression model is based on only the first subset as opposed to all of the available data (i.e., the combination of the two subsets). After the evaluation of the regression model was completed, NIOSH should have re-estimated the regression model based on all of the available data.
- f. The predicted EO concentrations from the exposure regression model change dramatically from year to year before 1978. However, these changes before 1978 are not based on the Calendar Year variable in the regression model. These changes are based on the effects of the other variables in the regression model. The effects of these other variables are all based on data after 1976 and the behavior of these other variables after

1976. The effects of these other variables are joint effects with a changing Calendar Year and not separate effects independent of Calendar Year.

As Hornung et al. state: “although we feel that this model produces relatively accurate estimates of ETO exposure levels for the NIOSH epidemiologic study, there is a broader problem which we could not address. The accuracy of this model (or any other method of exposure assessment relying on IH measurements) depends heavily upon the representativeness of the measured data. If the industrial hygienists who collected the original data used a sampling strategy weighted toward identifying overexposure problems, exposure estimates will probably be biased on the high side. This, in turn, would bias risk estimates based on such data toward the null” (p. 835).

NIOSH did not use any exposure values before 1976.

NIOSH recognized the considerable extent of the missing exposure values. Hornung et al. states that “the majority of cells in a job-exposure matrix dating back as early as 1943 were missing and would require estimation, using the model” (p. 829).

Going back to the individual worker exposure histories that Sielken & Associates have from NIOSH and UCC, 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&UCC, M&F, Lag=0	12%	23%	7%	49%	72%	68%	56%	81%	77%
NIOSH&UCC, M&F, Lag=15	12%	24%	7%	49%	72%	65%	56%	82%	73%
NIOSH&UCC, M&F, Lag=20	12%	28%	7%	49%	84%	65%	56%	94%	75%
NIOSH&UCC, M, Lag=0	17%	29%	10%	51%	76%	69%	57%	84%	77%
NIOSH&U	17%	31%	10%	51%	77%	64%	57%	85%	71%

CC, M, Lag=15									
NIOSH&U CC, M, Lag=20	17%	35%	10%	51%	87%	64%	57%	95%	72%
NIOSH&U CC, F, Lag=0	5%	8%	3%	47%	61%	67%	55%	73%	76%
NIOSH&U CC, F, Lag=15	5%	8%	3%	47%	62%	65%	55%	74%	74%
NIOSH&U CC, 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.

The following tables show that proportions of exposure before 1976 and/or 1978 are also high in the UCC and NIOSH and UCC cohorts combined.

Data Set (Lag in Years)	% of perso n years befor e Janua ry 1, 1960	% of ppm- years ETO expos ure before Januar y 1, 1960	Average % of individu al's cumulati ve exposure (account ing for any lag) before January 1, 1960	% of perso n years befor e Janua ry 1, 1976	% of ppm- years ETO expos ure before Januar y 1, 1976	Average % of individu al's cumulati ve exposure (account ing for any lag) before January 1, 1976	% of perso n years befor e Janua ry 1, 1978	% of ppm- years ETO expos ure before Januar y 1, 1978	Average % of individu al's cumulati ve exposure (account ing for any lag) before January 1, 1978
NIOSH&U CC, M&F, Lag=0	12%	23%	7%	49%	72%	68%	56%	81%	77%
NIOSH&U CC, M&F, Lag=15	12%	24%	7%	49%	72%	65%	56%	82%	73%
NIOSH&U CC, M&F, Lag=20	12%	28%	7%	49%	84%	65%	56%	94%	75%
NIOSH&U CC, M, Lag=0	17%	29%	10%	51%	76%	69%	57%	84%	77%

NIOSH&U CC, M, Lag=15	17%	31%	10%	51%	77%	64%	57%	85%	71%
NIOSH&U CC, M, Lag=20	17%	35%	10%	51%	87%	64%	57%	95%	72%
NIOSH&U CC, F, Lag=0	5%	8%	3%	47%	61%	67%	55%	73%	76%
NIOSH&U CC, F, Lag=15	5%	8%	3%	47%	62%	65%	55%	74%	74%
NIOSH&U CC, F, Lag=20	5%	11%	3%	47%	76%	66%	55%	92%	77%

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
UCC, M, Lag=0	24%	67%	36%	54%	100%	94%	58%	100%	97%
UCC, M, Lag=15	24%	68%	35%	54%	100%	88%	58%	100%	91%
UCC, M, Lag=20	24%	69%	35%	54%	100%	85%	58%	100%	87%

The NIOSH regression model fixed the calendar year effect to 1978.

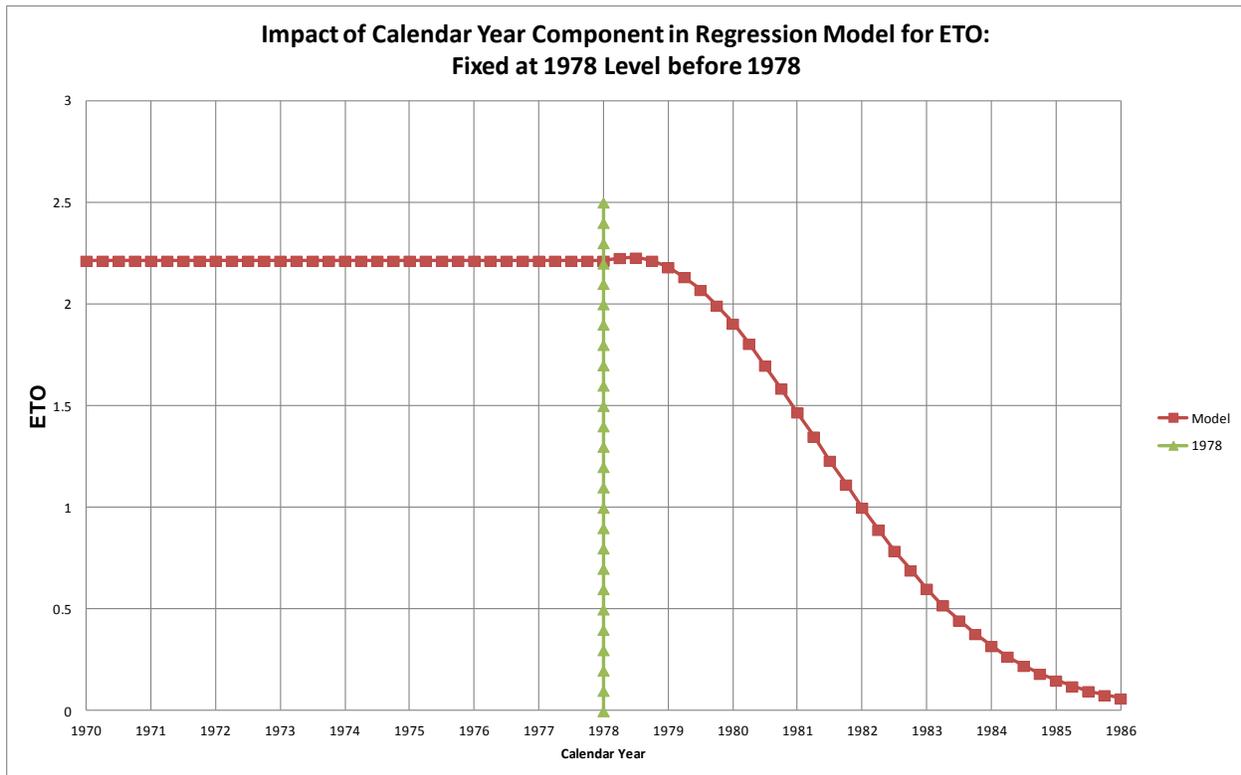
Hornung et al. recognize the importance of calendar year, stating “However, no combination of variables could be found to allow removal of calendar year from the model” and “A decreasing trend in ETO exposures with calendar year of operation was a highly significant factor.” (p. 831)

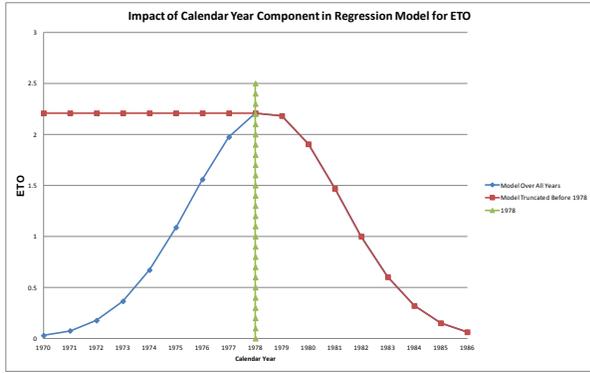
NIOSH set exposure for the years (yr. variable) before 1978 in the multiple regression to what it was in 1978. See Hornung et al., p. 831 (“Since we felt that the decrease in ETO levels after 1978 (independent of engineering controls) was explained by improved work practices after ETO was identified as a potential carcinogen, we set each predicted ETO level prior to 1978 equal to the predicted level in 1978. Variation in exposure levels prior to 1978 were modeled as a function of the remaining terms in the model with the calendar year effect fixed at 1978. Therefore, there was no extrapolation by calendar year prior to 1978.”). Calendar year is a major predictor of exposure after 1978, but is not allowed in the model to impact exposures prior to 1978. If exposures were higher before 1978, this would influence cancers with long latencies.

Hornung et al., p. 834, shows

$$\ln \text{ETO} = \dots - 0.446 \times (\text{Year} - 82) - 0.062 \times (\text{Year} - 82)^2 \dots$$

This component of the exposure regression model implies that the impact of calendar year is as follows:

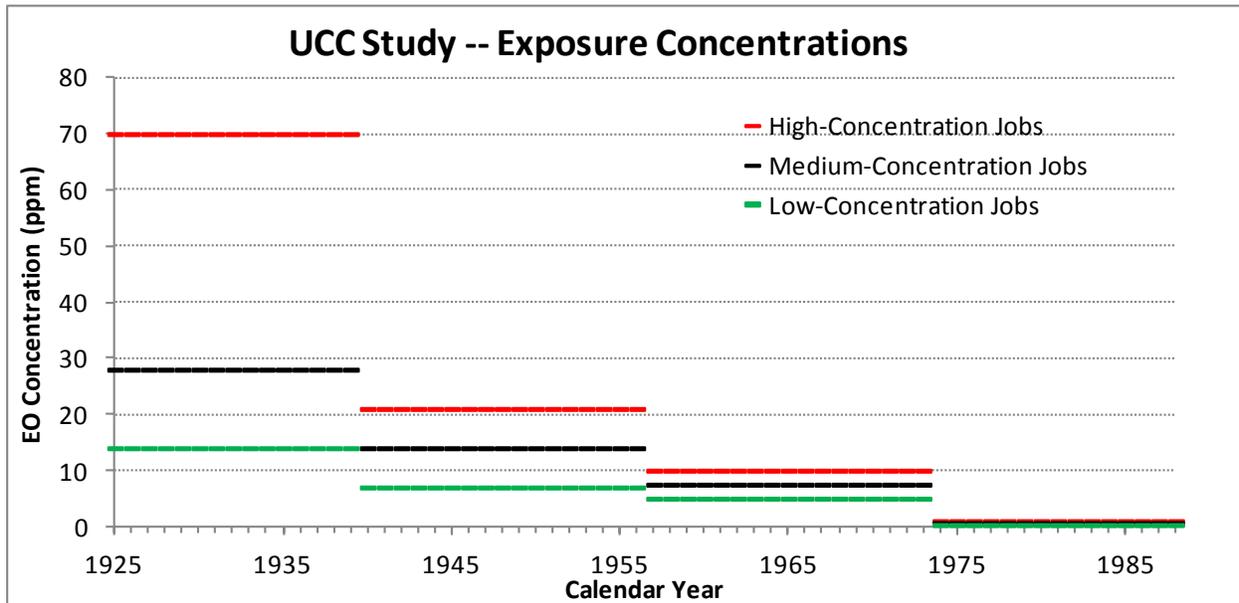


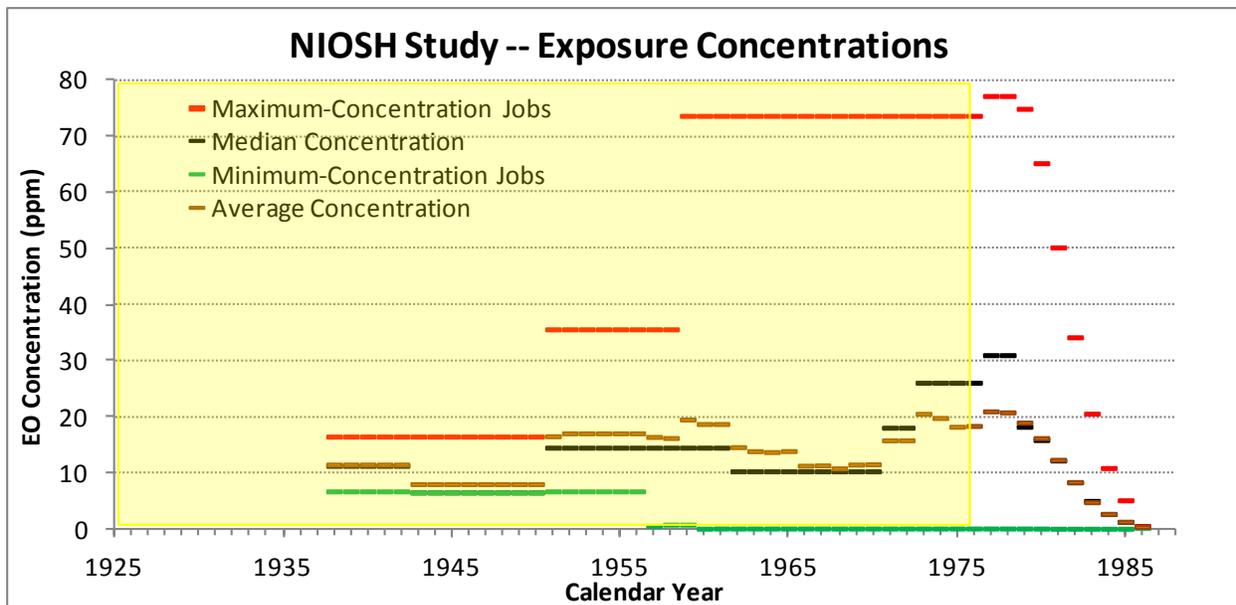


Blue portion (i.e., before 1978) not used by NIOSH.

There is a marked difference in the pattern of the time profile of EO concentrations in the NIOSH and UCC studies.

While the UCC study has EO concentrations that decrease with calendar year (equivalently, they increase as you move back in time to earlier calendar years), the NIOSH study has maximum EO concentrations that increase with calendar year, for years before 1978, and decrease with calendar year, for years after 1978, as shown in the following two figures, respectively.





Although the NIOSH exposure model assumes that the effect of calendar year for years before 1978 remained constant and equal to the effect in 1978, there is a clear decrease in the maximum EO concentrations for years before 1978 as you go back in time to earlier years. (This is opposite of what you would expect and opposite to what is in the UCC data). NIOSH used EO concentration data between 1976 and 1985 to fit a model but did not have any EO concentration data before 1976 to validate their model estimates.

UCC used sparse data throughout most of the exposure period to derive their EO concentration estimates. For example, Swaen et al. (2009) indicate that

Hogstedt et al in a 1979 publication provided “rough” estimates of EO exposures to be probably below 14 ppm in the distillation department of chlorohydrin-based EO production from 1941 to 1947. He notes, however, that there were occasional exposures to EO up to the odor threshold (715 ppm) based on sampling data and that levels from the 1950 seconds to 1963 averaged 5 to 25 ppm.

Some of the estimates of EO concentrations in the UCC study are based on different plants with similar exposure conditions. Still other estimates in the UCC data are based on actual measurements taken at UCC plants and validated with measurements taken at some other plants with similar conditions. For example, Swaen et al. (2009) say that

A morbidity study of EO production workers was conducted at this plant by Joyner¹⁵ that included an industrial hygiene monitoring survey in the early 1960 seconds over a 22-month period that included 200 separate measurements in 14 to 17 locations in three production units.

Not only is the effect of calendar year based on 1976 through 1985, so are the effects of all variables.

Hornung et al. (1994) state “Variation in exposure levels prior to 1978 were modeled as a function of the remaining terms in the model with the calendar year effect fixed at 1978.”

Multiple Linear Regression Model used by Hornung et al (p. 834) is:

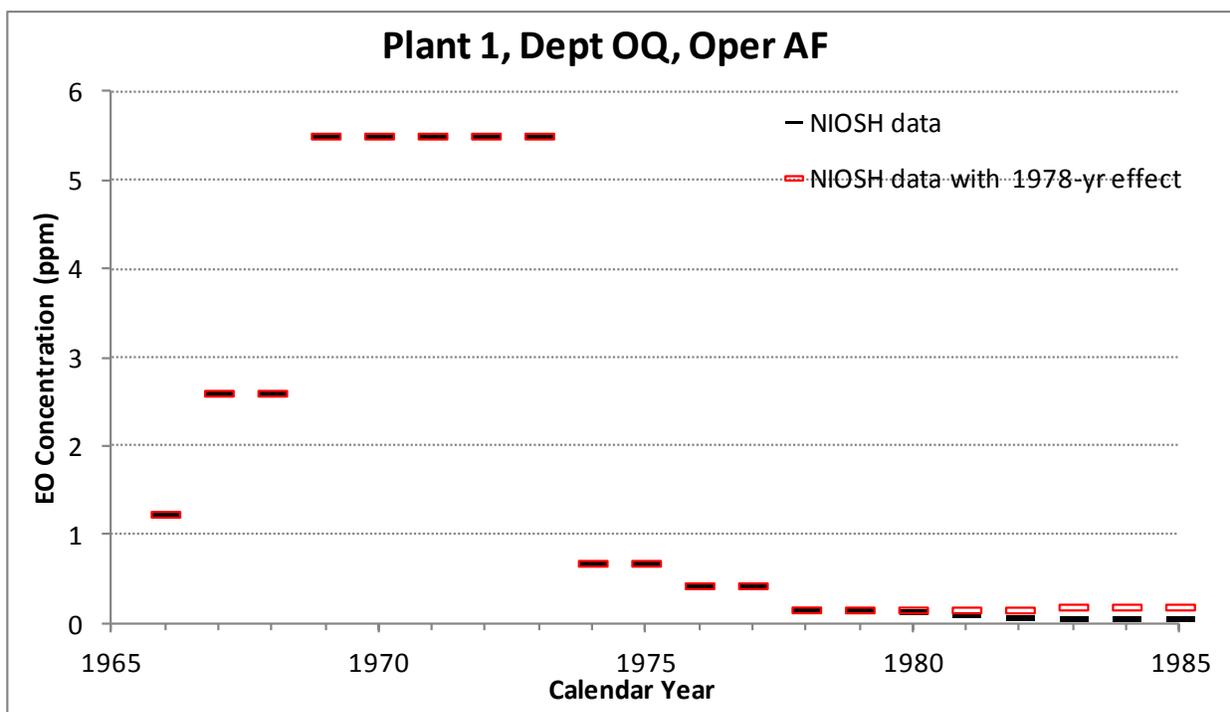
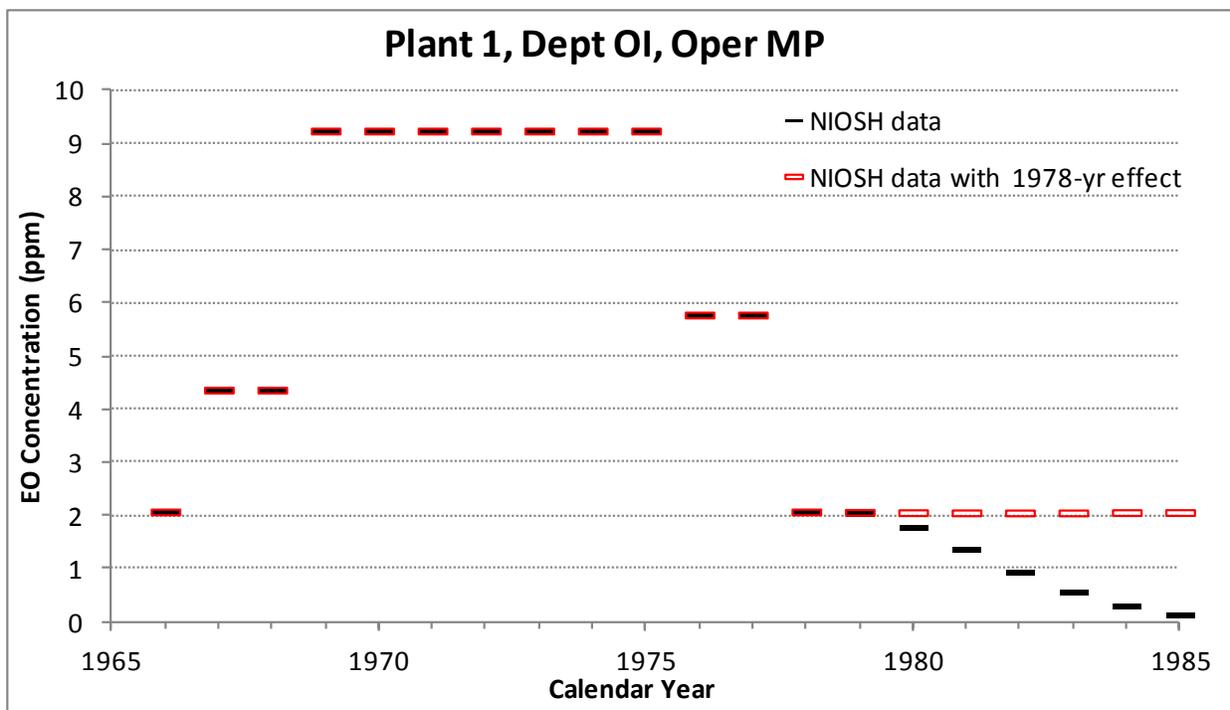
$\ln \text{eto} = -0.946$

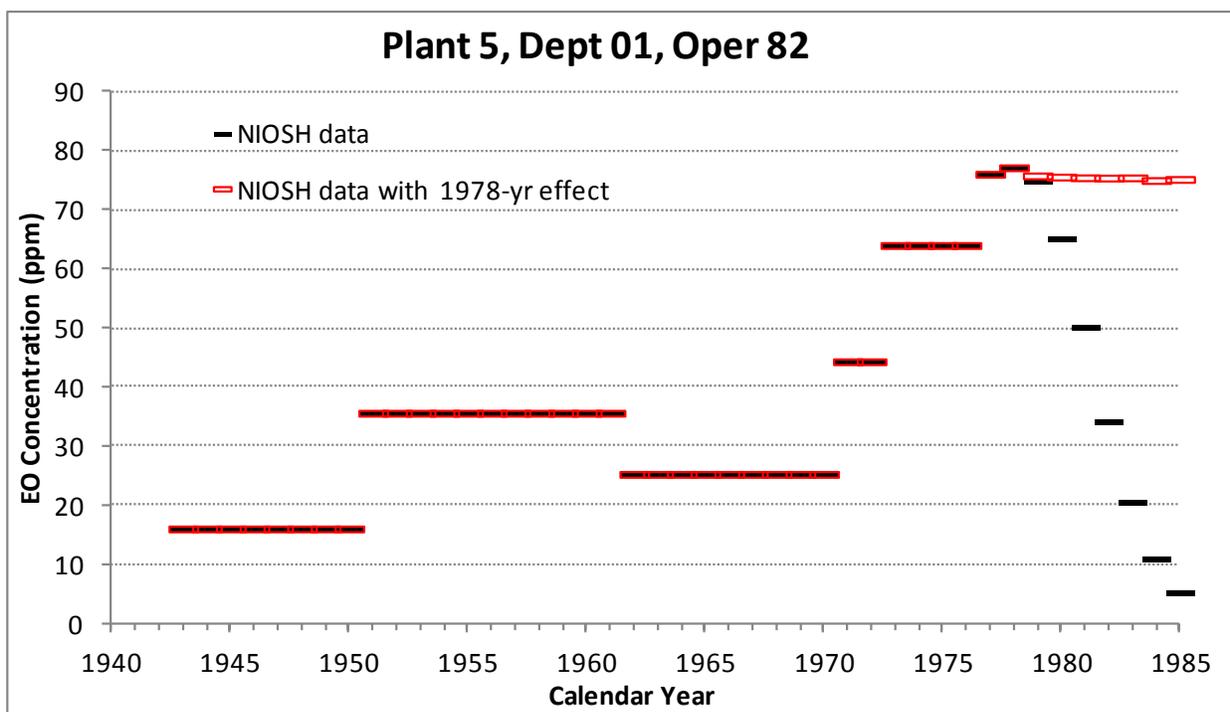
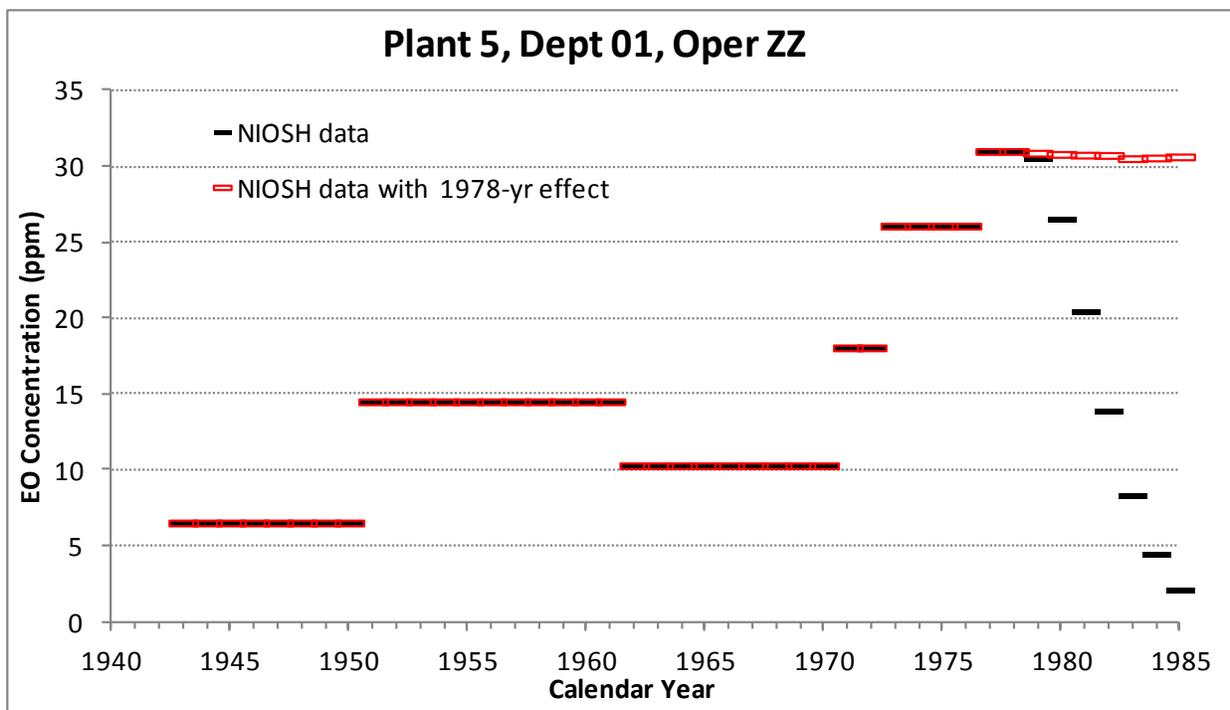
$$\begin{aligned} & -0.289 \times \text{AERATION} \text{ (which is a 0,1 indicator variable)} \\ & - 0.181 \times \text{EXP1} - 0.880 \times \text{EXP2} - 0.188 \times \text{EXP3} - 0.606 \times \text{EXP4} \\ & - 0.207 \times \text{EXP5} - 0.087 \times \text{EXP6} + 0.292 \times \text{EXP7} \\ & \quad \text{(which are 0,1 indicator variables for 8 exposure categories)} \\ & + 0.279 \times \text{PROD1} + 0.939 \times \text{PROD2} + 0.688 \times \text{PROD3} + 2.059 \times \text{PROD4} \\ & \quad \text{(which are 0,1 indicator variables for 5 product types)} \\ & - 0.233 \times (\text{AGE} - 4) \\ & \quad \text{(e.g., freshly sterilized is AGE = 1)} \\ & - \mathbf{0.466} \times (\mathbf{\text{YEAR}-82}) - \mathbf{0.062} \times (\mathbf{\text{YEAR}-82})^2 \\ & \quad \text{(which refers to calendar year)} \\ & - 0.624 \times \text{EXHAUST} \\ & \quad \text{(which is a 0, 1 indicator variable for rear exhaust)} \\ & + 0.114 \times (\text{CUBICFT} - 1000)/100 - 0.0021 \times [(\text{CUBICFT} - 1000)/100]^2 \\ & \quad \text{(which is a continuous variable for cubic feet).} \end{aligned}$$

The regression model was NOT cross-validated across different calendar years. For example, the data were not split into two disjoint sets – one set with early years (e.g., 1976 to 1980) and a second set of later years (e.g., 1981 to 1985). The model was not estimated on the basis of one set of calendar years and then validated against the second set of calendar years. All the model was based on exposures after 1976. However, there was extrapolation of the effects of the terms in the regression model to calendar years before 1978. These terms were assumed to have the same effect before 1978 as they did between 1976 and 1985.

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.

In these examples, the black dashes are NIOSH’s values. The red dashes are NIOSH’s values for 1978 and before and also what NIOSH’s values would have been if the Calendar Year effect were fixed at its 1978 value throughout. Red dashes are for comparison purposes after 1978.





In the regression model, the $\ln(\text{ETO})$ does not change with the variable Calendar Year except for 1978 through 1985. However, in all four of the above examples (which were randomly selected), the predicted EO concentration (and hence the value in the Job Exposure Matrix and NIOSH's epidemiological studies) changes dramatically from year to year before 1978.

These changes before 1978 are not based on Calendar Year. These changes are based on the effects of the other variables – but the effects of these other variables are all based on data after 1976 and the behavior of these other variables after 1976. In fact, the effects of these other variables are estimated in a model that contains both them and Calendar Year. That is, the effects of these other variables are joint effects with a changing Calendar Year and not separate effects independent of Calendar Year.

NIOSH’s final regression model seems to be based on only Set 1 and NOT on Set 1 and 2 combined.

NIOSH split their data into two data sets.²

Set 1. Data used for Model Development:

- i. 205 annual arithmetic means
based upon 2,350 full-shift charcoal tube measurements
- ii. 12 different plants
- iii. no data before 1976
- iv. Hornung et al., p. 831: “7 means based on 23 samples in 1976-1978”

Set 2. Data used for Model Evaluation:

- i. 46 annual arithmetic means
based upon 350 full-shift charcoal tube measurements
- ii. 6 different plants
- iii. data only between 1979 and 1985

After evaluation of the regression model was completed, it would be standard practice to re-estimate the regression model based on Set 1 and 2 combined. NIOSH does not even provide a sensitivity analysis of the regression model based on Set 1 versus the regression model based on Set 1 and 2 combined (i.e., the complete data set). Hornung et al. state “After the results of the validation procedure indicated a reliable model, it was used to predict annual exposures for-each worker in the epidemiologic study” (p. 832), suggesting that the model was not refit to data Set 1 and 2 combined.

The authors started with a working model and then revised it several times but never re-estimated it on the basis of data sets 1 and 2 combined: “Based upon the results of the validation procedure described earlier, we made further modifications to the model. By observing the pattern of differences between the model’s predictions and the actual measurements (Table IV), we determined that the interaction terms between exposure category and product type, as well as exposure category and calendar year, should be removed.” Hornung et al., p. 831.

It appears that NIOSH could have refit their regression model to data Set 1 and 2 combined since they refit the model at least a few times after their “Evaluation of the Model”: “It was then determined that eight values previously coded as “office” or “supervisor” should actually have

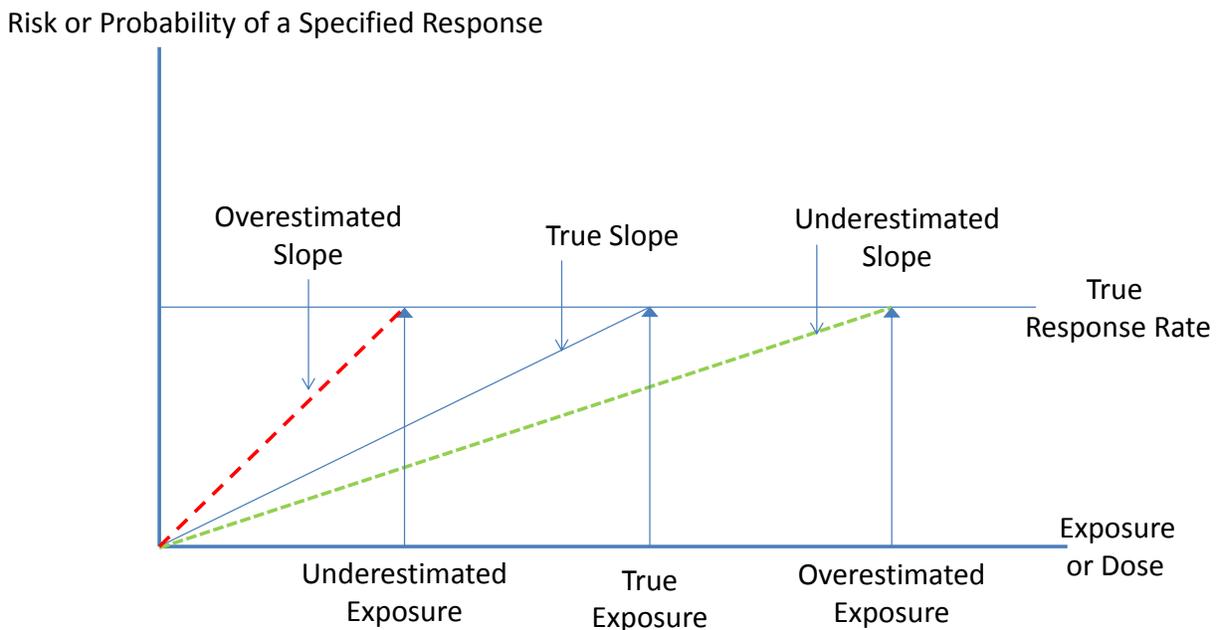
² All of the testing or performance evaluation of the regression model was based on ETO values observed between 1976 and 1985. No comparisons of the model predictions versus observed ETO values were made before 1976 because there no observed ETO values before 1976.

been assigned to warehouse locations. The data were corrected and the model refit.” Hornung et al., p. 833.

Greife et al. mention underestimation whereas Hornung et al. discuss overestimation of model predictions.

The following figure illustrates the impact of overestimation or underestimation.

Explanation of the Impact of Under or Over Estimation



Multiplicative Effect of “CUBICFT” on ETO Concentration

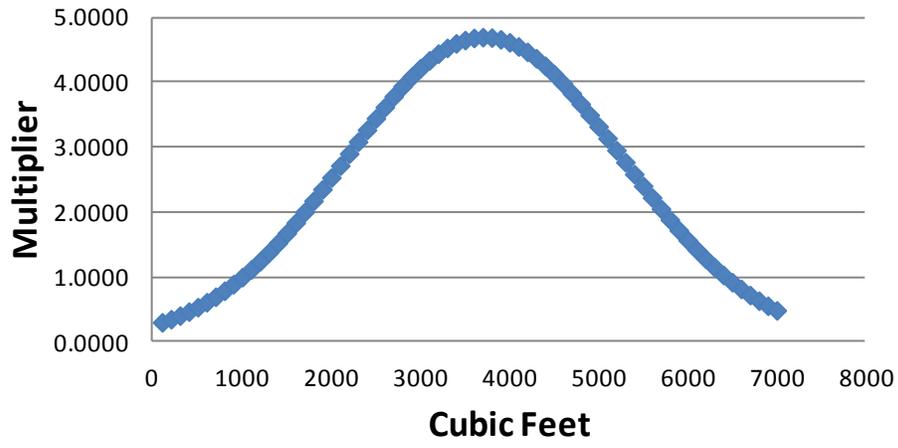
The impact of cubic feet in the regression model for ln(ETO) is as follows

$$+ 0.114 \times [(CUBICFT - 1000)/100] - 0.0021 \times [(CUBICFT - 1000)/100]^2$$

(which is a continuous variable for cubic feet).

This additive effect on ln(ETO) is a multiplicative effect on ETO concentration.

Multiplicative Effect on ETO Conc



American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #4
October 2014

Charge Question #4. Uncertainty in the cancer risk estimates. Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

For breast cancer mortality, lymphohematopoietic cancer mortality, and lymphoid cancer mortality, EPA’s models over predict the observed number of cancer mortalities in the NIOSH cohort.

In almost all cases the over prediction is statistically significant. The 95% confidence intervals on the predicted number of cancer mortalities rarely contain the observed number of cancer mortalities. These over predictions occur despite the fact they assume that the slope in the exposure-response model is zero (flat) in the “plateau” region corresponding to higher exposures.

For example, the 95% confidence intervals on the predicted number of cancer mortalities using in EPA’s preferred linear model with its 95% Upper Confidence Limit are as follows:

- [126, 188] versus 102 observed – Breast Cancer Mortality
 $126/102 = 1.24$ to $188/102 = 1.84$ fold over prediction
– [Fig. A.1](#), [Table A.1](#)
- [166, 266] versus 74 observed – Lymphohematopoietic Cancer Mortality
 $166/74 = 2.24$ to $266/74 = 3.59$ fold over prediction
– [Fig. C.1](#), [Table C.1](#)
- [99, 173] versus 53 observed – Lymphoid Cancer Mortality
 $99/53 = 1.87$ to $173/53 = 3.26$ fold over prediction
– [Fig. E.1](#), [Table E.1](#)

Only the log-linear rate ratio Cox proportional hazards models actually fit to the observed individual worker data do not routinely over predict the number of observed cancer mortalities (i.e., models 1&2 by Sielken & Associates and models 3&4 by Steenland et al. (2010) for EPA -- [Fig. A.2](#), [Table A.1](#), [Fig. C.2](#), [Table C.1](#), [Fig. E.2](#), [Table E.1](#)).

We have used EPA model predictions only when the cumulative exposures are below the “plateau” region and not assumed any further increase with EO exposures in the “plateau” region (that is, the model is assumed to be flat in the “plateau” region) (see example display below) for Models 11 to 16. If we had used the models without the flattening after the knot, then the 95% confidence intervals on the predicted number of cancer mortalities using in EPA’s preferred linear model with its 95% Upper Confidence Limit would have been as follows:

- [180, 267] versus 102 observed – Breast Cancer Mortality
 $180/102 = 1.76$ to $267/102 = 2.62$ fold over prediction
– [Table A.1](#)
- [369, 590] versus 74 observed – Lymphohematopoietic Cancer Mortality

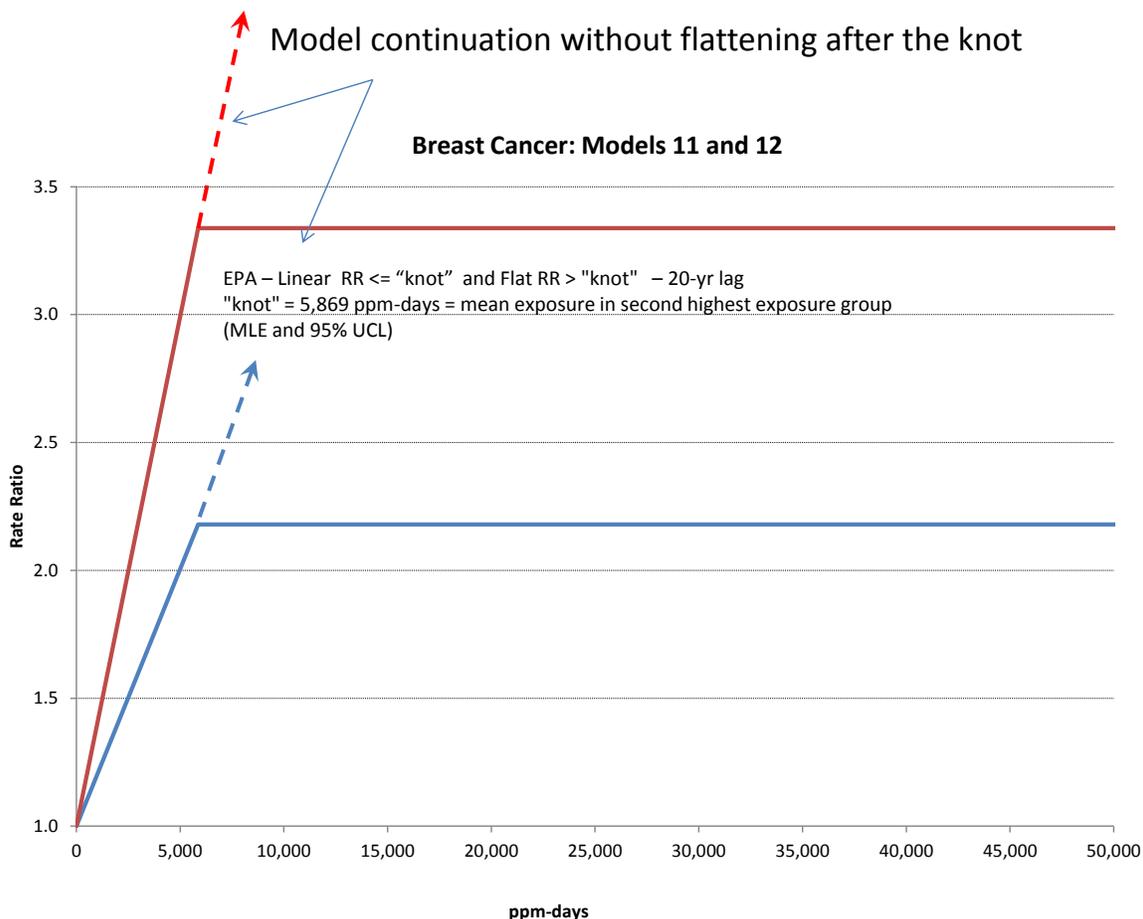
$369/74 = 4.99$ to $590/74 = 7.97$ fold over prediction

– [Table C.1](#)

[231, 403] versus 53 observed – Lymphoid Cancer Mortality

$231/53 = 4.36$ to $403/53 = 7.60$ fold over prediction

– [Table E.1.](#)



The models EPA uses to characterize occupational risks also statistically significantly over predict the observed cancer mortalities -- Models 17 to 22 in [Tables A.1, C.1,](#) and [E.1.](#)

Breast Cancer

For breast cancer, 102 deaths were observed in the NIOSH study, which is 1 fewer than expected (103) based on US background cancer mortality rates. Using EPA's exposure response model for breast cancer mortality and EPA's 95% upper confidence limit, the predicted number of breast cancer mortalities in the study is 153, which is 50 more than expected and 51 more than the actual observed. (See Appendix A.)

Based on the ratios of the observed number of deaths to the model-based predicted number of breast cancer deaths in Table A.1, and using the corresponding 95% confidence intervals on the ratios, only the Sielken & Associates and the Steenland et al. (2010) log-linear models result in

95% confidence intervals on the ratios that include 100%. That is, the ratio between the observed and predicted number of breast cancer deaths is NOT statistically significantly different than one for these two models. This also means that the observed number of breast cancer deaths in the NIOSH cohort is not statistically significantly different than the predicted number of breast cancer deaths using the corresponding model.

All other models used by the EPA result in 95% confidence intervals on the ratios that do NOT include 100%. That is, the ratio between the observed and predicted number of breast cancer deaths IS statistically significantly different than one for all other models used by EPA. This also means that the observed number of breast cancer deaths in the NIOSH cohort is statistically significantly less than the predicted number of breast cancer deaths using the corresponding model.

Moreover, as shown in Table A.2, the SMRs for breast cancer are not statistically significantly greater than 100% for any of the exposure intervals. The SMR in the workers in the lowest cumulative exposure is equal to 100%. That is, the breast cancer mortality rate in the lowest cumulative exposure group of the NIOSH female cohort is approximately equal to the background breast cancer mortality in the US population. The SMRs are less than 100% in all exposure intervals except the highest exposure group, which has an SMR greater than 100% that is not statistically significant. The SMR in the highest exposure group (with lagging) is statistically significantly greater than 100% (Table A.3). The SMR in the unexposed workers (controls and zero lagged exposures) is unusually low but not statistically significantly less than 100%.

Lymphohematopoietic Cancer

There were 79 male and female workers who died with lymphohematopoietic cancer in the NIOSH study and 74 of those workers had exposure estimates. Steenland et al. 2004 reported in their Table 1 an SMR of 100 (95% CI: 79, 124) when all male and female workers that included individuals without exposure estimates, Sielken & Associates calculated an SMR of 95.4 (95% CI: 74.9, 119.8) when only male and female workers with exposure estimates were included in the analysis. (See Appendix C).

Based on the ratios of the observed number of deaths to the model-based predicted number of lymphohematopoietic cancer deaths in Table C.1, and using the corresponding 95% confidence intervals on the ratios, Only the Sielken & Associates and the Steenland et al. (2010) log-linear models result in 95% confidence intervals on the ratios that include 100%. That is, the ratio between the observed and predicted number of lymphohematopoietic cancer deaths is NOT statistically significantly different than one for these two models. This also means that the observed number of lymphohematopoietic cancer deaths in the NIOSH cohort is not statistically significantly different than the predicted number of lymphohematopoietic cancer deaths using the corresponding model.

All other models used by the EPA result in 95% confidence intervals on the ratios that do NOT include 100%. That is, the ratio between the observed and predicted number of lymphohematopoietic cancer deaths IS statistically significantly different than one for all other

models used by EPA. This also means that the observed number of lymphohematopoietic cancer deaths in the NIOSH cohort is statistically significantly less than the predicted number of lymphohematopoietic cancer deaths using the corresponding model.

Moreover, as shown in Table C.2, the SMRs are not statistically significantly greater than 100% for any of the exposure intervals. The SMR in the workers in the lowest cumulative exposure is equal to 74.0%. That is, the lymphohematopoietic cancer mortality rate in the lowest cumulative exposure group of the NIOSH male and female cohort is less than the background lymphohematopoietic cancer mortality in the US population. The SMRs are less than 100% in all exposure intervals except the second lowest exposure group, which has an SMR greater than 100% that is not statistically significant. The SMRs in all exposure groups (with lagging) are not statistically significantly greater than 100% (Table C.3). The SMR in the unexposed workers (controls and zero lagged exposures) is unusually low but not statistically significantly less than 100% at the 2.5% significance levels but is statistically significantly less than 100% at the 5% significance level (one-sided p-value=0.0325).

Lymphoid Cancer

For lymphoid cancer, 53 deaths were observed in the NIOSH study, which is 3 more than expected (50) based on US background cancer mortality rates. Using EPA's exposure response model for lymphoid cancer mortality and EPA's 95% upper confidence limit, the predicted number of lymphoid cancer mortalities in the study is 130, which is 80 more than expected and 77 more than the actual observed. (See Appendix E.)

Based on the ratios of the observed number of deaths to the model-based predicted number of lymphoid cancer deaths in Table E.1, and using the corresponding 95% confidence intervals on the ratios, only the Sielken & Associates and the Steenland et al. (2010) log-linear models result in 95% confidence intervals on the ratios that include 100%. That is, the ratio between the observed and predicted number of lymphoid cancer deaths is NOT statistically significantly different than one for these two models. This also means that the observed number of lymphoid cancer deaths in the NIOSH cohort is not statistically significantly different than the predicted number of lymphoid cancer deaths using the corresponding model.

All other models used by the EPA result in 95% confidence intervals on the ratios that do NOT include 100%. That is, the ratio between the observed and predicted number of lymphoid cancer deaths IS statistically significantly different than one for all other models used by EPA. This also means that the observed number of lymphoid cancer deaths in the NIOSH cohort is statistically significantly less than the predicted number of lymphoid cancer deaths using the corresponding model.

Moreover, as shown in Table E.2, the SMRs are not statistically significantly greater than 100% for any of the exposure intervals. The SMR in the workers in the lowest cumulative exposure is equal to 75.7%. That is, the lymphoid cancer mortality rate in the lowest cumulative exposure group of the NIOSH male and female cohort is less than the background lymphoid cancer mortality in the US population. The SMRs are greater than 100% in all exposure intervals except the lowest exposure group, which has an SMR less than 100% that is not statistically significant.

The SMRs in all exposure groups (with lagging) are not statistically significantly greater than 100% (Table E.3). The SMR in the unexposed workers (controls and zero lagged exposures) is unusually low but not statistically significantly less than 100%.

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.

Valdez-Flores et al. (2010) state that “Cox model estimates of the concentrations corresponding to a 1-in-a-million extra environmental cancer risk are all greater than approximately 1 ppb and are more than 1500-fold greater than the 0.4 ppt estimate in the 2006 EPA draft IRIS risk assessment.”¹

Using the numerical values in the 2013 draft IRIS assessment, the impact of the exposure-response model for a specific health endpoint rather than a more appropriate model fit directly to the individual data ranges between approximately 10 and 100-fold. In addition, the choices EPA made in its method of calculating risk estimates from the slope in the exposure-response model – including choice of incidence or mortality background hazard rates, using an 85-year exposure period instead of a 70-year exposure period, using LEC01 instead of the EC01, and using NIOSH data only instead of NIOSH and UCC data – have multiplicative impacts. These further impacts can increase the risk estimates by approximately another 10-fold.

In addition, the formulas underlying EPA’s life-table method of calculating extra risks are incorrect for incidence background hazard rates² and the method of implementing an age-dependent adjustment factor (ADAF) is inconsistent with the Cancer Guidelines.³

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¹ Valdez-Flores, Ciriaco, Robert L. Sielken Jr., M. Jane Teta. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56: 312-20 (Attachment 1).

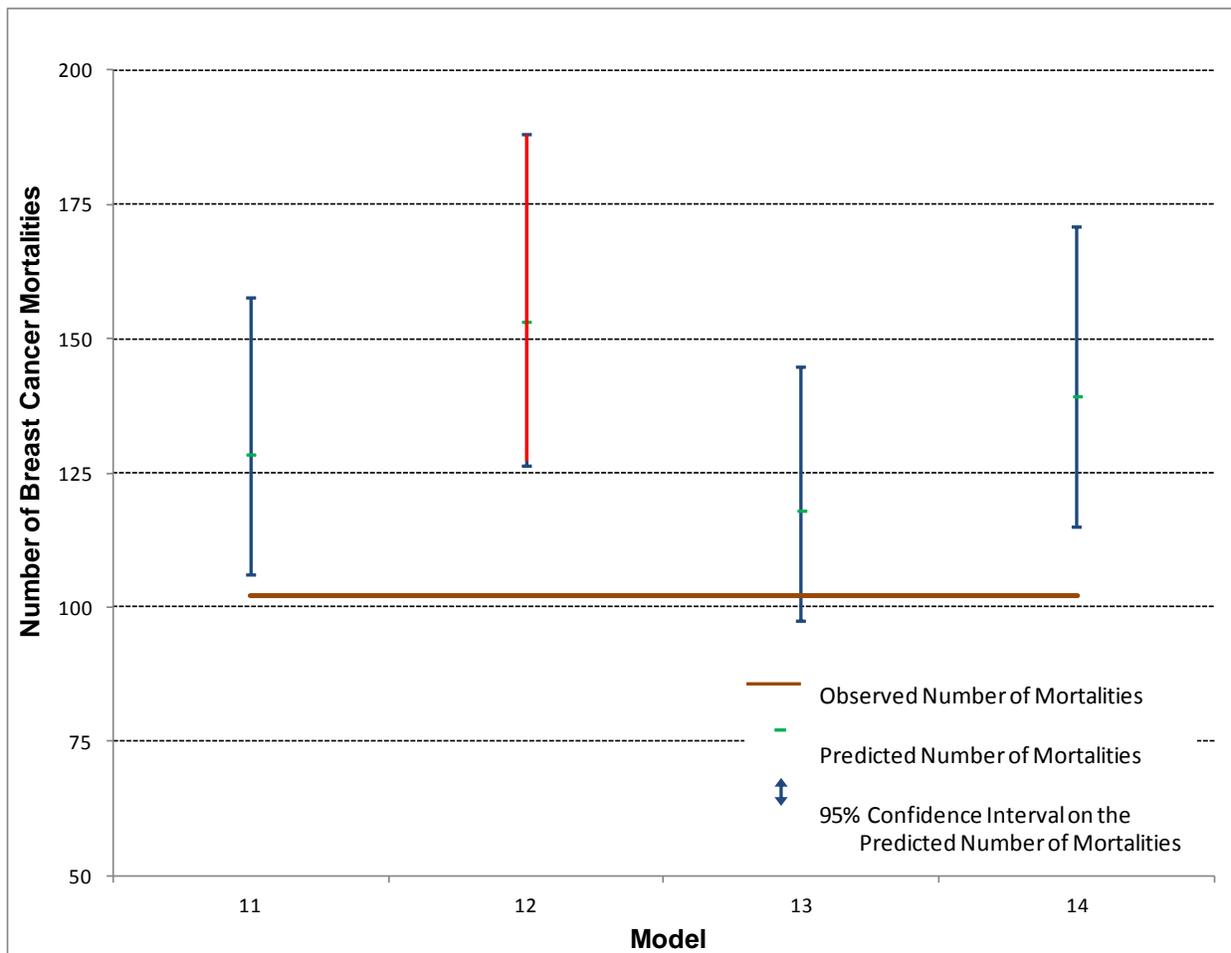
² Robert L. Sielken Jr. and Ciriaco Valdez-Flores. (2009). Life-table calculations of excess risk for incidence versus mortality: Ethylene oxide case study. Regulatory Toxicology and Pharmacology, 55: 82-89 (Attachment 2).

³ Robert L. Sielken Jr. and Ciriaco Valdez-Flores. (2009). Life-table calculations of excess risk for incidence versus mortality: Ethylene oxide case study. Regulatory Toxicology and Pharmacology, 55: 76-81 (Attachment 3)..

Appendix A

Comparison of Epidemiological Exposure-Response Model Results for Ethylene Oxide and Breast Cancer Mortality

Figure A.1. EPA Models Assuming that the Model is Flat After the “Knot.”



Models:

Results using EPA models but assuming that slope for RR is zero (flat) after the “knot”

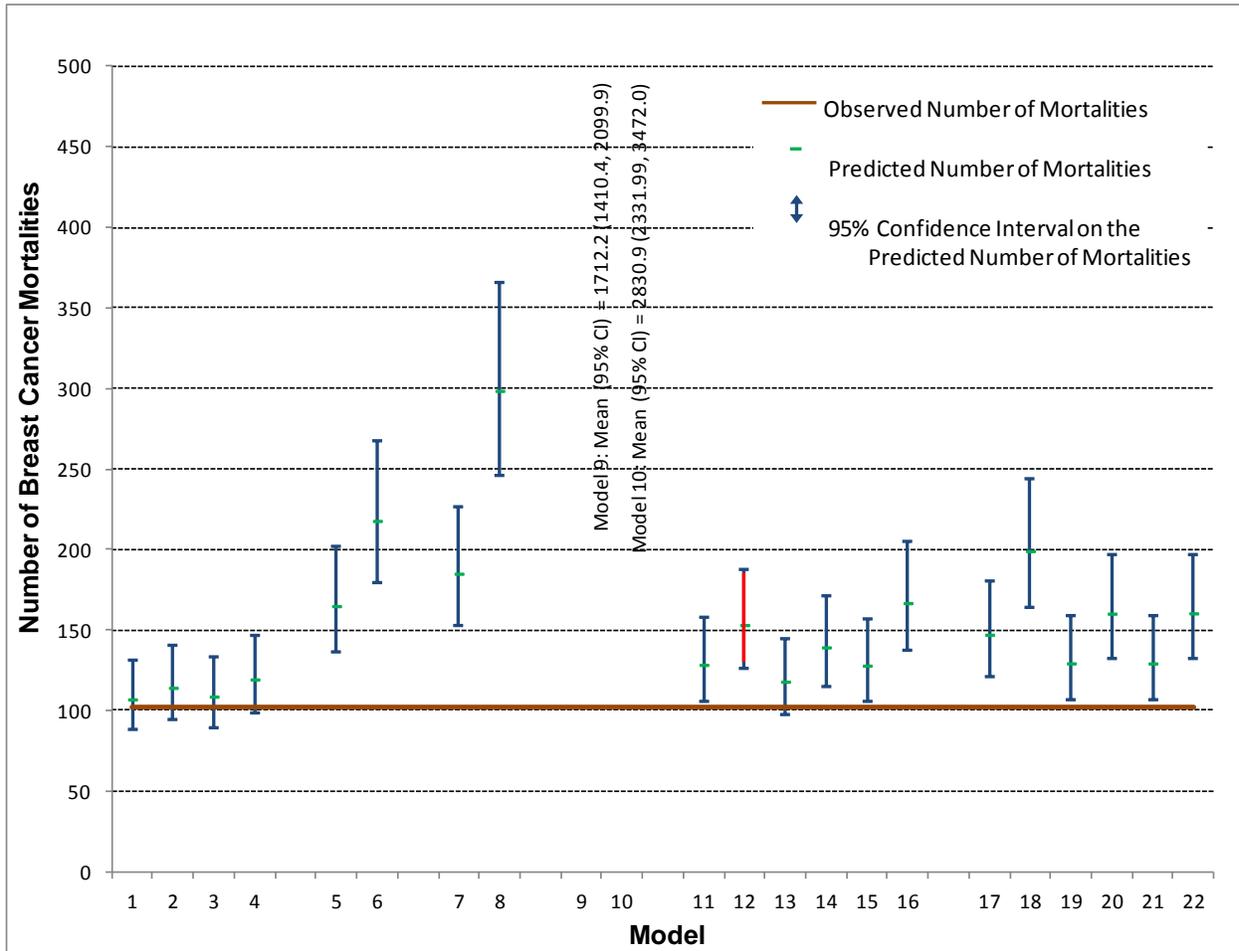
11. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8 and page 4-25 – “knot” = 5,869 ppm-days = mean exposure in second highest exposure group

12. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8 and page 4-25 – “knot” = 5,869 ppm-days = mean exposure in second highest exposure group

13. EPA – Loglinear Spline – 20-yr lag (MLE) – EPA Table 4-8 -- Knot @ 13,000 ppm-days

14. EPA – Loglinear Spline – 20-yr lag (95% UCL) – EPA Table 4-0 -- Knot @ 13,000 ppm-days

Figure A.2. All Models



Models:

1. Sielken & Associates – Loglinear – 20-yr lag (MLE)
2. Sielken & Associates – Loglinear – 20-yr lag (95% UCL)
3. Steenland et al. (2010) for EPA – Loglinear – 20-yr lag (MLE) – EPA Table 4-7
4. Steenland et al. (2010) for EPA – Loglinear – 20-yr lag (95% UCL) – EPA Table 4-7
5. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8
6. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8
7. EPA – Loglinear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 13,000 ppm-days
8. EPA – Loglinear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 13,000 ppm-days
9. EPA – Loglinear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 700 ppm-days
10. EPA – Loglinear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 700 ppm-days

Results using above EPA models but assuming that slope for RR is zero (flat) after the “knot”

11. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8 and page 4-25 – “knot” = 5,869 ppm-days = mean exposure in second highest exposure group
12. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8 and page 4-25 – “knot” = 5,869 ppm-days = mean exposure in second highest exposure group

13. EPA – Loglinear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 13,000 ppm-days
14. EPA – Loglinear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 13,000 ppm-days
15. EPA – Loglinear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 700 ppm-days
16. EPA – Loglinear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 700 ppm-days

Results using EPA models considered for occupational exposure levels

17. EPA -- log cumulative exposure -- 20-yr lag (MLE) -- Table 4-7
18. EPA -- log cumulative exposure -- 20-yr lag (95% UCL) -- Table 4-7
19. EPA -- Linear $\leq 5,869$ ppm-day Table 4-8 and page 4-25, log cumulative exposure $>5,869$ ppm-day Table 4-7 -- 20-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model.
20. EPA -- Linear $\leq 5,869$ ppm-day Table 4-8 and page 4-25, log cumulative exposure $>5,869$ ppm-day Table 4-7 -- 20-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model.
21. EPA -- Linear $\leq 5,240$ ppm-day Table 4-8, log cumulative exposure $>5,240$ ppm-day Table 4-7 -- 20-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.
22. EPA -- Linear $\leq 5,240$ ppm-day Table 4-8, log cumulative exposure $>5,240$ ppm-day Table 4-7 -- 20-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.

Table A.1. Model Predictions for Breast Cancer Mortalities—102 Observed
Using the breast cancer mortality models in the July 2013 draft IRIS assessment for EO and the model estimated by Sielken & Associates using the individual data

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
Background (No Model)	n/a	103.0	100.9%	(84.8, 126.3)
1. S&A – Log-linear – 20-yr lag (MLE) ¹¹	9.42E-06	107.0	104.9%	(88.1, 131.2)
2. S&A – Log-linear – 20-yr lag (95% UCL) ¹	1.84E-05	114.2	111.9%	(94.1, 140.0)
3. Steenland et al. (2010) for EPA – Log-linear – 20-yr lag (MLE) – EPA Table 4-7 ¹	1.22E-05	108.7	106.6%	(89.6, 133.3)
4. Steenland et al. (2010) for EPA – Log-linear – 20-yr lag (95% UCL) – EPA Table 4-7 ¹	2.27E-05	119.4	117.0%	(98.3, 146.4)
EPA Final Mortality Model – Linear – EPA Only Used the Second Model with the 95% UCL on Slope				
5. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8	2.01E-04	165.0	161.7%	(135.9, 202.3)
6. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8	3.98E-04	217.8	213.6%	(179.5, 267.2)
EPA Spline Model with Knot at 13,000 ppm-days				
7. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 13,000 ppm-days	6.07E-05	185.1	1678.6%	(1,410.4, 2,099.9)

¹ The models used by Sielken & Associates and Steenland et al. (2010) [appearing as an appendix in EPA (2013)] are the same models; however, Steenland et al. did not use all of the individual data – Steenland et al. only used a subsample of the individual data.

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
8. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 13,000 ppm-days	1.12E-04	298.7	2775.4%	(2,332.0, 3,471.9)
EPA Spline Model with Knot at 700 ppm-days				
9. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 knot @ 700 ppm-days	6.88E-04	1712.2	2775.4%	(2,332.0, 3,471.9)
10. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 knot @ 700 ppm-days	1.37E-03	2830.9	1678.6%	(1,410.4, 2,099.9)
Results using above EPA models but assuming that slope for RR is zero after the “knot”				
11. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8 – knot = 5,869 ppm-days	2.01E-04	128.5	125.9%	(105.8, 157.5)
12. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8 – knot = 5,869 ppm-days	3.98E-04	153.2	150.2%	(126.2, 187.9)
13. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 13,000 ppm-days	6.07E-05	118.0	115.7%	(97.2, 144.7)
14. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 13,000 ppm-days	1.12E-04	139.3	136.6%	(114.8, 170.9)
15. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 700 ppm-days	6.88E-04	127.9	125.4%	(105.4, 156.9)

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
16. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 700 ppm-days	1.37E-03	166.8	163.6%	(137.4, 204.6)
EPA models used for occupational exposures and occupational risks				
17. EPA -- log cumulative exposure -- 20-yr lag (MLE) -- Table 4-7	8.40E-02	147.1	144.2%	(121.2, 180.5)
18. EPA -- log cumulative exposure -- 20-yr lag (95% UCL) -- Table 4-7	1.42E-01	199.1	195.2%	(164.0, 244.2)
19. EPA -- Linear <= 5,869 ppm-day Table 4-8, log cumulative exposure >5,869 ppm-day Table 4-7 -- 20-yr lag (MLE)	2.01E-04	129.4	126.8%	(106.6, 158.7)
20. EPA -- Linear <= 5,869 ppm-day Table 4-8, log cumulative exposure >5,869 ppm-day Table 4-7 -- 20-yr lag (95% UCL)	3.98E-04	160.3	157.1%	(132.0, 196.6)
21. EPA -- Linear <= 5,240 ppm-day Table 4-8, log cumulative exposure >5,240 ppm-day Table 4-7 -- 20-yr lag (MLE)	2.01E-04	129.3	126.8%	(106.5, 158.6)

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
22. EPA -- Linear <= 5,240 ppm-day Table 4-8, log cumulative exposure >5,240 ppm-day Table 4-7 -- 20-yr lag (95% UCL)	3.98E-04	160.5	157.3%	(132.2, 196.8)

Table A.2. SMRs for breast cancer mortality in the NIOSH female cohort for unlagged exposures to EO (from Table 5 in Steenland et al. 2004):

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)			
(0, 647]	26	26.00	100.0 (65.3, 146.5)
(647, 2780]	24	28.24	85.0 (54.4, 126.5)
(2780, 12322]	26	28.26	92.0 (60.1, 134.8)
> 12322	26	20.47	127.0 (82.9, 186.1)
All	102	102.9	99.1 (80.8, 120.3)

Table A.3. SMRs for breast cancer mortality in the NIOSH female cohort for 20-year lagged exposures to EO (from Table 5 in Steenland et al. 2004):

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)	42	52.50	80.0 (57.7, 108.1)
(0, 647]	17	16.19	105 (61.1, 168.1)
(647, 2780]	15	14.85	101 (56.5, 166.6)
(2780, 12322]	15	13.04	115 (64.3, 189.7)
> 12322	13	6.28	207 (110.1, 354.0)
All	102	102.9	99.1 (80.8, 120.3)

Appendix B

Graphical representation of the rate ratio functions for the 22 models used in the analyses

- Figure B.1. 1. Sielken & Associates – Log-linear – 20-yr lag (MLE) – blue
2. Sielken & Associates – Log-linear – 20-yr lag (95% UCL) – red

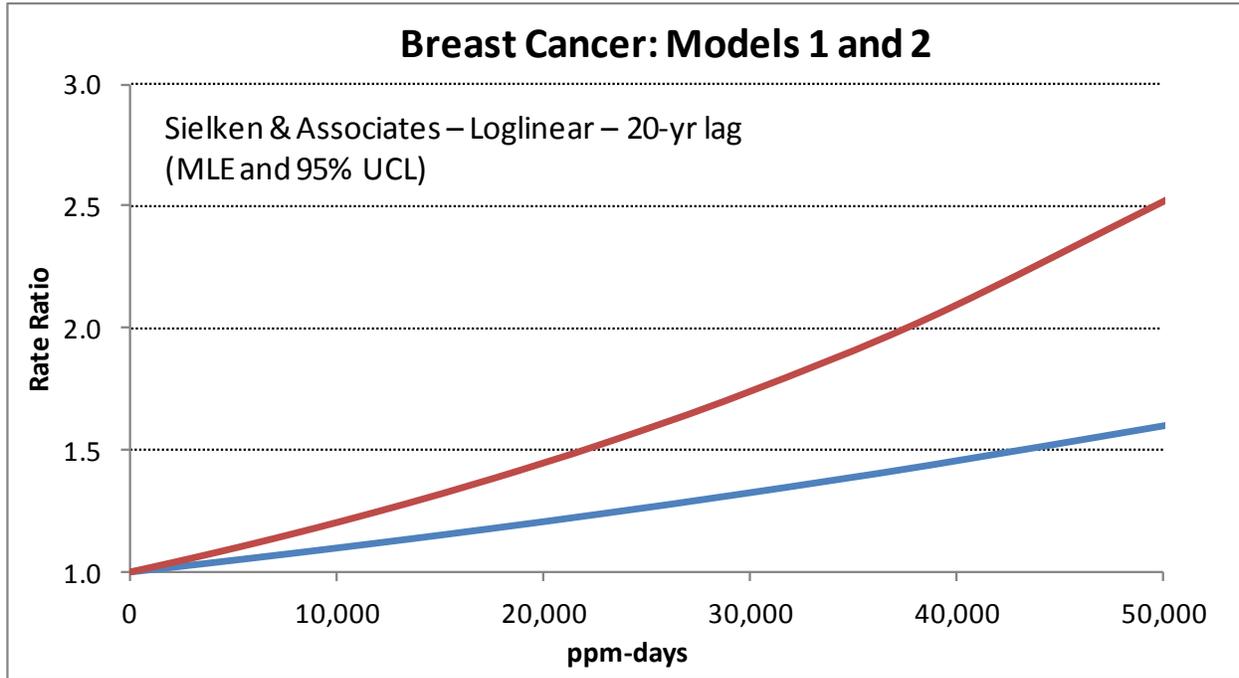


Figure B.2 3. Steenland et al. (2010) for EPA – Log-linear – 20-yr lag (MLE) – EPA Table 4-7 – blue
4. Steenland et al. (2010) for EPA – Log-linear – 20-yr lag (95% UCL) – EPA Table 4-7 – red

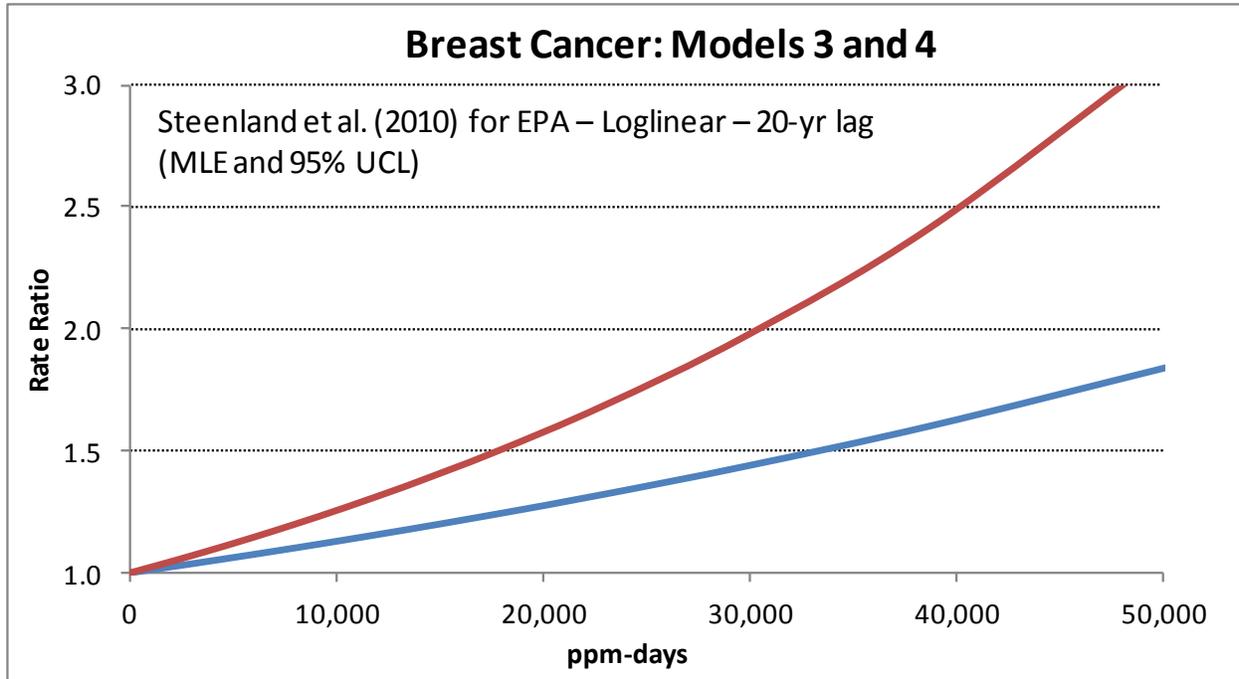


Figure B.3 5. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8 – blue
6. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8 – red

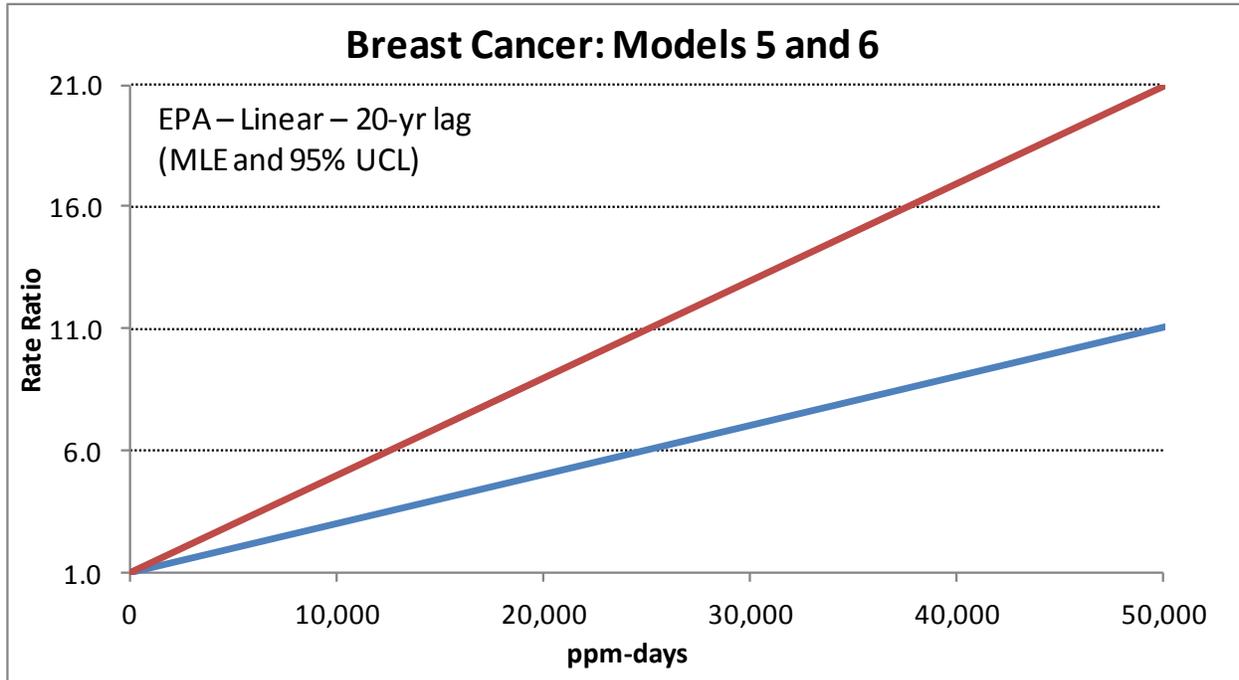


Figure B.4 7. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 13,000 ppm-days – blue
8. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 13,000 ppm-days – red

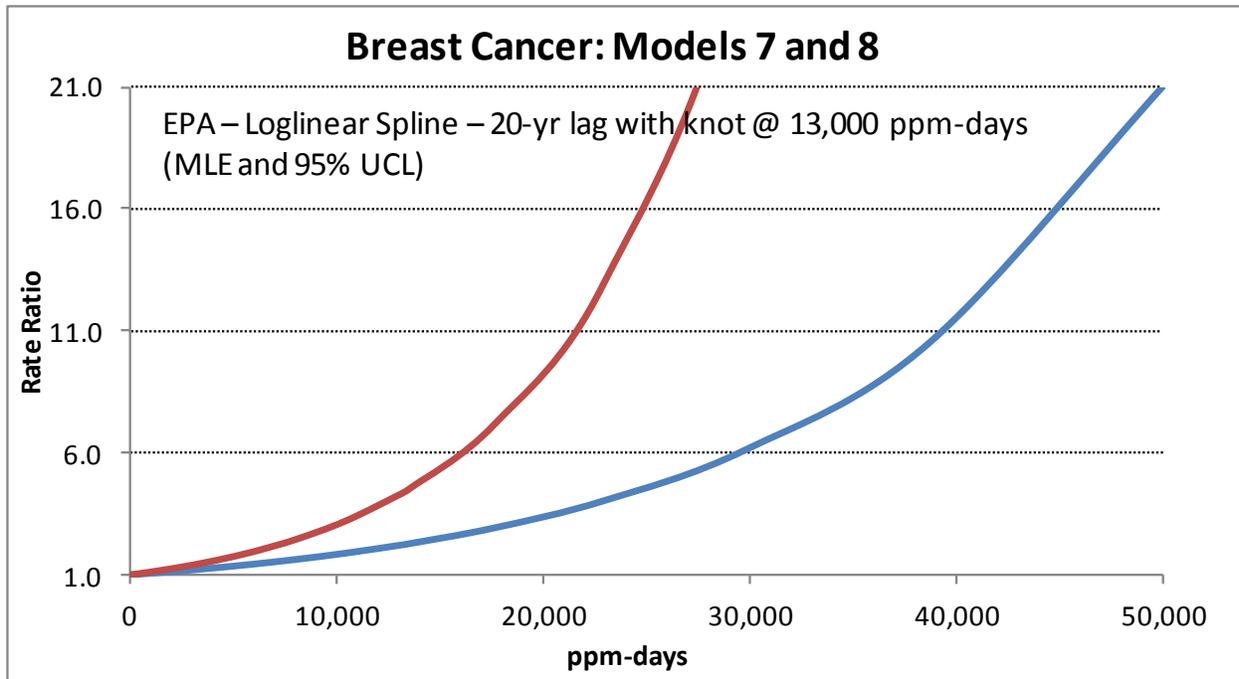


Figure B.5 9. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 700 ppm-days – blue
10. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 700 ppm-days – red

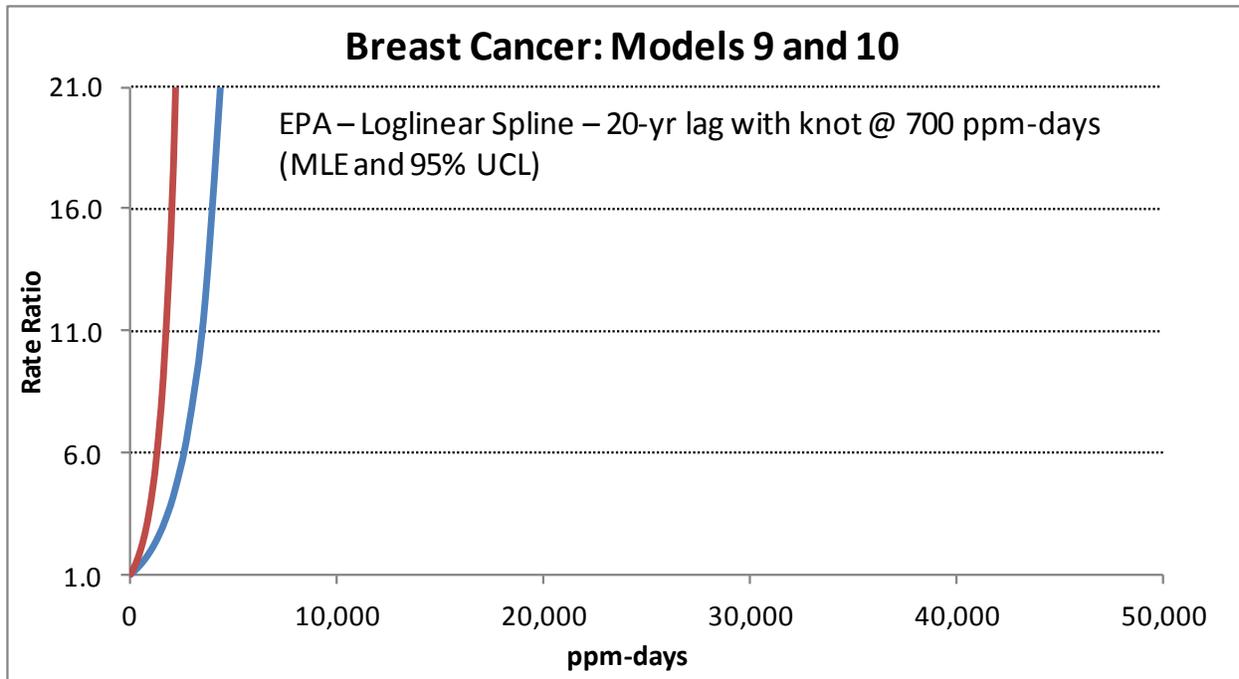


Figure B.6 11. EPA – Linear – 20-yr lag (MLE) – EPA Table 4-8 - “knot” = 5,869 ppm-days = mean exposure in second highest exposure group – blue
12. EPA – Linear – 20-yr lag (95% UCL) – EPA Table 4-8 - “knot” = 5,869 ppm-days = mean exposure in second highest exposure group – red

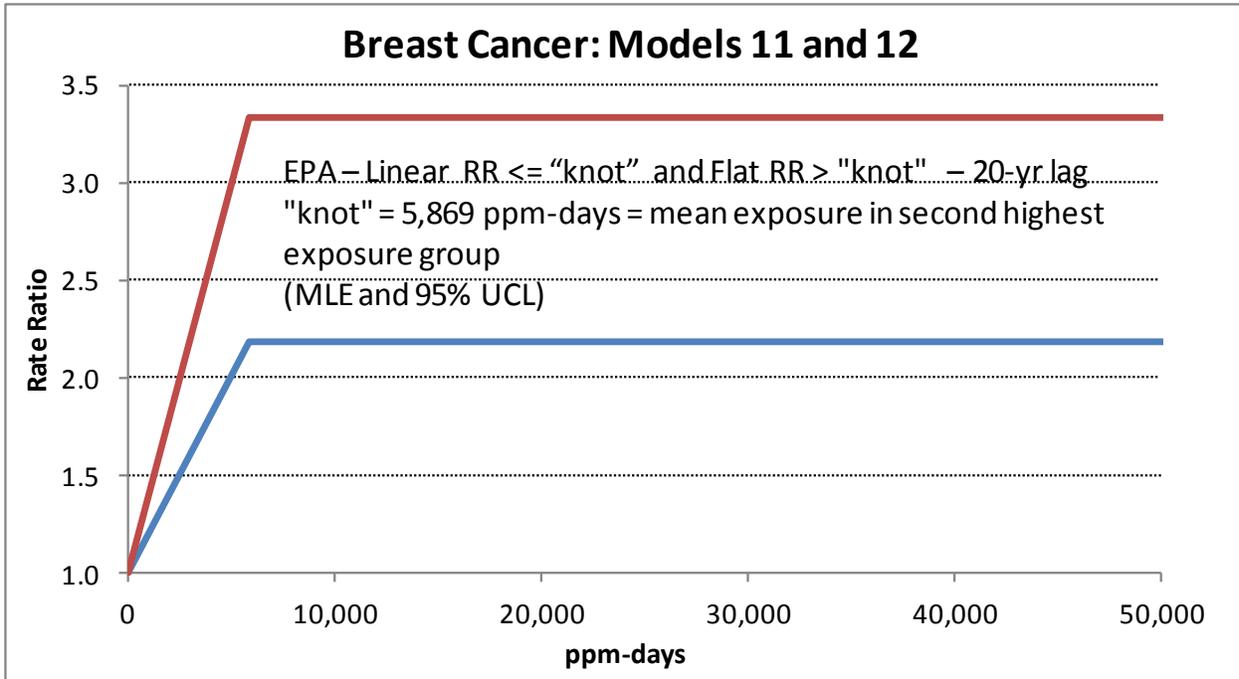


Figure B.7 13. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 13,000 ppm-days – blue
14. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 13,000 ppm-days – red

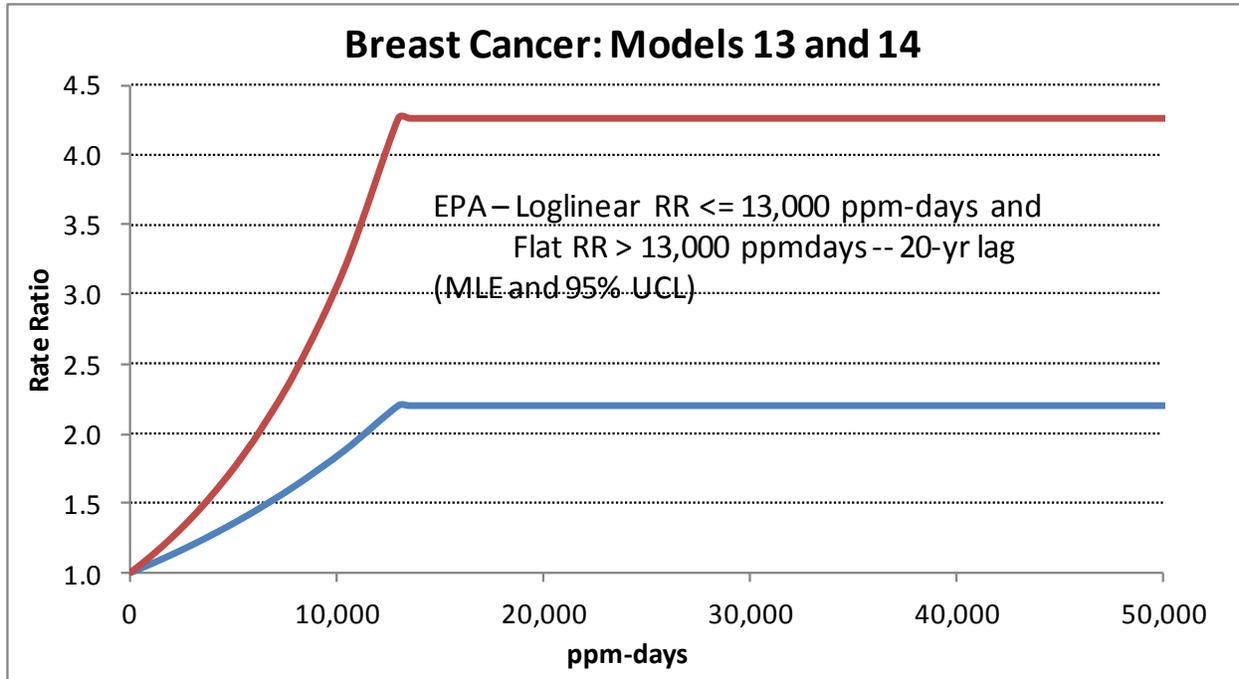


Figure B.8 15. EPA – Log-linear Spline – 20-yr lag (MLE) – EPA Table 4-8 - knot @ 700 ppm-days – blue
16. EPA – Log-linear Spline – 20-yr lag (95% UCL) – EPA Table 4-8 - knot @ 700 ppm-days – red

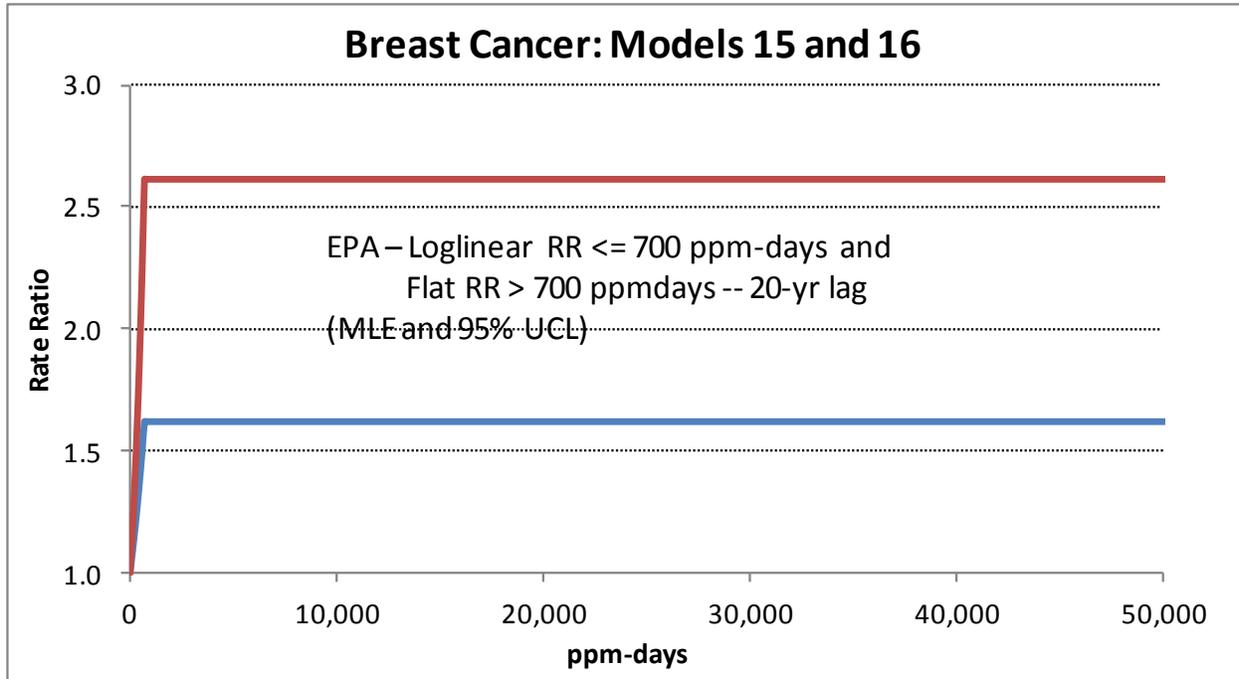


Figure B.9 17. EPA -- log cumulative exposure -- 20-yr lag (MLE) -- Table 4-7 -- blue
18. EPA -- log cumulative exposure -- 20-yr lag (95% UCL) -- Table 4-7 -- red

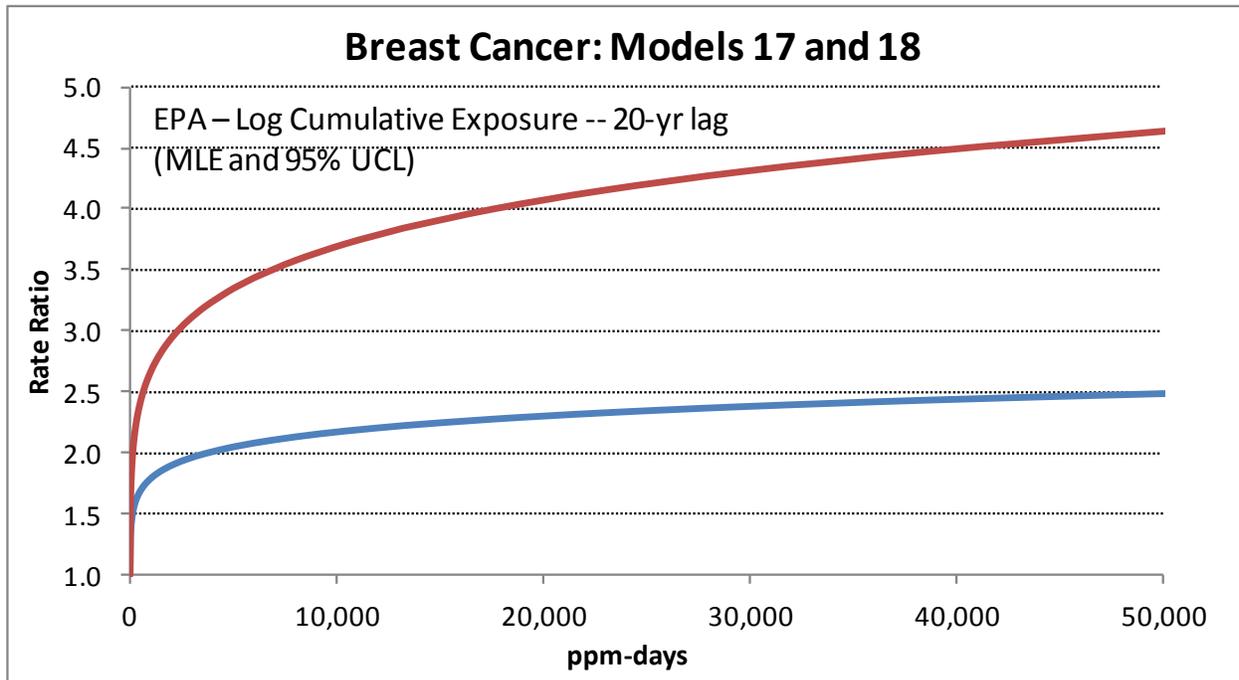


Figure B.10 19. EPA -- Linear $\leq 5,869$ ppm-day Table 4-8, log cumulative exposure $>5,869$ ppm-day Table 4-7 -- 20-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model – blue
 20. EPA -- Linear $\leq 5,869$ ppm-day Table 4-8, log cumulative exposure $>5,869$ ppm-day Table 4-7 -- 20-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model – red

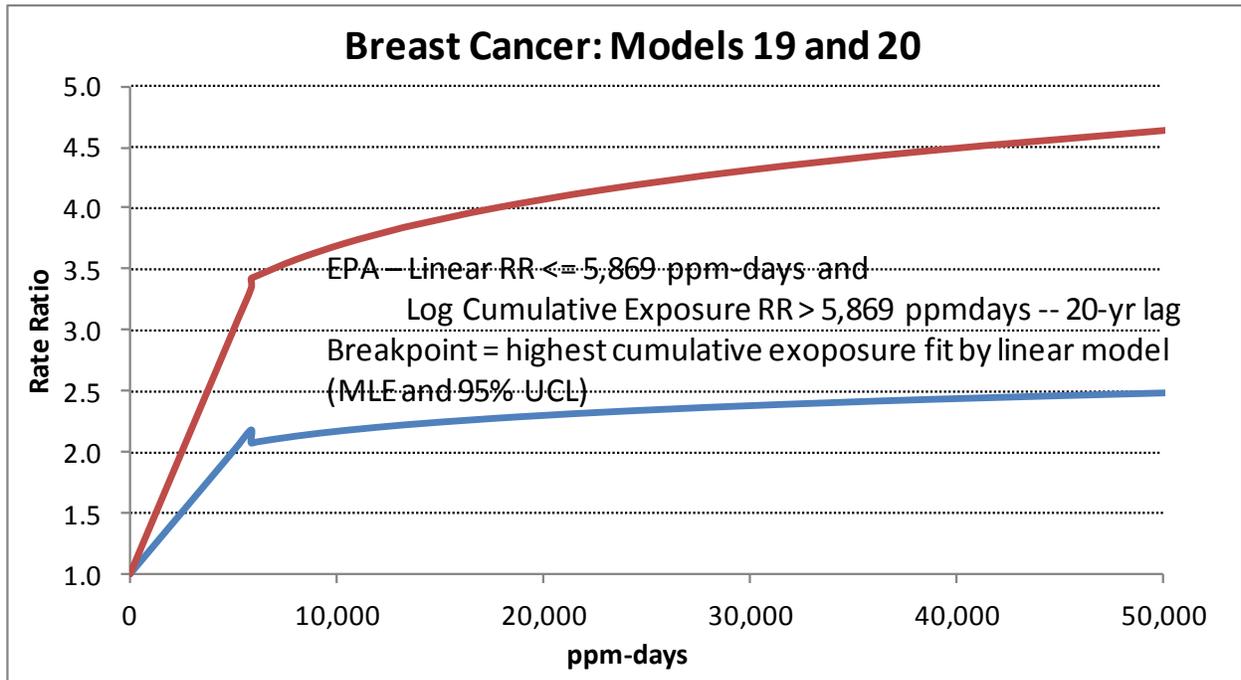
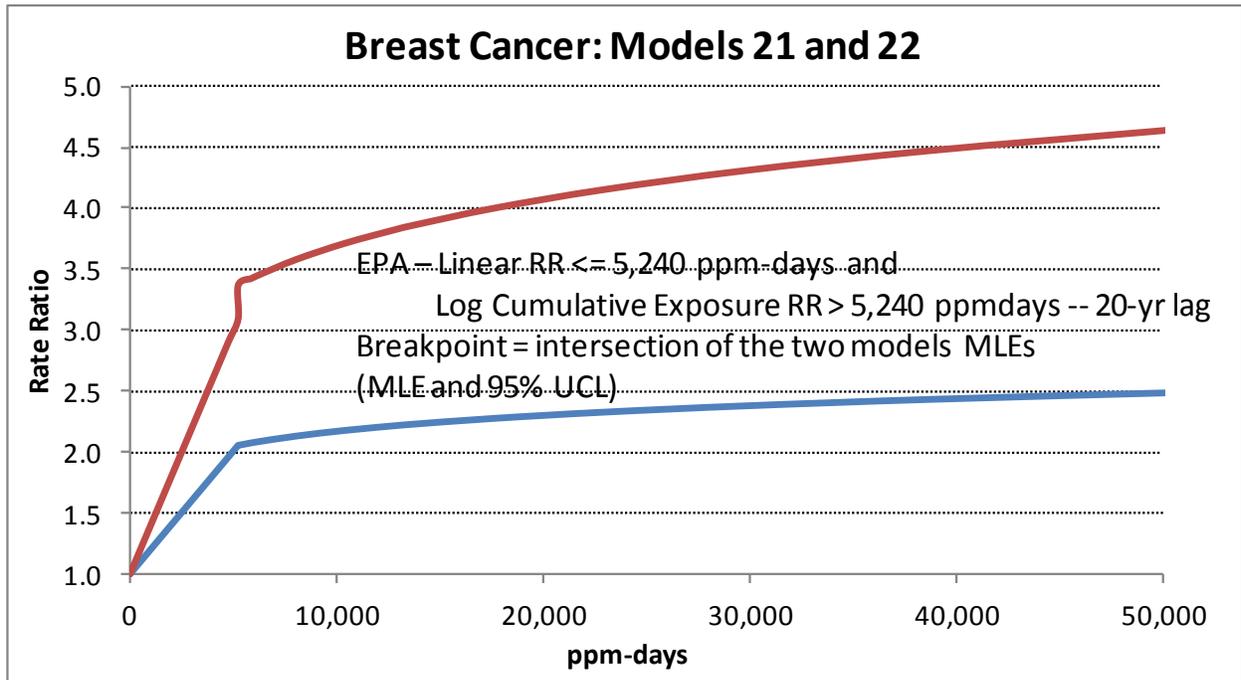


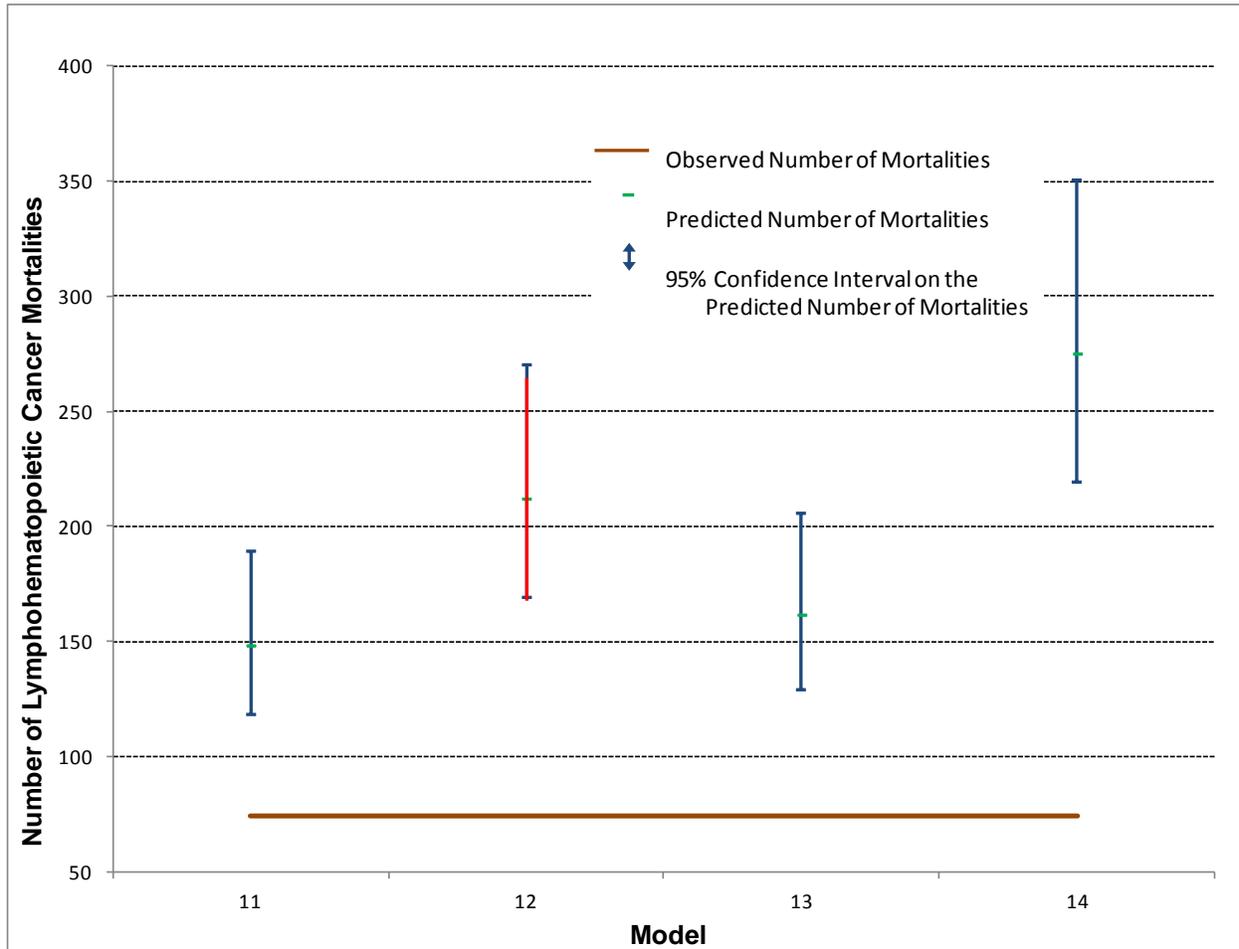
Figure B.11 21. EPA -- Linear $\leq 5,240$ ppm-day Table 4-8, log cumulative exposure $>5,240$ ppm-day Table 4-7 -- 20-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – blue
 22. EPA -- Linear $\leq 5,240$ ppm-day Table 4-8, log cumulative exposure $>5,240$ ppm-day Table 4-7 -- 20-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – red



Appendix C

Comparison of Epidemiological Exposure-Response Model Results for Ethylene Oxide and Lymphohematopoietic Cancer Mortality

Figure C.1. EPA Models Assuming that the Model is Flat After the “Knot”



Models:

Results using EPA models but assuming that slope for RR is zero (flat) after the “knot”

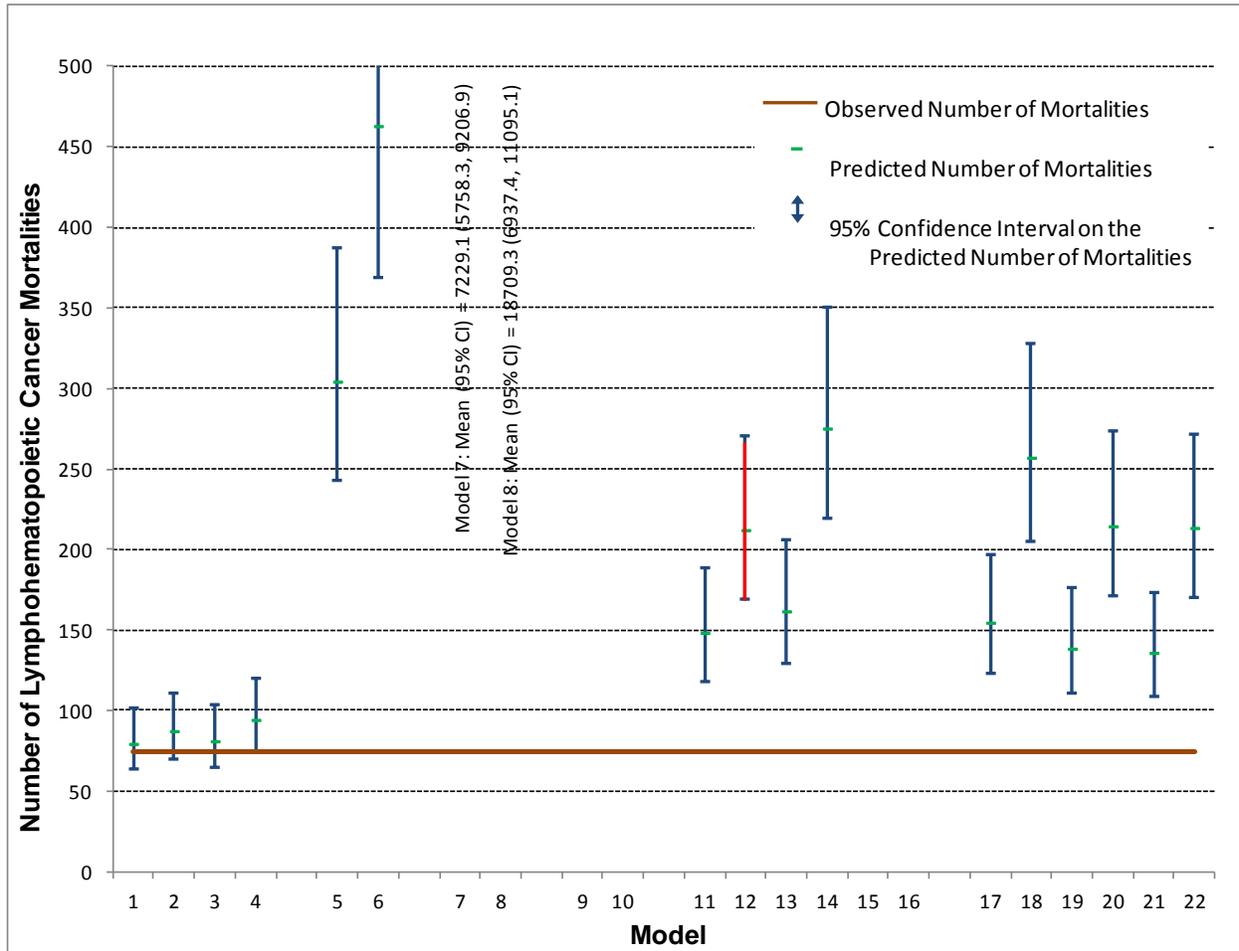
11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – footnote page 4-12 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – footnote page 4-12 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

13. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 500 ppm-days

14. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 500 ppm-days

Figure C.2. All Models



Models:

1. Sielken & Associates – Loglinear – 15-yr lag (MLE)
2. Sielken & Associates – Loglinear – 15-yr lag (95% UCL)
3. Steenland et al. (2010) for EPA – Loglinear – 15-yr lag (MLE) – EPA Table 4-2
4. Steenland et al. (2010) for EPA – Loglinear – 15-yr lag (95% UCL) – EPA Table 4-2
5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3
7. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 500 ppm-days
8. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 500 ppm-days
9. EPA – Loglinear Spline – 15-yr lag (MLE) – knot @ (for lymphohematopoietic cancer mortality EPA did not fit the loglinear spline model with an alternative knot)
10. EPA – Loglinear Spline – 15-yr lag (95% UCL) – knot @ (for lymphohematopoietic cancer mortality EPA did not fit the loglinear spline model with an alternative knot)

Results using above EPA models but assuming that slope for RR is zero (flat) after the “knot”

11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – footnote page 4-12 - “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – footnote page 4-12 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group
13. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 500 ppm-days
14. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 500 ppm-days
15. EPA – Loglinear Spline – 15-yr lag (MLE) – knot @ (for lymphohematopoietic cancer mortality EPA did not fit the loglinear spline model with an alternative knot)
16. EPA – Loglinear Spline – 15-yr lag (95% UCL) – knot @ (for lymphohematopoietic cancer mortality EPA did not fit the loglinear spline model with an alternative knot)

Results using EPA models considered for occupational exposure levels

17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2
19. EPA -- Linear \leq 7,335 ppm-day Table 4-3, log cumulative exposure $>$ 7,335 ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model.
20. EPA -- Linear \leq 7,335 ppm-day Table 4-3, log cumulative exposure $>$ 7,335 ppm-day Table 4-2 -- 15-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model.
21. EPA -- Linear \leq 4,160 ppm-day Table 4-3, log cumulative exposure $>$ 4,160 ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.
22. EPA -- Linear \leq 4,160 ppm-day Table 4-3, log cumulative exposure $>$ 4,160 ppm-day Table 4-2 -- 15-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.

Table C.1. Model Predictions for Lymphohematopoietic Cancer Mortalities—74 Observed Using the lymphohematopoietic cancer mortality models in the July 2013 draft IRIS assessment for EO and the model estimated by Sielken & Associates using the individual data

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
Background (No Model)	n/a	77.53	104.8%	(61.8, 98.7)
1. S&A – Log-linear – 15-yr lag (MLE) ¹	1.90E-06	79.34	107.2%	(63.2, 101.1)
2. S&A – Log-linear – 15-yr lag (95% UCL) ¹	6.54E-06	87.29	118.0%	(69.5, 111.2)
3. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (MLE) – EPA Table 4-2 ¹	3.26E-06	81.00	109.5%	(64.5, 103.2)
4. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (95% UCL) – EPA Table 4-2 ¹	9.00E-06	94.26	127.4%	(75.1, 120.0)
EPA Final Mortality Model – Linear – EPA Only Used the Second Model with the 95% UCL on Slope				
5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3	3.46E-04	304.35	411.3%	(242.4, 387.6)
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3	6.65E-04	463.10	625.8%	(368.9, 589.8)
EPA Spline Model with Knot at 500 ppm-days				
7. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 500 ppm-days	2.01E-03	7229.11	9769.1%	(5,758.3, 9,206.9)

¹ The models used by Sielken & Associates and Steenland et al. (2010) [appearing as an appendix in EPA (2013)] are the same models; however, Steenland et al. did not use all of the individual data – Steenland et al. only used a subsample of the individual data.

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
8. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 500 ppm-days	3.28E-03	8709.33	11769.4%	(6,937.4, 11,092.1)
EPA Spline Model with Knot at ALTERNATIVE ppm-days				
9. EPA – Log-linear Spline – 15-yr lag (MLE) – Knot @	(for lymphohematopoietic cancer mortality EPA did not fit the log-linear spline model with an alternative knot)			
10. EPA – Log-linear Spline – 15-yr lag (95% UCL) – Knot @	(for lymphohematopoietic cancer mortality EPA did not fit the log-linear spline model with an alternative knot)			
Results using above EPA models but assuming that slope for RR is zero after the “knot”				
11. EPA – Linear – 15-yr lag (MLE) – Table 4-3 - footnote page 4-12 – knot = 7,335 ppm-days	3.46E-04	148.33	200.6%	(118.2, 188.9)
12. EPA – Linear – 15-yr lag (95% UCL) – Table 4-3 footnote page 4-12 – knot = 7,335 ppm-days	6.65E-04	212.16	286.7%	(169.0, 270.2)
13. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 500 ppm-days	2.01E-03	161.71	218.5%	(128.8, 205.9)
14. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 500 ppm-days	3.28E-03	275.22	371.9%	(219.2, 350.5)
15. EPA – Log-linear Spline – 15-yr lag (MLE) – Knot @	(for lymphohematopoietic cancer mortality EPA did not fit the log-linear spline model with an alternative knot)			
16. EPA – Log-linear Spline – 15-yr lag (95% UCL) – Knot @	(for lymphohematopoietic cancer mortality EPA did not fit the log-linear spline model with an alternative knot)			

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
EPA models used for occupational exposures and occupational risks				
17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2	1.07E-01	154.64	209.0%	(123.2, 197.0)
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2	1.76E-01	257.09	347.4%	(204.8, 327.4)
19. EPA -- Linear <= 7,335 ppm-day Table 4- 3, log cumulative exposure >7,335 ppm- day Table 4-2 -- 15-yr lag (MLE)	3.46E-04	138.48	187.1%	(110.3, 176.4)
20. EPA -- Linear <= 7,335 ppm-day Table 4- 3, log cumulative exposure >7,335 ppm- day Table 4-2 -- 15-yr lag (95% UCL)	6.65E-04	214.53	289.9%	(170.9, 273.2)
21. EPA -- Linear <= 4,160 ppm-day Table 4- 3, log cumulative exposure >4,160 ppm- day Table 4-2 -- 15-yr lag (MLE)	3.46E-04	135.90	183.7%	(108.3, 173.1)
22. EPA -- Linear <= 4,160 ppm-day Table 4- 3, log cumulative exposure >4,160 ppm- day Table 4-2 -- 15-yr lag (95% UCL)	6.65E-04	213.46	288.5%	(170.0, 271.9)

Table C.2. The SMRs for lymphohematopoietic cancer mortality in the NIOSH female cohort for unlagged exposures to EO (Sielken & Associates)

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)			
(0, 1461]	19	25.7	74.0 (44.5, 115.6)
(1461, 3835]	19	13.9	137.0 (82.5, 214.0)
(3835, 15523]	18	19.1	94.1 (55.7, 148.7)
> 15523	18	18.9	95.5 (56.6, 150.9)
All	74	77.5	95.4 (74.9, 119.8)

Table C.3. SMRs for lymphohematopoietic cancer mortality in the NIOSH female cohort for 15-year lagged exposures to EO (Sielken & Associates calculated):

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)	13	21.7	60.0 (31.9, 102.7)
(0, 1461]	18	20.2	89.1 (52.8, 140.8)
(1461, 3835]	16	10.4	154.2 (88.1, 250.4)
(3835, 15523]	13	13.5	96.1 (51.1, 164.3)
> 15523	14	11.8	119.0 (65.0, 199.6)
All	74	77.5	95.4 (74.9, 119.8)

Appendix D

Graphical representation of the rate ratio functions for the 22 models used in the analyses

Figure D.1 1. Sielken & Associates – Log-linear – 15-yr lag (MLE) – blue
2. Sielken & Associates – Log-linear – 15-yr lag (95% UCL) – red

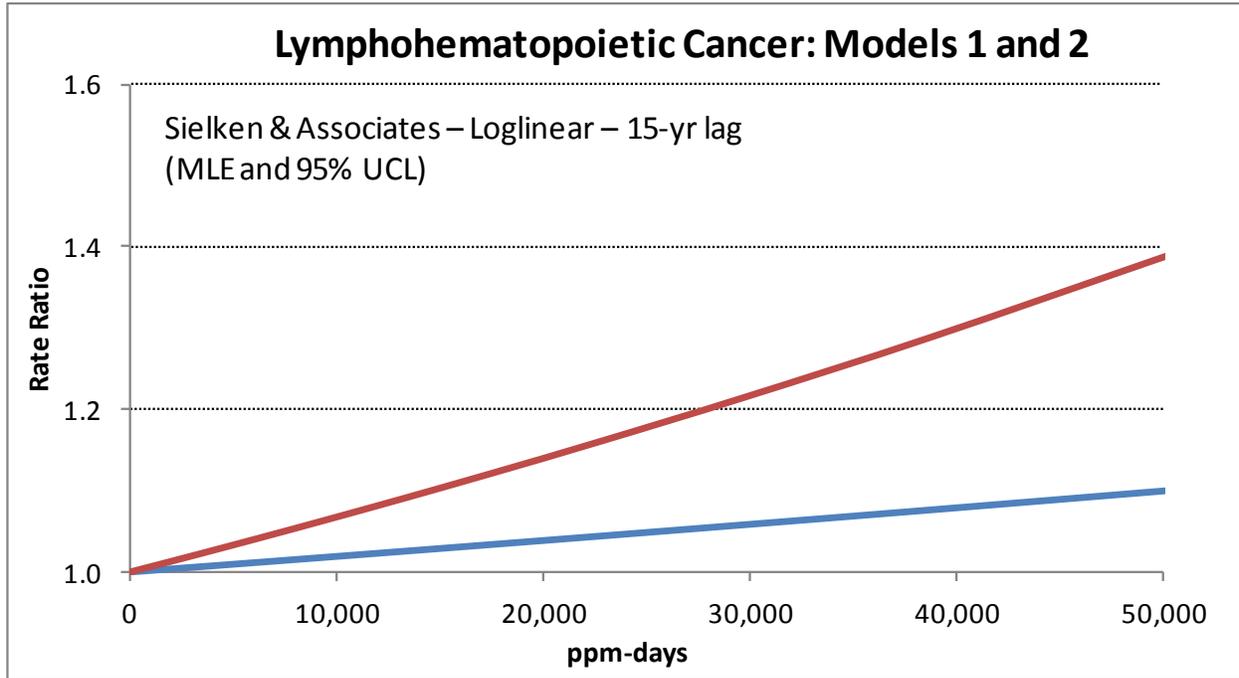


Figure D.2 3. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (MLE) – EPA Table 4-2 – blue
4. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (95% UCL) – EPA Table 4-2 – red

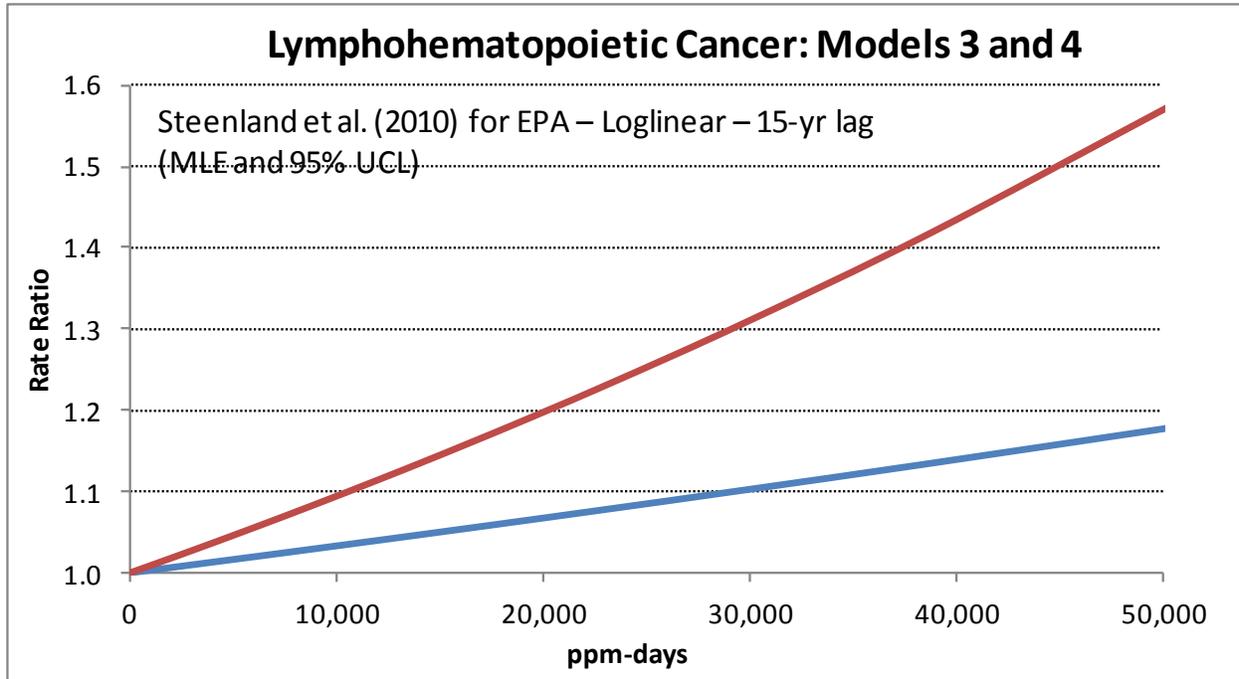


Figure D.3 5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – blue
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – red

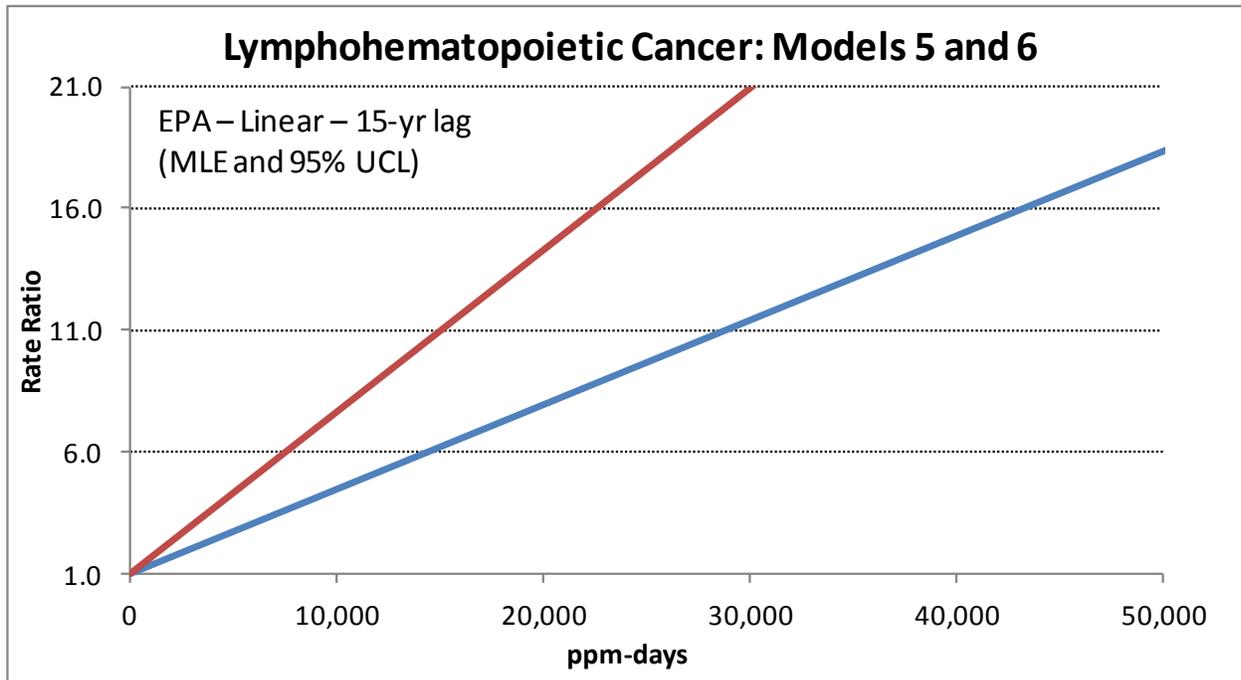


Figure D.4 7. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 500 ppm-days – blue
8. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 500 ppm-days – red

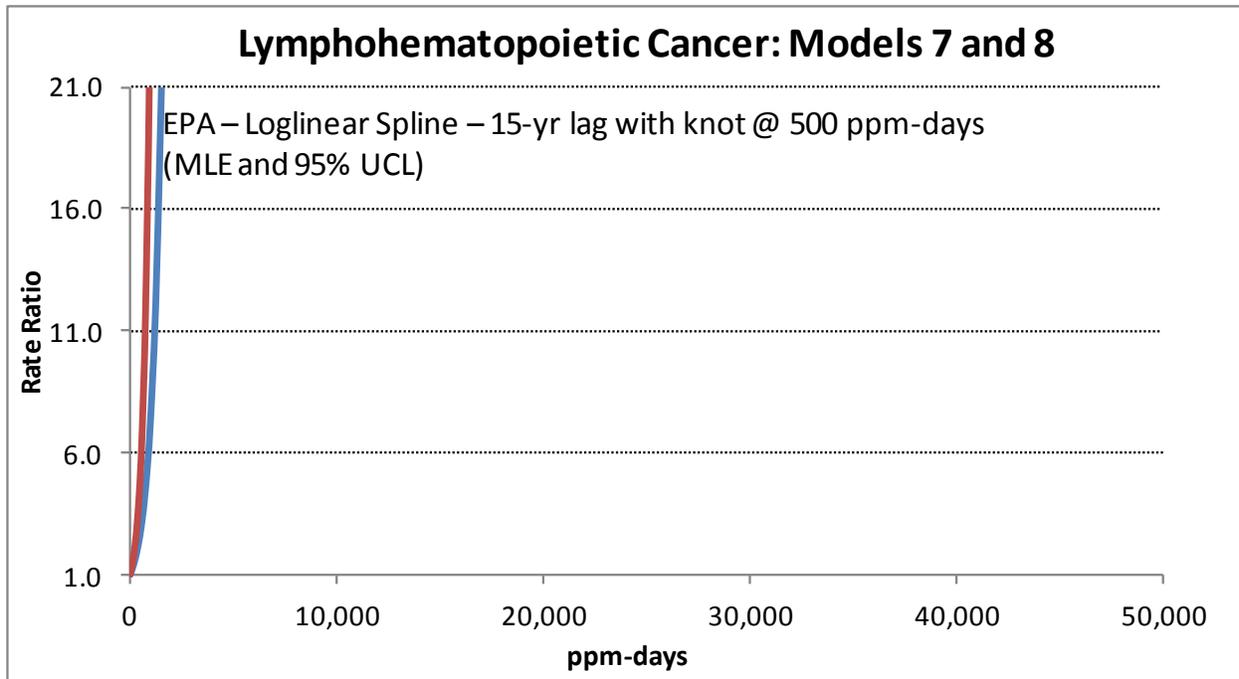


Figure D.6 11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group – blue
12. EPA – Linear – 15-yr lag (95% UCL) – EPA page Table 4-3 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group – red

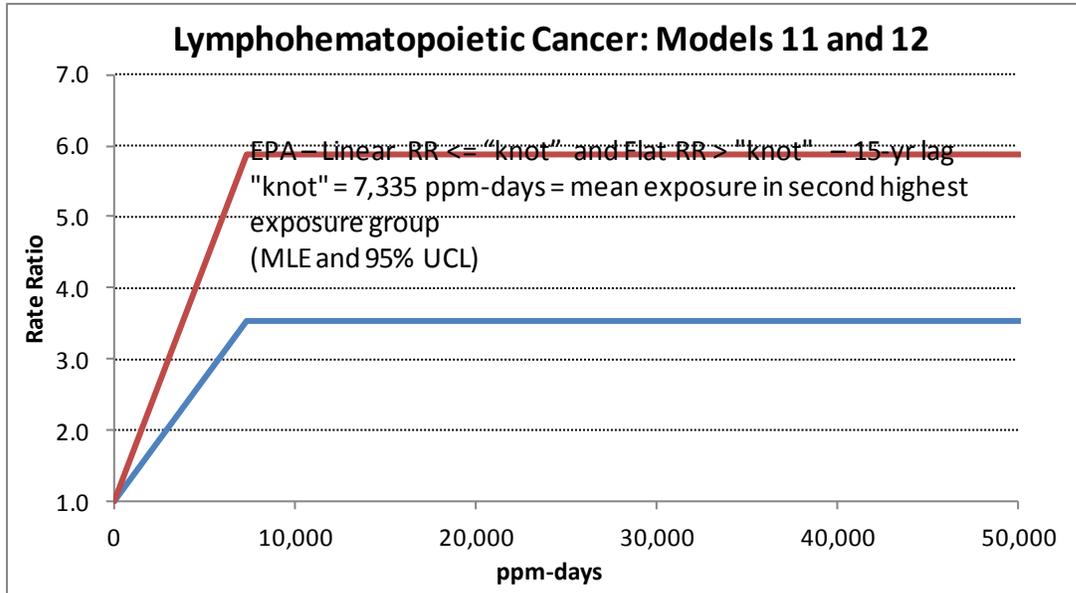


Figure D.7 13. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 500 ppm-days – blue
14. EPA – Log-linear Spline – 15-yr lag (95% UCL) – Table 4-3 - knot @ 500 ppm-days – red

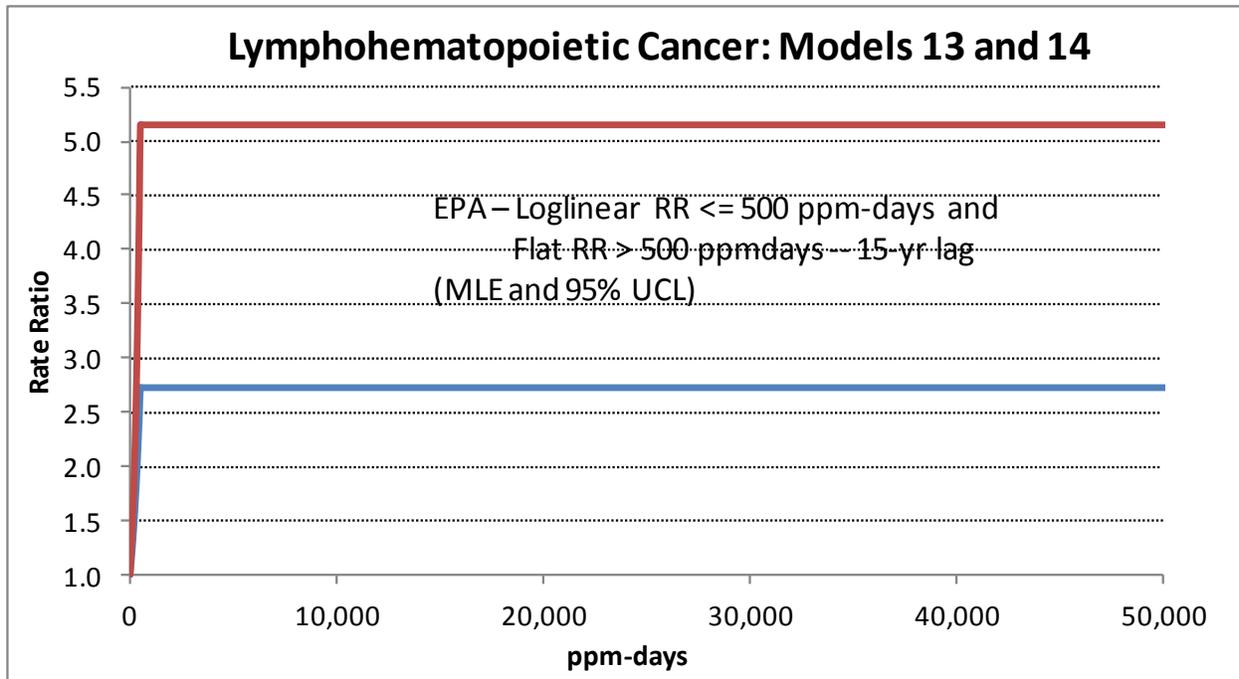


Figure D.8 17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2 -- blue
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2 -- red

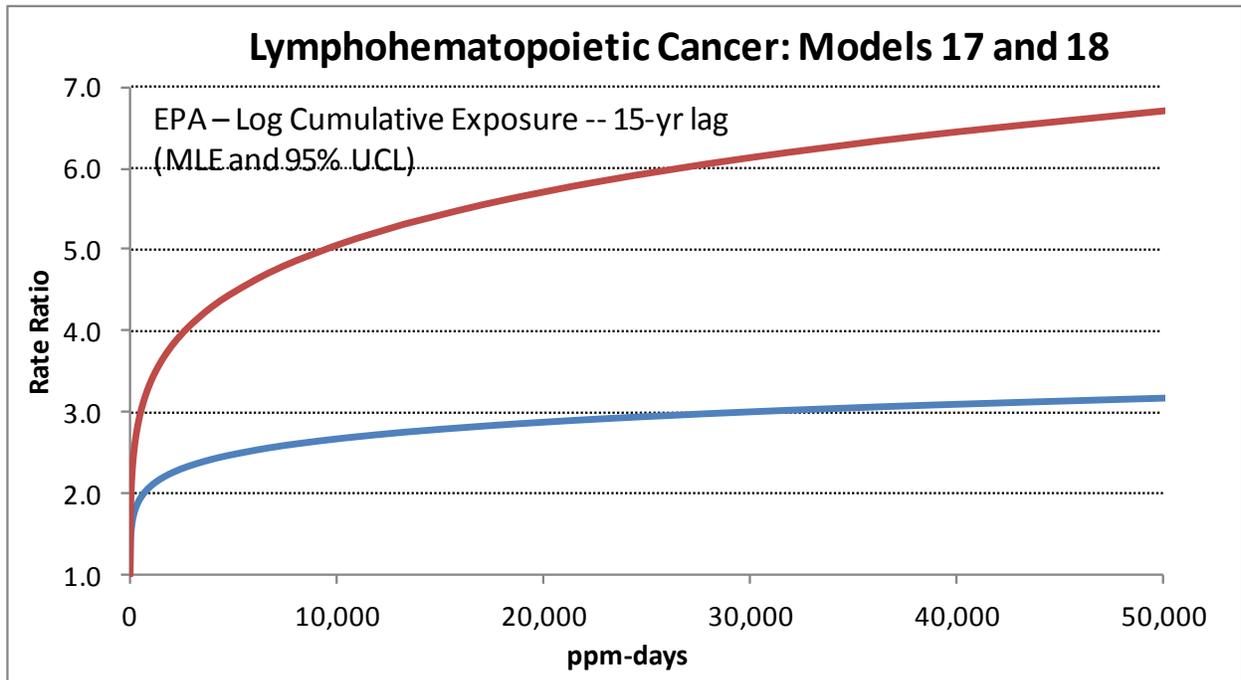
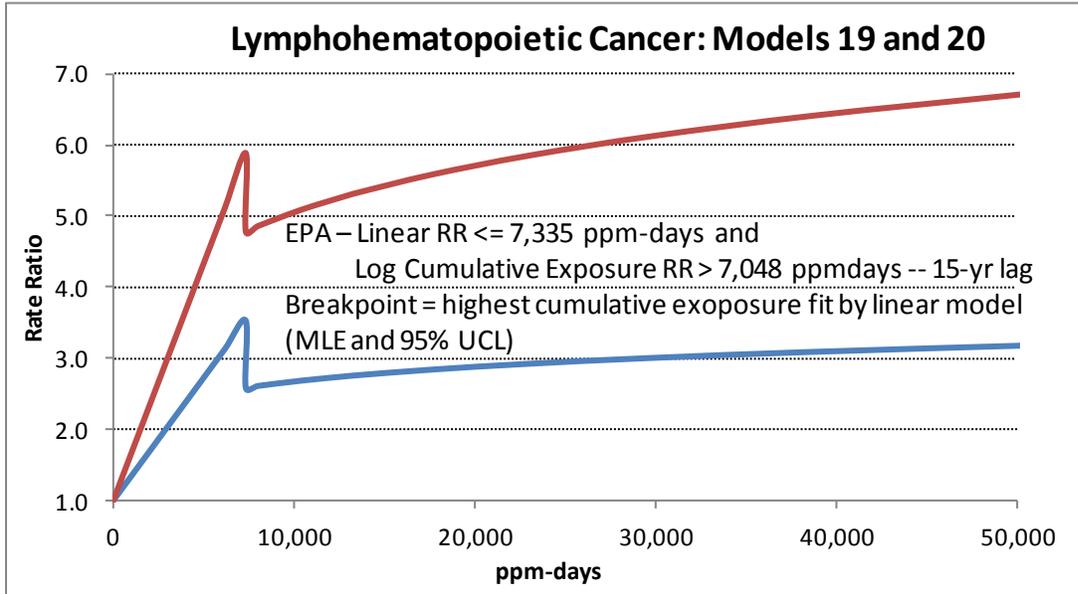
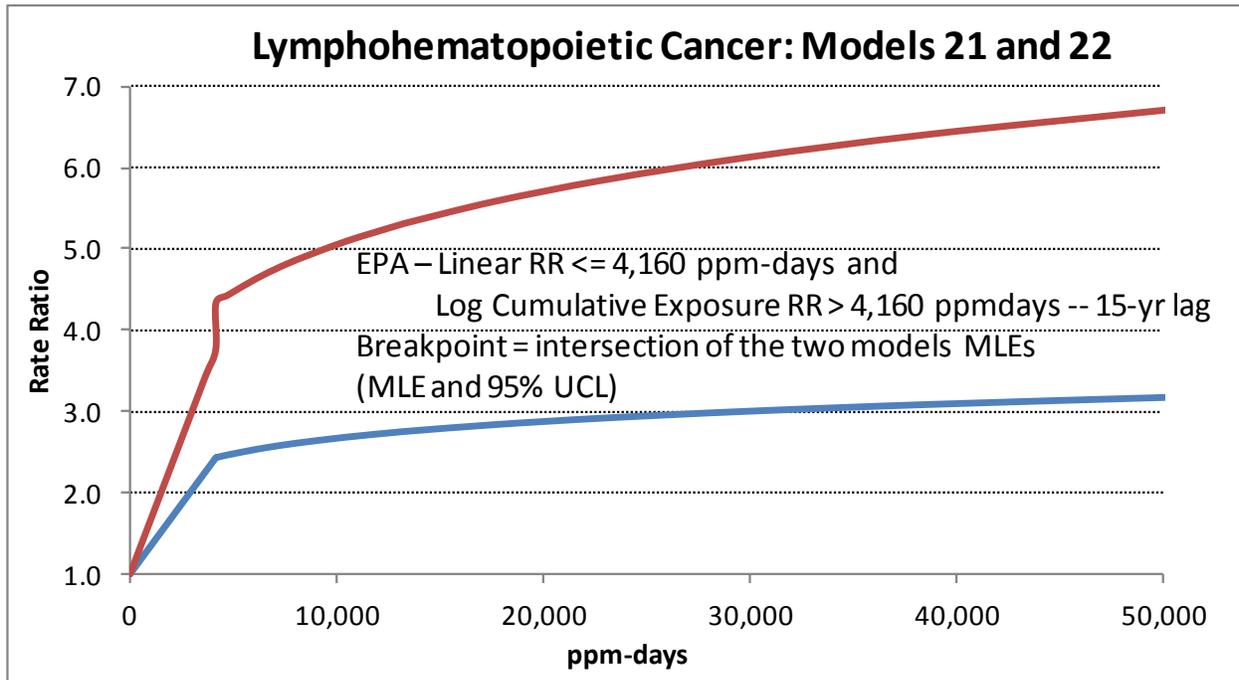


Figure D.9 19. EPA -- Linear $\leq 7,335$ ppm-day Table 4-3, log cumulative exposure $>7,335$ ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model – blue
 20. EPA -- Linear $\leq 7,335$ ppm-day Table 4-3, log cumulative exposure $>7,335$ ppm-day Table 4-2 -- 15-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model – red



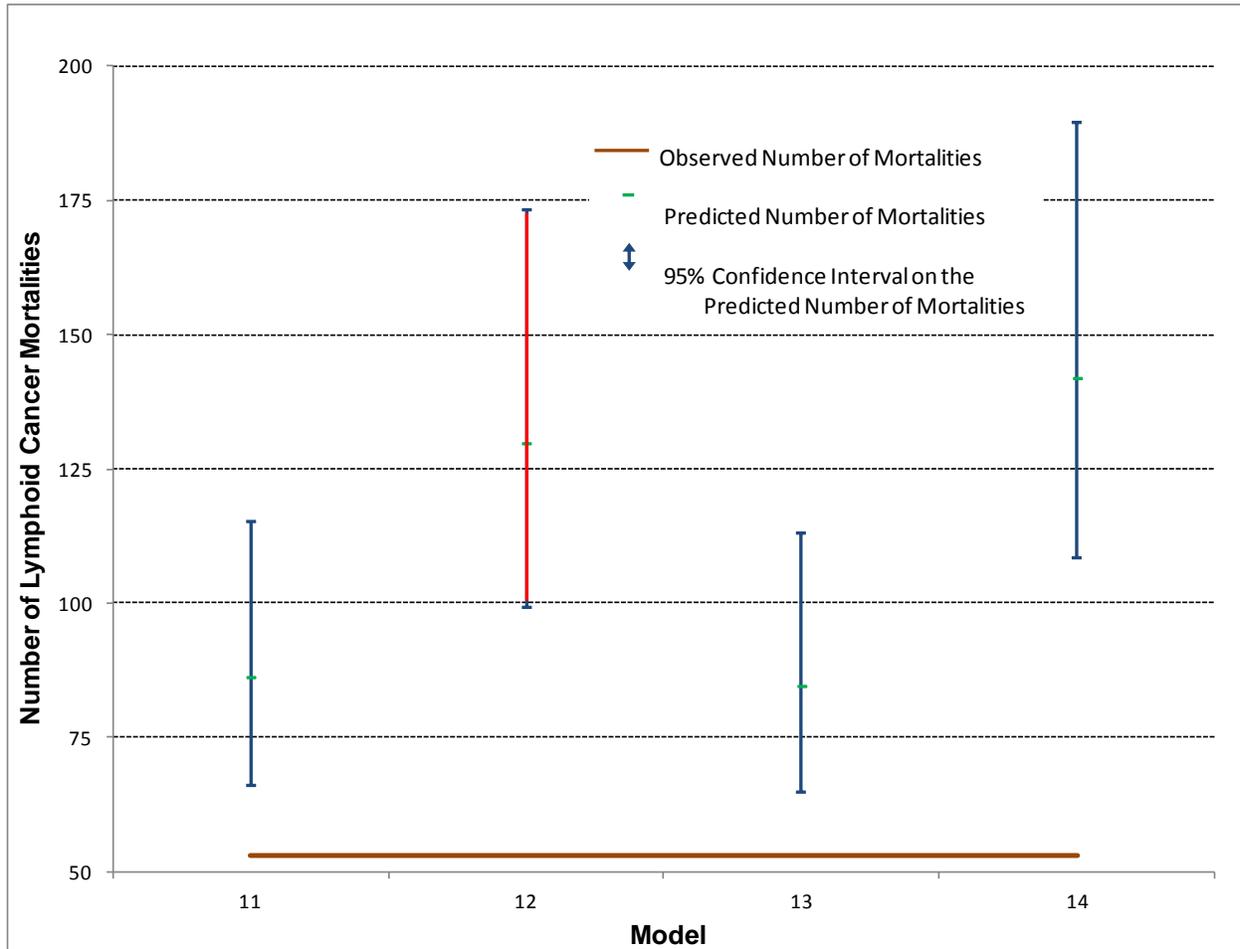
- Figure D.10
- 21. EPA -- Linear $\leq 4,160$ ppm-day Table 4-3, log cumulative exposure $>4,160$ ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – blue
 - 22. EPA -- Linear $\leq 4,160$ ppm-day Table 4-3, log cumulative exposure $>4,160$ ppm-day Table 4-2 -- 15-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – red



Appendix E

Comparison of Epidemiological Exposure-Response Model Results for Ethylene Oxide and Lymphoid Cancer Mortality

Figure E.1. EPA Models Assuming that the Model is Flat After the “Knot”



Models:

Results using EPA models but assuming that slope for RR is zero (flat) after the “knot”

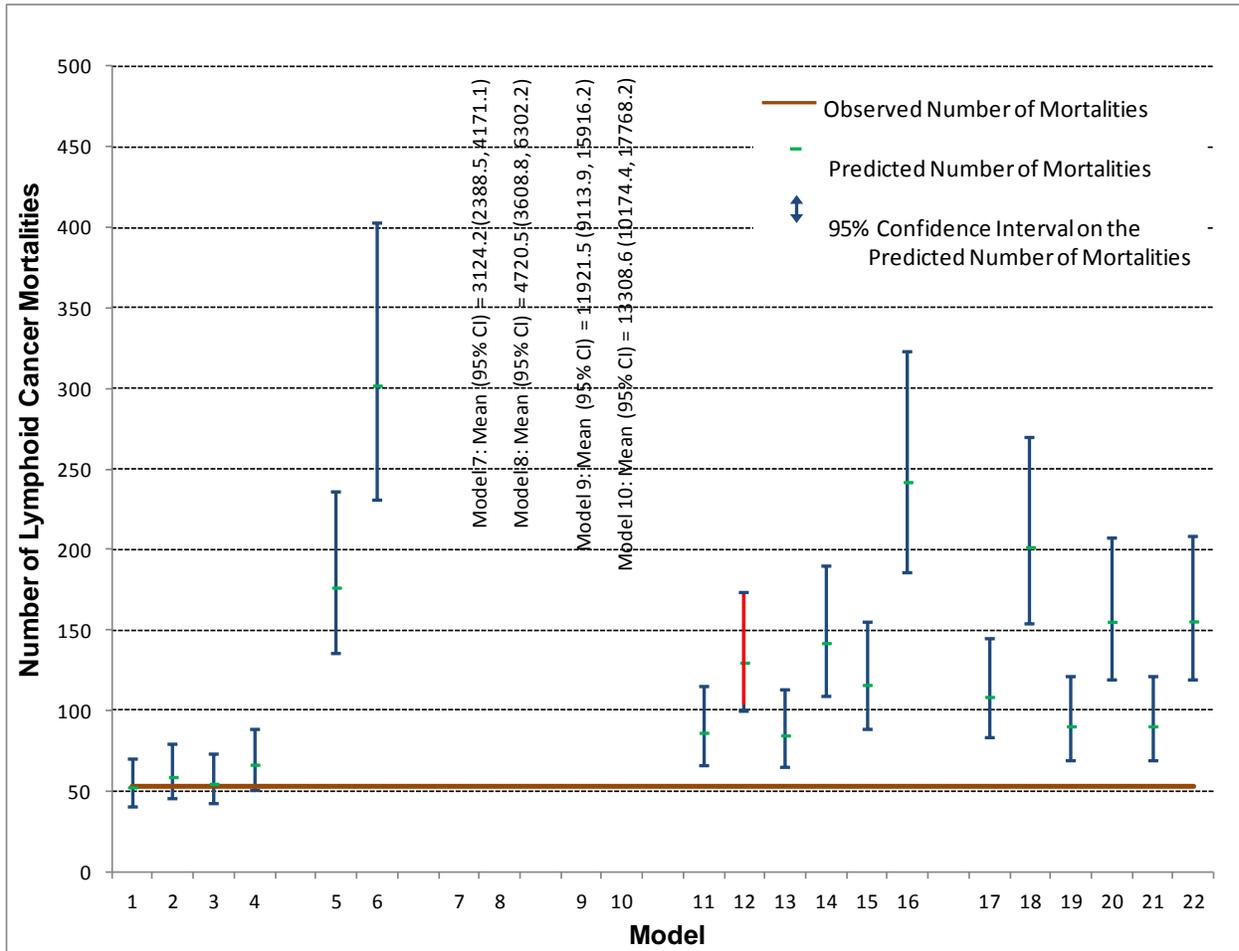
11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – footnote page 4-12 “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – footnote page 4-12 “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

13. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 1,600 ppm-days

14. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 1,600 ppm-days

Figure E.2. All Models



Models:

1. Sielken & Associates – Loglinear – 15-yr lag (MLE)
2. Sielken & Associates – Loglinear – 15-yr lag (95% UCL)
3. Steenland et al. (2010) for EPA – Loglinear – 15-yr lag (MLE) – EPA Table 4-2
4. Steenland et al. (2010) for EPA – Loglinear – 15-yr lag (95% UCL) – EPA Table 4-2
5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4.3
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4.3
7. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 1,600 ppm-days
8. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 1,600 ppm-days
9. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 100 ppm-days
10. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA f Table 4-3 knot @ 100 ppm-days

Results using above EPA models but assuming that slope for RR is zero (flat) after the “knot”

11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – footnote page 4-12 “knot” = 7,335 ppm-days = mean exposure in second highest exposure group
12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – footnote page 4-12 “knot” = 7,335 ppm-days = mean exposure in second highest exposure group

13. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 1,600 ppm-days
14. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 1,600 ppm-days
15. EPA – Loglinear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 100 ppm-days
16. EPA – Loglinear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 100 ppm-days

Results using EPA models considered for occupational exposure levels

17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2
19. EPA -- Linear \leq 7,335 ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure $>$ 7,335 ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model.
20. EPA -- Linear \leq 7,335 ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure $>$ 7,335 ppm-day Table 4-2 -- 15-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model.
21. EPA -- Linear \leq 6,835 ppm-day Table 4-3, log cumulative exposure $>$ 6,835 ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.
22. EPA -- Linear \leq 6,835 ppm-day Table 4-3, log cumulative exposure $>$ 6,835 ppm-day Table 4-2 -- 15-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect.

Table E.1 Model Predictions for Lymphoid Cancer Mortalities—53 Observed
 Using the lymphoid cancer mortality models in the July 2011 draft IRIS assessment for EO and
 the model estimated by Sielken & Associates using the individual data

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
Background (No Model)	n/a	50.39	95.1%	(38.5, 67.3)
1. S&A – Log-linear – 15-yr lag (MLE) ¹	2.81E-06	52.42	98.9%	(40.1, 70.0)
2. S&A – Log-linear – 15-yr lag (95% UCL) ¹	7.17E-06	58.75	110.8%	(44.9, 78.4)
3. Steenland et al. (2010) for EPA – Log- linear – 15-yr lag (MLE) – EPA Table 4-2 ¹	4.74E-06	54.52	102.9%	(41.7, 72.8)
4. Steenland et al. (2010) for EPA – Log- linear – 15-yr lag (95% UCL) – EPA Table 4-2 ¹	1.03E-05	66.41	125.3%	(50.8, 88.7)
EPA Final Mortality Model – Linear – EPA Only Used the Second Model with the 95% UCL on Slope				
5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3	2.47E-04	176.41	332.8%	(134.9, 235.5)
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3	5.51E-04	301.89	569.6%	(230.8, 403.1)
EPA Spline Model with Knot at 1,600 ppm-days				
7. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 1,600 ppm- days	4.89E-04	3124.21	5894.7%	(2,388.4, 4,171.1)

¹ The models used by Sielken & Associates and Steenland et al. (2010) [appearing as an appendix in EPA (2013)] are the same models; however, Steenland et al. did not use all of the individual data – Steenland et al. only used a subsample of the individual data.

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
8. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 1,600 ppm-days	9.08E-04	4720.47	8906.5%	(3,608.8, 6,302.2)
EPA Spline Model with Knot at 100 ppm-days				
9. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 100 ppm-days	1.01E-02	11921.46	22493.3%	(9,113.9, 15,916.2)
10. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 100 ppm-days	1.82E-02	13308.64	25110.6%	(10,174.4, 17,768.2)
Results using above EPA models but assuming that slope for RR is zero after the “knot”				
11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 – footnote page 4-12 – knot = 7,335 ppm-days	2.47E-04	86.24	162.7%	(65.9, 115.1)
12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 – footnote page 4-12 – knot = 7,335 ppm-days	5.51E-04	129.82	244.9%	(99.2, 173.3)
13. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 1,600 ppm-days	4.89E-04	84.59	159.6%	(64.7, 112.9)
14. EPA – Log-linear Spline – 15-yr lag (95% UCL) – Table 4-3 - knot @ 1,600 ppm-days	9.08E-04	141.97	267.9%	(108.5, 189.5)

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
15. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 100 ppm-days	1.01E-02	115.97	218.8%	(88.7, 154.8)
16. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 100 ppm-days	1.82E-02	241.97	456.5%	(185.0, 323.0)
EPA models used for occupational exposures and occupational risks				
17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2	1.12E-01	108.52	204.8%	(83.0, 144.9)
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2	1.92E-01	201.52	380.2%	(154.1, 269.1)
19. EPA -- Linear <= 7,335 ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure >7,335 ppm-day Table 4-2 -- 15-yr lag (MLE)	2.47E-04	90.30	170.4%	(69.0, 120.6)
20. EPA -- Linear <= 7,335 ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure >7,335 ppm-day Table 4-2 -- 15-yr lag (95% UCL)	5.51E-04	155.18	292.8%	(118.6, 207.2)

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% x Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
21. EPA -- Linear <= 6,835 ppm-day Table 4-3, log cumulative exposure >6,835 ppm-day Table 4-2 -- 15-yr lag (MLE)	2.47E-04	90.27	170.3%	(69.0, 120.5)
22. EPA -- Linear <= 6,835 ppm-day Table 4-3, log cumulative exposure >6,835 ppm-day Table 4-2 -- 15-yr lag (95% UCL)	5.51E-04	155.45	293.3%	(118.8, 207.5)

Table E.2. SMRs for lymphoid cancer mortality in the NIOSH female cohort for unlagged exposures to EO (Sielken & Associates)

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)			
(0, 1826]	14	18.49	75.7 (41.4, 127.0)
(1826, 6575]	13	11.85	109.7 (58.4, 187.6)
(6575, 20089]	13	9.61	135.2 (71.9, 231.2)
> 20089	13	10.43	124.6 (66.3, 213.1)
All	53	50.39	105.2 (78.8, 137.6)

Table E.3. SMRs for lymphoid cancer mortality in the NIOSH female cohort for 15-year lagged exposures to EO (Sielken & Associates calculated)

Cumulative Exposure to EO (ppm-days)	Observed	Expected	SMR (95% Confidence Interval)
0 (lagged out)	9	11.5	78.4 (35.8, 148.8)
(0, 647]	15	15.7	95.6 (53.4, 157.6)
(646, 2780]	9	9.5	94.6 (43.2, 179.7)
(2780, 12322]	11	6.9	159.9 (79.7, 286.2)
> 12322	9	6.8	132.0 (60.2, 250.5)
All	53	53.4	105.2 (78.8, 137.6)

Appendix F

Graphical representation of the rate ratio functions for the 22 models used in the analyses

Figure F.1 1. Sielken & Associates – Log-linear – 15-yr lag (MLE) – blue
2. Sielken & Associates – Log-linear – 15-yr lag (95% UCL) – red

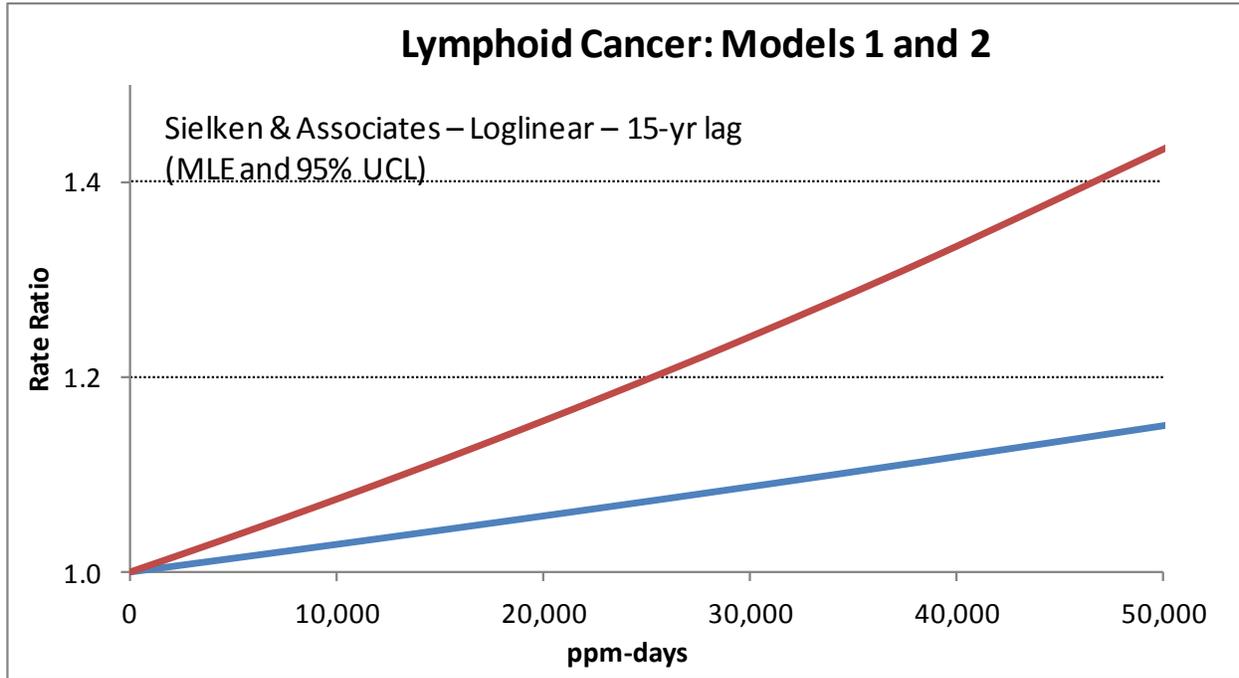


Figure F.2 3. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (MLE) – EPA Table 4-2 – blue
4. Steenland et al. (2010) for EPA – Log-linear – 15-yr lag (95% UCL) – EPA Table 4-2 – red

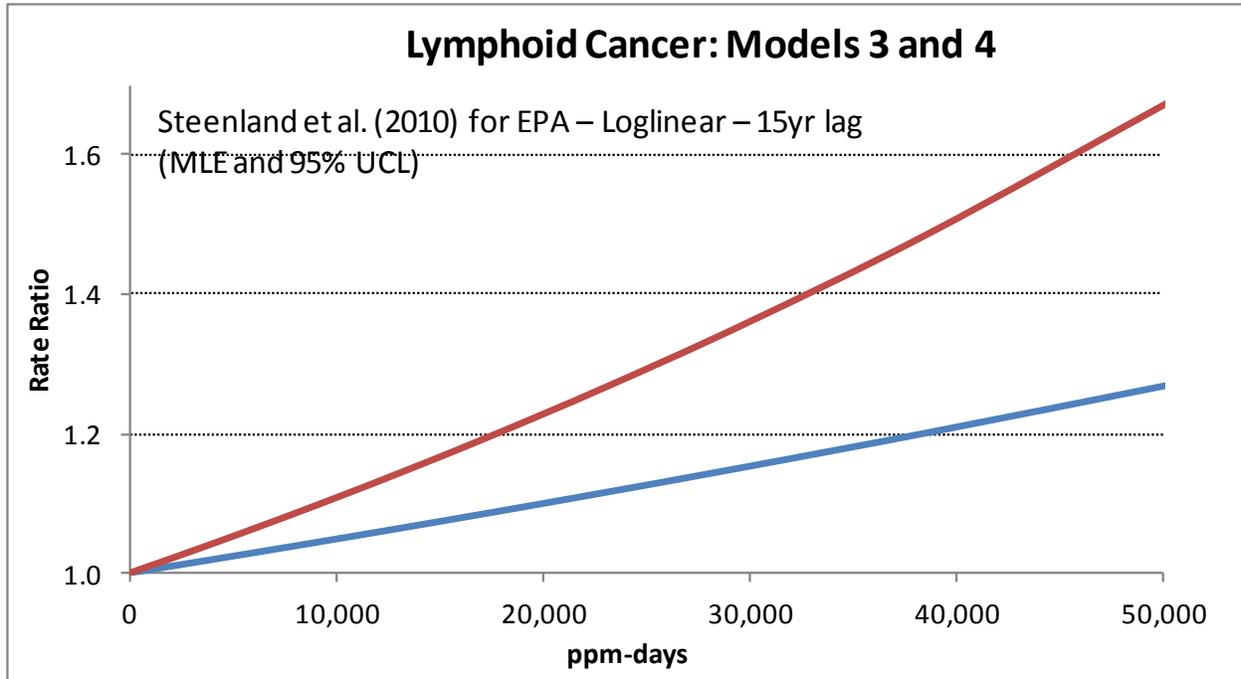


Figure F.3 5. EPA – Linear – 15-yr lag (MLE) – EPA Table 4.3 – blue
6. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4.3 – red

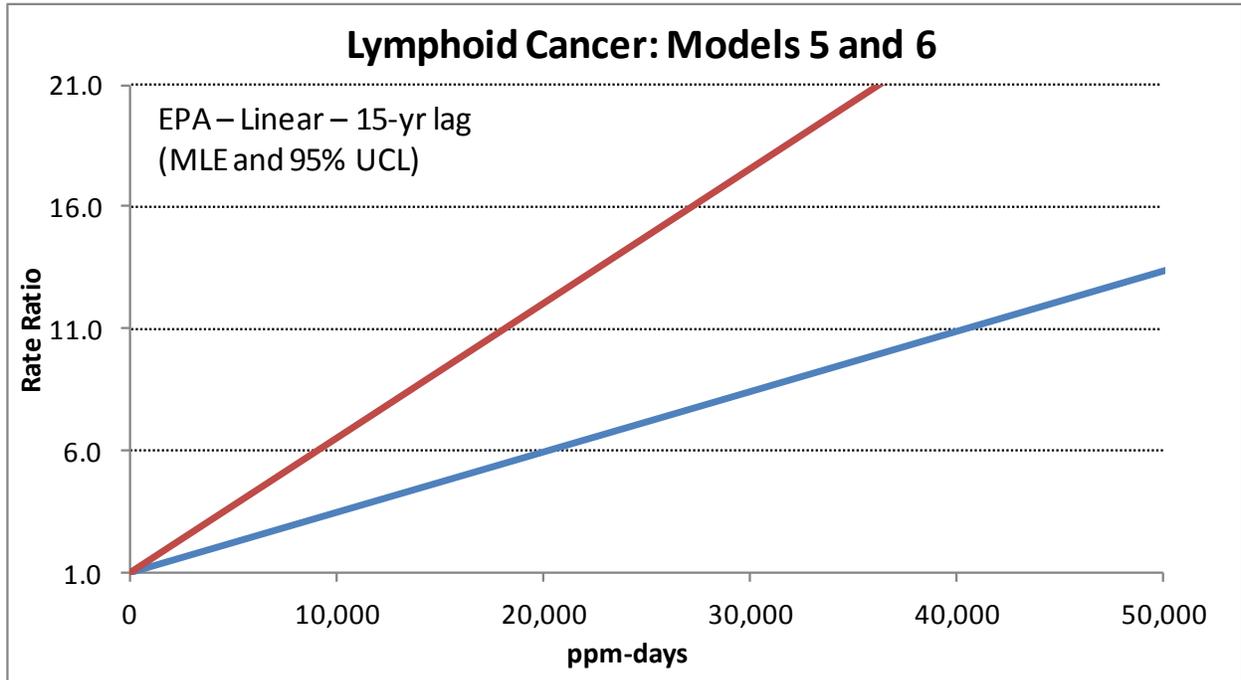


Figure F.4 7. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 1,600 ppm-days – blue
8. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 1,600 ppm-days – red

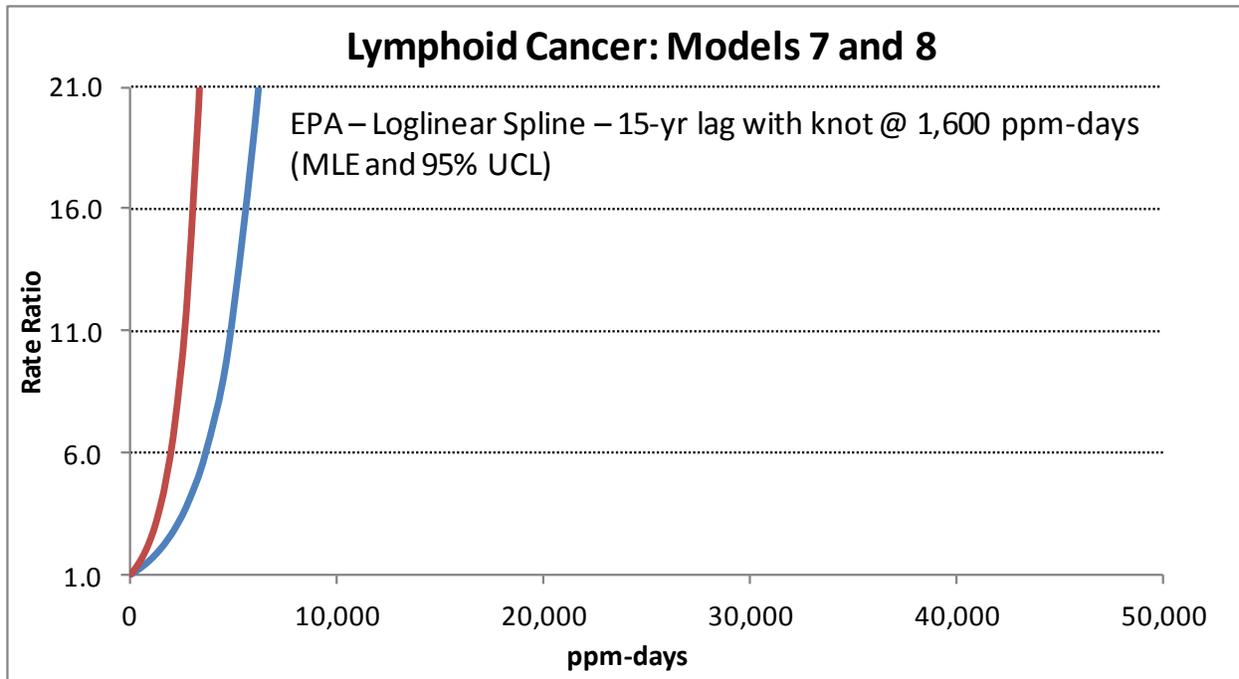


Figure F.5 9. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 knot @ 100 ppm-days – blue
10. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 knot @ 100 ppm-days – red

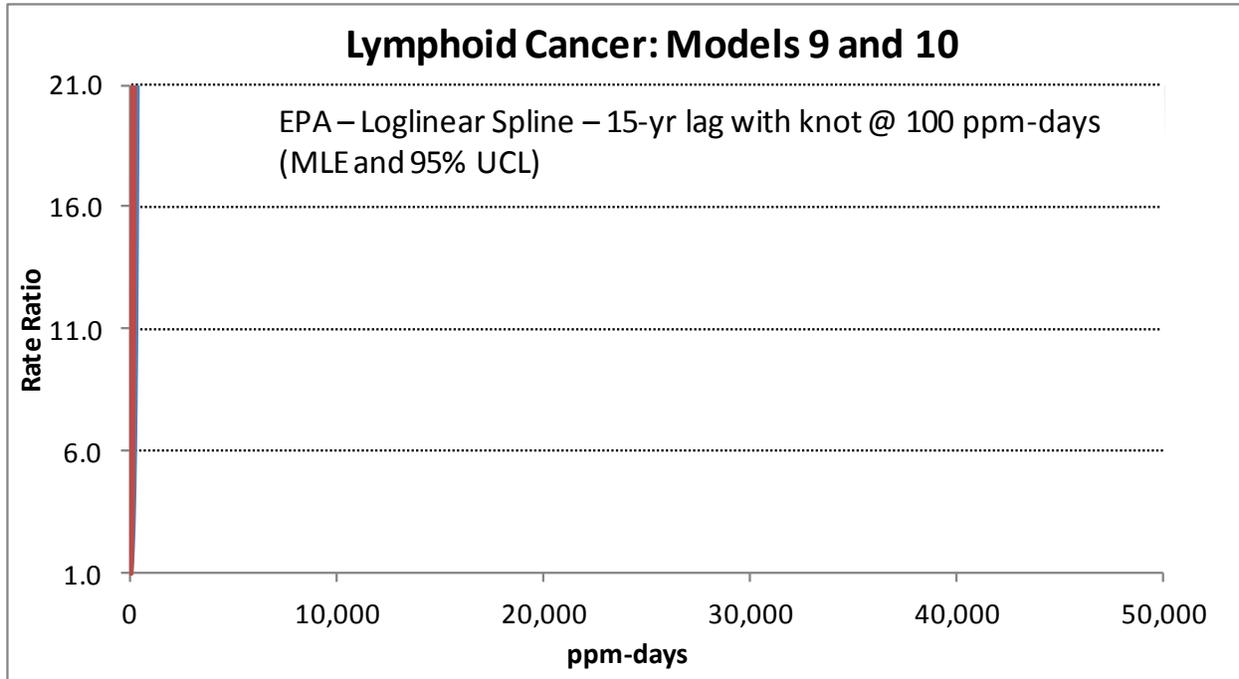


Figure F.6 11. EPA – Linear – 15-yr lag (MLE) – EPA Table 4-3 and footnote page 4-12 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group – blue
 12. EPA – Linear – 15-yr lag (95% UCL) – EPA Table 4-3 and footnote page 4-12 – “knot” = 7,335 ppm-days = mean exposure in second highest exposure group – red

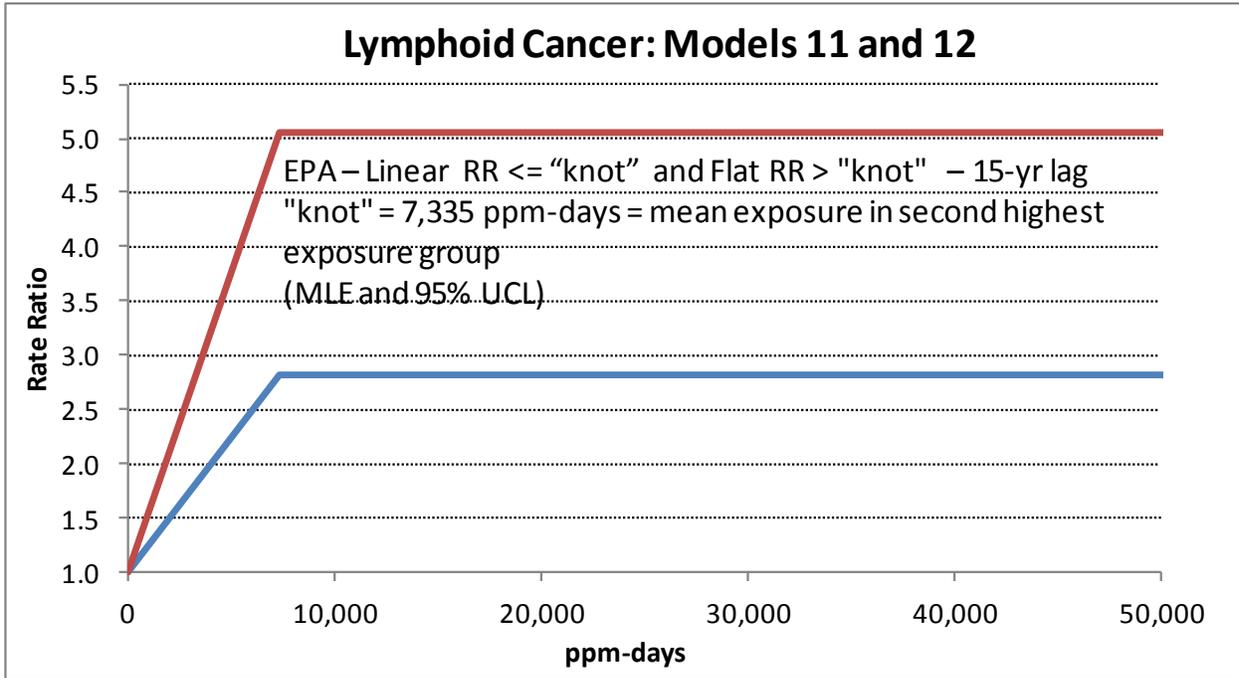


Figure F.7 13. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 1,600 ppm-days – blue
14. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 1,600 ppm-days – red

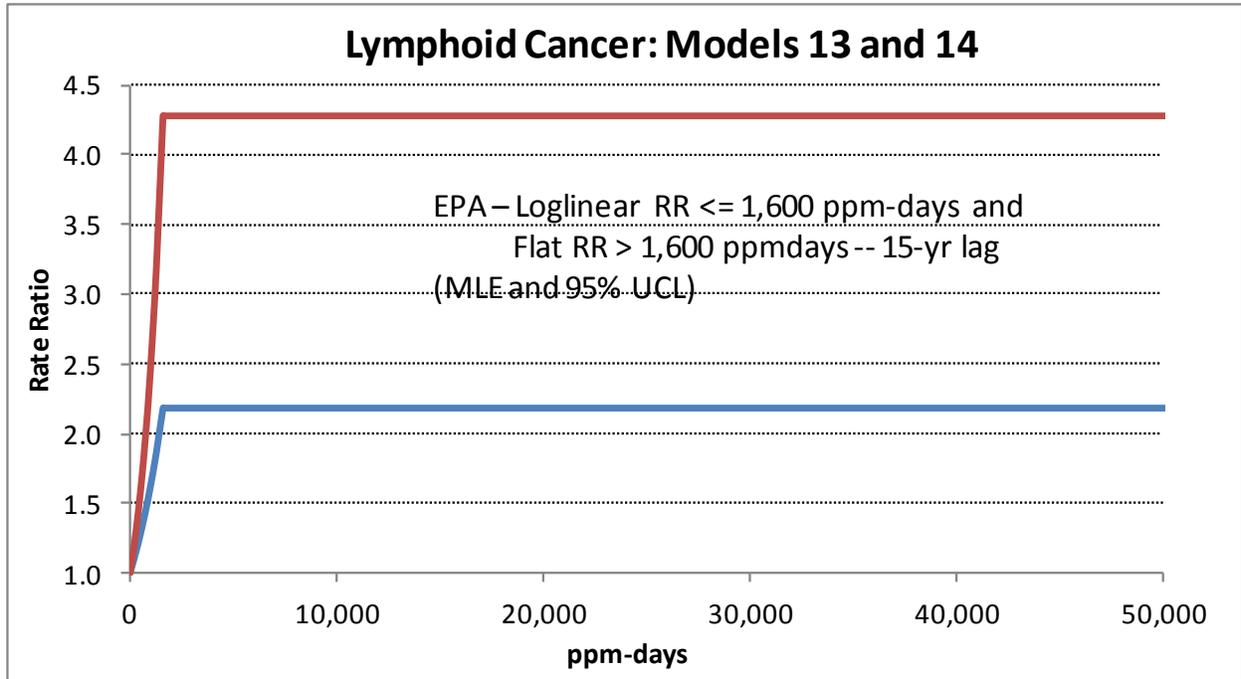


Figure F.8 15. EPA – Log-linear Spline – 15-yr lag (MLE) – EPA Table 4-3 - knot @ 100 ppm-days – blue
16. EPA – Log-linear Spline – 15-yr lag (95% UCL) – EPA Table 4-3 - knot @ 100 ppm-days – red

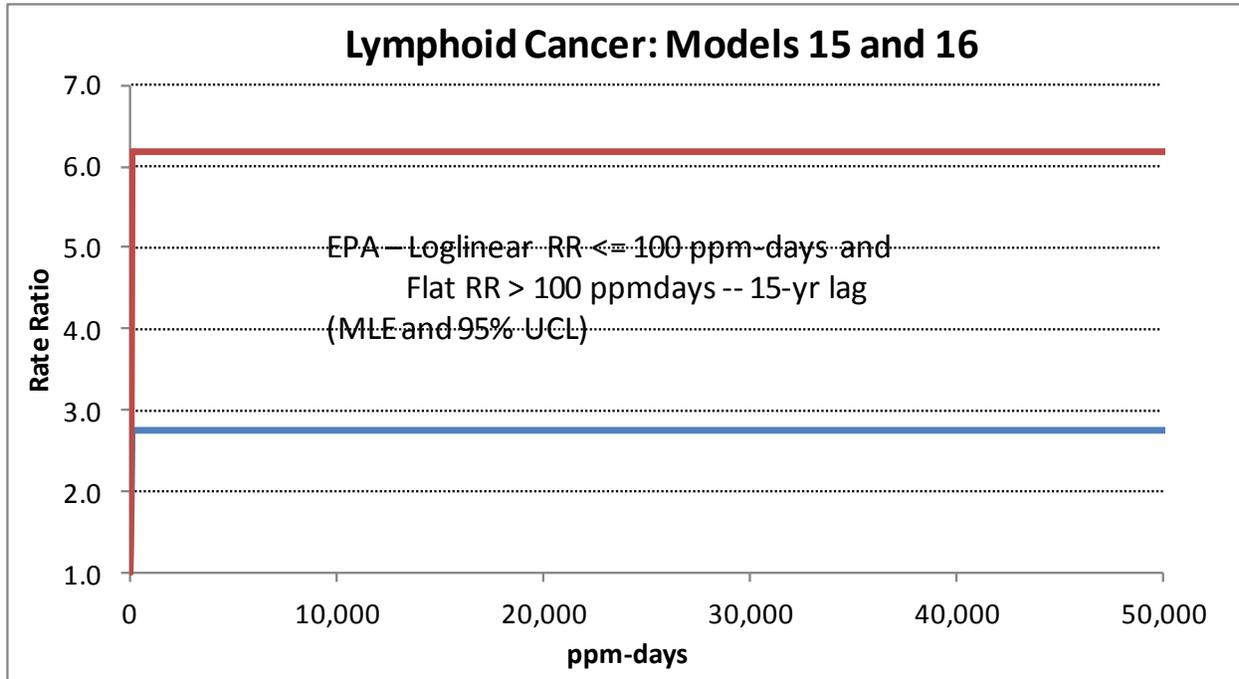


Figure F.9 17. EPA -- log cumulative exposure -- 15-yr lag (MLE) -- Table 4-2 -- blue
18. EPA -- log cumulative exposure -- 15-yr lag (95% UCL) -- Table 4-2 -- red

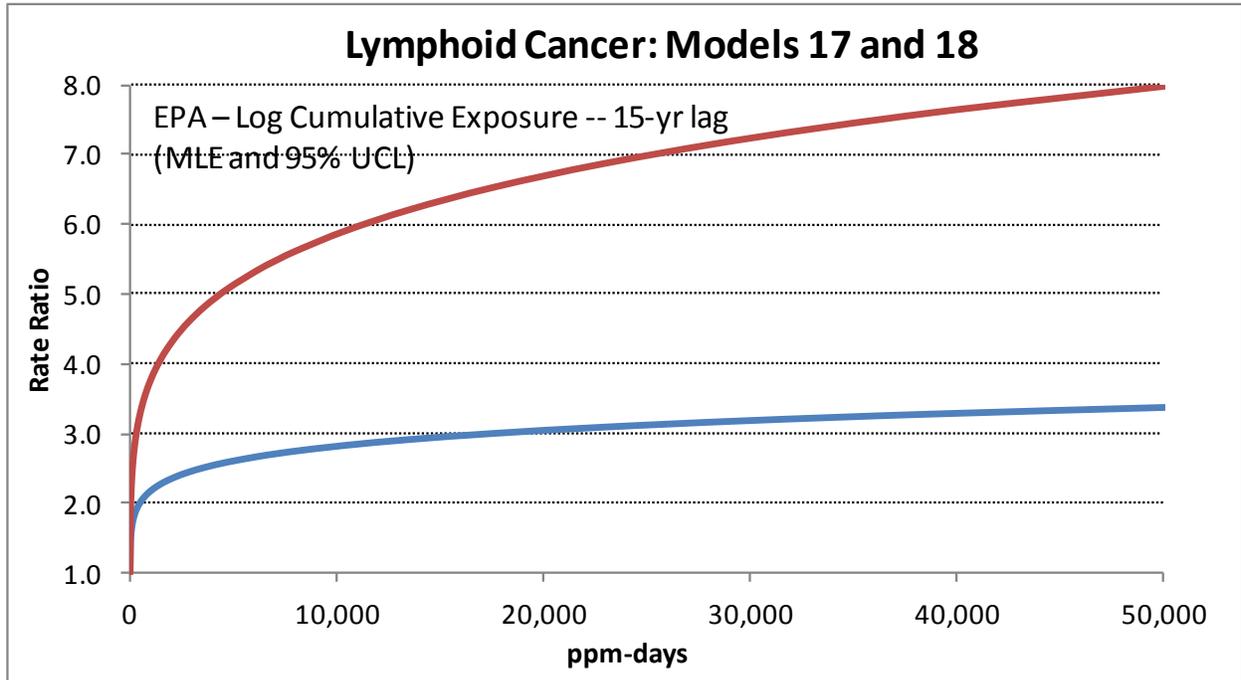


Figure F.10 19. EPA -- Linear $\leq 7,335$ ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure $>7,335$ ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = highest cumulative exposure fit by linear model – blue
 20. EPA -- Linear $\leq 7,335$ ppm-day Table 4-3 and footnote page 4-12, log cumulative exposure $>7,335$ ppm-day Table 4-2 -- 15-yr lag (95% UCL) – Breakpoint = highest cumulative exposure fit by linear model – red

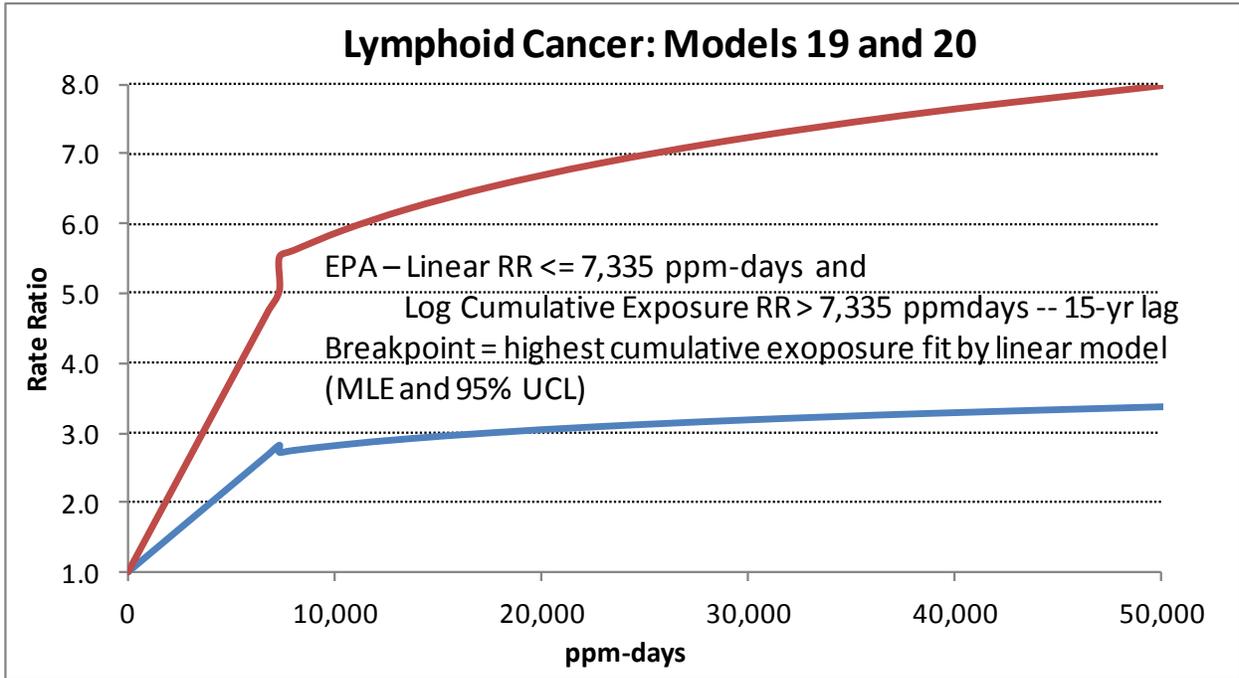
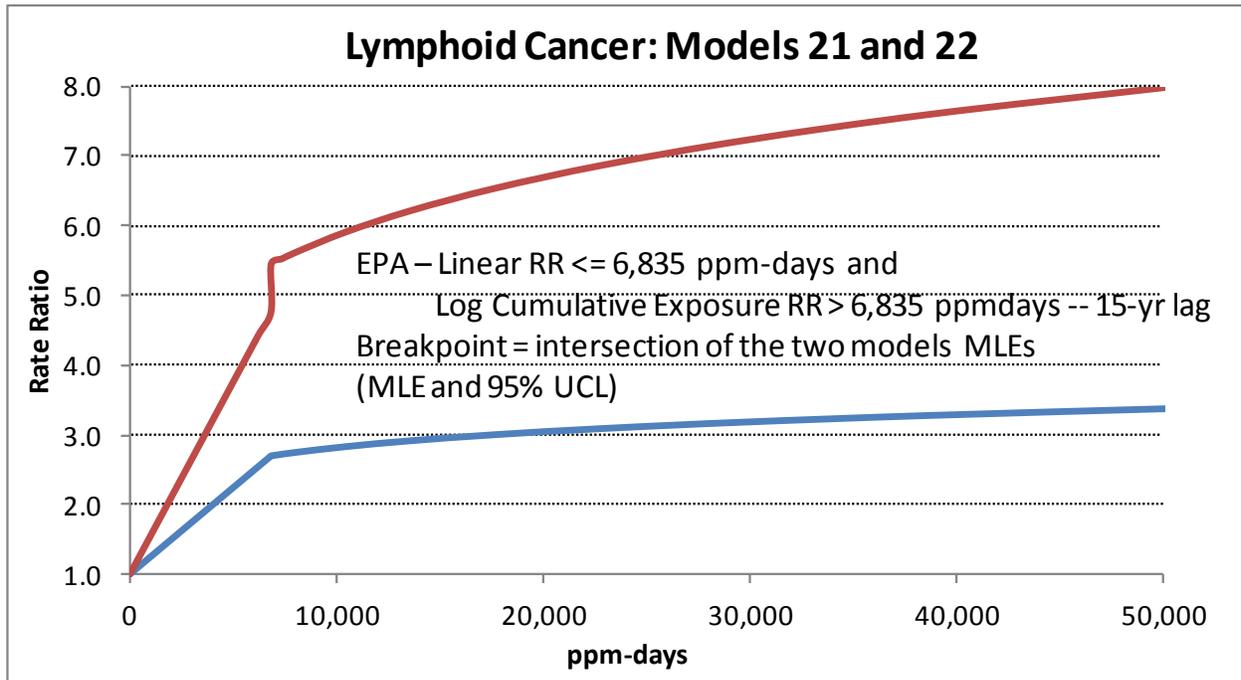


Figure F.11 21. EPA -- Linear $\leq 6,835$ ppm-day Table 4-3, log cumulative exposure $>6,835$ ppm-day Table 4-2 -- 15-yr lag (MLE) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – **blue**
 22. EPA -- Linear $\leq 6,835$ ppm-day Table 4-3, log cumulative exposure $>6,835$ ppm-day Table 4-2 -- 15-yr lag (95% UCL)) – Breakpoint = cumulative exposure where the linear model and the log cumulative exposure model intersect – **red**



American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #5
October 2014

Charge Question #5. Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:

- Section 3.3.3 and Appendix C (genotoxicity)

ACC recommended on September 23, 2014 the following addition to this charge question:

How well is it demonstrated that a direct, DNA reactive mutagenic MOA is the only MOA for all tumors attributed to ethylene oxide?

Determination of a direct, DNA-reactive mutagenic MOA

- Positive genotoxicity data in the absence of additional supporting data do not constitute sufficient evidence to determine this MOA.
- Application of a MOA analysis framework based on “KEY EVENTS” for assessing a chemical carcinogen’s cancer MOA provides clarity and scientific rigor to the process.
- Key events are early, necessary and quantifiable precursor steps in the pathogenesis of cancer.
- The earliest of the key events in tumor development due to chemicals acting via a direct, DNA reactive mutagenic MOA deal with mutation induction in the target tissue before tumor development.
- To establish a direct, DNA-reactive mutagenic MOA, it necessary to demonstrate pro-mutagenic DNA adducts in the target tissue for cancer. This has not been done for EO.
- EPA should specify which tumors it deems to be induced via a direct, DNA reactive mutagenic MOA and their reasons for these determinations.

Several recent publications discuss modern approaches to data organization in the determination of a chemical’s MOA for cancer, specifically a direct, DNA reactive mutagenic MOA. One key paper, Pottenger et al. (2014), outlines a process (with examples) that is both scientifically rigorous and provides transparency as to how the data support such an MOA. In addition, Phillipin et al. (2014) provides unambiguous evidence that the ethylene oxide DNA adduct that is abundantly produced in tissues at low to moderate exposure levels, i.e. N7HEdG, is not a promutagenic adduct. Rusyn et al. (2005) demonstrates that apurinic sites, which could result from incomplete repair of the N7dG adduct and be promutagenic, do not accumulate following exposure to ethylene oxide. There is a data gap in critical information on DNA adducts in target tissues following ethylene oxide exposures associated with tumors in that only a limited number have been investigated. Abstracts for these publications are attached.

In the discussion of vinyl chloride, a chemical that does induce cancer with a direct, DNA reactive mutagenic MOA, Pottenger et al. (2014) state that if the abundant N7dG adduct produced by that chemical was the only one found in the target tissue, such a designation could not have been made. The N7dG adduct produced by vinyl chloride is analogous to the N7HEdG

adduct produced by ethylene oxide. Rather, in the case of vinyl chloride, a promutagenic -ethno-dG adduct is produced that allowed the designation.

Alternative biologically plausible modes of action

- Initial amplification of pre-existing (background) K-Ras mutations in lung mediated by oxidative stress modifying Ras signaling in mice exposed to EO, with experimental support, has been postulated as an early event in lung tumor production in this animal model.
- Modern studies of the pathogenesis of human lymphoid tumors suggest a MOA independent of initiation by a “single hit” resulting from an external mutagen. Lymphomas are typically associated with immunological factors such as infections, immunosuppression and autoimmunity rather than chemicals. Double strand breaks (DSBs) due to physiological processes (V(D)J recombination, class switching, AID hypermutation) coupled with pathological DSB (e.g. due to ROS, aberrant immune response) conspire to initiate these malignancies.

The first of these biologically plausible MOAs is based on research reported by Parsons et al. (2013) (this open-access publication is attached). EPA dismissed the data and hypothesis presented in the paper because the data were variable, because there was no other supporting evidence in the literature for the hypothesis put forward and because these data, *per se*, did not prove the hypothesis put forward. In essence, EPA peer reviewed the paper and rejected it. One EPA criticism of the paper is that the focus was only on *Ras* mutations even though EPA, in its review of the genotoxicity of ethylene oxide, cited the Hong et al. (2007) paper reporting these mutations as evidence that ethylene oxide’s mutagenicity is important in the etiology of lung tumors.

The second of these biologically plausible MOAs deals with lymphoid tumors. The supporting literature is being submitted by Dr. Richard Irons.

My remarks are not intended to disprove a direct, DNA reactive mutagenic MOA for any tumor associated with ethylene oxide. However, neither scientific rigor nor transparency has been demonstrated by EPA in making this designation. Furthermore, alternative biologically plausible MOAs have been suggested for at least of some of the tumors attributed to ethylene oxide. For these reasons, EPA should reconsider its insistence on only a linear, non-threshold extrapolation for risk assessment for all tumors.

Richard J. Albertini M.D., Ph.D.

References

Philippin et al. (2014). Ethylene oxide and propylene oxide derived N7-alkylguanine adducts are bypassed accurately in vivo. *DNA Repair*, 22: 133-36.

Abstract

Adducts formed at the nucleophilic N7 position of guanine are the most abundant lesions produced by alkylating agents such as ethylene oxide (EO) and propylene oxide (PO). In order to investigate the intrinsic mutagenic potential of N7-alkylguanine adducts, we prepared single-stranded DNA probes containing a single well-defined N7-alkylguanine adduct under conditions that minimize the presence of depurinated molecules. Following introduction of these probes into *Escherichia coli* cells, the effect of the N7-alkylguanine adducts on the efficiency and fidelity of replication was determined. To investigate the effect on replication we monitored the relative transformation efficiency of the lesion containing constructs with respect to the control construct. The methyl adduct was found not to be toxic, while the N7-(2-hydroxyethyl)guanine (N7-heG) and N7-(2-hydroxypropyl)guanine (N7-hpG) adducts reduce the transformation efficiency to $\approx 70\%$ and 40% , respectively. Within the detection limits of our assay, replication across the N7-alkylguanine adducts in vivo is essentially error-free, as no mutant colony was observed among ≈ 300 individual sequenced colonies (i.e., mutation frequency $< 0.3\%$).

Pottenger et al. (2014). An organizational approach for the assessment of DNA adduct data in risk assessment: case studies for aflatoxin B1, tamoxifen and vinyl chloride. *Crit Rev Toxicol*, 44(4): 348-91.

Abstract

The framework analysis previously presented for using DNA adduct information in the risk assessment of chemical carcinogens was applied in a series of case studies which place the adduct information into context with the key events in carcinogenesis to determine whether they could be used to support a mutagenic mode of action (MOA) for the examined chemicals. Three data-rich chemicals, aflatoxin B1 (AFB1), tamoxifen (Tam) and vinyl chloride (VCl) were selected for this exercise. These chemicals were selected because they are known human carcinogens and have different characteristics: AFB1 forms a unique adduct and human exposure is through contaminated foods; Tam is a pharmaceutical given to women so that the dose and duration of exposure are known, forms unique adducts in rodents, and has both estrogenic and genotoxic properties; and VCl, to which there is industrial exposure, forms a number of adducts that are identical to endogenous adducts found in unexposed people. All three chemicals produce liver tumors in rats. AFB1 and VCl also produce liver tumors in humans, but Tam induces human uterine tumors, only. To support a mutagenic MOA, the chemical-induced adducts must be characterized, shown to be pro-mutagenic, be present in the tumor target tissue, and produce mutations of the class found in the tumor. The adducts formed by AFB1 and VCl support a mutagenic MOA for their carcinogenicity. However, the data available for Tam

shows a mutagenic MOA for liver tumors in rats, but its carcinogenicity in humans is most likely via a different MOA.

Rusyn et al. (2005). Effects of ethylene oxide and ethylene inhalation on DNA adducts, apurinic/apyrimidinic sites and expression of base excision DNA repair genes in rat brain, spleen, and liver. *DNA Repair*, 4(10)-1099-110.

Abstract

Ethylene oxide (EO) is an important industrial chemical that is classified as a known human carcinogen (IARC, Group 1). It is also a metabolite of ethylene (ET), a compound that is ubiquitous in the environment and is the most used petrochemical. ET has not produced evidence of cancer in laboratory animals and is "not classifiable as to its carcinogenicity to humans" (IARC, Group 3). The mechanism of carcinogenicity of EO is not well characterized, but is thought to involve the formation of DNA adducts. EO is mutagenic in a variety of in vitro and in vivo systems, whereas ET is not.

Apurinic/apyrimidinic sites (AP) that result from chemical or glycosylase-mediated depurination of EO-induced DNA adducts could be an additional mechanism leading to mutations and chromosomal aberrations. This study tested the hypothesis that EO exposure results in the accumulation of AP sites and induces changes in expression of genes for base excision DNA repair (BER). Male Fisher 344 rats were exposed to EO (100 ppm) or ET (40 or 3000 ppm) by inhalation for 1, 3 or 20 days (6h/day, 5 days a week). Animals were sacrificed 2h after exposure for 1, 3 or 20 days as well as 6, 24 and 72 h after a single-day exposure. Experiments were performed with tissues from brain and spleen, target sites for EO-induced carcinogenesis, and liver, a non-target organ. Exposure to EO resulted in time-dependent increases in N7-(2-hydroxyethyl)guanine (7-HEG) in brain, spleen, and liver and N7-(2-hydroxyethyl)valine (7-HEVal) in globin. Ethylene exposure also induced 7-HEG and 7-HEVal, but the numbers of adducts were much lower. No increase in the number of aldehydic DNA lesions, an indicator of AP sites, was detected in any of the tissues between controls and EO-, or ET-exposed animals, regardless of the duration or strength of exposure. EO exposure led to a 3-7-fold decrease in expression of 3-methyladenine-DNA glycosylase (Mpg) in brain and spleen in rats exposed to EO for 1 day. Expression of 8-oxoguanine DNA glycosylase, Mpg, AP endonuclease (Ape), polymerase beta (Pol beta) and alkylguanine methyltransferase were increased by 20-100% in livers of rats exposed to EO for 20 days. The only effects of ET on BER gene expression were observed in brain, where Ape and Pol beta expression were increased by less than 20% after 20 days of exposure to 3000 ppm. These data suggest that DNA damage induced by exposure to EO is repaired without accumulation of AP sites and is associated with biologically insignificant changes in BER gene expression in target organs. We conclude that accumulation of AP sites is not a likely primary mechanism for mutagenicity and carcinogenicity of EO.

American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #5
October 2014

Charge Question #5: Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:

- Section 3.3.3 and Appendix C (genotoxicity)
- Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard characterization (p. H-3).

EPA should follow the recommendation of members of the SAB to include a nonlinear approach.

When the EPA Science Advisory Board (SAB) reviewed EPA's previous 2007 draft assessment of the carcinogenicity of EO, "[w]ith appropriate discussion of the statistical and biological uncertainties, several Panel members strongly advocated that both linear and nonlinear calculations be considered in the final EtO Risk Assessment" (EPA 2007, at 4). In the 2013 draft IRIS assessment, however, EPA states that it "considered this suggestion but judged that the support for a nonlinear approach was inadequate" (EPA 2013 at 4-43, EPA 2014 at 4-46).

The Cancer Guidelines state:

A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. Special attention is important when the data support a nonlinear mode of action but there is also a suggestion of mutagenicity. Depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches. (EPA 2005, at 3-22) (emphasis in original).

The Cancer Guidelines refer to chemicals with direct mutagenic activity as "generally considered to be linear" (EPA 2005, at 3-21). However, this does not mean that EPA must use a linear approach if the science does not support it.¹ By contrast, EO genetic toxicity data indicate the EO assessment should at least consider both linear and nonlinear modes-of-action, in accordance

¹ The Cancer Guidelines state: "These cancer guidelines are intended as guidance only. They do not establish any substantive "rules" under the Administrative Procedure Act or any other law and have no binding effect on EPA or any regulated entity, but instead represent a non-binding statement of policy. EPA believes that the cancer guidelines represent a sound and up-to-date approach to cancer risk assessment, and the cancer guidelines enhance the application of the best available science in EPA's risk assessments. However, EPA cancer risk assessments may be conducted differently than envisioned in the cancer guidelines for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment. The science of risk assessment continues to develop rapidly, and specific components of the cancer guidelines may become outdated or may otherwise require modification in individual settings" (EPA 2005, at 1-2 to 1-3).

with the Cancer Guidelines. Moreover, as discussed in Dr. Albertini's comments, EO should be considered a weak mutagenic substance, further justifying the inclusion of both linear and nonlinear modes of action.

EPA should follow the recommendation that both linear and nonlinear calculations be considered in the EO assessment.

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

EPA has misinterpreted Marsden et al. (2009) to support linearity of risk at low doses. The 2013 draft IRIS assessment states:

Using sensitive detection techniques and an approach designed to separately quantify both endogenous N7-HEG adducts and "exogenous" N7-HEG adducts induced by EtO treatment in rats, Marsden et al. (2009) reported increases in exogenous adducts in DNA of spleen and liver consistent with a linear dose-response relationship ($P < 0.05$) down to the lowest dose administered (0.0001 mg/k injected i.p. daily for 3 days) (EPA 2013, at 3-29 to 3-30; EPA 2014, at 4-79).

This statement, however, applies only to exogenously derived N7-HEG adducts. Figure 2 in Marsden et al. (2009) shows that the total level of N7-HEG adducts (endogenous + exogenous) only becomes significantly greater than the level of endogenous adducts alone at the highest doses of EO administered.

Appendix A provides the details of a statistical review of the results in Marsden et al. (2009). For all study endpoints (liver, spleen, and stomach), there are no statistically significant differences between the response level in the control group and the response level in the lower dose groups (for the lowest 3 doses for liver, the lowest 2 doses for spleen, and the lowest dose for stomach). Furthermore, in the 2013 draft IRIS assessment, EPA does not address the authors' major conclusion: "In summary, by using a dual-isotope approach combining HPLC-AMS with LC-MS/MS analysis, we have provided evidence supporting a linear dose-response relationship for the major EO DNA adduct after exposure to low occupationally relevant doses. More importantly, we have proven that the extent of damage arising from this route is insignificant compared with the background level of N7-HEG naturally present" (Marsden et al. 2009, at 3058). Therefore, Marsden et al. (2009) does not support linearity of risk at low EO doses.

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Appendix A

Statistical Review of the Results in

Debbie A. Marsden, Donald J. L. Jones, and Robert G. Britton et al. (2009). Non-Linearity of N7-(2-Hydroxyethyl) Guanine Induced by Low-Dose [¹⁴C]Ethylene Oxide: Evidence for a Novel Mechanism of Endogenous Adduct Formation. Cancer Res, 69:3052-3059 (attached).

The data on adducts per 10¹² nucleotides as extracted from Marsden et al. (2009) are shown in Table 1.

Table 1. Levels of endogenously and exogenously derived DNA adducts in tissues of [¹⁴C]EO-treated rats measured by LC-MS/MS and AMS, respectively

[¹⁴ C]EO dose (mg/kg)	[¹⁴ C]N7-HEG levels of DNA adducts per 10 ¹² nucleotides (mean ± SE)*		
	Liver	Spleen	Stomach
Control	16 ± 9	8 ± 5	0 ± 0
0.0001	25 ± 13	22 ± 5	0 ± 0
0.0005	55 ± 28	22 ± 10	27 ± 7*
0.001	649 ± 509	1068 ± 126*	419 ± 73
0.005	445 ± 104*	612 ± 138	617 ± 360
0.01	3616 ± 392	2931 ± 1091	843 ± 30
0.05	9760 ± 1673	12023 ± 2214	18800 ± 6402
0.1	38857 ± 5154	23967 ± 1659	17215 ± 4361

NOTE: Values are the mean ± SE for three rats per group. For the [¹⁴C]N7-HEG adducts only, formed by direct reaction of [¹⁴C]EO with DNA, the first level of damage identified as being significantly higher than the background radiocarbon in control animals is designated by * (P < 0.05). The highlighted cell for each organ indicates the lowest dose that is consistent with a positive trend.

Table 2. Significance levels for the comparison of each dose group to the controls using a one sided t-test

[¹⁴ C]EO dose (mg/kg)	Significance level for a two-sample one-sided t-test comparing the mean [¹⁴ C]N7-HEG levels to the controls		
	Liver	Spleen	Stomach
Control	na	na	na
0.0001	0.2998	0.0594	0.5000
0.0005	0.1277	0.1394	0.0091
0.001	0.1408	0.0005	0.0023
0.005	0.0074	0.0060	0.0809
0.01	0.0004	0.0276	<0.0001
0.05	0.0022	0.0028	0.0213
0.1	0.0008	0.0001	0.0084

Table 3. Significance levels for the slope of the linear least squares fit to all the dose groups less than or equal to each dose group

[¹⁴ C]EO dose (mg/kg)	Significance level for a trend test that includes the [¹⁴ C]N7-HEG levels at and below each dose group		
	Liver	Spleen	Stomach
Control	na	na	na
0.0001	na	na	na
0.0005	0.0204	0.5456	0.1210
0.001	0.0958	0.1163	0.0929
0.005	0.3412	0.4327	0.0506
0.01	0.0103	0.0144	0.0105
0.05	0.0001	<0.0001	<0.0001
0.1	0.0001	<0.0001	0.0019

In Table 1 the NOAEL is 0.001, 0.0005 and 0.0001 mg/kg/day based on the liver, spleen and stomach, respectively. The same NOAELs occur in Table 2. Note that the results of the tests reported in Table 1 compared the mean in the dose group with the mean of all the levels below the dose group as opposed to the results in Table 2 that compared the mean in each dose group to the mean in the control group.

From Table 3, it can be concluded that there is no statistically significant trend (at the 5% significance level) for doses below 0.005 mg/kg/day for any of the three organs, suggesting a possible threshold between 0.005 and 0.01 mg/kg/day. The results in Table 3 show that the following statement on page 3-29 of the 2013 draft IRIS assessment is inaccurate:

Marsden et al. (2009) reported increases in exogenous adducts in DNA of spleen and liver consistent with a linear dose-response relationship ($p < 0.05$), down to the lowest dose administered (0.0001 mg/kg injected i.p. daily for 3 days).

A similar discussion appears in the 2014 draft IRIS assessment at page 4-79.

Table 4. Significance levels for the increase in the coefficient of determination (r^2) of different polynomial models with one higher degree fit to all dose groups using least squares

Degree of Polynomial	Liver		Spleen		Stomach	
	r^2	p-value	r^2	p-value	r^2	p-value
1	0.9425	0.0001	0.9976	<0.0001	0.8222	0.0019
2	0.9937	0.0008	0.9976	0.9961	0.9634	0.0045
3	0.9985	0.0163	0.9976	0.9906	0.9994	0.0001

Table 4 shows that for liver and spleen, the quadratic model fits the data statistically significantly better than the linear model. However, the quadratic model fit to the stomach levels is concave when all the data are included. However, the model is far from being linear.

Figure 1. Relationship between [^{14}C]EO dose and level of exogenous [^{14}C]N7-HEG formed in rat liver tissues. Points, mean of three animals per treatment group; bars, SE

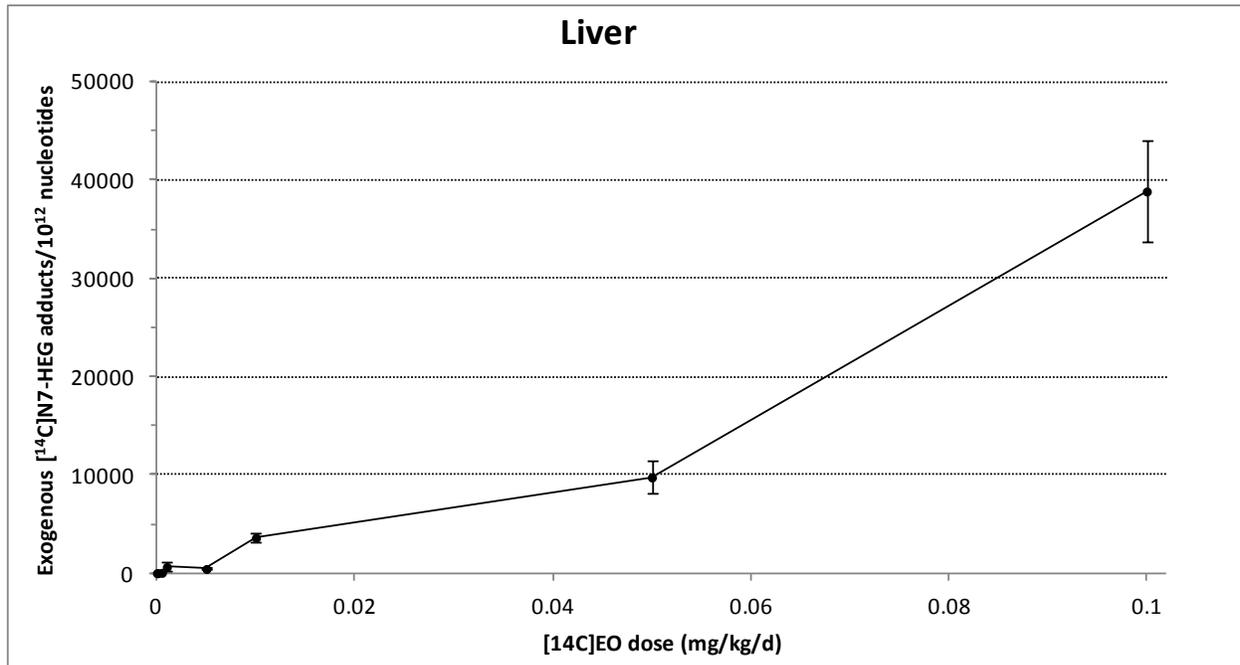


Figure 2. Relationship between [^{14}C]EO dose and level of exogenous [^{14}C]N7-HEG formed in rat spleen tissues. Points, mean of three animals per treatment group; bars, SE

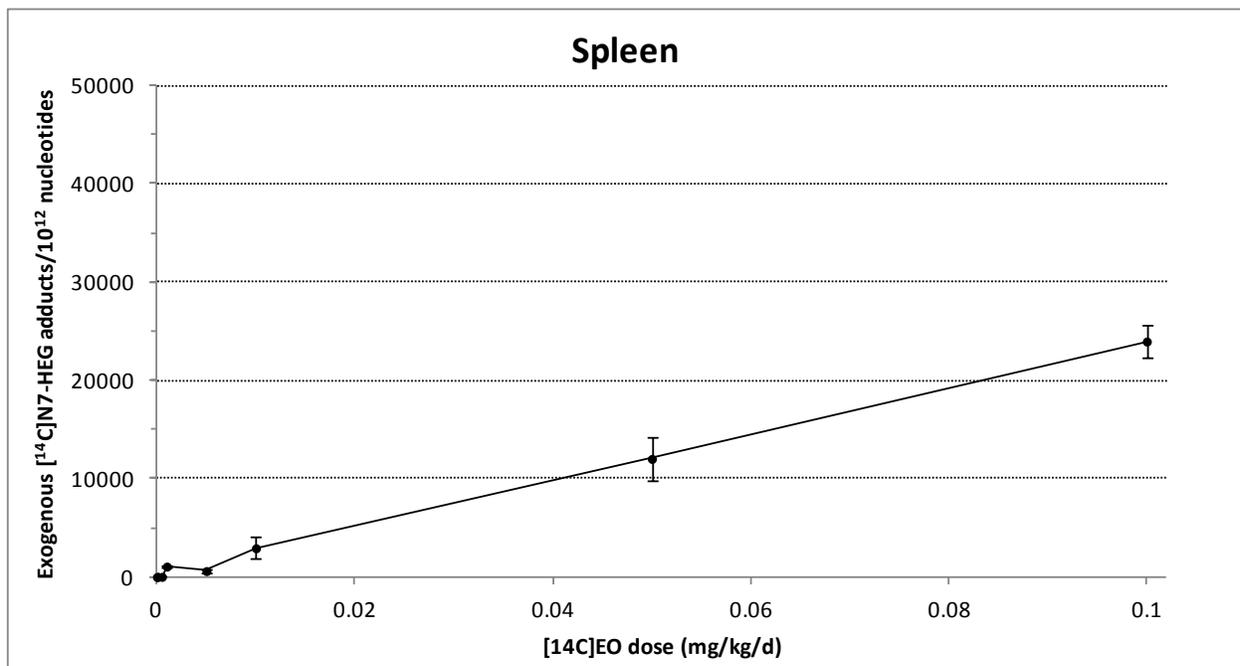
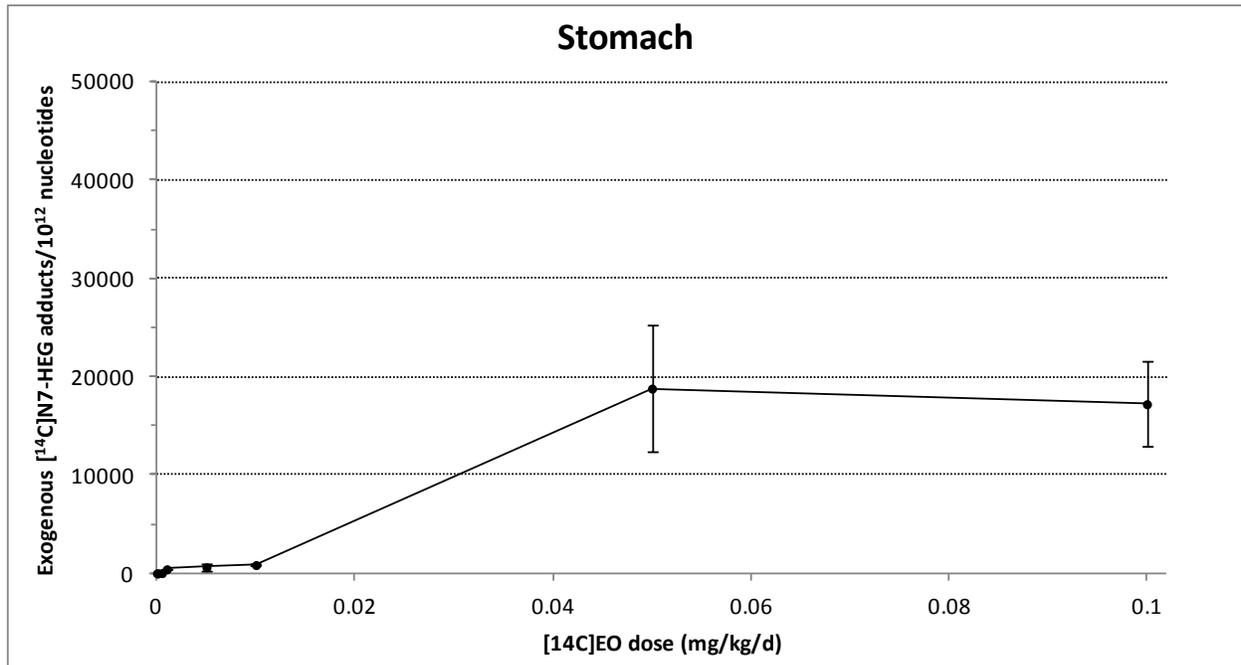


Figure 3. Relationship between [¹⁴C]EO dose and level of exogenous [¹⁴C]N7-HEG formed in rat spleen tissues. Points, mean of three animals per treatment group; bars, SE



American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #6
October 2014

Charge Question #6: Please comment on the completeness and clarity of the appendix describing major new studies published since the first external review draft but not included in the revised assessment (Appendix J) and on the conclusion presented in that appendix that the inclusion of these new studies would not substantially alter the hazard or quantitative findings of the assessment.

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 response in Appendix J.3.1. As part of the public docket we submitted "Comments from Robert L. Sielken, Sielkin [sic] & Associates Consulting - Appendix J." 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.

See related attachments:

1. Valdez-Flores and Sielken (2013).pdf
2. Final_Supplementary_Material_for_Valdez-Flores_and_Sielken_2013.pdf
3. EPA's_Appendix_J_3_1_with_SA_Comments_Added-Final.pdf

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American Chemistry Council Ethylene Oxide Panel
Supplemental Information Related to Charge Question #7
October 2014

Charge Question #7: EPA solicited public comments on a July 2013 public comment draft of the IRIS carcinogenicity assessment of EtO and has revised the assessment to respond to the scientific issues raised in the comments. A summary of the major public comments and EPA's responses are provided in Appendix L. Has EPA adequately addressed the scientific issues raised in the public comments? For example, please comment on EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a total cancer unit risk estimate.

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.

The "lymphoid" category includes a large number of diverse cancers. An approach that combines breast and lymphoid cancers is inconsistent with the NIOSH studies where women showed some association with breast cancer in the highest exposure category, but had no increase in "lymphoid" tumors. Restricting exposure to a 1-in-a-million risk for the category with the greatest unit risk would result in less than a 1-in-a-million risk for the other disease category, making combining the two unit risks unnecessarily conservative.

There is no cogent biological rationale to conclude that lymphoid neoplasms, comprised of either B- or T- lymphocytes at any level of maturity, share common origins with carcinoma of the breast or any somatic cell. The differential embryology of these various tissues is outlined in the material prepared by Drs. Iron and Albertini.

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

We question why EPA did not model the **combined** response directly from the individual data rather than model the two **separate** responses and then try to combine the two separate results. It makes a difference.

EPA combines the 95% UCL on the unit risk estimate for breast cancer incidence and the 95% UCL on the unit risk estimate for lymphoid neoplasm incidence. Although the mathematical rationale to calculate the 95% UCL on the combined unit risk estimate is correct, provided some assumptions are met, there are several issues that make the combination of the individual risk estimates invalid.

1. Accounting for Competing Risks. Combining unit risks calculated using separate life-table analyses leaves out part of the effect of competing risks. For example, EPA has inadvertently double counted the risk of the incidence by allowing that a person with in-situ or invasive breast cancer be counted as a person at risk of lymphoid neoplasm, and vice versa. This results in an

exaggeration of the risk that depends on the frequency of the co-occurrence of breast cancer and lymphoid neoplasm.

2. Different Background Populations at Risk. The unit risk for in-situ and invasive breast cancer is an estimate for the US female population. In contrast, the unit risk for lymphoid neoplasm is an estimate for the US male and female populations combined. In addition to inappropriately accounting for competing risks (item 1 above), the life-table analyses for the two endpoints apply different distributions of the competing risks in the calculation of extra risks. The assessment then combines a unit risk factor for the US female population (in situ and invasive breast cancer) with a unit risk factor for the US male and female population (lymphoid neoplasm).

3. Incidence vs. Mortality. Risk estimates for the two endpoints are based on different assumptions. The risk estimates based on breast cancer incidence are based on a model for breast cancer incidence. The risk estimates for the lymphoid neoplasm incidence, however, are based on a model for lymphoid mortality and an assumption that the exposure-response relationship for incidence is the same as the exposure-response relationship for mortality. The specific relationship between the underlying exposure-response model for lymphoid neoplasm incidence and the underlying exposure-response model for lymphoid neoplasm mortality is unknown; however, a mortality model and incidence model can be significantly different.

For breast cancer and the 2014 draft IRIS Assessment, the unit risks based on incidence are 1.04 to 3.39 times greater than the unit risks based on mortality.

	Slope ^a (S.E.)	EC ₀₁ ^b	LEC ₀₁ ^b	Unit Risk ^b for Incidence	Ratio ^c Unit Risks
Model for breast cancer mortality and risk estimates for breast cancer mortality					
Linear regression of categorical results, excluding the highest exposure quartile	0.000201 (0.000120)	0.0387 ^b	0.0195 ^b	0.513 ^b	na
Model for breast cancer incidence and risk estimates for breast cancer incidence					
Full Incidence Cohort: Linear regression of categorical results, excluding the highest exposure quintile	0.0000264 (0.0000269)	0.0503	0.0188	0.532	1.04
Sub-cohort with Interviews: Linear regression of categorical results, excluding the highest exposure quintile	0.0000517 (0.0000369)	0.0257	0.0118	0.847	1.65
Sub-cohort with Interviews: 2-piece linear spline (knot at 5,800 ppm × days)	0.000119 (0.0000677)	0.0112	0.00576	1.74	3.39

^aTable 4-8 for mortality model and Table 4-11 for incidence models

^bTable 4-9 for mortality model and Table 4-13 for incidence models

^cRatio Unit Risks = unit risk based on model for breast cancer incidence to unit risk based on model for breast cancer mortality

4. Exposure-response model. The model used for the exposure response model of lymphoid neoplasm is a linear model fit to the summary categorical results after excluding the highest exposure quartile (Table 4-3). For breast cancer incidence, however, EPA uses a 2-piece linear spline (knot at 5,800 ppm×days) fit to the individual data. EPA combines the unit risk factors calculated from very differently shaped models thereby increasing the uncertainty in the estimates of risk.

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