Comments to the U.S. EPA SAB Ethylene Oxide Review Panel Reviewing the Agency's Draft Assessment "Evaluation of the Carcinogenicity of Ethylene Oxide"

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1. EPA's draft risk assessment grossly over predicts the observed number of lymphohematopoietic cancer mortalities in the NIOSH study upon which the assessment is based.

In NIOSH data on individual subjects made available to Sielken & Associates

-- 7,634 male workers with exposure data and known birth date

-- 37 observed lymphohematopoietic (LH) cancer mortalities

-- 34.4 expected # of lymphohematopoietic (LH) cancer mortalities
using 1990 US male background survival and LH cancer mortality rates

-- 2.6 = 37 - 34.4 = observed excess # of LH cancer mortalities

-- 334.7 = expected # using the 95% upper confidence limit
(0.000760 per ppm-day) on the slope in EPA's linear regression

-- 300.3 = 334.7 - 34.4 = expected excess using EPA's slope

-- 115.5 = 300.3 / 2.6 > 100 fold over prediction
of excess LH cancer mortalities

2. EPA should not have relied exclusively on the male LH data without a mechanistic justification for treating males and females differently with respect to LH which EPA's analysis lacked.

In the NIOSH retrospective study,
increased risks of lymphohematopoietic (LH) cancer
were observed in males but not females,
even though the NIOSH cohort was large and diverse
and consisted of more women than men.

This discrepancy raises fundamental questions
about EPA's exclusive reliance on the male LH data.

Furthermore, from a statistical perspective,
it is invalid
to estimate a dose-response relationship
based on one population (here males)
and claim that that dose-response relationship
is applicable to a different population (here females).

If EPA wants to make an inference about
the combined population of Males & Females,
then EPA should estimate the dose-response relationship
in the combined population of Males & Females
using the combined data on Males & Females.

3. EPA's should have used the Individual Subject Data and not just Odd Ratios.

EPA's linear regression using Odds Ratios
instead of the Individual Subject Data
was mathematically FLAWED.

The Individual Subject Data provides more information than simple summary statistics like Odds Ratios.

In addition, EPA's linear regression using Odds Ratios does not include the uncertainty
in the observed response rate in the controls

Simply stated,

EPA’s use of Odds Ratios

instead of Individual Subject Data

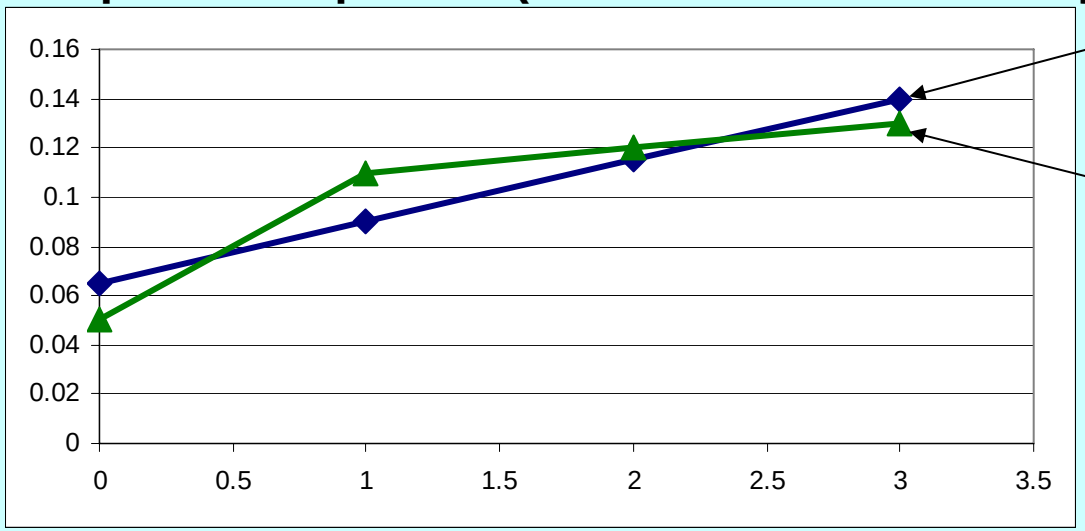
leads to invalid results

-- invalid estimates of the slope.

Illustrative hypothetical examples:

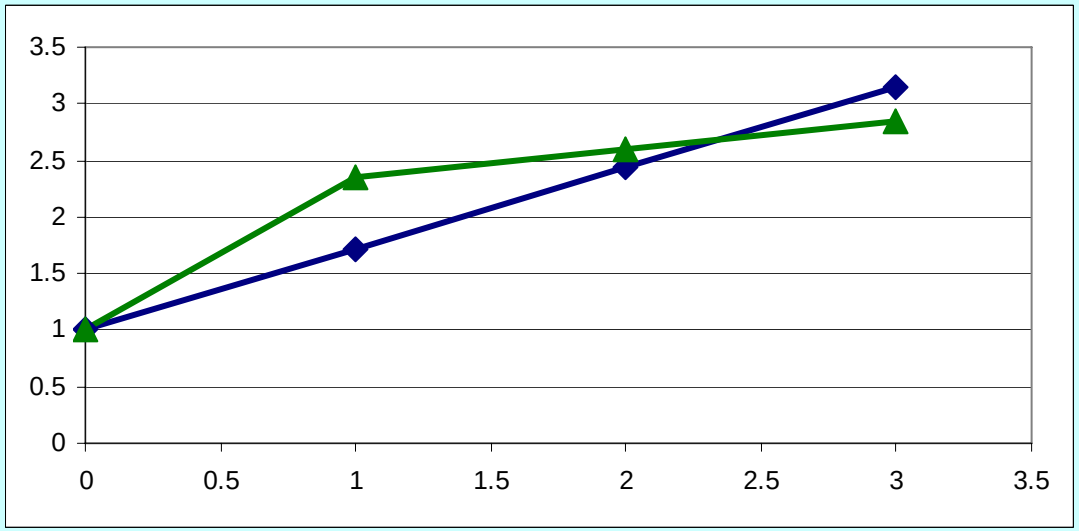
Using Individual Subject Data: slope = 0.39

Response Proportion (based on Individual Subject Data)



Using Only Odds Ratios: slope = 0.72

Odds Ratio (based on Response Proportions)



Wrong Answer:
Wrong Magnitude:
2-fold too high

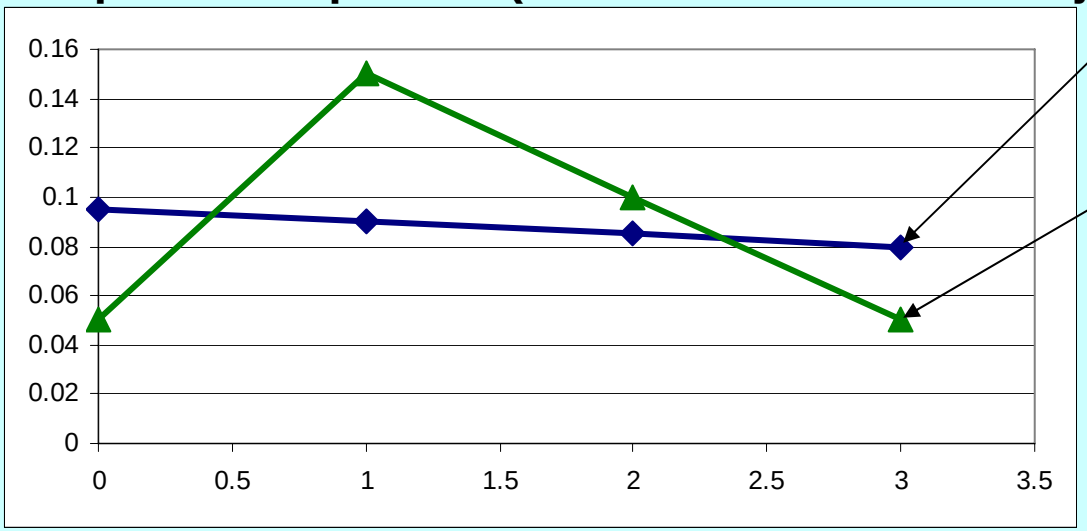
Illustrative hypothetical examples:

Using Individual Subject Data:
slope = - 0.05
Negative

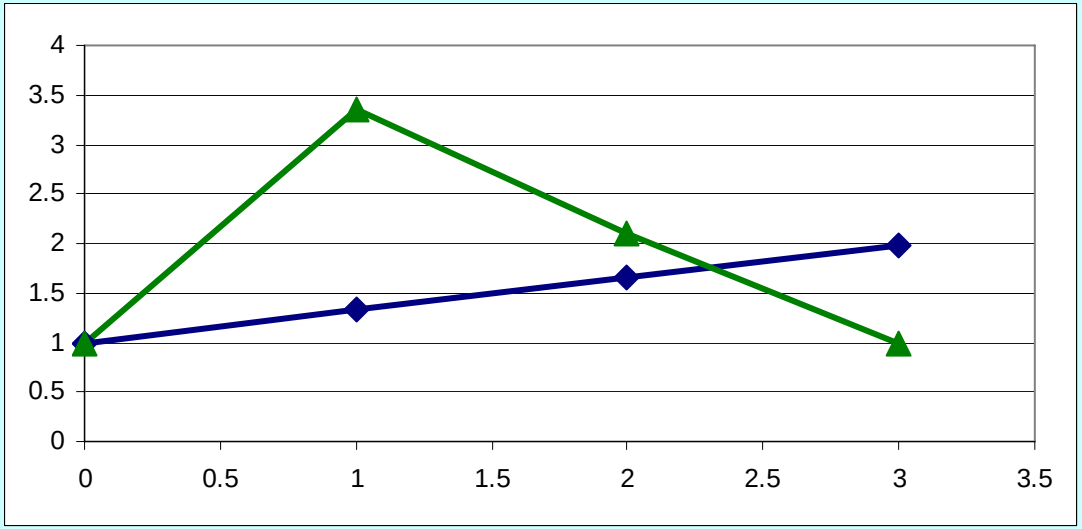
Using Only Odds Ratios:
slope = + 0.33
Positive

Wrong Answer: Positive when should have been Negative.

Response Proportion (based on Individual Subject Data)



Odds Ratio (based on Response Proportions)



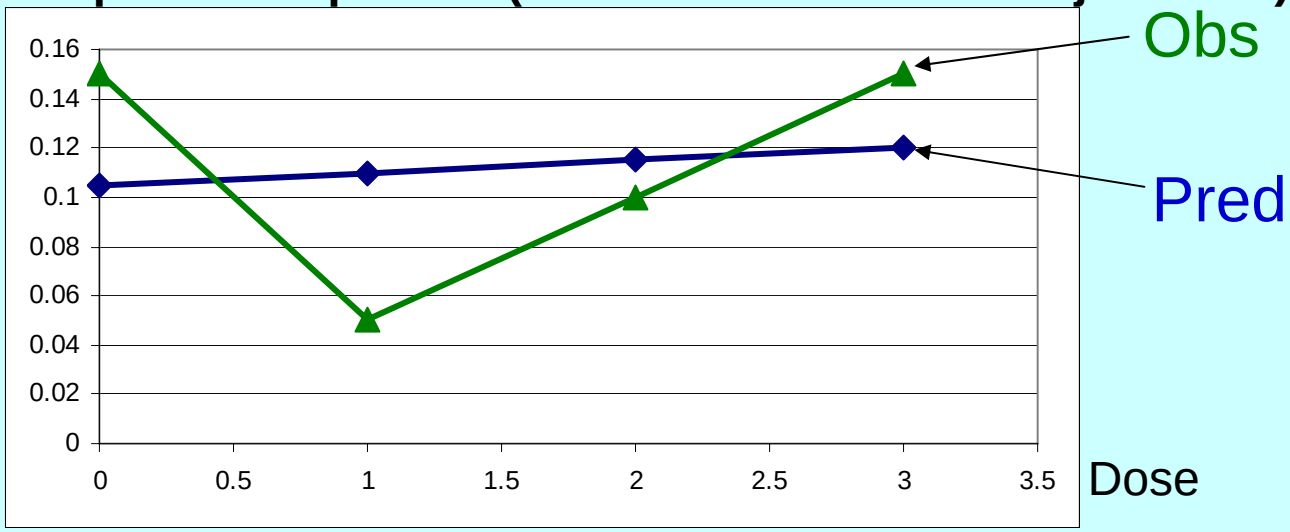
Illustrative hypothetical examples:

Using Individual Subject Data:
slope = + 0.05
Positive

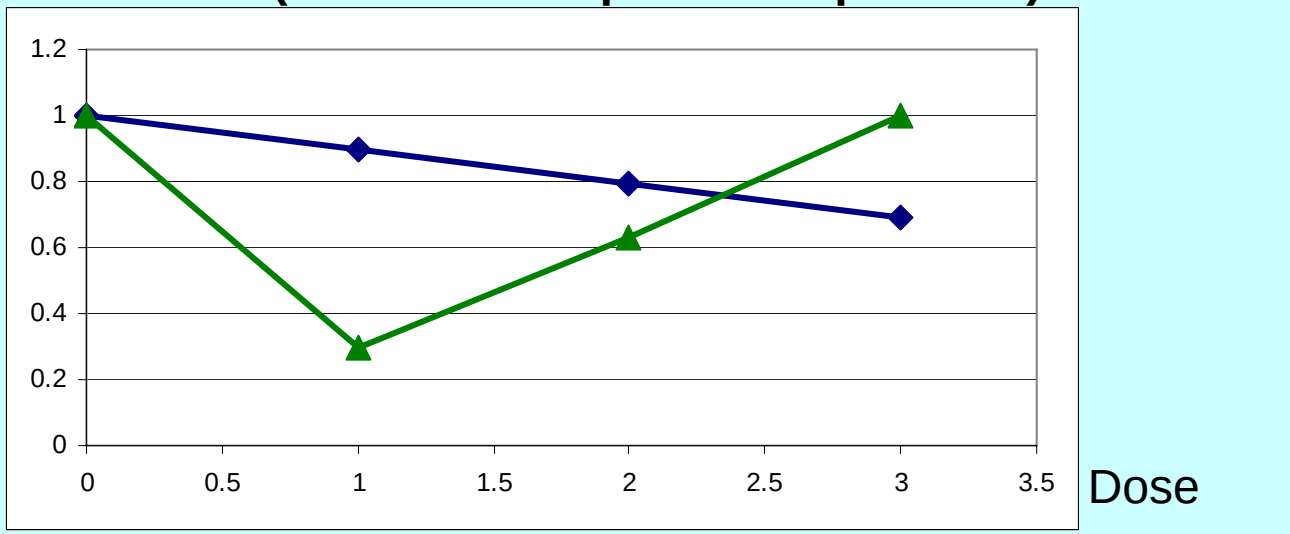
Using Only Odds Ratios:
slope = - 0.10
Negative

Wrong Answer: Negative when should have been Positive.

Response Proportion (based on Individual Subject Data)



Odds Ratio (based on Response Proportions)



4. EPA's Un-reviewed Policy Decisions implemented in the Draft Cancer Assessment are Scientifically Unsupported, Unprecedented, Overly Conservative, and Inappropriate.

Even though EPA was using human data,
EPA relied on the lower bound on the point of departure (POD),
rather than the best estimate.

Historically, when the risk assessment is based on human data,
the best estimate (e.g., EC) is used
rather than a 95% lower confidence limit (e.g., LEC).

Using the best estimate
would make the Cancer Assessment for EtO
more comparable to the Cancer Assessments
for other chemicals with human data.

Assuming an 85-year period of continuous exposure
and cumulative risk, rather than the traditional 70-year period
makes the Cancer Assessment for EtO
less comparable to the Cancer Assessments for other chemicals.

Furthermore, the dose-response modeling and
available cancer incidence and mortality data are
less stable (more uncertain) for older ages.

96% of the NIOSH workers had ceased exposures by age 70.

Only 3% of the NIOSH workers were observed at age $\geq$ 85.

5. EPA conducted a Flawed Statistical Analysis of the data.

a. EPA's rationale and methodology for exclusion of the highest exposure group are inappropriate.

b. Computational Errors:

b.1 Not only was EPA's weighted least squares regression an inappropriate methodology, but also EPA's slope and its standard error were calculated incorrectly.

b.2 EPA's spreadsheet calculation of excess risk is a mathematically incorrect implementation of the methodology of BIER IV (1988) and is mathematically inappropriate for incidence as opposed to mortality.

c. Using an ADAF for EtO is inappropriate. Furthermore, EPA's method of incorporating an ADAF does not properly incorporate age-dependence and is mathematically incorrect.

d. Using rodent data for EtO is inappropriate. Furthermore, EPA's method of estimating carcinogenic risk based on rodent data is mathematically incorrect -- the sum of 95% UCLs is not a 95% UCL, endpoints are not necessarily independent, etc.

Some Conclusions:

1. EPA's draft risk assessment grossly over predicts the observed number of lymphohematopoietic cancer mortalities in the NIOSH study upon which the assessment is based.

2. EPA should not have relied exclusively on the male LH data without a mechanistic justification for treating males and females differently with respect to LH which EPA's analysis lacked.

3. EPA's should have used the Individual Subject Data and not just Odd Ratios.

4. EPA's Un-reviewed Policy Decisions implemented in EPA's Draft Cancer Assessment are Scientifically Unsupported, Unprecedented, Overly Conservative, and Inappropriate.

5. EPA conducted a Flawed Statistical Analysis of the data.

Thank You