American Chemistry Council Ethylene Oxide Panel Comments on the OEHHA DRAFT IUR

ACC EO Panel's Toxicology Research Task Group (TRTG) and Scientific Advisory Team

July 14, 2023

Proposed Agenda

- ACC: Presentation (60 min)
- Discussion and Questions (20 min)

Overview

- Why epidemiological data and biological plausibility should be the primary basis for model selection, in contrast to EPA's reliance on statistical and visual fit
- The epidemiological data is not consistent with the low dose steep model
- Why healthy worker effect (HWE) should not be a basis to ignore epidemiological weight of evidence based on both external and internal comparisons
- Why breast cancer **incidence** should not be used for quantitative risk assessment
- The biological data is more consistent with the CPH model
- Reality checks of model selection and concluding remarks
  - Consideration of background endogenous and ambient air exposures

Why epidemiological and biological plausibility should be the primary basis for selection of model

In contrast to EPA's reliance on statistical and visual fit

Comparison of OEHHA (2023, draft)/IRIS (2016) vs. TCEQ (2020) IURs **(w/o ADAF)**

	OEHHA (2023, draft) EPA IRIS (2016) w/o ADAF	**TCEQ (2020) w/o ADAF**
Cohort	NIOSH Human (Steenland et al. 2003, 2004)	NIOSH Human (Steenland et al. 2004)
Critical Cancer endpoint	M + F **lymphoid cancer incidence derived from mortality** and **F breast cancer incidence**	M lymphoid cancer **mortality** (more conservative than M+F)
Model (with 15 year lag)	**2-piece linear spline model (2-slope model)**	**Standard Cox proportional hazard (CPH; linear in exposure range of interest)**
Age limit for life table	85 yrs	70 yrs
ADAF factor	none	none
P-Value (compared to null)	**P=0.14 (recalculated from 0.07 to include all 3 parameters)**	**P=0.3**
Point-of-departure	LEC 1/100	LEC 1/100,000
IUR (per ppm)	6.1	2.5E-03
1/100,000 RSC (ppt)	**1.7**	**4000**
References	OEHHA (2023), IRIS (2016), Steenland et al. (2003, 2004)	Steenland et al. (2003), Valdez-Flores et al. (2010), TCEQ (2020)

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The major reason for the >2000-fold difference is the model selected

EPA IRIS rationale for 2-slope model

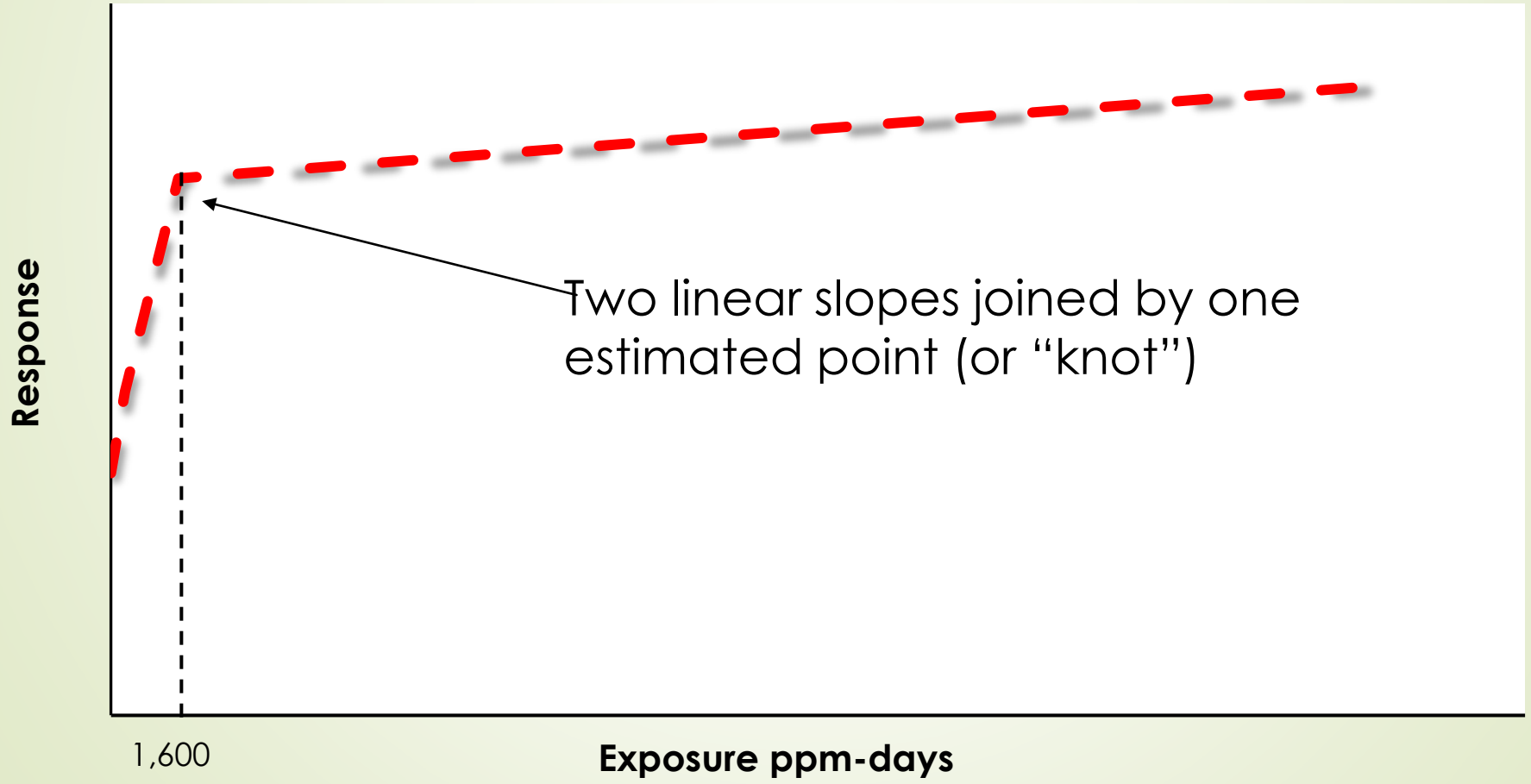
- Statistical fit
- Visual fit
- Significant log cumulative exposure models

EPAs rationale for 2-slope model

- Statistical fit with incorrect degrees of freedom
- Visual fit based on graphs not fit for purpose
- Significant log cumulative exposure models that are biologically implausible

Statistical fit with incorrect degrees of freedom

OEHHA URL is based on EPA IRIS URL
The IRIS Model is based on a 2-slope model with the initial slope steeper than the second slope (IRIS describes it as "supralinear")



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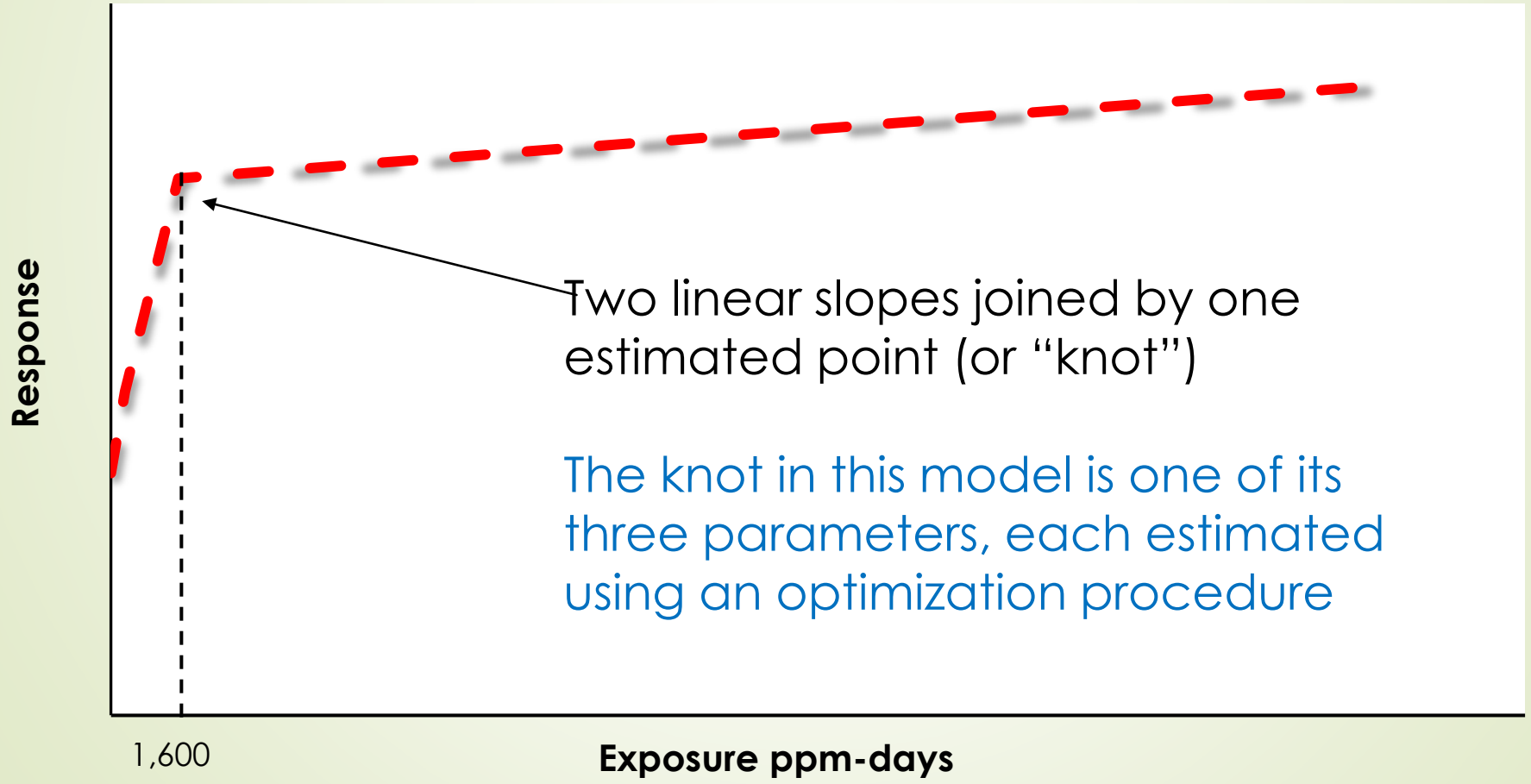
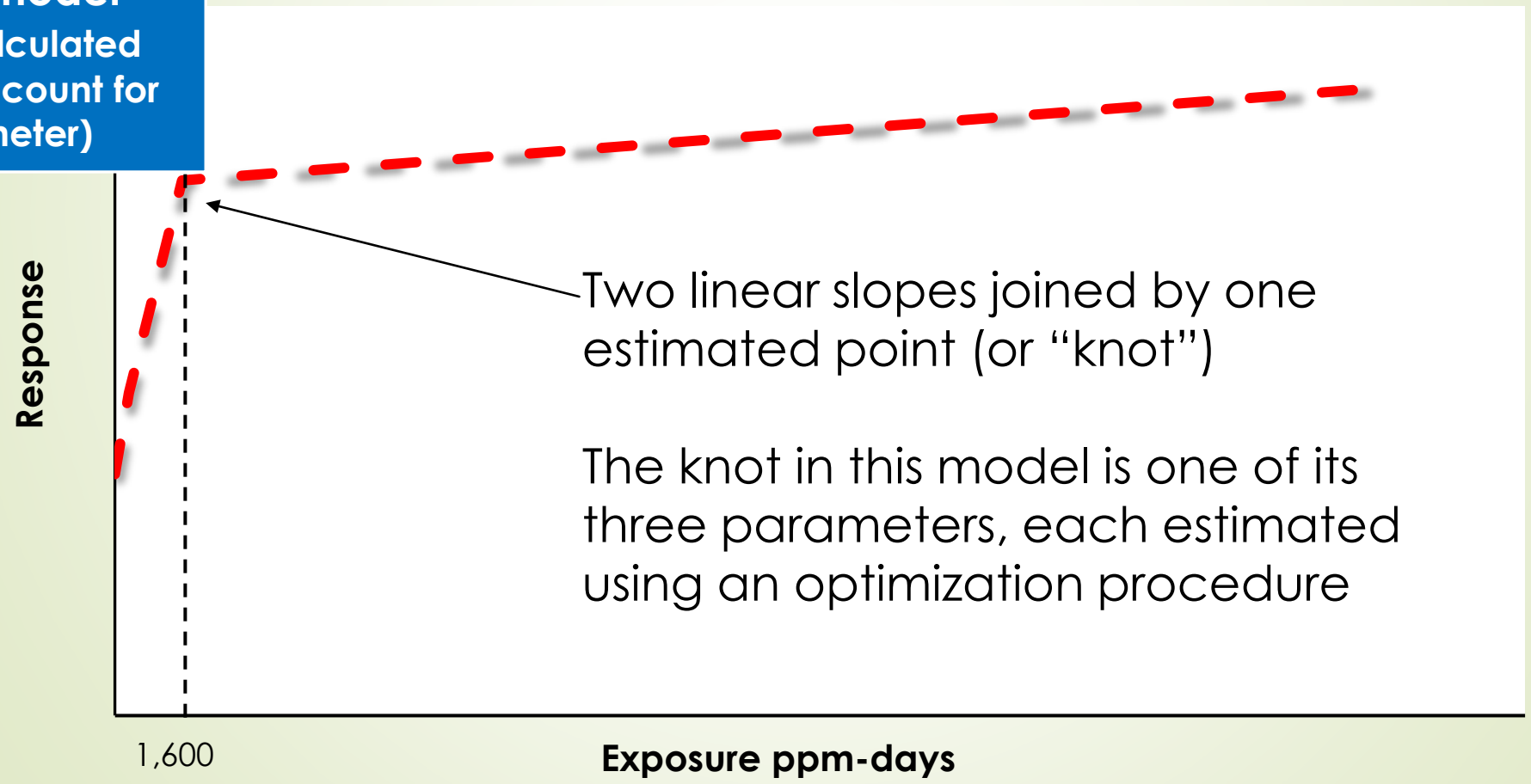


TCEQ peer reviewers with statistical modeling expertise agree the knot is a parameter and with TCEQ's correction of p-values

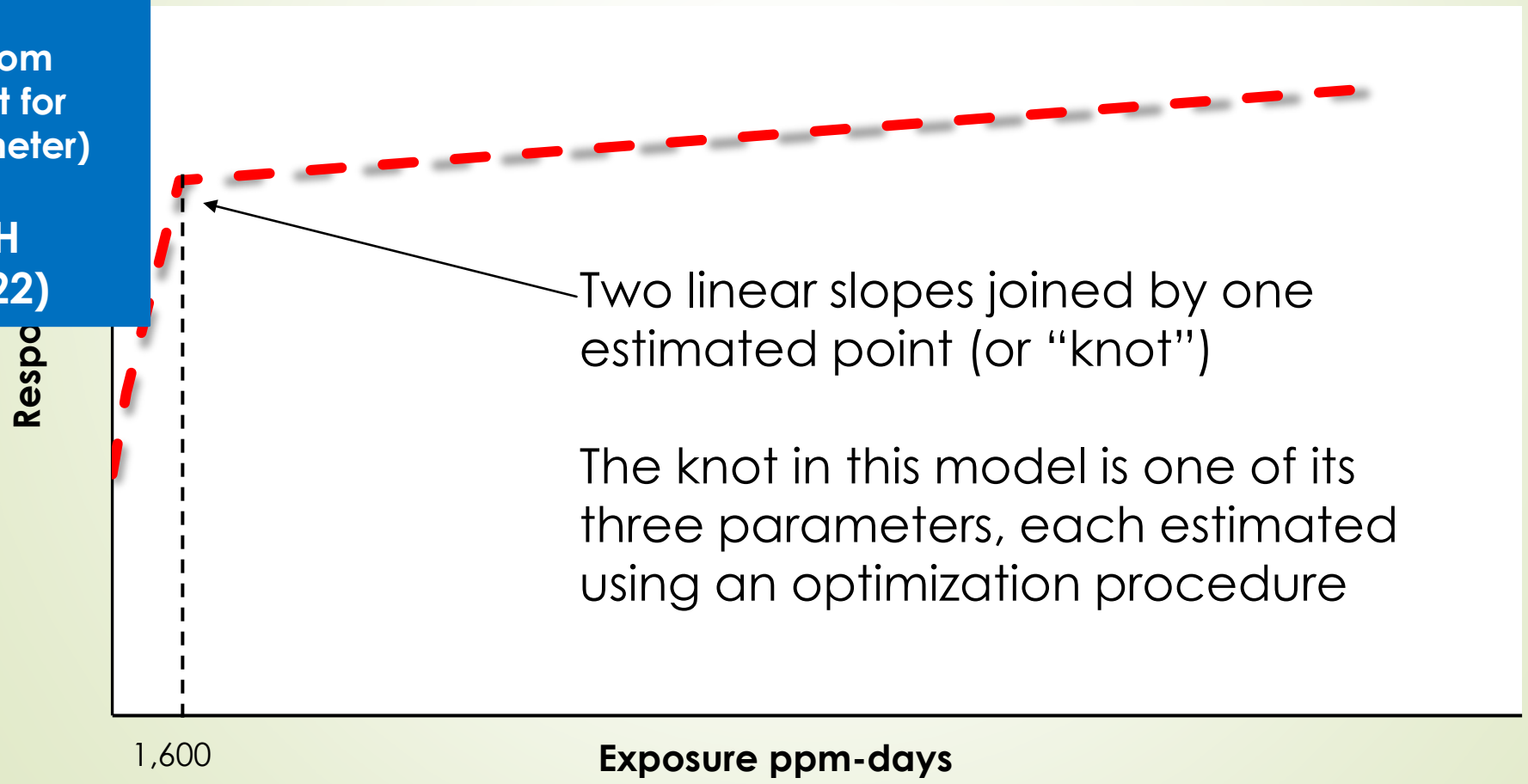
IRIS 2-slope model (p=0.14, recalculated from 0.07 to account for the knot parameter)



The p-values are similar for the 2-slope and standard CPH models

IRIS 2-slope model (p=0.14, recalculated from 0.07 to account for the knot parameter)

Standard CPH model (p=0.22)



Statistical evaluation should account for all modeled parameters

The strategy to pick the "best model" for regulatory decision making should be "*subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters versus having a parsimonious description*"

(NRC 2007 Models in Environmental Regulatory Decision Making, p. 174).

Statistically, there is no difference in p-value or AIC between the standard CPH model and the IRIS 2-slope model, but the standard CPH model is a simpler (more parsimonious) single-slope model.

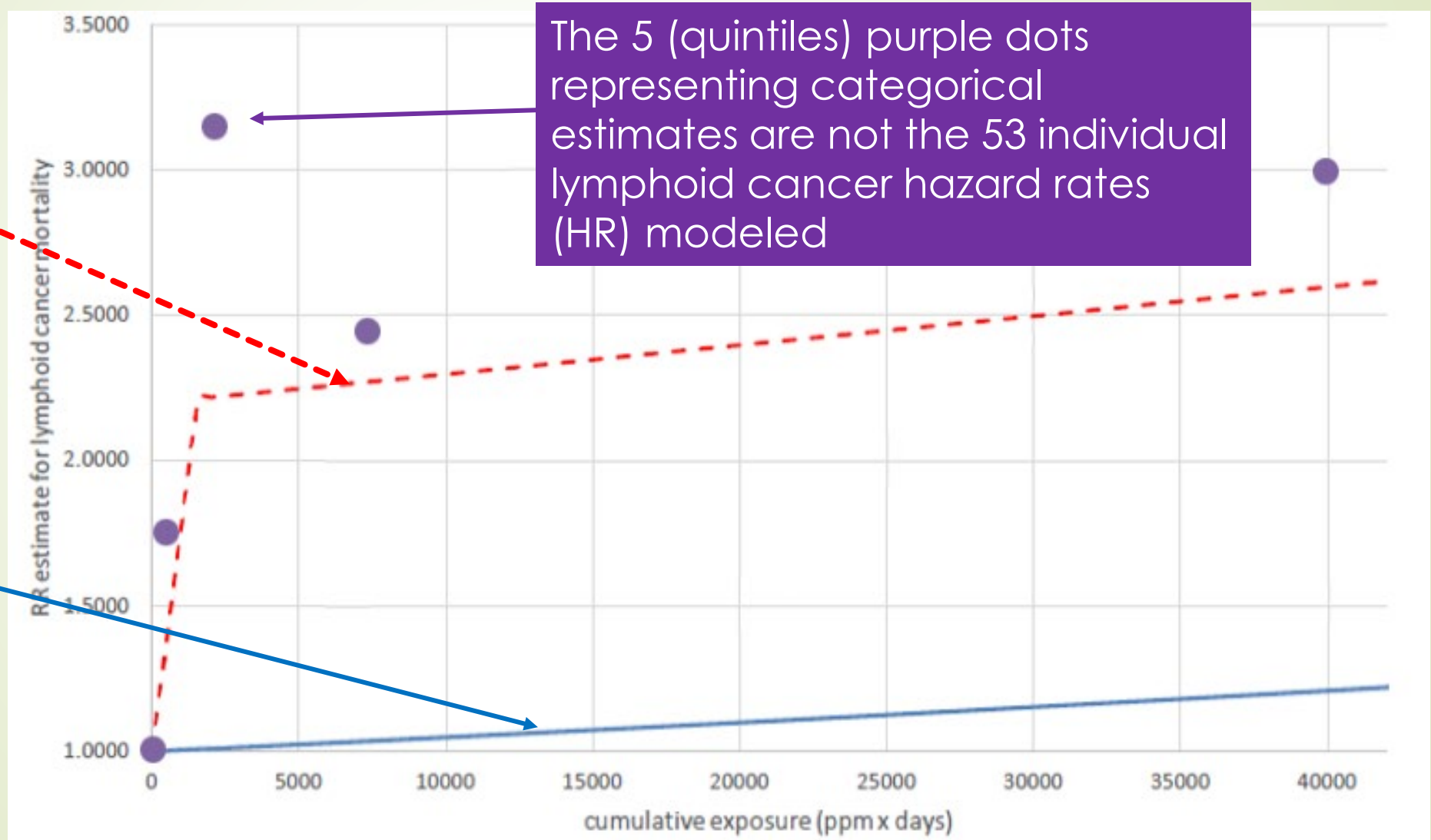
Visual fit based on graphs not fit for purpose

IRIS "visual fit" figures do not convey the actual data that were fit

IRIS 2-slope model (p=0.14)

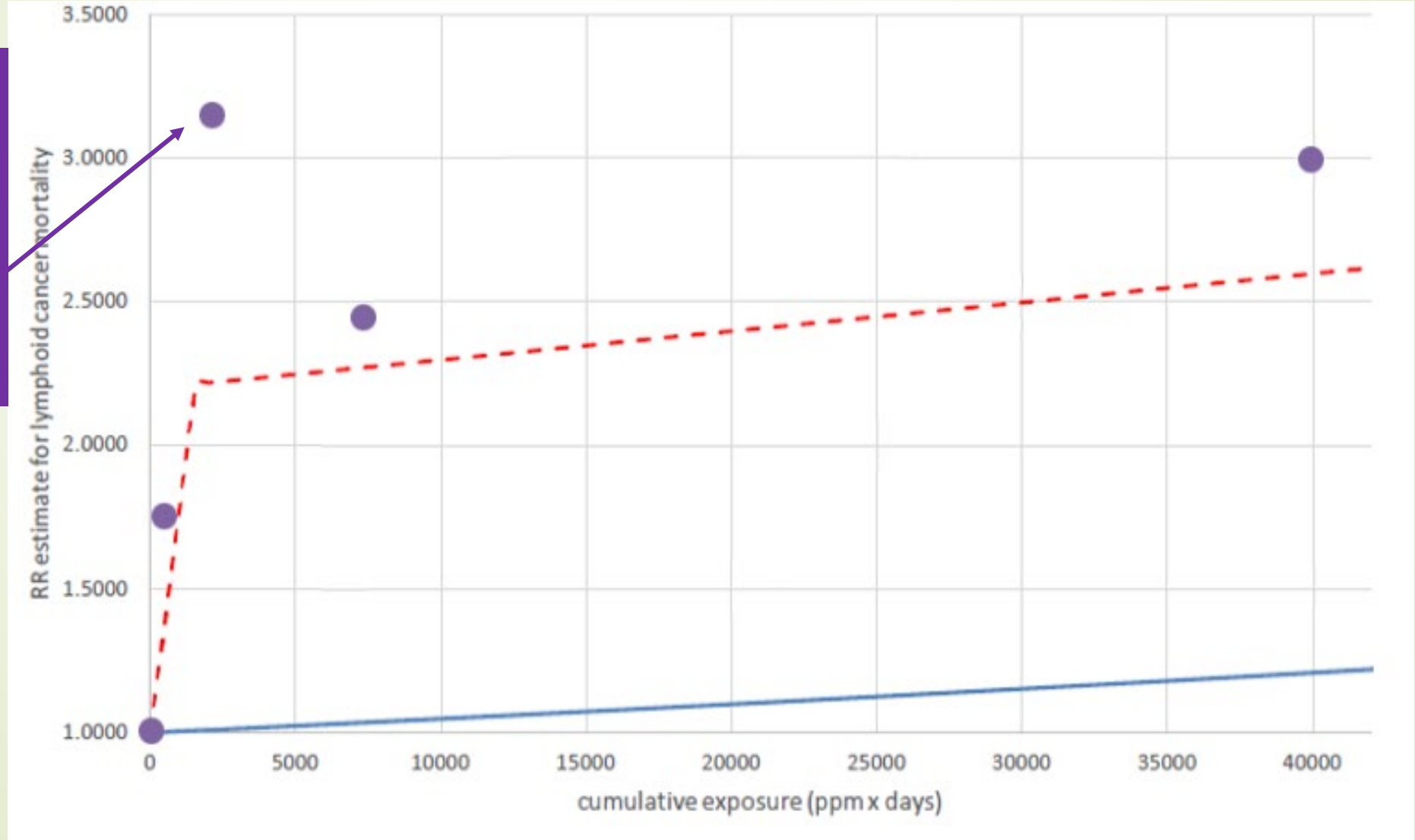
Standard CPH model (p=0.22)

The 5 (quintiles) purple dots representing categorical estimates are not the 53 individual lymphoid cancer hazard rates (HR) modeled



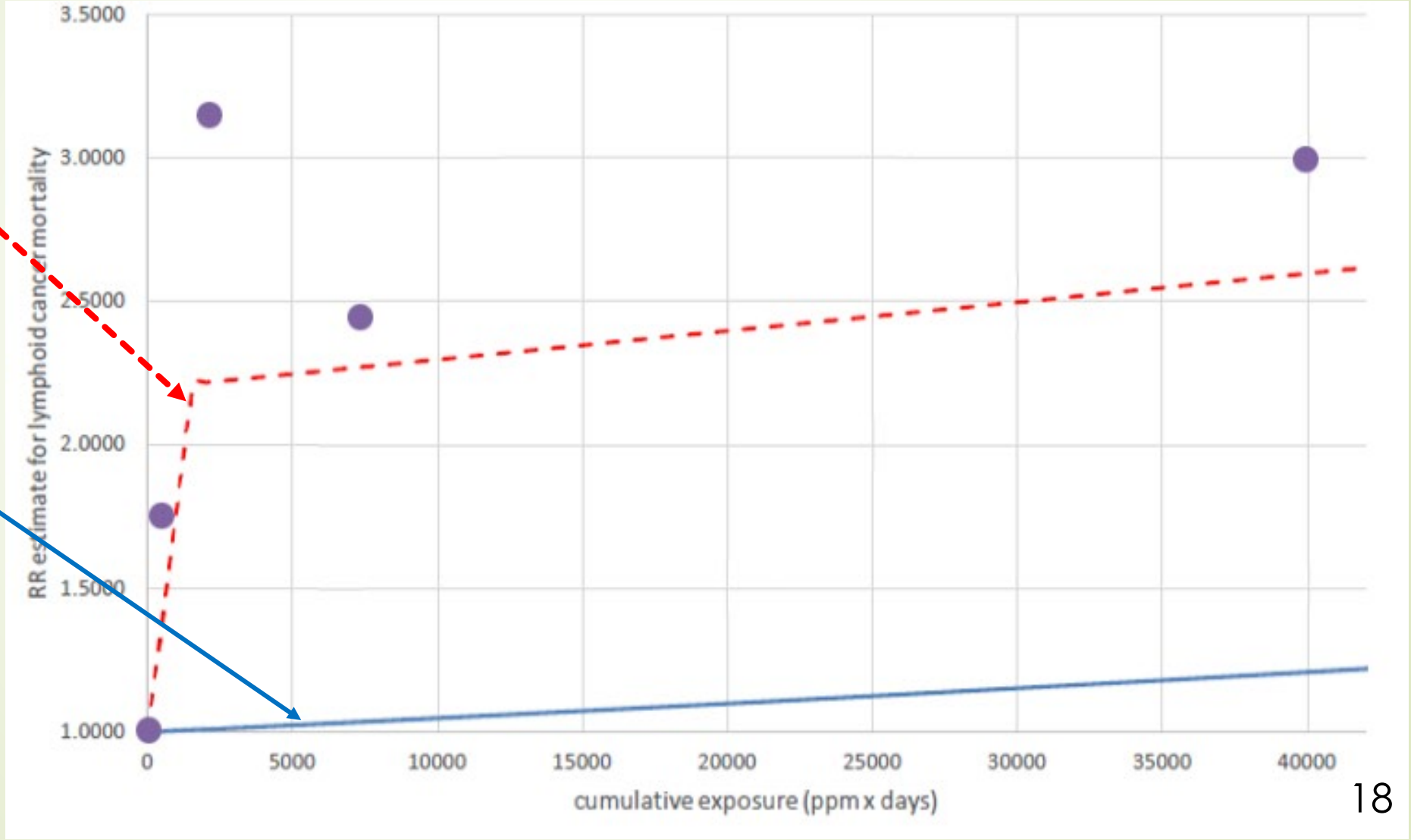
IRIS "visual fit" figures do not reflect the distinctly different male and female exposure-response pattern

Steenland et al. (2004) reported effects in males only at the highest exposure level compared to no effect in females



EPA figure legends correctly warn that comparisons along the y-axis are not appropriate

Each continuous model of *hazard rate has* a different implicit y-intercept which is then forced to 1 on graphs of relative rates

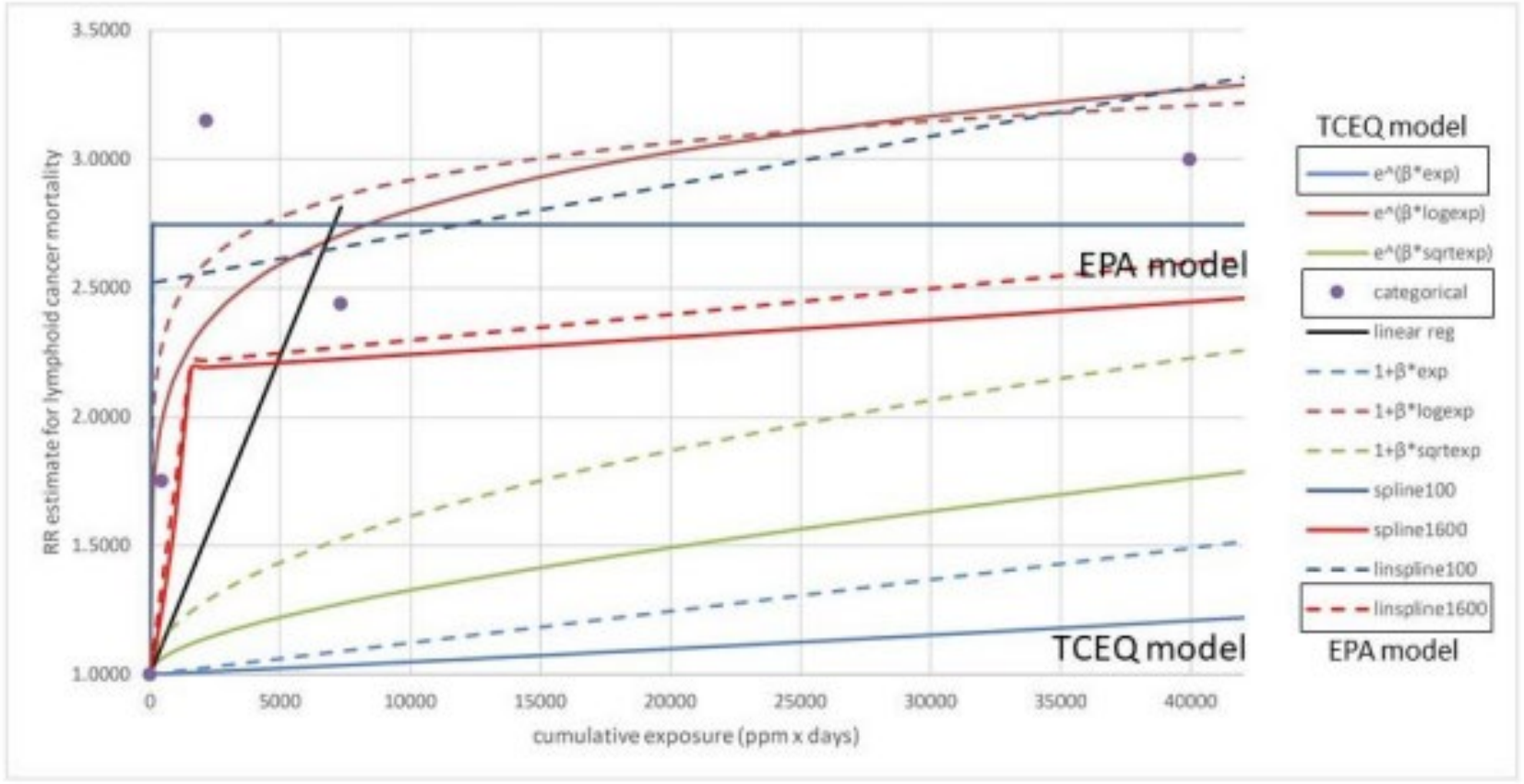


Yet, the figures give the false impression that the CPH model "underestimates" the categorical RR estimates

UCSF public comments to TCEQ (p. 15)*

"Comparing TCEQ's model, depicted by the solid blue curve near the bottom of the graph, to the nonparameteric categorical RR estimates, depicted by the filled purple circles, **shows that the model selected by the TCEQ substantially underestimates the nonparametric categorical RR estimates.** In contrast, the EPA model depicted by the dashed red line (linspline 1600) is a much better predictor of the nonparametric categorical RR estimates."

Figure from UCSF public comments to TCEQ

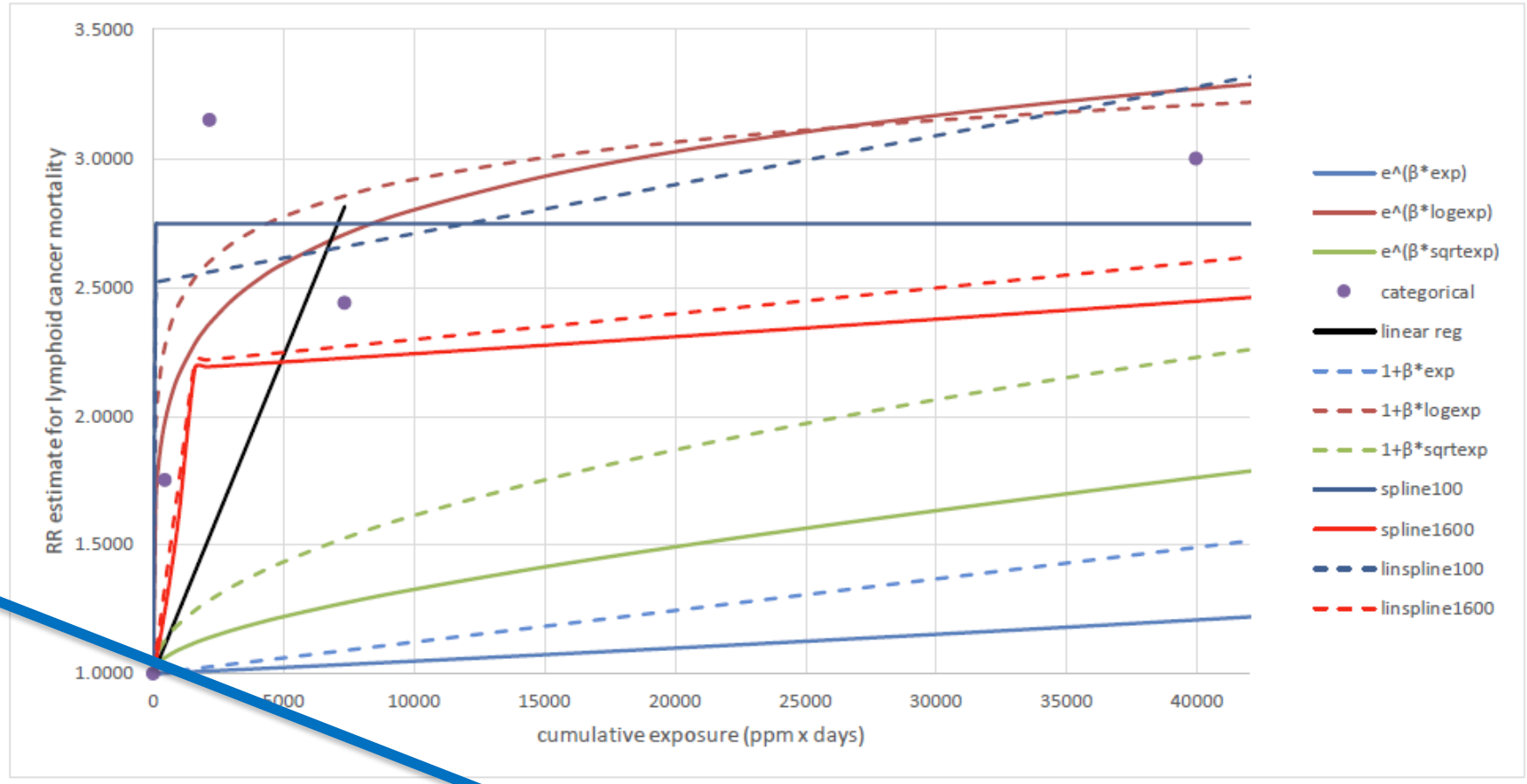


Reproduction of Figure 4-3 from EPA assessment, with black rectangles and text added to highlight TCEQ's model, the categorical RR estimates, and EPA's selected model.[54]

*TCEQ response to public comments p. 41 notes the first author is also first author of EPA IRIS (2016)

EPA IRIS (2016) note in all figure legends is easy to miss:

"Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; ***thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis."***



e^(β*exp): $RR = e^{(\beta \times exposure)}$; e^(β*logexp): $RR = e^{(\beta \times \ln(exposure))}$; e^(β*sqrtexp): $RR = e^{(\beta \times sqrt(exposure))}$; categorical: $RR = e^{(\beta \times exposure)}$ with categorical exposures, plotted at the mean cumulative exposure; linear reg: weighted linear regression of categorical results, excluding highest exposure group (see text); 1 + β*exp: $RR = 1 + \beta \times exposure$; 1 + β*logexp: $RR = 1 + \beta \times \ln(exposure)$; 1 + β*sqrtexp: $RR = 1 + \beta \times sqrt(exposure)$; spline100(1,600): Two-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text); linspline100(1,600): Two-piece linear spline model with knot at 100 (1,600) ppm × days (see text). (Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the *y*-axis. They are, however, comparable in terms of general shape.)

Source: Steenland reanalyses for males and females combined; see Appendix D (except for linear regression of categorical results, which was done by EPA).

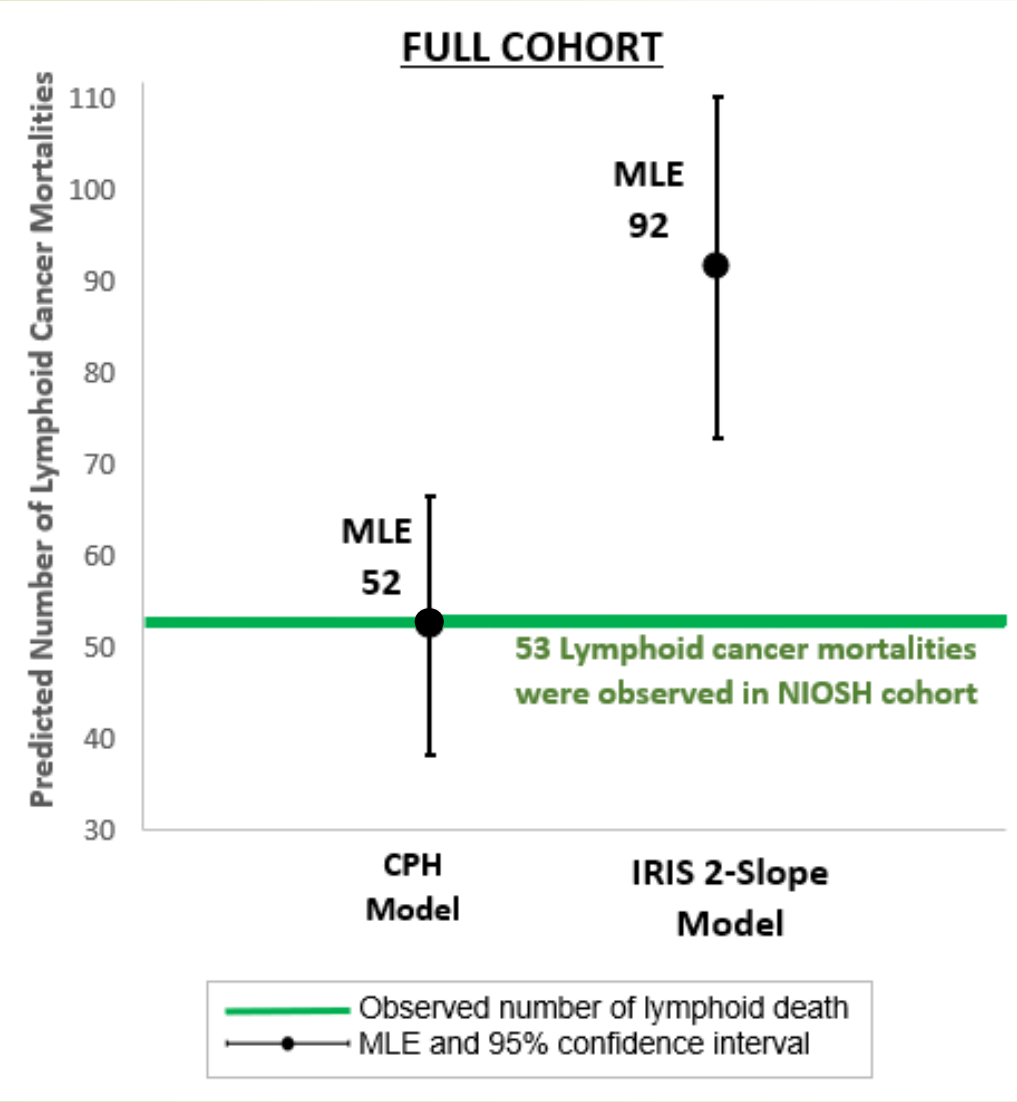
Figure 4-3. Exposure-response models for lymphoid cancer mortality vs. occupational cumulative exposure (with 15-year lag).

"Other models, including the log-linear models (e.g., Cox regression) and the models using categorical data or exposure transformations, generally resulted in slopes **that appeared to dramatically over- or under-predict the actual study results**, especially in the lower-exposure ranges"

OEHHA Draft IUR Appendix B p. 36

ACC's comments explain why conclusions about over- or under-prediction should not be made based on visual comparisons of misleading graphs not fit for this purpose.

TCEQ's Ground-truthing exercise is a more objective method than IRIS's visual fit comparisons to address how well the models predict the actual number of cancer mortalities



Results of Ground-truthing Exercise (TCEQ, 2020; Table 6 and 7)

- The CPH model prediction for the **full cohort** is more accurate than the IRIS 2-slope model

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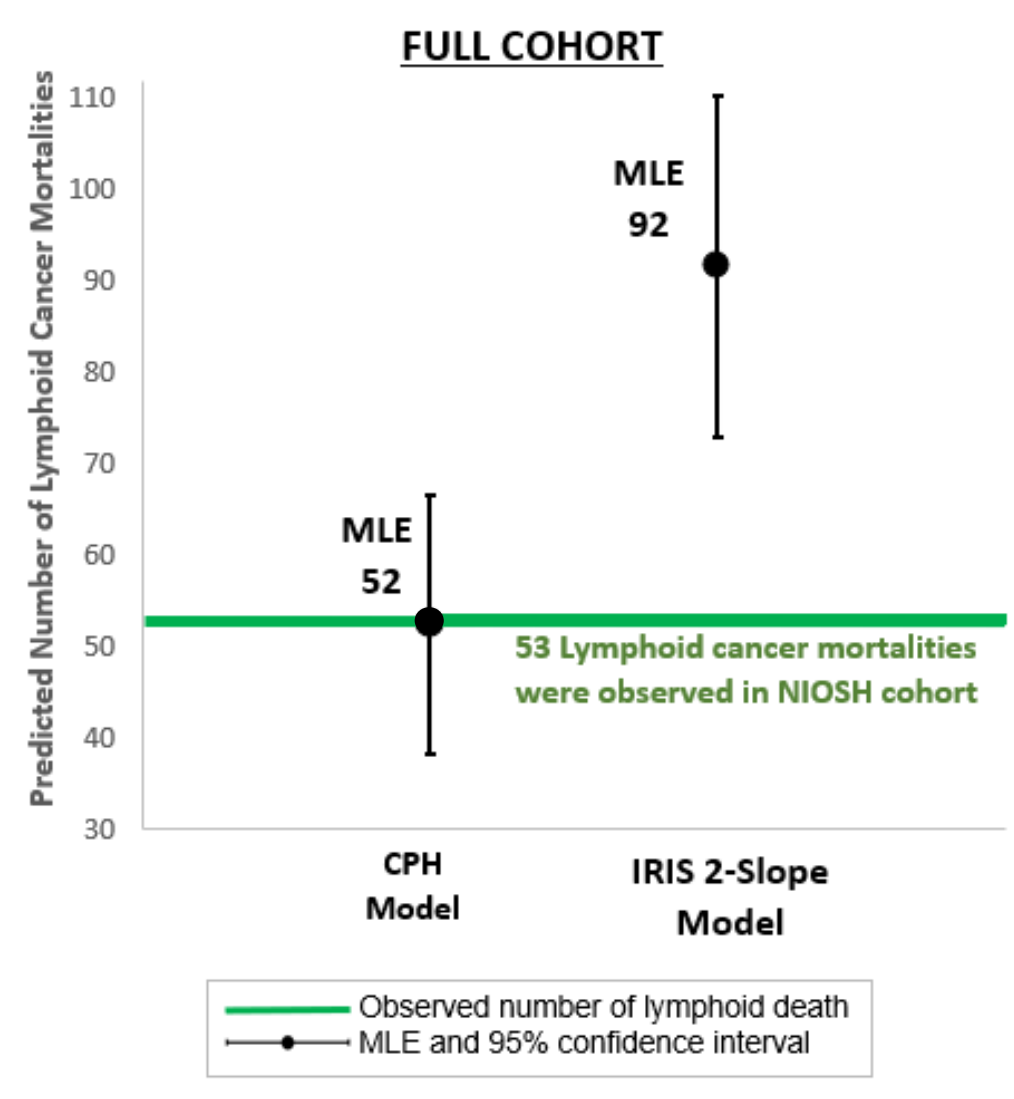

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  - HWE of 15% is included to represent differences between the NIOSH and general population
  - Different methods for calculating confidence intervals are used

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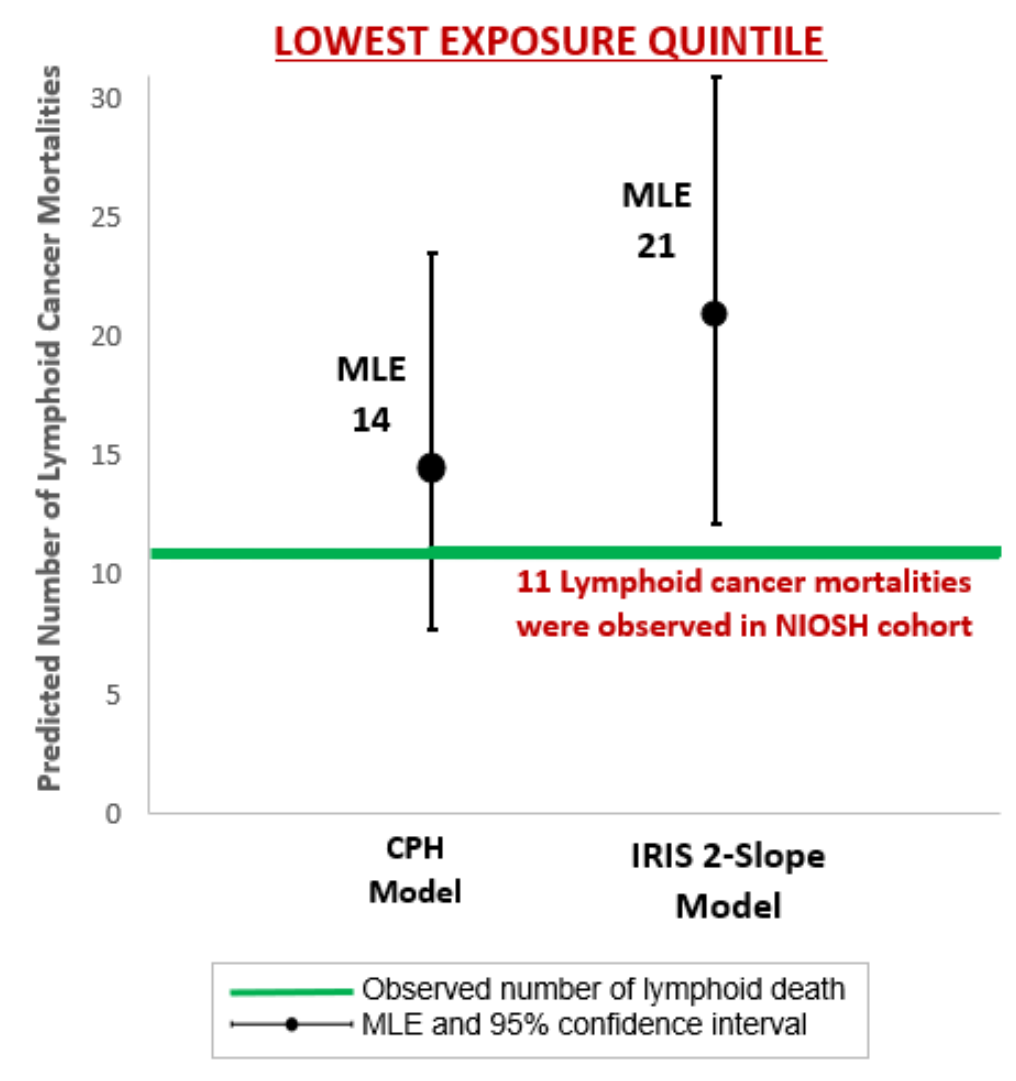

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  - HWE of 15% is included to represent differences between the NIOSH and general population (TCEQ, 2020)
  - Different methods for calculating confidence intervals are used
- The CPH model prediction is also more accurate for each exposure quintile **including the lowest exposure category (>0 to ~1550 ppm-days)**

Significant log cumulative exposure models that are biologically implausible

Log-cumulative CPH model was the only model statistically significant out of >50 model runs for each cancer in Steenland et al. (2004)

- Steenland et al. (2004) applied a large number of curve-fitting models (>50 for each cancer) in an exploratory statistical modeling exercise
  - 5 different exposure metrics (duration, average, maximum, cumulative and log cumulative)
  - 5 different lags for each exposure metric (0, 5, 10, 15, 20)
  - Males, females, and both sexes reported
- Steenland et al. (2004) reported only 3 continuous models with specific lags to be statistically significant for the mortality study.
  - **Log cumulative CPH model of lymphohematopoietic (LH) cancers in males (15-yr lag)**
  - **Log cumulative CPH model of male lymphoid cancers (15-yr lag)**
  - **Log cumulative CPH model of female breast cancer mortality (20-yr lag)**

EPA uses significant log cumulative model as the basis for supporting a supralinear 2-piece spline model

- EPA emphasis on log cumulative models as the driving force for justifying a steep exposure response model is inappropriate
  - EPA dismissed the log cumulative exposure model because it is biologically implausible, yet uses this model to support the steep 2-piece spline model
  - Log cumulative exposure models force a steep slope at low exposures based on the mathematical formula, regardless of the observed response data (Valdez-Flores et al., 2010, section 4.3)

Statistics alone is not an appropriate basis to select an exposure-response model for EtO

"*Any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.*" EPA SAB (2015)

EPA SAB's advice is consistent with the caution in the EPA (2005) Cancer Risk Assessment Guidelines on applying multiple statistical models

- *"Another problem occurs when a multitude of alternatives are presented without sufficient context to make a reasoned judgment about the alternatives.*
- *"This form of model uncertainty reflects primarily the availability of different computer models and not biological information about the agent being assessed or about carcinogenesis in general."*

Supralinear 2-Slope models and the log cumulative models are inconsistent with epidemiologic and biological evidence

- Epidemiology studies do not suggest a steep increase at low cumulative exposures, i.e., a potent carcinogen.
- Dose-response patterns for early key events for the hypothesized tumor mode of action do not support a model with a very steep initial slope.
- Taken together, the epidemiological and biological data overwhelmingly support a standard CPH cancer dose-response model used by TCEQ

Epidemiology studies do not suggest steep increase at low cumulative exposures, i.e., a potent carcinogen.

NIOSH and the UCC Data Sets of Workers Exposed to Ethylene Oxide

Endpoint (**Males only**)	NIOSH (Steenland et al. 2004)	UCC (Swaen et al. 2009)
Lymphohematopoietic Tissue	37	27
Lymphoid Tumors	27	17
Non-Hodgkin's Lymphoma	18	12
Multiple Myeloma	4	3
Leukemia	10	11
All Workers	7,634	2,063
% Deceased	19%	51%
Avg. follow-up	25 yr.	37 yr.
ppm-yr. exp.	27	67

Epidemiologic evidence does not support IRIS model of a potent carcinogen

- Most informative studies:
  - **NIOSH Sterilant workers (Steenland et al., 2003, 2004)**
    - No overall excesses in lymphoid cancer mortality or breast cancer incidence in external comparisons
    - Increased lymphoid cancer mortality for males only at highest exposure group in select internal analyses
  - **UCC Chemical workers (Swaen et al., 2009)**
    - No increased lymphoid cancer mortality in external comparisons nor in internal worker to worker comparisons
    - Additional analyses (lagged, categorical) in Valdez-Flores et al. (2010)
- *Published epidemiology data conflicts with IRIS model*

OEHHA's Erroneous Assumption of a HWE

- IARC (1999) "HWE is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce."

- NIOSH and UCC studies have very long avg. follow ups 27 and 35 yr.

- Steenland et al. (2004) notes the disappearing of the HWE in NIOSH study
  - "The healthy worker effect has diminished (all cause mortality was up to an 0.90 from the prior SMR of 0.81) as would be expected with increased follow up"

  - The authors do not use HWE to dismiss non-positive findings:

"The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons"

IRIS visual fit and unit risk analysis combined male and female data with opposing associations

	Males	Female
LH 13,500+ppm-d **SMR**	1.46 (13)	0.46 (3)
NHL SMR	1.29 (95% CI: 0.78-2.01)	0.73 (95% CI: 0.38-1.29)
NHL 13,500+ppm-d **SMR**	**2.37*** (8)	**0.37** (1)
Lymphoid CPH cum exp	p = 0.06, positive slope	p = 0.78, negative slope
Lymphoid CPH categorical cum exp	**p = 0.49** **OR = 1.00, 2.45, 1.85, 2.44***	**p = 0.42** **OR = 1.00, 2.05, 1.25, 0.87**
Log cum 15 yr lag	p = 0.02*	NA
Categorical cum 15 yr lag	**OR = 1.00, 0.90, 2.89, 2.74, 3.76***	NA
* Statistical significance		

"Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect are not known." (Steenland et al., 2004)

Breast Cancer Incidence Data should not be used for Quantitative Risk Assessment

"Our data suggest that EtO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment."

Steenland et al. (2003)

Missing Breast Cancer Cases in IRIS Analysis

- 319 identified cases, 367 expected in 7,576 women
  - **48** or more missed cases (either no association or a positive one)

- 233 cases included in 5,139 interviewed women (32% women did not participate, mostly due to inability to locate)
  - **86** cases lost (Went from 319 to 233 cases)

- If all women were interviewed, the analysis would have included:

  48 or more + 86= **134 or more** breast cancer cases in addition to the 233

Breast cancer incidence- Quantitative Risk Assessment Uncertainties

- Under-ascertainment of incident cases in overall and interviewed substudy
  - Missing cases due mostly to location problems of short-term workers, i.e., those with lower cumulative exposures
  - Serious concern about selection bias where proportionally more cases found and interviewed among long-term workers, fewer cases found and interviewed in short term workers
  - Association with duration of exposure much stronger than with cumulative exposure
  - Consequence: apparent positive slope, regardless of model
- Breast cancer mortality is fully ascertained

Quantitative Risk Assessment of Epidemiology Data

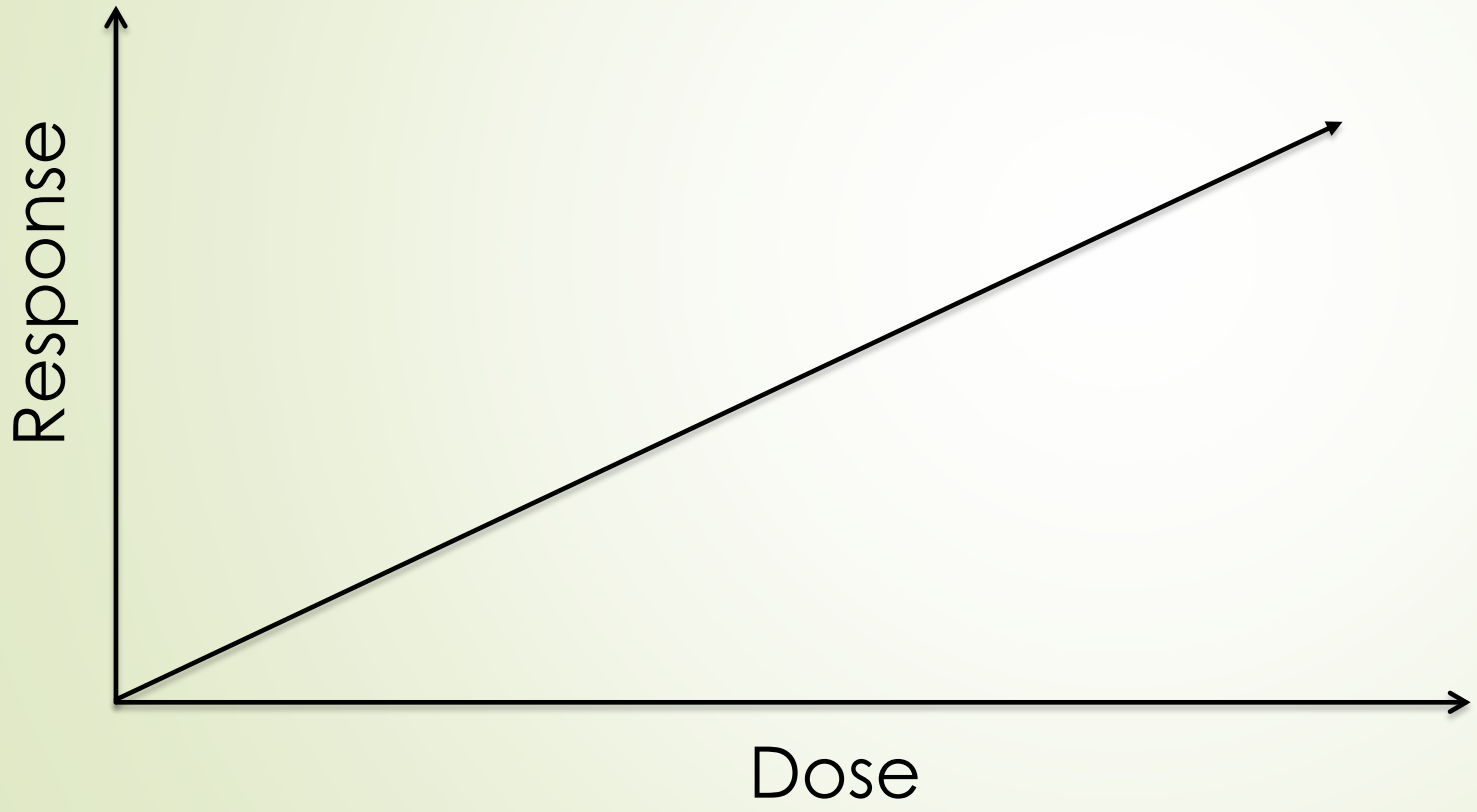
- Breast cancer incidence data **should not** be used for quantitative risk assessment purposes
  - Steenland et al. (2003) refers to findings as suggestive with additional uncertainties
  - The authors report a large number of missing cases (underascertainment) raising serious concern about selection bias, supported by an unusually strong association with duration of employment
  - Data is not publicly available
- Breast cancer **mortality** data, which is fully ascertained, is more consistent with the standard CPH model

Biological evidence is more consistent with the standard CPH model

Biological Evidence

- Mutagenicity is the presumed MoA for EtO Carcinogenicity
- EtO is direct-acting alkylating agent
  - Metabolic activation not required for its reactivity.
  - Detoxified via GSH conjugation and epoxide hydrolysis
- DNA adduction is the molecular initiating event,
  - Repair processes expected to afford protection.
- A relatively weak mutagen,
  - Requires high doses and long exposure durations.
- Data for DNA adduction, mutagenicity, and carcinogenicity conservatively support CPH model vs. 2-piece spline model with steep initial slope.

Default Dose-Response for Direct-Acting Alkylating Agents Such as EtO



Linear Response

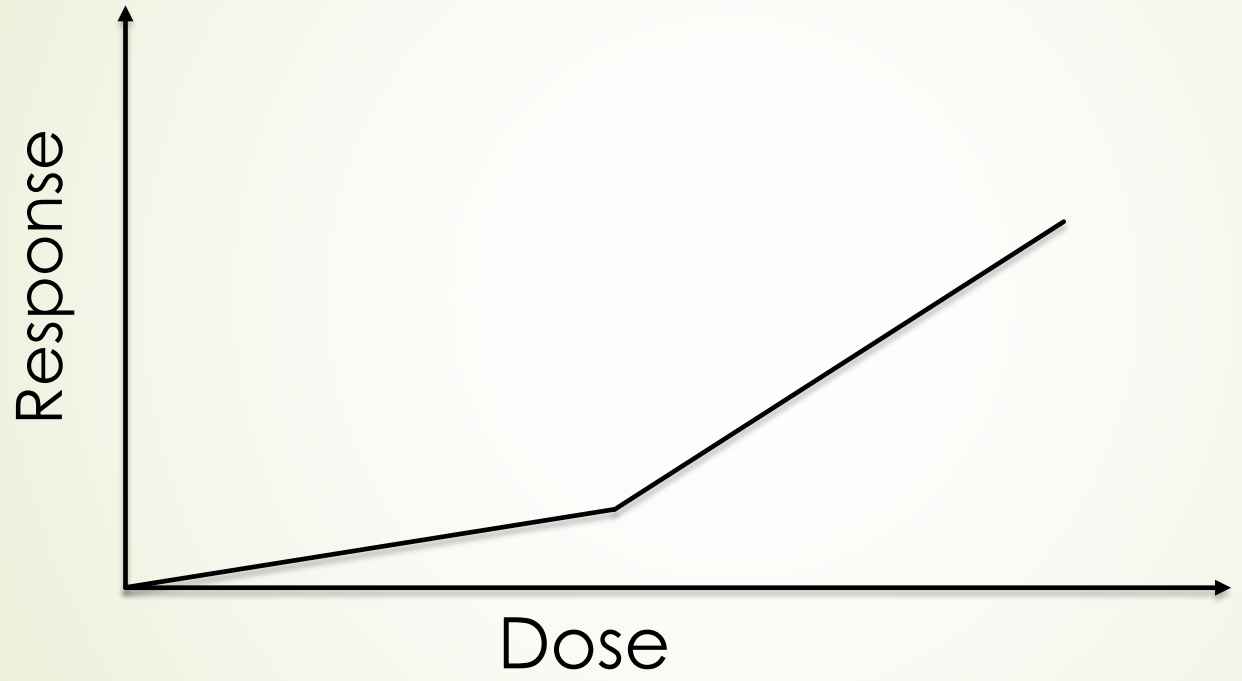
Single Slope

Worst-case Scenario

One-hit → one-effect

No thresholds

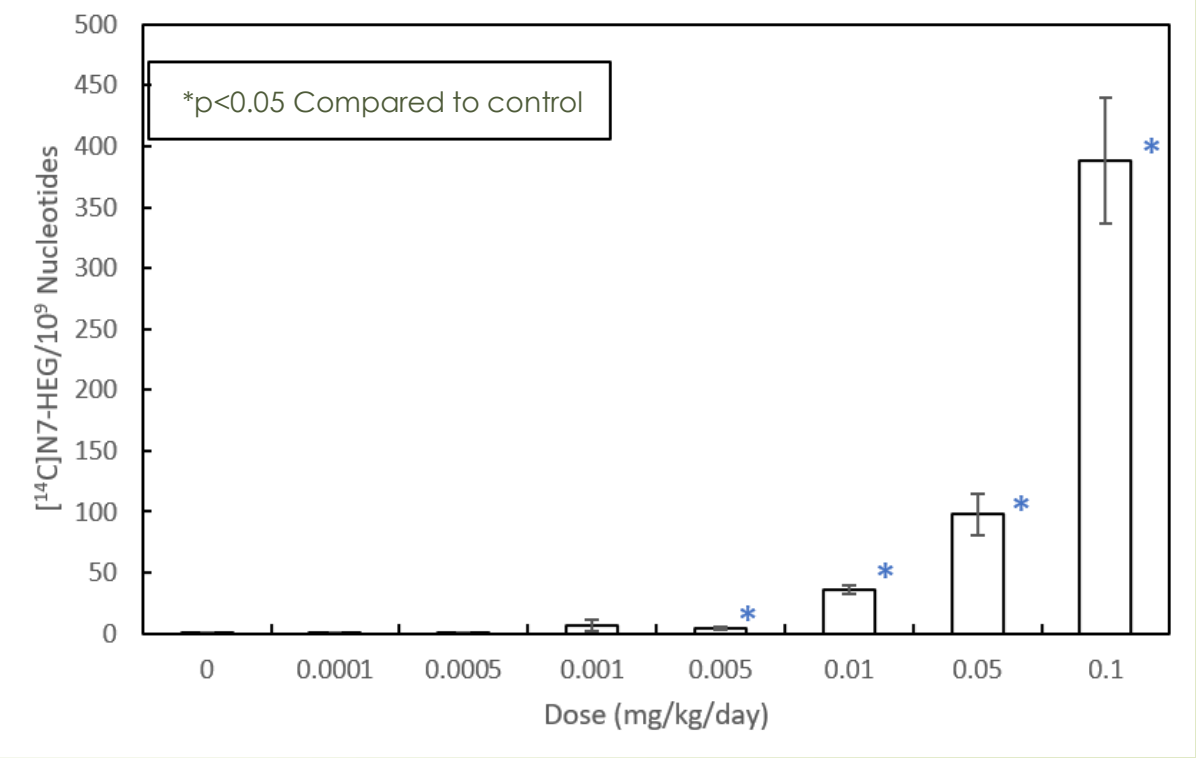
Linear Response with 2-Slopes
Shallow initial slope and steep second slope



Plausible and most likely for EtO based on available data

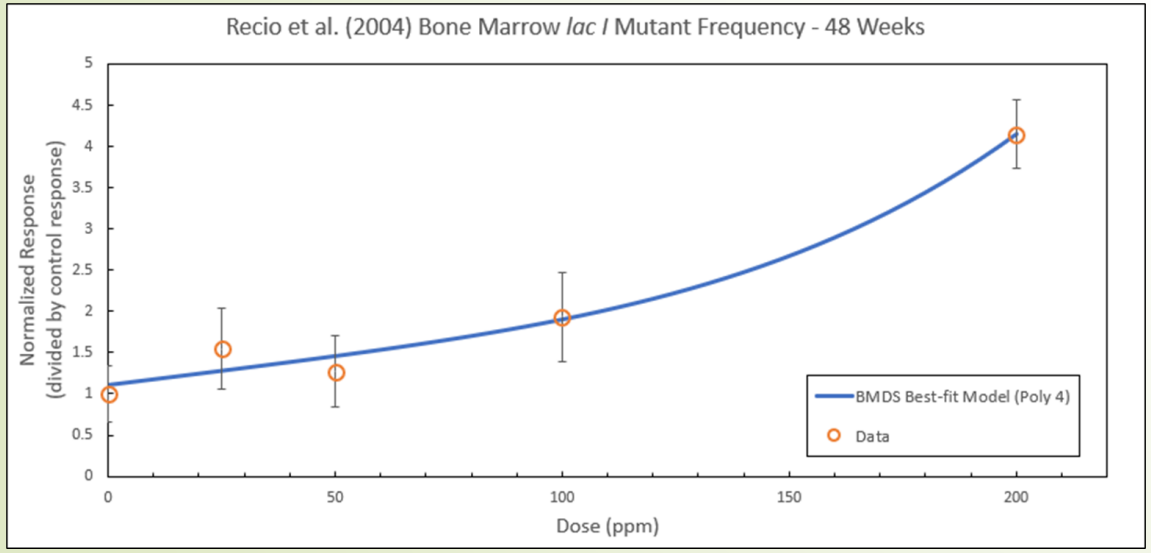
Experimental Evidence:
Dose-Response for N7-HEG Adducts in Rats (Marsden et al., 2009)

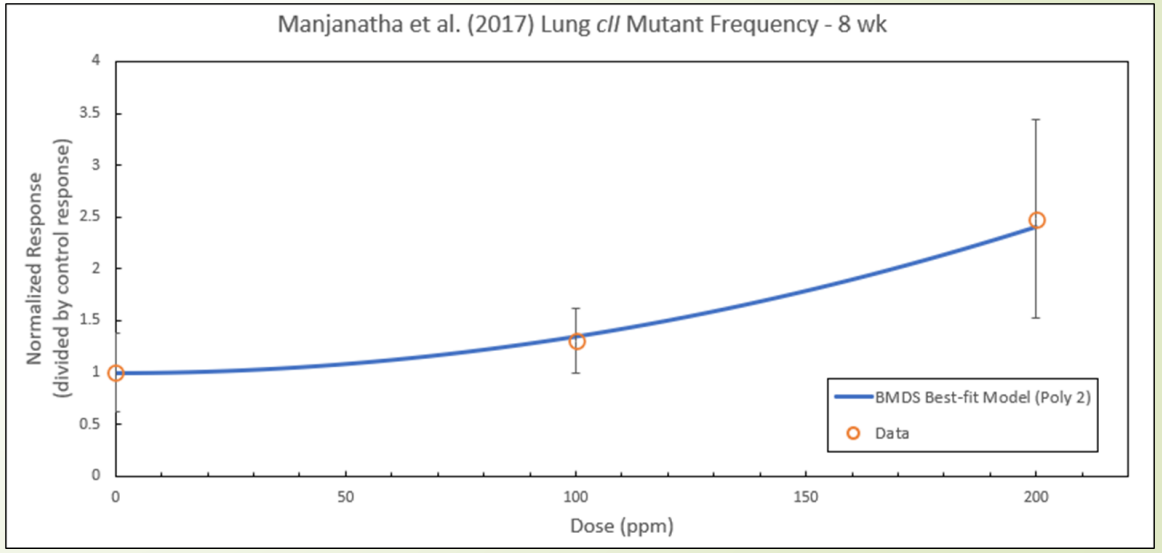
- N7-HEG is the most abundant, but not mutagenic, adduct formed following EtO exposure.
- Dose-response for N7-HEG is the worst case scenario for all EtO adducts, including mutagenic O^6-HEG with 300X lower abundance.
- N7-HEG formation at best has a linear response with single slope



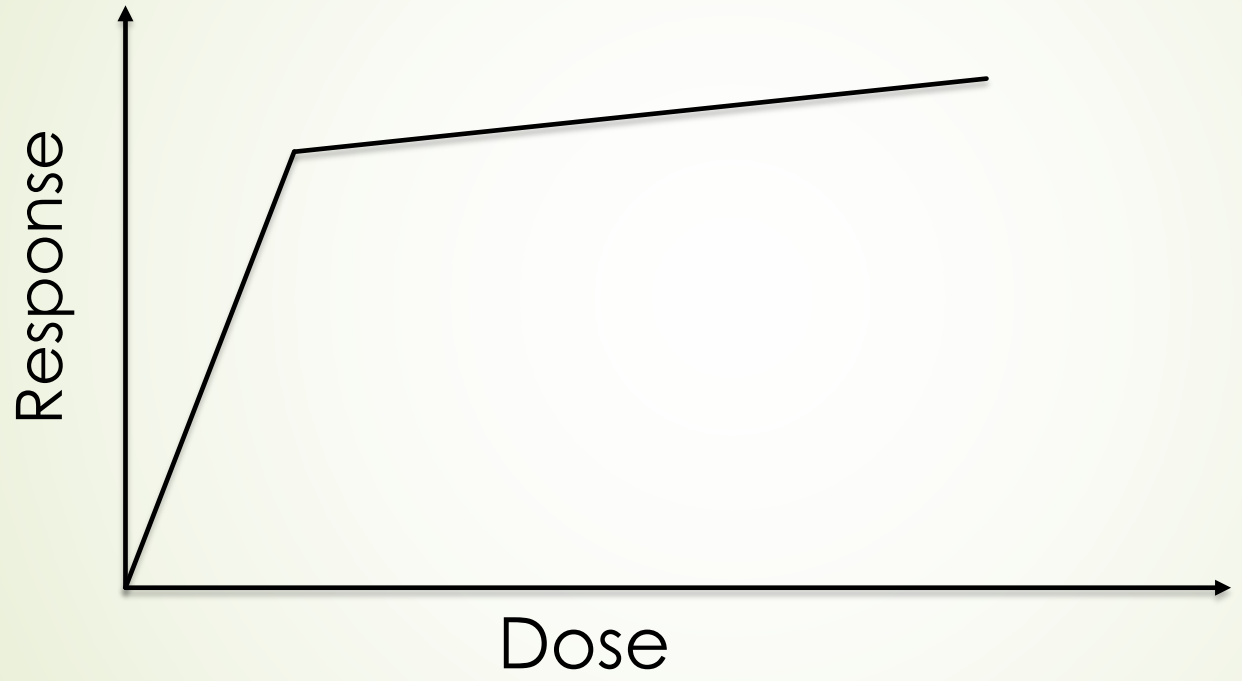
Experimental Evidence:
Dose-Response for EtO-Induced Mutations in Mice

- Most relevant target tissues for biological plausibility
  - Mutagenic in mouse bone marrow after 48 weeks, but not at 12 or 24 weeks, at concentrations of ≥100 ppm (Recio et al., 2004).
  - In mouse lung only after 8 weeks of exposure to 200 ppm (Manjanatha et al., 2017).





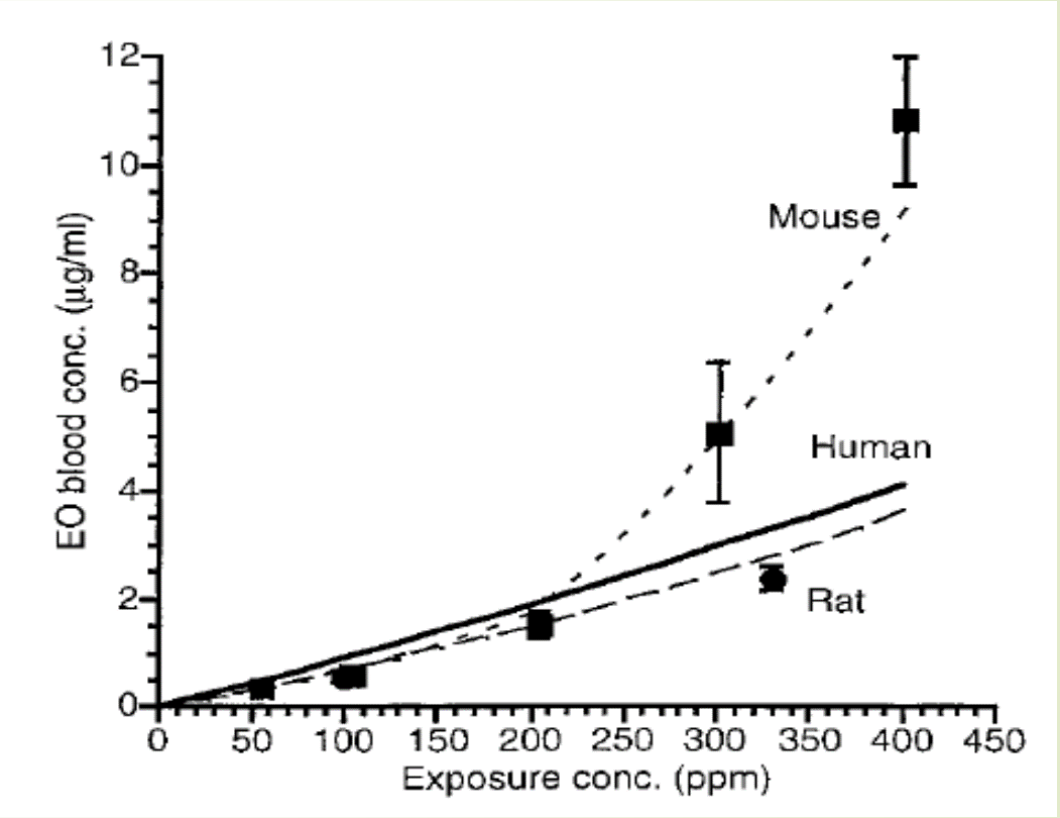
Linear Response with 2-Slopes
Steeper initial slope and shallow second slope



Not plausible for EtO based on the toxicokinetic data

No Plausibility for Steeper Initial Slope Based on Toxicokinetic Data (Fennell and Brown, 2001)

- Blood concentrations of EtO increased linearly with exposure between 50 and 200 ppm.
- Only in mice, dose-disproportionate increases in blood EtO occurred at >200 ppm due to GSH depletion.
- These observations do not support the plausibility of an initial steeper slope for EtO-induced biological effects.



Permitted Daily Exposure (PDE) Value Based on EtO Mutagenicity Data (Gollapudi et al., 2021)

- Growing consensus at international level for using mutagenicity to derive PDE.
- Quantitative analysis of 40 sets of EtO in vivo genotoxicity studies to calculate point-of-departure (POD) for wide range of endpoints.
- Composite adjustment factors used to derive PDE.
- The lowest POD (0.075 ppm) resulted in a PDE value of 238 ppt.
- The PDE is similar to TCEQ's 1/M extra risk concentration of 240 ppt.

Rat ethylene bioassay data does not support IRIS cancer risk specific concentration (RSC)

- EtO 1/M RSC of 0.1 ppt is one of the most conservative IRIS standards which is based on an assumption of a low dose steep or supra-linear exposure-response
- If EtO were such a potent carcinogen, one should expect tumors at low ppm exposure to EtO in the ethylene animal carcinogenicity study
- Yet, exposure of rats to 300-3000 ppm ethylene (equivalent to 2.4-5.5 ppm EtO based on DNA adducts) did not result in tumors.
- The ethylene data provides additional evidence that the exposure-response is not supralinear or steep at lower exposures

Biological Evidence: Conclusions

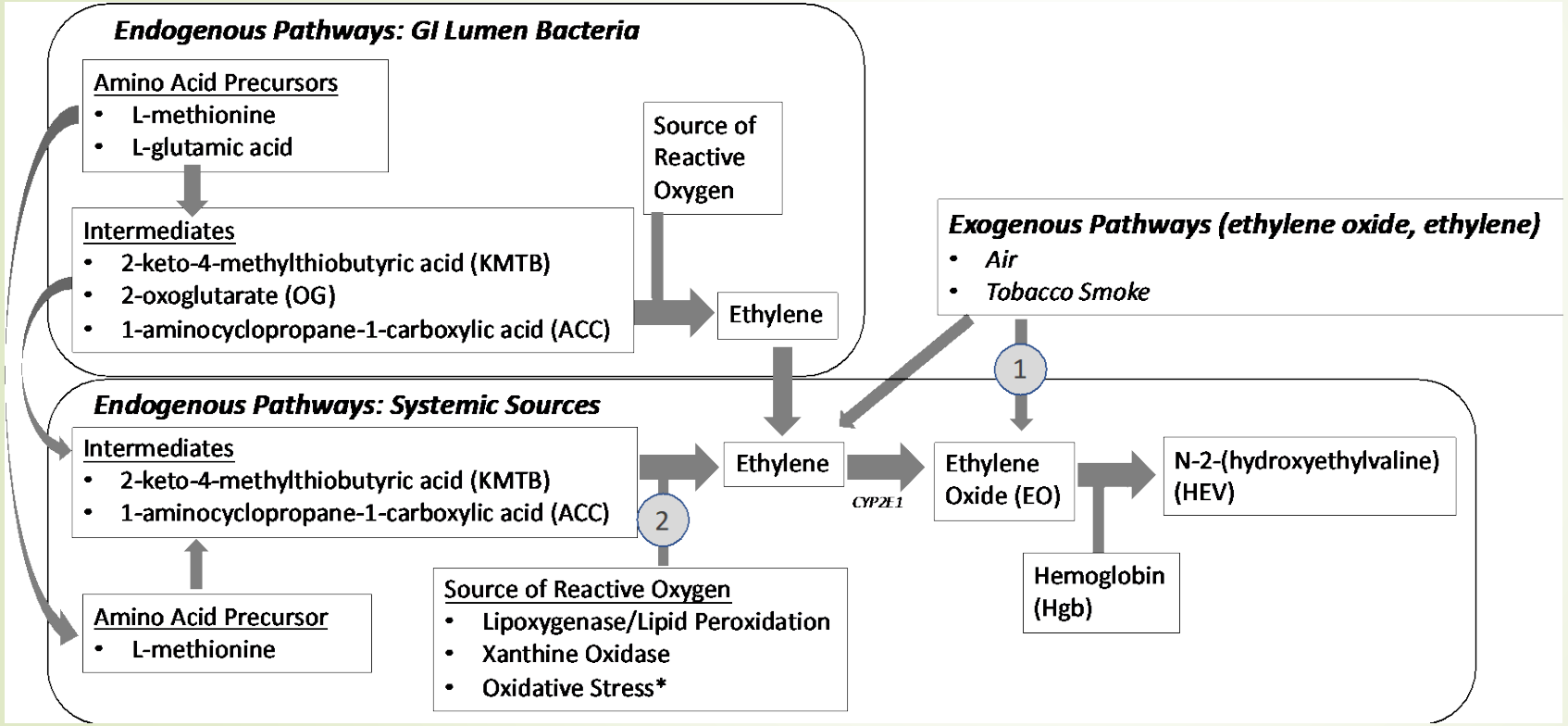
- DNA adduction and mutagenicity are early key events (KE) in the presumed mode of action (MoA) for EtO-induced tumors.
- Dose-response for early KE do not support a 2-piece spline linear model with a very steep first slope.
- In contrast, the biological data provide support for the conservative selection of the CPH dose-response model used by TCEQ

Reality Checks and Concluding Remarks

Background Endogenous EtO Overview

- Great that a section for endogenous EtO is included in OEHHA documents!
- HEV are useful biomarkers of exposure for EtO
  - HEV serves as the basis for Germany's long-term Biological Reference Value for EtO
  - Paucity of data relating to DNA adducts (as potential biomarkers of effect) does not detract from this conclusion
  - DNA adduct measurements are more difficult & more variable than hemoglobin adducts (temporal & analytical method differences) making them less useful as potential biomarkers
- Endogenous EtO has been well characterized in animals
- Linear correlation between HEV and EtO in air used to estimate endogenous EtO in humans is well supported and show no indication of low-dose sublinearity
- Understanding endogenous level provides a reality check and provides a reference frame for risk managers put risk-based values into context.
- Confidence in endogenous exposure estimates is high

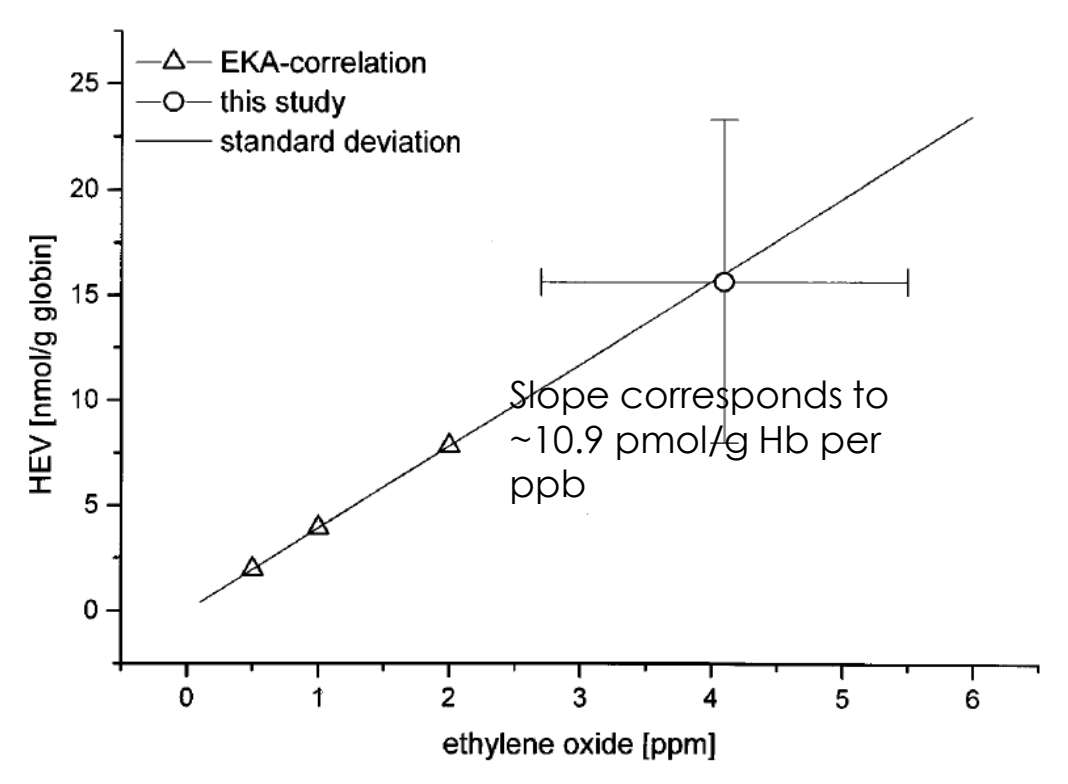
The pathways for endogenous EO production are well characterized in laboratory animals (see figure), and serves as the best explanation for the levels of HEV measured in the US population (NHANES)



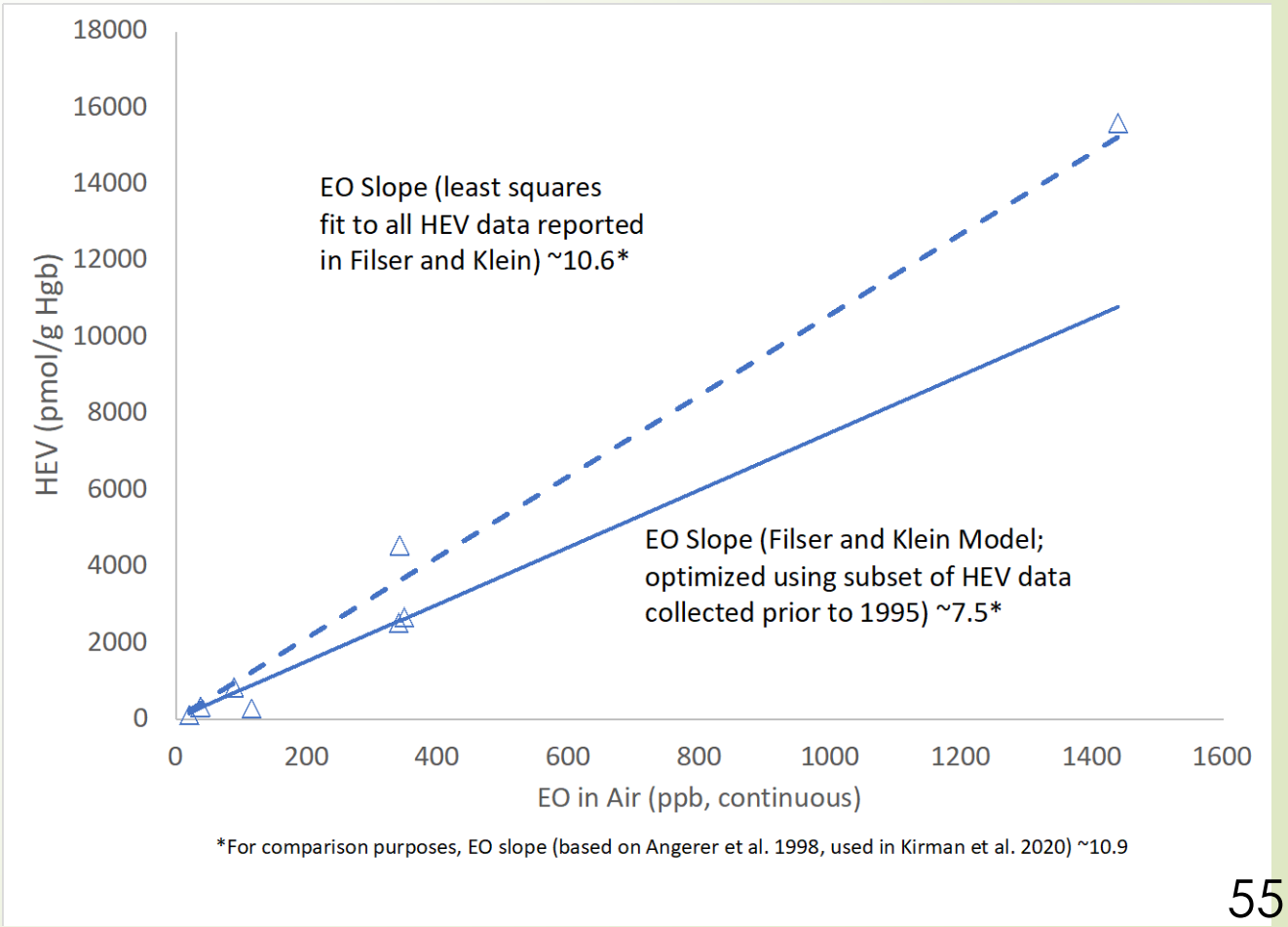
- *Germ-free animals have internal EtO dose (HEV) reduced by ~half*
- *Dietary factors (fatty acid composition) can modulate EtO internal dose*
- *Exogenous EtO induces endogenous production (Marsden et al., 2009)*
- *PBPK model encoding endogenous pathways would be nice to have, but is not necessary to use HEV data*
- *Exogenous exposures to EO cannot explain the levels of HEV measured by CDC in US population.*
- *Endogenous EtO is the only other viable explanation*

Relationship Between Measured HEV and EO Exposure is Linear Based on PBPK Predictions & Worker Data

Angerer et al. (1998); basis for Germany's BAR for EtO

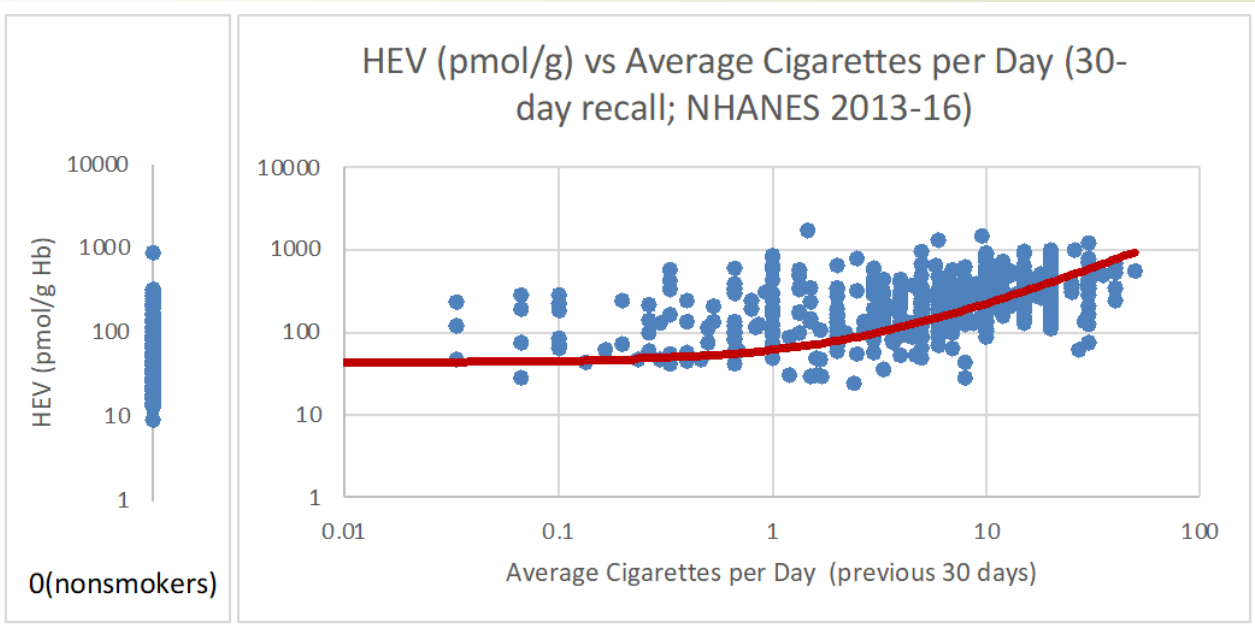


Adapted from Filser and Klein (2018)



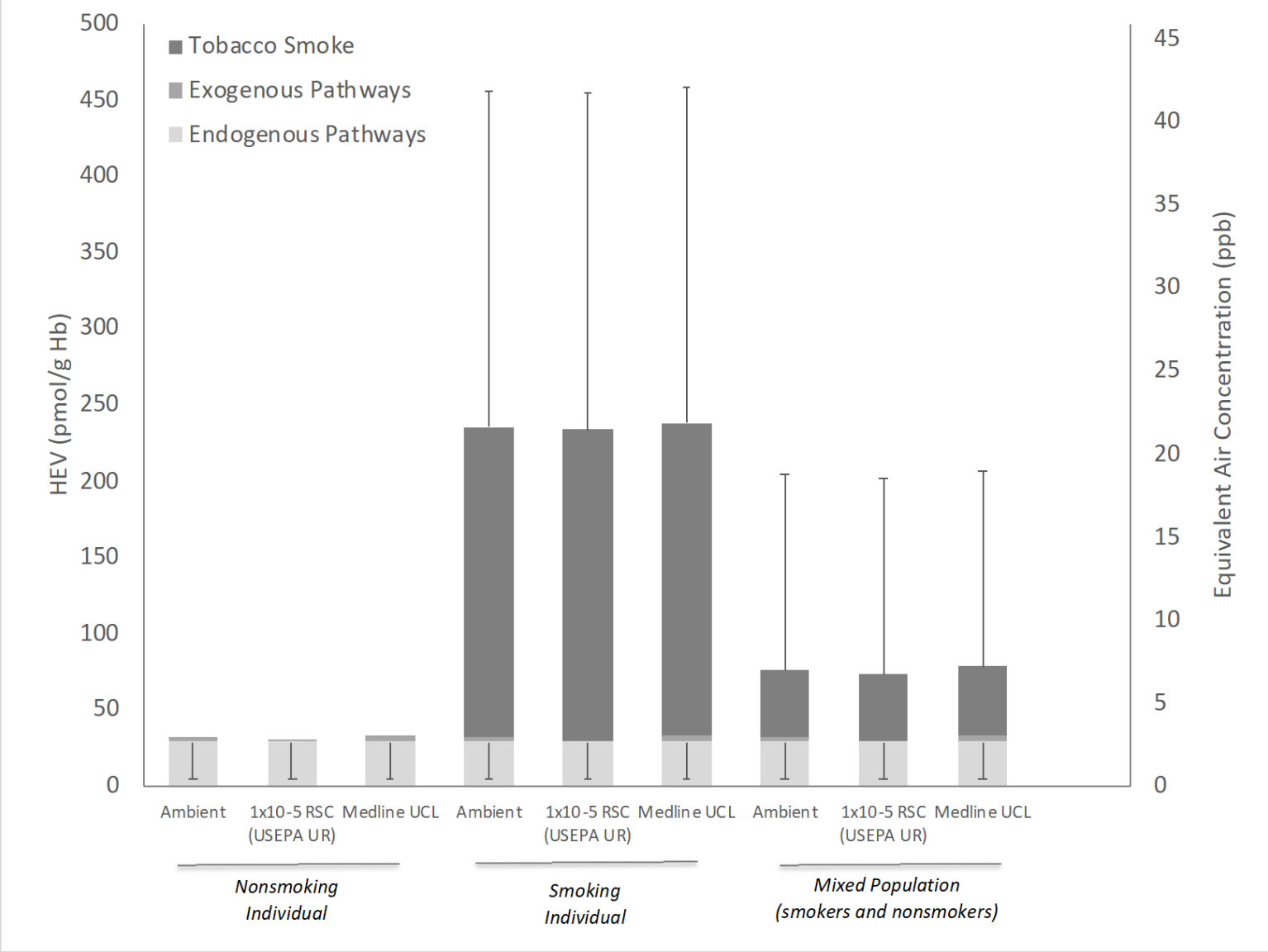
CDC NHANES HEV Data Also Support Linearity

- **EPA (2022, p. 69) suggested:**
  - ***For validation of the HEV based projections, "forwards" determinations of smokers total exposures to EtO (e.g., as might be assessed using exhaled breath measurements) could be compared with "backwards" calculations of projected EtO exposure levels hypothesized from HEV from adduct level.***
- Confirmation of linear relationship between HEV exposure
  - EtOHEV (pmol/g) = 10.9 × EtO (continuous exposure, ppb)
  - Figure showing HEV (pmol/g) vs Average Cigarettes per Day (30-day recall; NHANES 2013-16)
    - Slope = 18 pmol/g per cig/day = 10.9 pmol/g per ppb (continuous exposure), if using a conversion factor of **0.6 ppb per cig/day**.
  - Consistent with forward analysis
    - Estimated daily EtO exposure concentration 9 ppb / 17 (cig/day) = **0.53 ppb per cig/day.**



- *Note – the red line in this figure is linear, but distorted due to log-log plot*
- ***Smoker data agree with worker data on previous slide, and are linear across the entire exposure range***

Source Characterization: Putting Exogenous Exposures into Perspective



- *Exogenous EtO is not an important contributor to total EtO exposure*
- *Proposed RSC for 10^{-5} cancer risk is 0.002 ppb, which*
  - *can't be measured,*
  - *is more than 60 time below the mean background concentration in ambient air in CA, and*
  - *more than 1100 times below the below the median endogenous equivalent concentration*
- *Endogenous EtO predominates in nonsmokers*
- *EtO from cigarettes predominates in smokers*
- *Risk management for the exogenous pathway does not have a meaningful impact of total EtO exposures or associated health risks*
- *Source contribution is important for risk communication purposes*

Confidence in Endogenous EtO Exposure Estimates is High

- Estimates rely on data sets that are of high quality
  - HEV data collected by CDC as part of NHANES are used to quantify total EtO exposure to U.S. population
  - Air sampling data collected by USEPA are used to quantify the exogenous EtO exposure pathway
- Linear correlation between EtO in air and HEV levels in blood is strongly supported by available data
  - Consistent with available worker exposure data
  - Consistent with NHANES smoker data
  - There is no evidence to support any departures from linearity in these data

Summary

- **We have significant concerns with USEPA's 2-slope model of the NIOSH data**
- **Steep slope in low-dose region with high-dose plateau appears to be an artifact of embedded decisions made in the modeling, in particular:**
  - Combining men & women data exhibiting dramatically different exposure-response behaviors
  - Incorrect statistics, misleading visual fit comparisons, over-reliance on biologically implausible log-cumulative models
- **Steep slope in low dose-region is inconsistent with the epidemiology data**
  - Signals for LH, lymphoid and breast cancer are weak and inconsistent across available studies

Summary (continued)

- **Steep slope in low-dose region is inconsistent with the biological evidence**
  - EtO toxicokinetics do not exhibit the behavior of the EPA's steep initial slope
  - HEV data do not exhibit this behavior
  - Genotoxicity for EtO and carcinogenicity data for ethylene and EtO do not exhibit this behavior
- **EPA's 2-slope model overpredicts risk**
  - Overestimates cases in the range of observation
  - Resulting IUR predicts unacceptable excess risk in ambient air, exhaled air and fruits (Kirman and Hays, 2017; Kirman et al., 2021; Sheehan et al., 2021; Lewis et al., 2022)
  - As such, the use of USEPA's inhalation unit risk to assess, manage, and communicate risks from EtO is not recommended

Inhalation Unit Risk Based on Cox Proportional Hazards Model are Recommended

- **CPH regression, as performed by TCEQ, is preferred**
  - Accurately predicts the number of cancer cases in range of observation for the NIOSH cohort
  - CPH model is approximately linear in the low-dose range without exhibiting a plateau
  - CPH is a standard model used for epidemiology and is more representative of the epidemiological weight of evidence
  - The behavior is consistent with the underlying biology
    - EtO toxicokinetics
    - HEV data
    - Genotoxicity and carcinogenicity data