Oral Comments on the OEHHA DRAFT IUR

Statistical and Biological Considerations

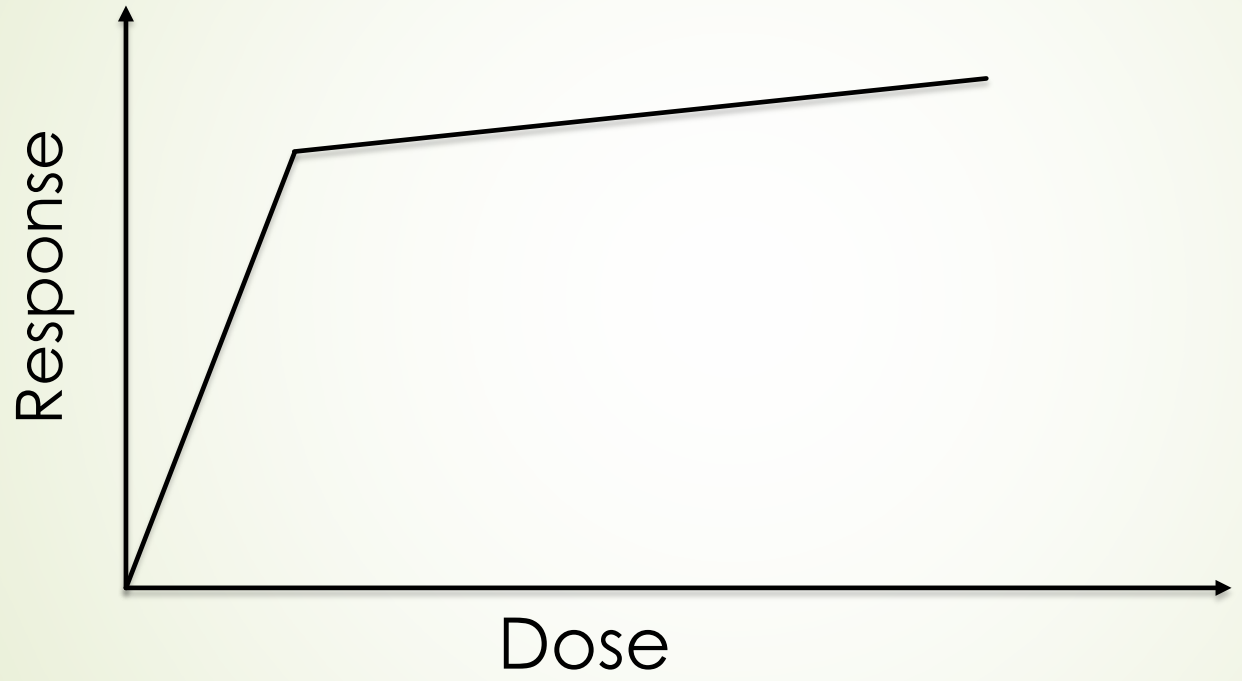
Abby Li, Jane Teta, Bhaskar Gollapudi, Kenneth Bogen, Steave Su, James Bus,
Written Comments and Published Research Supported by the American Chemistry Council's Ethylene Oxide Panel

Presented to the California Air Resources Board
Scientific Review Panel on Toxic Air Contaminants
February 2, 2024 Public Meeting

Key Issue: Model Selection

EPA IRIS MODEL: 2-piece spline model

Steeper initial slope + shallower second slope (2-slope model)



Not plausible based on the biological and epidemiological data for EtO

EPA IRIS rationale for 2-slope linear model

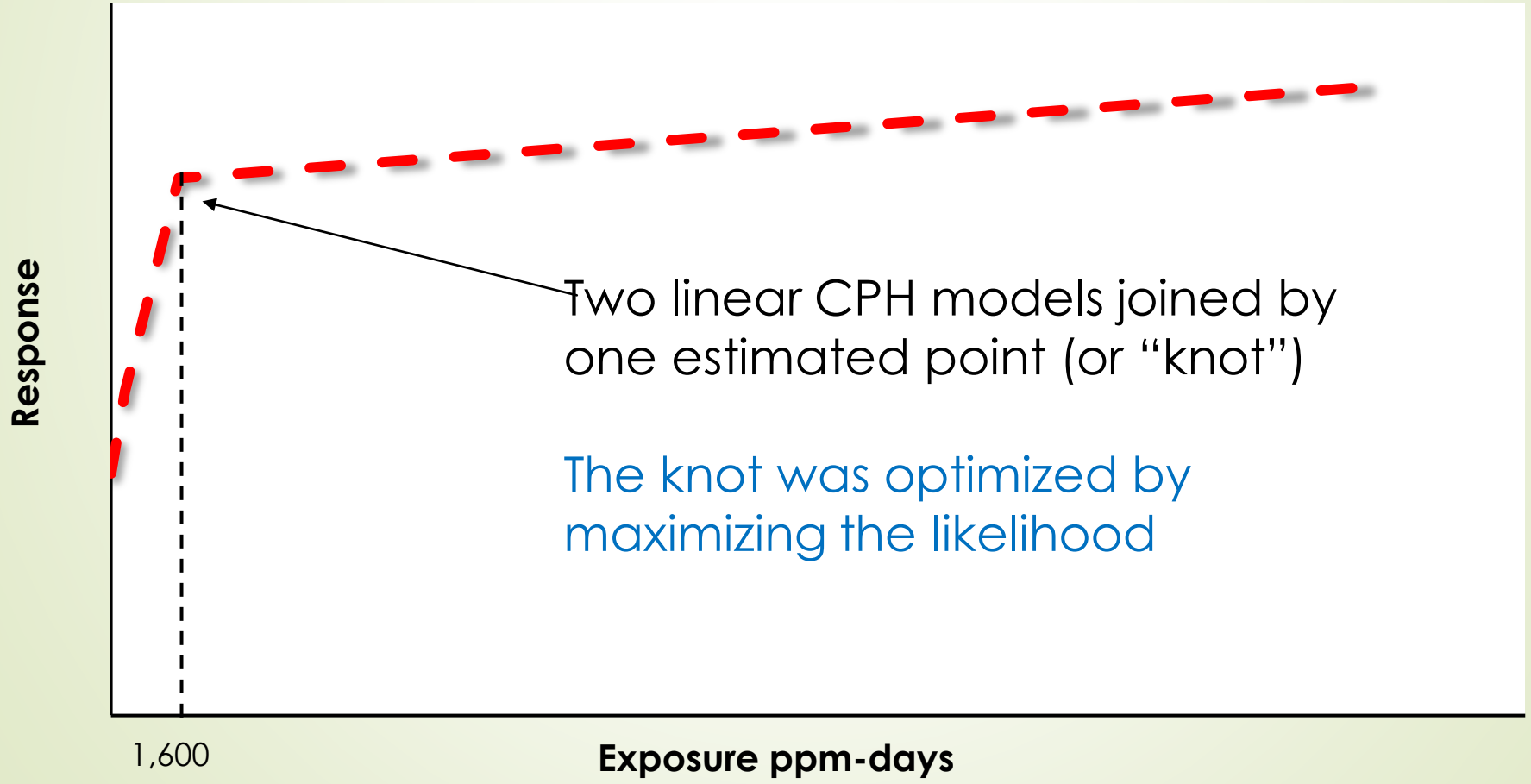
- Statistical fit
- Visual fit
- Significant log cumulative exposure models

EPA IRIS rationale for 2-slope linear model Is Flawed

- Statistical fit -incorrect p-values
- Visual fit -figures not fit for purpose
- Significant log cumulative exposure models - considered biologically implausible by EPA IRIS

Statistical correction (p=0.14) for Lymphoid

EPA IRIS p=0.07 did not account for the knot



Corrected p-values for TCEQ's Standard CPH and EPA's 2-slope model are comparable

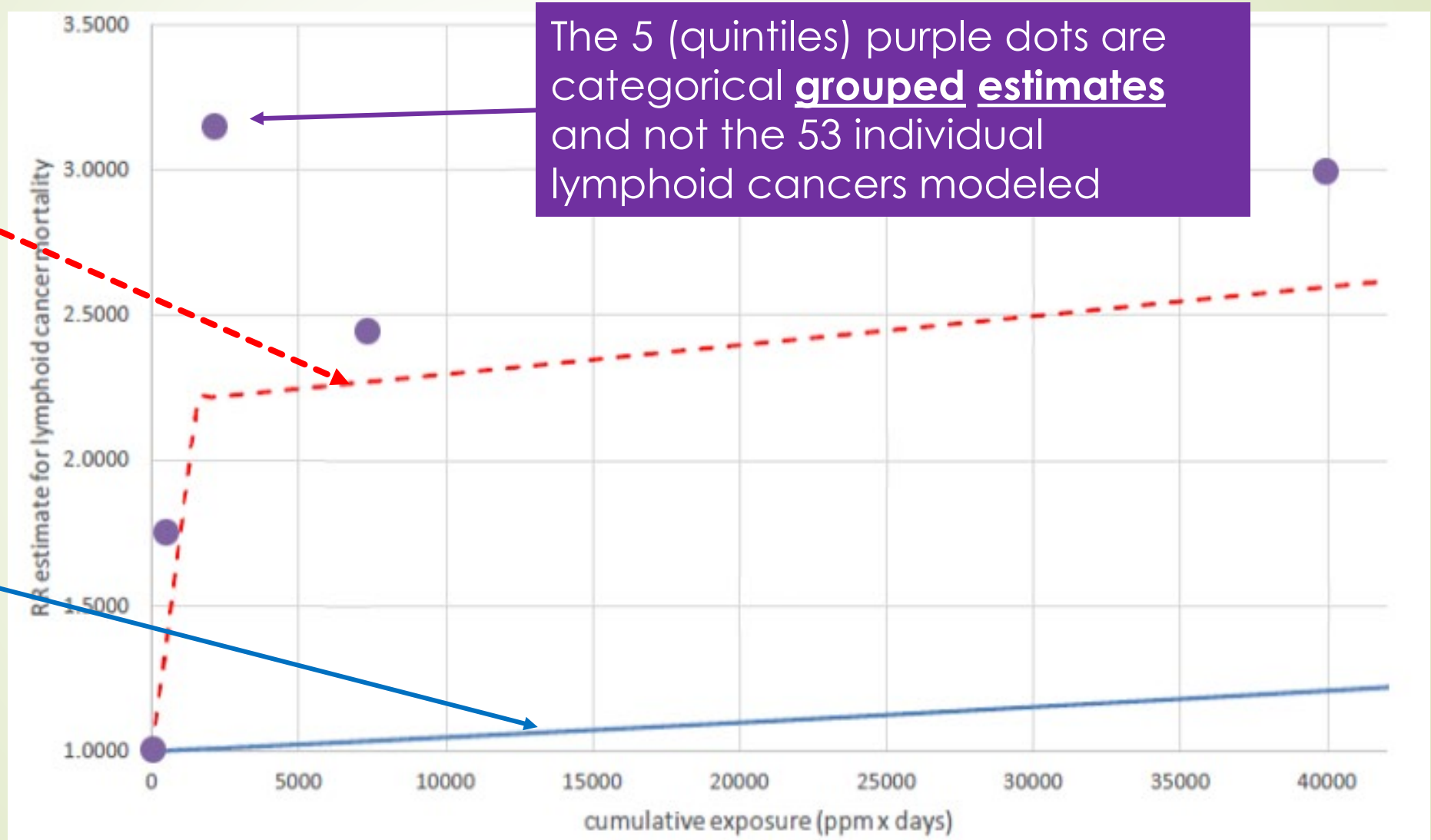
- TCEQ CPH model (p=0.22) ≈ IRIS 2-slope model (p=0.14)
  - TCEQ Peer reviewers with expertise in statistical modeling for risk assessment agreed with the correction
- The standard CPH model has the advantage of being a simpler (more parsimonious) single-slope model

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 are categorical **grouped estimates** and not the 53 individual lymphoid cancers modeled

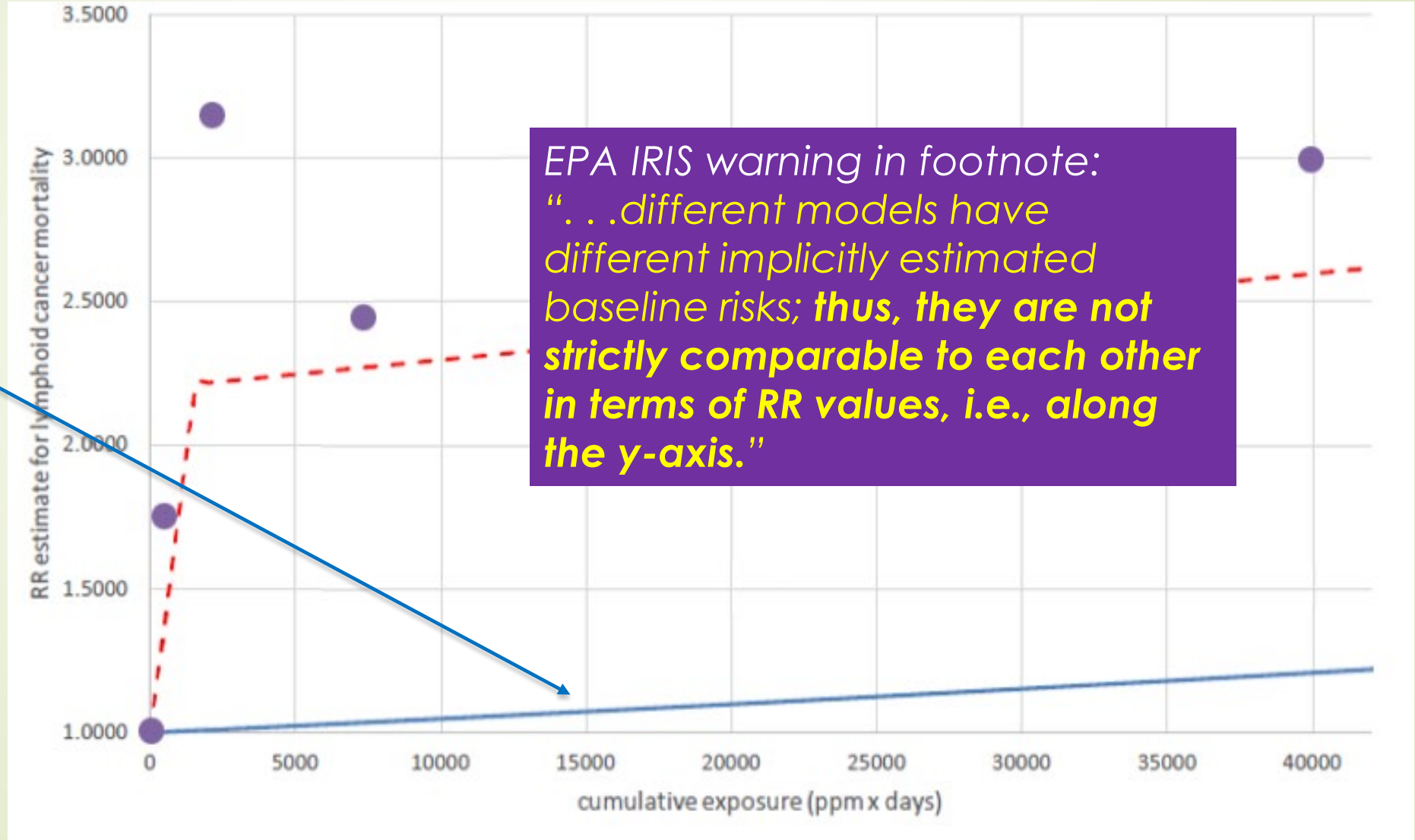


The Y-axis is Relative Rate: Conclusions about under- or over-estimation based on comparisons along the y-axis cannot be made

Common error:

". . .model selected by the TCEQ substantially underestimates the nonparametric categorical RR estimates."

Example from Public comments to TCEQ(p. 59) https://www.tceq.texas.gov/downloads/toxicology/dsd/comments/eto-public-comments.pdf;



EPA IRIS warning in footnote: ". . .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."***

Based on flawed visual comparisons, the Draft IUR incorrectly concludes:

"**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"

In fact, the TCEQ CPH model accurately predicts the observed number of lymphoid mortalities in the NIOSH study, while the EPA IRIS model statistically significantly overpredicts. This is true in the lowest exposure range as well as overall.

Based on flawed visual comparisons, the Draft IUR incorrectly concludes:

"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"

In fact, the TCEQ CPH model accurately predicts the observed number of lymphoid mortalities in the NIOSH study, while the EPA IRIS model statistically significantly overpredicts. This is true in the lower exposure ranges and overall.

EPA SAB (2015) emphasized

"*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*."

Standard CPH model is more consistent with the Biological Evidence (Detailed ACC Comments to SRP and OEHHA)

- Mutagenicity is the presumed MoA for EtO Carcinogenicity
- EtO is a 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
- EtO is a weak mutagen
  - Requires high doses and long exposure durations
- Dose-response data on TK, DNA adduction, mutagenicity, and carcinogenicity (ethylene and EtO) support the CPH model, but NOT a 2-piece spline model with steep initial slope

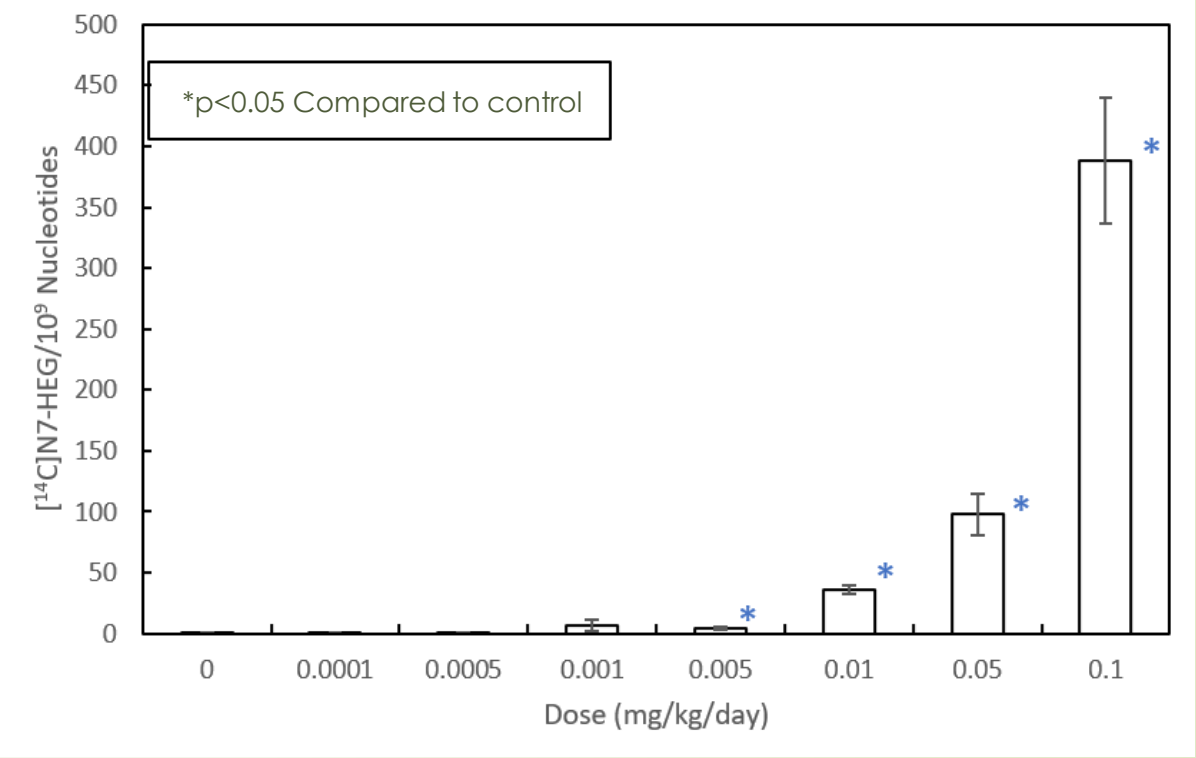
Recommendation: An IUR should be developed using a standard log-linear CPH model

- **Statistical Considerations:** Parsimonious model that better predicts the actual data.
- **Biological Plausibility**: Model is consistent with the underlying genotoxicity, carcinogenicity and toxicokinetics of EtO
- **Consistency with Observed data**: Is more representative of the NIOSH study and the epidemiological weight of evidence
- **Values needed to derive IUR based on Standard CPH are readily available**
  - Lymphoid Mortality (TCEQ and EPA IRIS)
  - Breast Cancer Mortality (EPA IRIS and Valdez-Flores et al. 2010)
  - Breast Cancer Incidence (EPA IRIS, but missing data)

Extra Slides

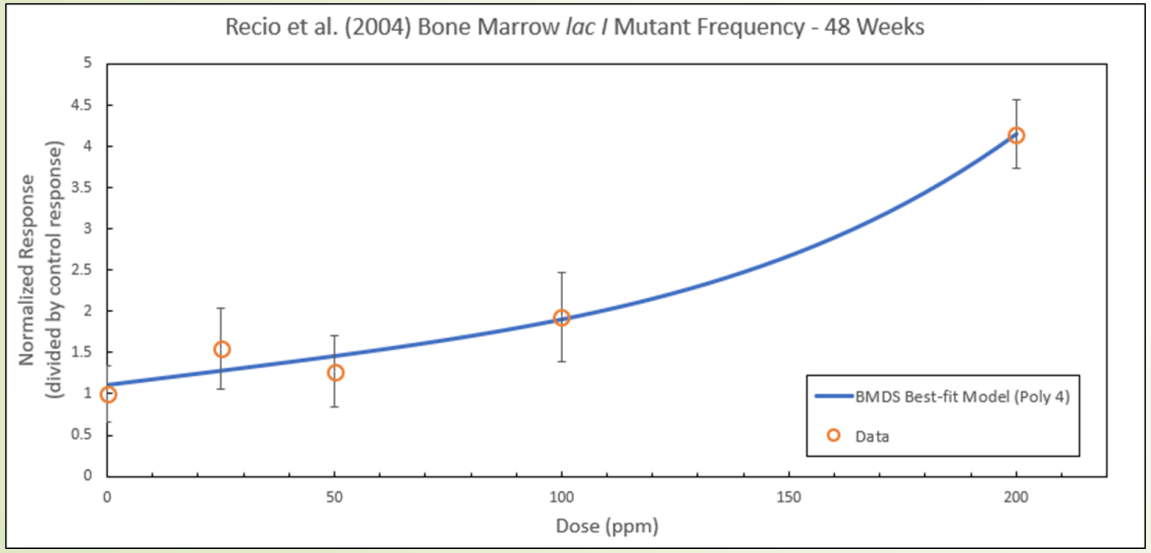
Experimental Evidence:
Dose-Response for N7-HEG Adducts in Rats (Marsden et al., 2009)

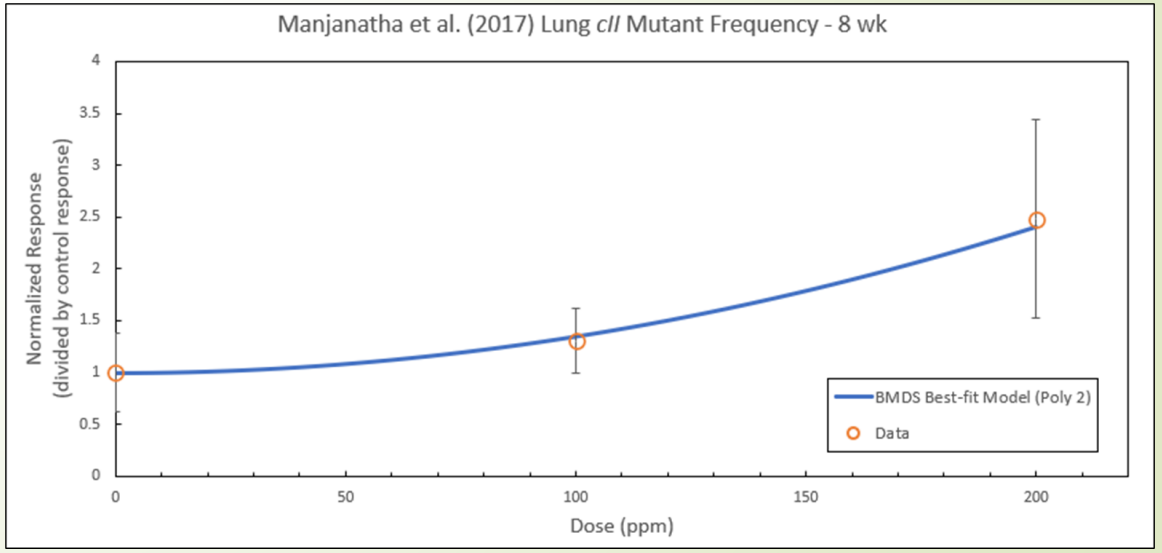
- N7-HEG is the most abundant, but not mutagenic, adduct formed following EtO exposure.
- Dose-response for N7-HEG is the worst case scenario for all EtO adducts, including mutagenic O^6-HEG with 300X lower abundance.
- N7-HEG formation at best has a linear response with single slope



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

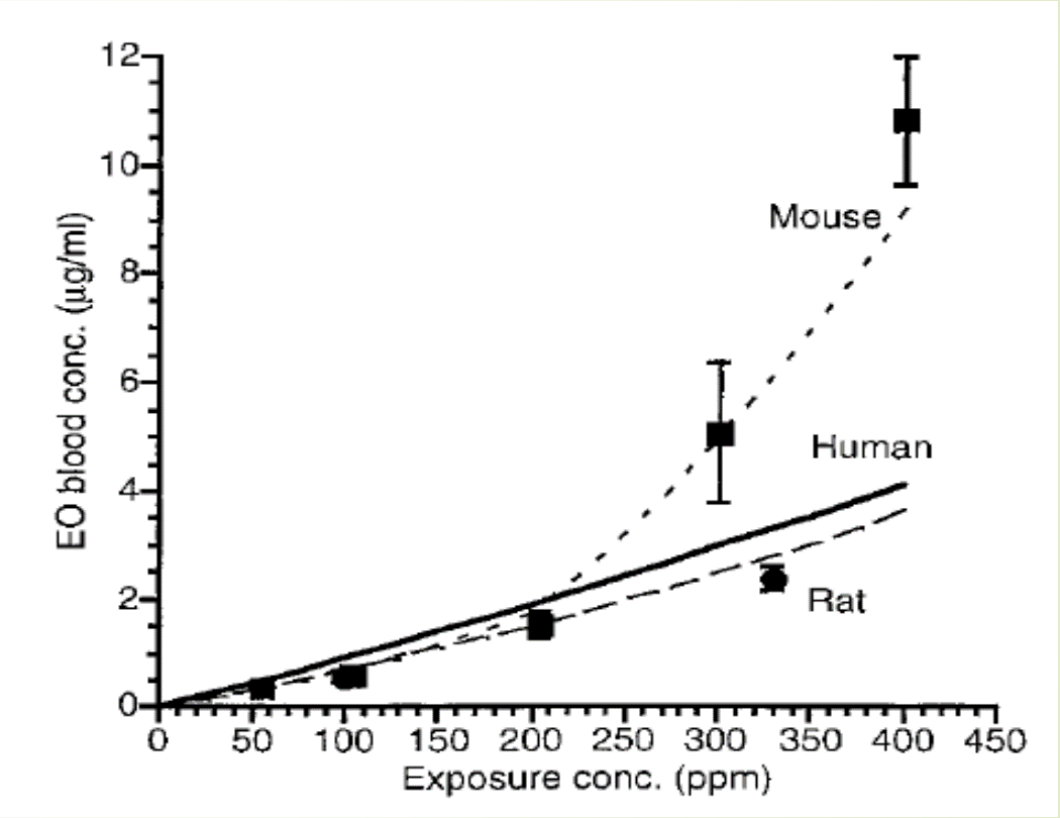
- Most relevant target tissues for biological plausibility
  - Mutagenic in mouse bone marrow after 48 weeks, but not at 12 or 24 weeks, at concentrations of ≥100 ppm (Recio et al., 2004).
  - In mouse lung only after 8 weeks of exposure to 200 ppm (Manjanatha et al., 2017).



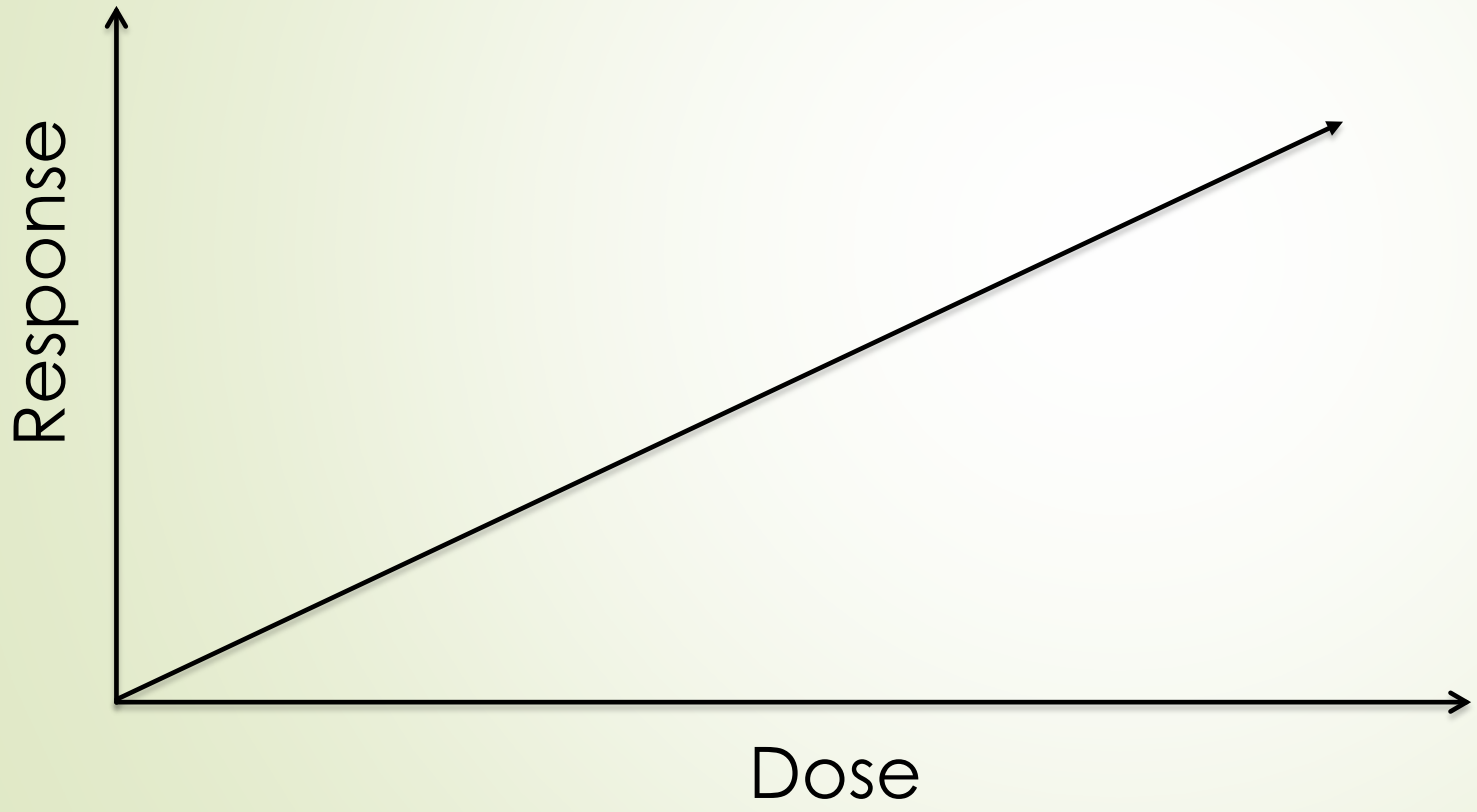


No Plausibility for Steeper Initial Slope Based on Toxicokinetic Data (Fennell and Brown, 2001)

- 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.



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



Linear Response

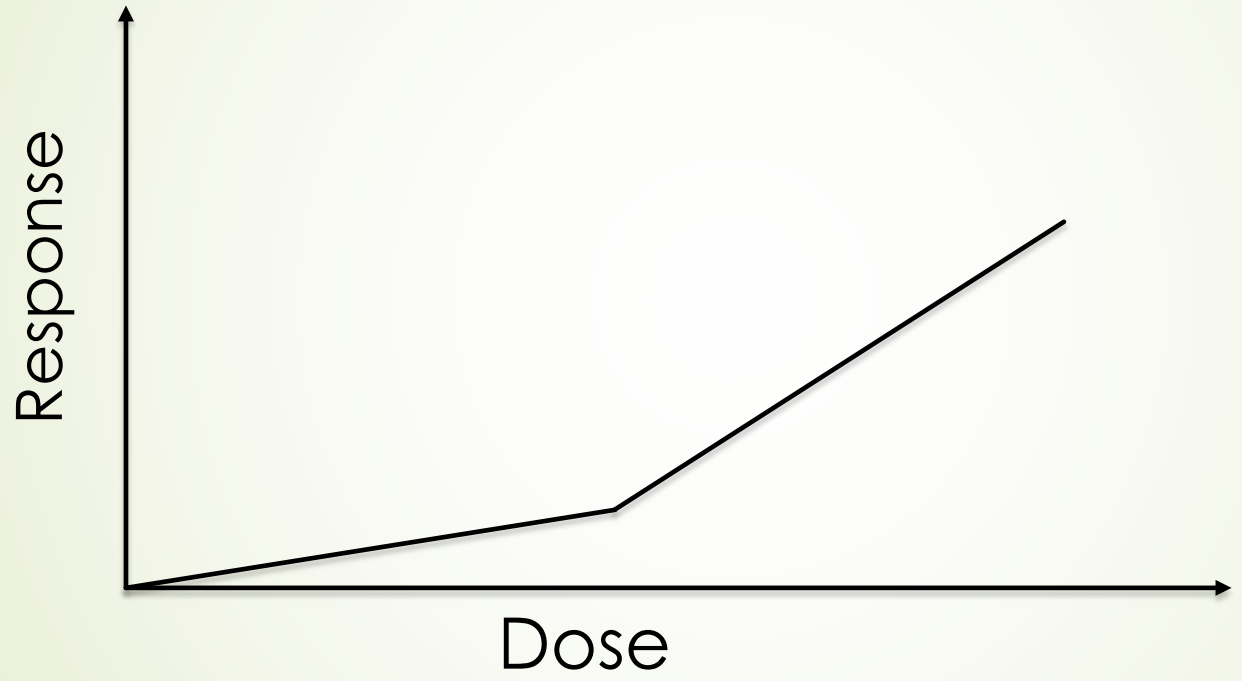
Single Slope

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