Scientific Issues in the Regulatory Assessment of Ethylene Oxide Cancer Risk

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TCEQ Toxicity Factor Guidelines

- Originally drafted in 2005
- External expert peer reviewed with 2 rounds of public comment
- Finalized in 2006
- Updated version drafted in 2011
- Also external expert peer reviewed with public comment
- Finalized in October 2012
- External peer reviews by a diverse group of external experts from government (e.g., USEPA, CalEPA), academia (e.g., UC, NYUSM, UTSPH), consulting (e.g., David Gaylor, Bruce Allen, John Christopher), and other relevant entities (e.g., Lovelace Respiratory Research Institute, NUATRC).
- Updated again in 2015 (323 page guidance document).
- *Our Goal: a state-of-the-science guidance document*.

Sound Science by TCEQ

- Our goal: *Use state-of-the-science guidelines to derive scientifically-sound toxicity factors*.
- Derivations can be found in Development Support Documents (DSDs) available on the web (https://www.tceq.texas.gov/toxicology/dsd/final.html).
- TCEQ has also published various derived values in the peer-reviewed scientific literature (e.g., 1,3-butadiene, nickel, arsenic, cadmium, hexavalent chromium, diethanolamine).

Sound Science Used Internationally

Ontario, Canada Ministry of Environment (MOE):

- ✓ *Deemed the assessment of 1,3-butadiene published by the TCEQ as the most scientifically-sound* after reviewing chemical assessments from Health Canada and Environment Canada, the Province of Quebec, the USEPA, the Swedish Institute of Environmental Medicine, the United Kingdom, and the World Health Organization (WHO), and the States of Louisiana, Massachusetts, Michigan, Minnesota, New Jersey, New York, Ohio, North Carolina, California, and Texas.

Sound Science Acknowledged by Peers

The Risk Assessment Specialty Section of the Society of Toxicology (SOT) recognized two of our 2015 papers on hexavalent chromium at the 2016 SOT conference as among the top 10 risk assessment application papers…

Regulatory Toxicology and Pharmacology 71 (2015) 93–100

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

ELSEVIER

Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium

J. Haney Jr.

Texas Commission on Environmental Quality (TCEQ), Austin, TX, United States

Regulatory Toxicology and Pharmacology 73 (2015) 834–852

Contents lists available at ScienceDirect

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ELSEVIER

Consideration of non-linear, non-threshold and threshold approaches for assessing the carcinogenicity of oral exposure to hexavalent chromium

J. Haney Jr.

Texas Commission on Environmental Quality (TCEQ), Austin, TX, United States

Sound Science Recognized by USEPA Experts

Peer Reviewers on USEPA's Proposed Mercury Air Toxics Standards (MATS) Rule in regard to nickel:

- ✓ *"I would recommend using the TCEQ URE*…The risk assessment leading to the derivation of this number was performed recently, included an updated and critical review of the literature, and appears to be comprehensive with an emphasis on health protection."
- ✓ *"Use the TCEQ URE*…This approach: (1) uses human data for the risk estimate, (2) takes advantage of a nickel-exposed cohort (Grimsrud 2003) for which there are data on the prevalence of smoking."
- ✓ *USEPA's own independent experts recommended that USEPA use our nickel cancer unit risk estimate (FYI they did not)*.

Sound Science Needed for EtO

- Medical sterilant and chemical intermediate (C_2H_4O).
- Recent USEPA (2016) unit risk factor (URF; excess cancer risk per unit lifetime exposure concentration) is primarily driven by lymphoid cancer, although breast cancer is also included.
- *EtO has not been conclusively demonstrated to cause cancer in people*.
- The USEPA and TCEQ agree that… *human data are insufficient to classify EtO as a known human carcinogen*.

Human Evidence Inconclusive for EtO Carcinogenicity

- Robust dataset in workers exposed to concentrations up to millions of times higher than environmental EtO levels (NIOSH cohort alone >17,500 workers).
- Some studies show an association with increased cancer risk (lymphoid, breast cancer) while others do not.
- Human evidence appears strongest for lymphoid cancer, although still inadequately strong as acknowledged by both USEPA and TCEQ.
- TCEQ's URF is based on lymphoid cancer.

Laboratory Animal Data of Questionable Relevance

- While some animals exposed to even higher EtO concentrations developed certain cancers, these data are of highly questionable relevance to humans…
  - Inconsistent rodent results (e.g., mammary tumors);
  - Irrelevant EtO exposure levels;
  - Interspecies site concordance not scientifically supported (per the International Agency for Research on Cancer 2019);
  - Major lung & brain tumor findings in EtO-exposed rodents appear to be inapplicable to humans (e.g., brain tumors statistically decreased and lung cancer not increased in workers exposed to EtO levels up to millions of times higher than the public).

TCEQ Assumes EtO is a Potent Carcinogen

- Despite the inconclusive human evidence, both the TCEQ and USEPA have chosen to assume that EtO causes cancer in people and derive cancer-based toxicity factors.
- This is a conservative assumption in order to protect the public from the potential carcinogenic effects of long-term EtO exposure.
- USEPA acceptable excess risk range is 1-in-a-million (1E-06) to 1-in-10,000 (1E-04), and based on their 2016 assessment:

  1E-06 excess risk air concentration = 0.1 ppt (0.0001 ppb)

  1E-05 excess risk air concentration = 1 ppt (0.001 ppb)

  1E-04 excess risk air concentration = 10 ppt (0.01 ppb)

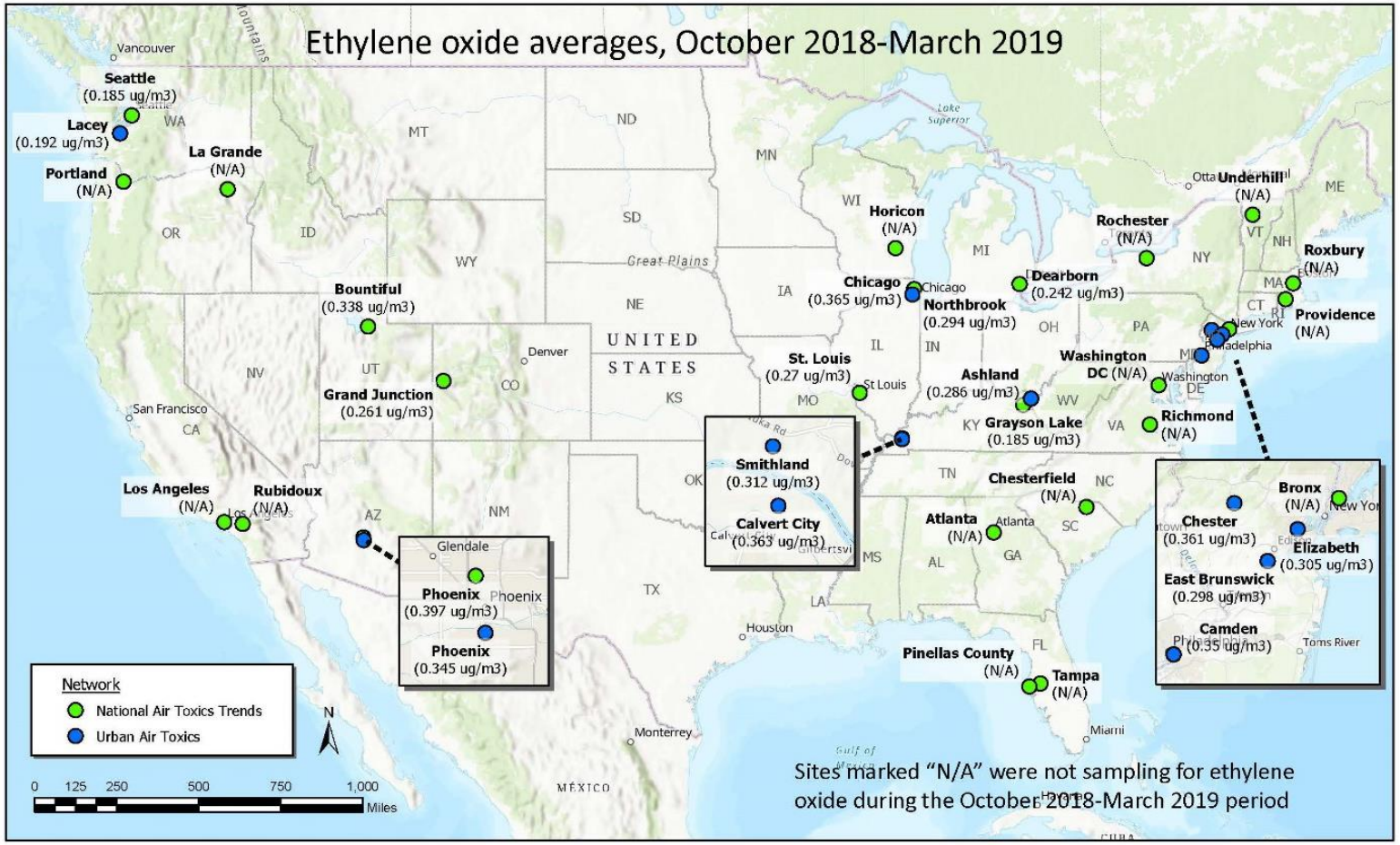
National Risk Driver Despite Inconclusive Human Evidence

- Based on theoretical excess risk estimates using USEPA's 2016 assessment, EtO has become the new national risk driver for the USEPA National Air Toxics Assessment (NATA).
- EtO is also naturally produced in the human body (i.e., endogenously) due to oxidation of ethylene.
- The range of the amount of EtO naturally present in the human body is equivalent to continuous exposure to ≈0.56-4.5 ppb in air, with a mean ≈1.9 ppb (Kirman and Hays 2017; GM ≈2.9 ppb per Jain 2020 analysis of NHANES data).

What is Range of Background Air Concentrations?

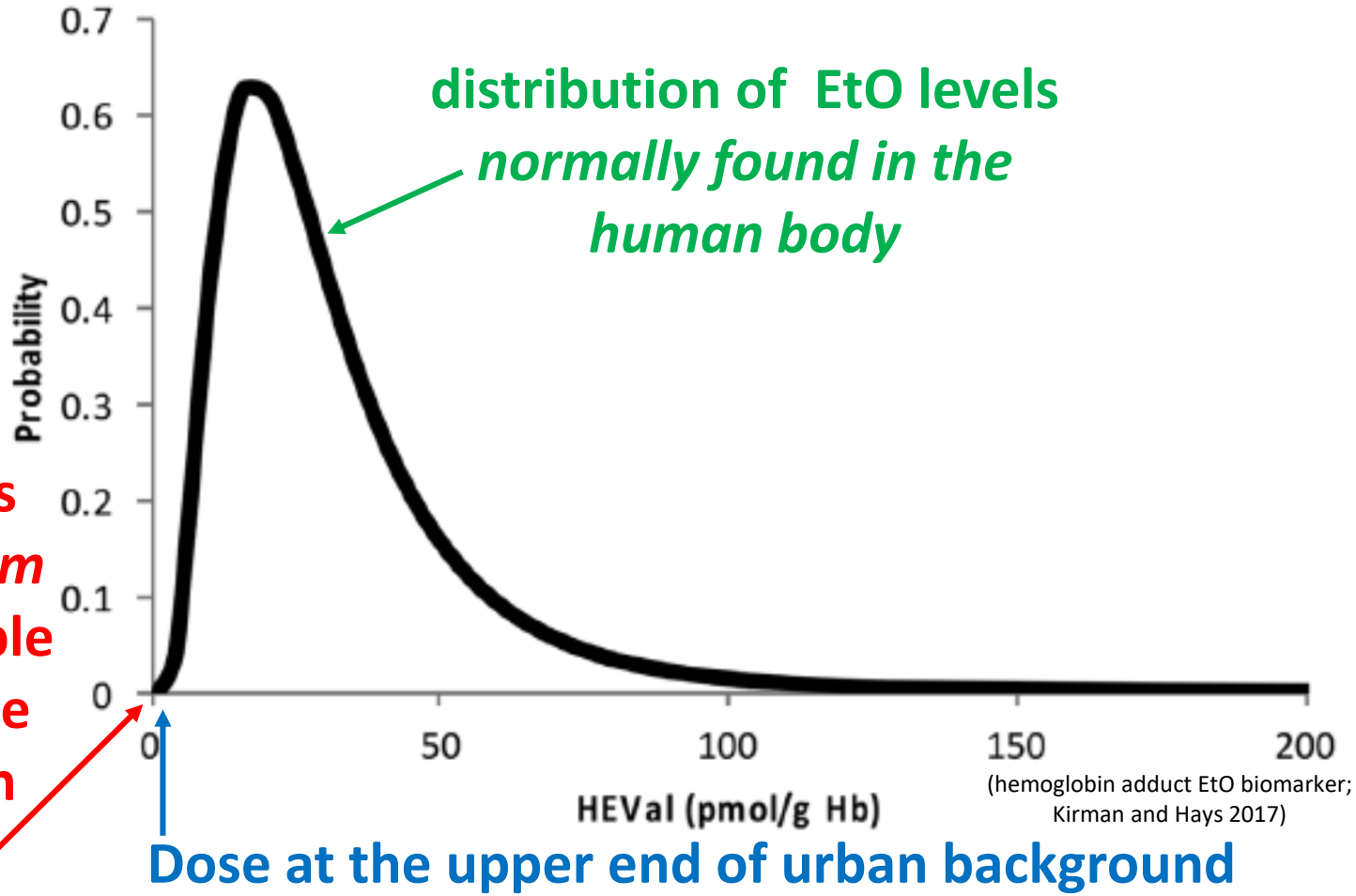
- 18-site urban air background of ≈0.2-0.4 µg/m³ (≈0.1-0.2 ppb)
- ≈10-20 times USEPA's maximum acceptable of 0.0185 µg/m³ (0.01 ppb)

National Air Toxics Trends and Urban Air Toxics monitoring sites



How do endogenous EtO, air background, and risk-based levels compare?

The amount of EtO naturally present in the human body corresponds to air concentrations much higher than urban background levels in air, which are themselves much higher than acceptable levels per USEPA's assessment…



Objective Scientific Perspective is Needed for EtO Risk

- Recognizing this, TCEQ's more recent EtO dose-response assessment is important and timely work.

The Public Needs Objective Scientific Perspective

- Some objective perspective based on best available science would be beneficial to the public and public officials in concerned communities…

2 Chicago plants shut down amid cancer concerns

Sean Reilly, E&E News reporter

Published: Monday, September 30, 2019

Protesters outside a Sterigenics International LLC facility. Stop Sterigenics/Twitter

Regulators Also Need Objective Scientific Perspective

- Some objective perspective based on best available science would also be beneficial for the NATA…

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Fact Sheet: EPA Taking Steps to Address Emissions of Ethylene Oxide

Latest National Air Toxics Assessment Shows Potential Long-Term Health Concerns in Some Areas

Print the Fact Sheet

- Download and print a copy of this fact sheet in PDF format

OVERVIEW

- **AUGUST 22, 2018 --** The U.S. Environmental Protection Agency (EPA) is taking steps to address emissions of the chemical *ethylene oxide* from some types of industrial facilities across the country.
- EPA is addressing ethylene oxide based on the results of the latest National Air Toxics Assessment (NATA), which identified the chemical as a potential concern in several areas across the country. NATA is the Agency's nationwide air toxics screening tool, designed to help EPA and state, local and tribal air agencies identify areas, pollutants or types of sources for further examination.
- The 2014 NATA uses emissions data from the latest National Emissions Inventory (2014 is the most recent data available), along with the latest scientific information on air toxics and health, to estimate long-term air toxics exposures and potential public health risk in census tracts across the United States.

So why is Sound Science needed for EtO?

- Because these grave concerns about the carcinogenic risk posed by EtO do not stem from EtO's carcinogenic potency, but rather the scientifically flawed assessment of it.
- The USEPA (2016) URF for EtO is based on a scientifically unjustified, overall supra-linear *two-piece spline dose-response model* that has been demonstrated by the TCEQ to be:
  1) statistically significantly over-predictive for two cohorts (NIOSH, UCC); AND
  2) not supported by the carcinogenic mode of action (MOA);
  3) not supported by data on EtO levels normally produced within the human body;
  4) not supported by reality checks on population background incidence; and
  5) not supported by appropriate standard model fit criteria.

What's new in TCEQ's assessment?

- To begin with, the TCEQ dose-response assessment considers *new data and/or analyses from the scientific literature* not available in 2016 (e.g., Vincent et al. 2019, Marsh et al. 2019, IARC 2019, Kirman and Hays 2017, Jain 2020).
- The assessment also considers *new TCEQ analyses* and *new data provided to TCEQ* (e.g., accuracy evaluation analyses for the dose-response models, evaluation of potential healthy worker effects for EtO-specific cancer endpoints, sensitivity analysis of the accuracy of model predictions to healthy worker effects for overall cancer mortality, as of yet unpublished summary results from a recent UCC cohort update, Cox proportional hazards modeling results for multiple exposure lag times, validation analyses of NIOSH-based dose-response models using the UCC lymphoid cancer mortality data).

TCEQ's EtO Assessment is Now Final

- TCEQ's draft EtO assessment (June 2019) underwent a public comment period.
- The agency received numerous and thorough comments from diverse groups, both for and against (e.g., NGOs, academia, industry, citizens, author of multiple EtO studies, first author of USEPA's assessment through another institution).
- Comments were not particularly difficult to fully address scientifically in written responses and appropriate revisions were made to the draft assessment, resulting in an even more scientifically robust TCEQ draft assessment (dated January 2020).
- The revised draft assessment (January 2020) underwent an independent external expert peer review, which has been concluded.
- Necessary changes were made to TCEQ's EtO dose-response assessment.
- This thorough and extensive scientific process has culminated in the final TCEQ assessment for EtO, which incorporates the best science currently available.

TCEQ's EtO Assessment is Now Final

- Development Support Document (DSD) homepage: https://www.tceq.texas.gov/toxicology/dsd/final
- Toxicology Division's ethylene oxide (EtO) homepage: https://www.tceq.texas.gov/toxicology/ethylene-oxide

TCEQ's final ethylene oxide ESL comes during a unique period of strain on the nation's medical industry. TCEQ's ethylene oxide cancer dose-response assessment demonstrates that this chemical, which is used to sterilize half of the approximately 40 billion medical devices used in the United States every year, poses less risk than was previously thought.

Previous assessments of the chemical's risk by other agencies forced the closure of some ethylene oxide sterilization facilities in other parts of the country and threaten more closures. These closures have already caused a shortage of pediatric tracheostomy (breathing) tubes, and the U.S. Food and Drug Administration has issued an alert about possible additional disruptions in the supply of sterile medical devices.

While the agency's assessment is a purely scientific exercise and does not consider the implications for the supply of sutures, surgical kits, and other medical devices, TCEQ's final ESL for ethylene oxide may help mitigate these supply chain risks. Using the most current science, the new limit remains protective for people living near facilities that emit ethylene oxide while providing flexibility for the medical sterilization industry to continue its own critical role in patient care in the state of Texas.

After years of careful review and analysis, TCEQ updates ethylene oxide exposure limit

May 15, 2020 – Chemical critical for sterilizing medical equipment safer than previously thought

FOR IMMEDIATE RELEASE

Contact	Andrew Keese
Phone	512-695-8072
After Hrs	512-695-8072

After years of extensive study, public input and peer review, TCEQ today finalized its updated safe exposure level for ethylene oxide.

The agency has established a long-term effects screening level of 2.4 parts per billion, which is the health-protective air concentration used to determine limits for proposed air permits in Texas. TCEQ's previous ethylene oxide ESL, a preliminary standard, was 1 ppb.

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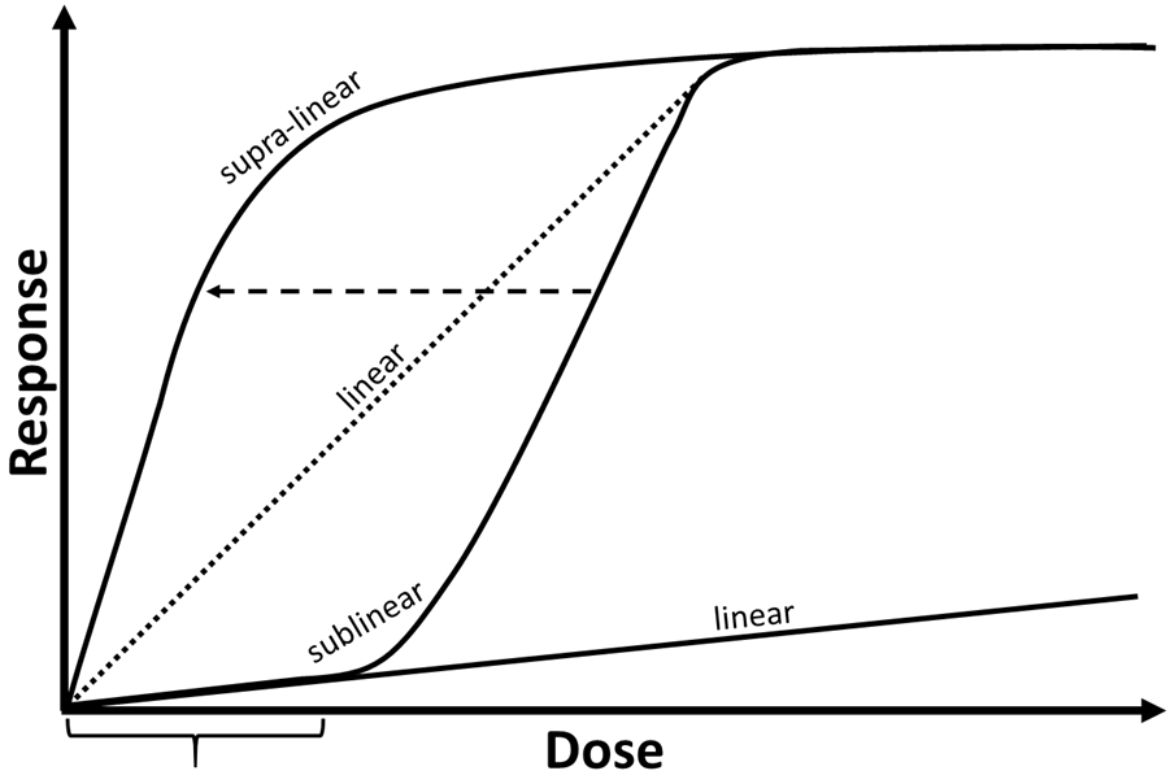
TCEQ began its cancer dose-response assessment for ethylene oxide in 2017 and published a draft assessment for public comment in 2019. A revised assessment was then peer reviewed by an independent, external panel of scientific experts, who completed their work in early 2020. The resulting rigorous final assessment, responses to public and expert comments, and other information regarding ethylene oxide can be found at **www.tceq.texas.gov/toxicology/ethylene-oxide (/toxicology/ethylene-oxide)**.

What's the key difference between the assessments?

Both the TCEQ and USEPA used results from the same NIOSH cohort (e.g., 17,500+ workers, 53 lymphoid cancer cases), but in different dose-response models:

- USEPA used an unconventional *Two-Piece Spline Model* – however, USEPA acknowledges *there are no MOA data that support its overall supra-linearity* (i.e., no MOA data support its biological plausibility).



Sublinearity expected in the endogenous range (as opposed to a steep low-dose slope from an overall supra-linear model), but in the absence of truly low-dose data and dose-response data only being available in the higher-dose region, the full dose-response would not be apparent and the dose-response would shift to the left, with only the portion defined by higher-dose data being defined and appearing supra-linear in nature.

TCEQ's Assessment is Supported by MOA + More

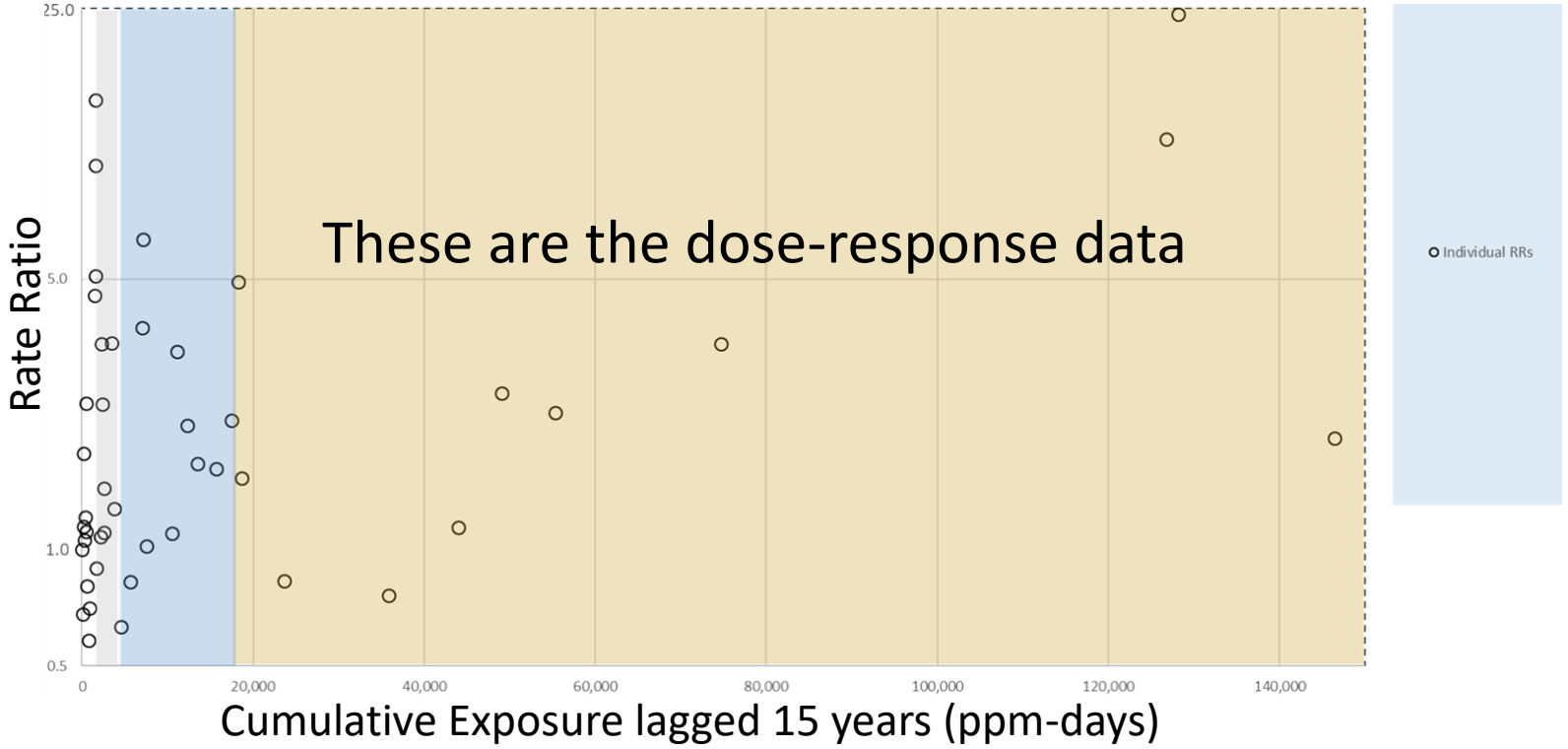
- TCEQ used a Cox Proportional Hazards Model – a standard dose-response model; its linearity across EtO doses of interest is supported by the mutagenic MOA determined by both agencies and other relevant considerations (e.g., the model and associated results are much more biologically plausible, TK of EtO also appear linear up to ≈200 ppm).

USEPA also *miscalculated model selection criteria* (e.g., Akaike information criteria (AIC) and model fit p-values) and visually misrepresented model fit to the data, whereas the TCEQ did not (see the DSD for details).

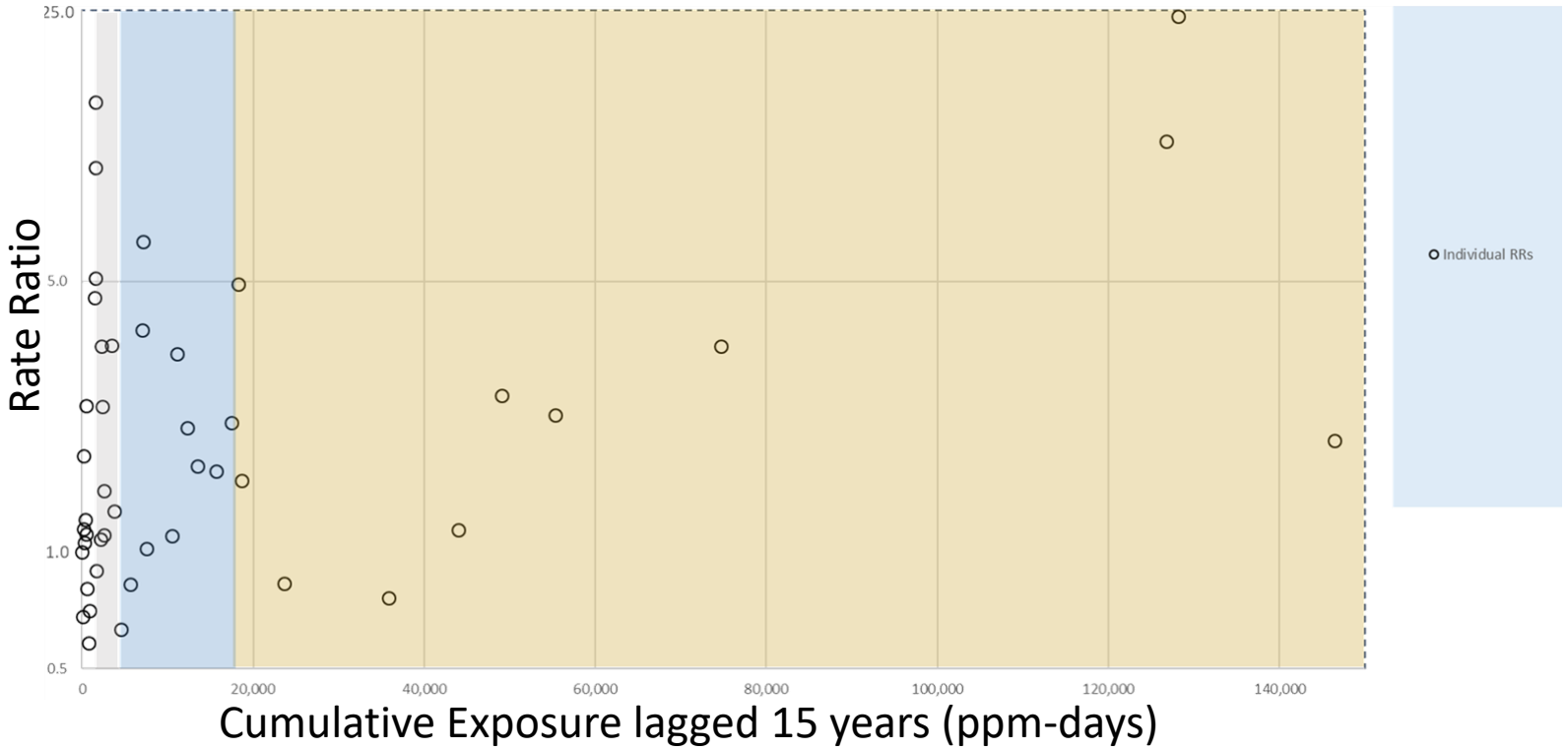
Key Cancer Data

- Here are the primary data at issue:

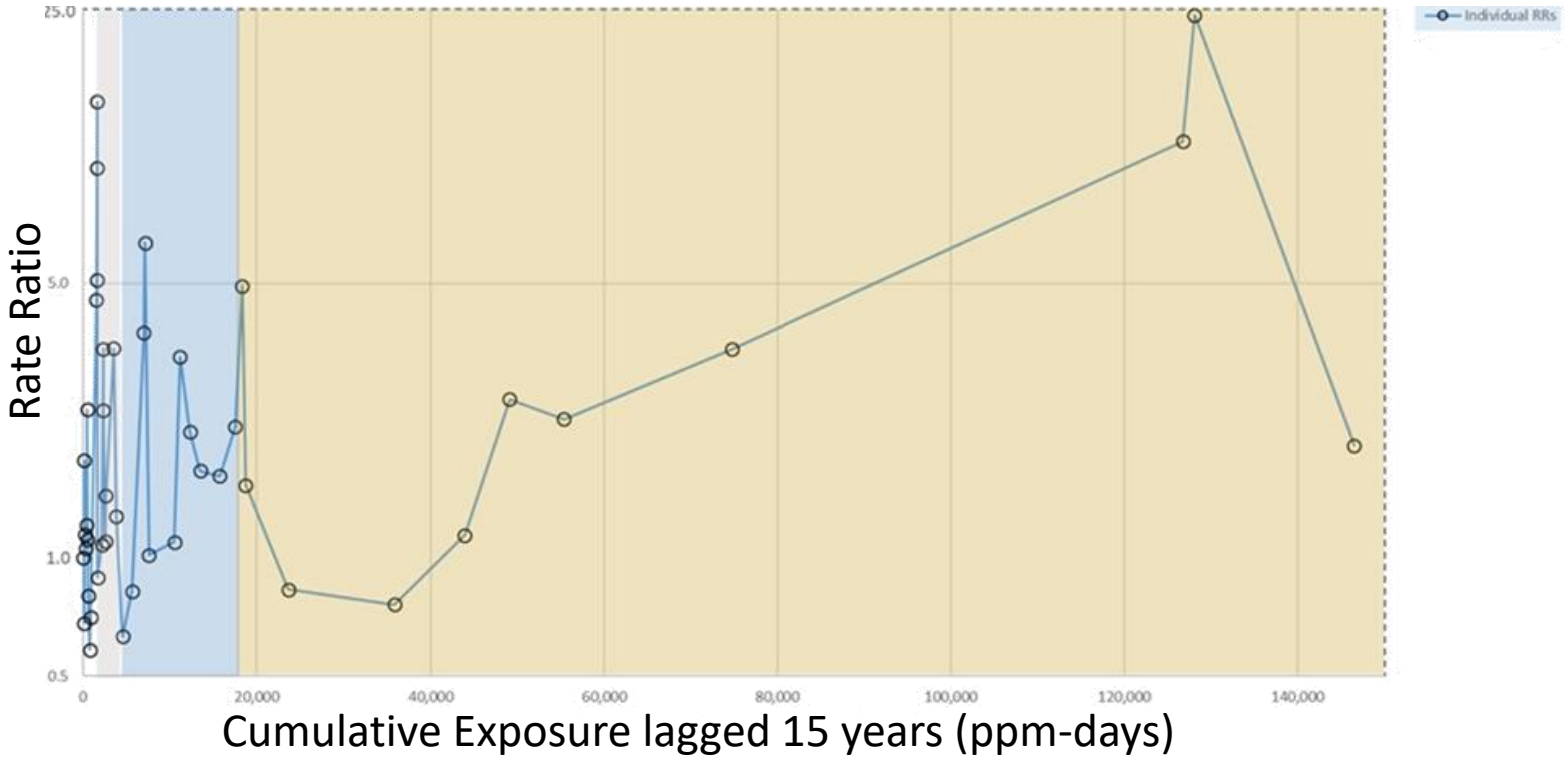
  53 lymphoid cancer mortalities in the NIOSH cohort…



Is there a dose-response and what is it?

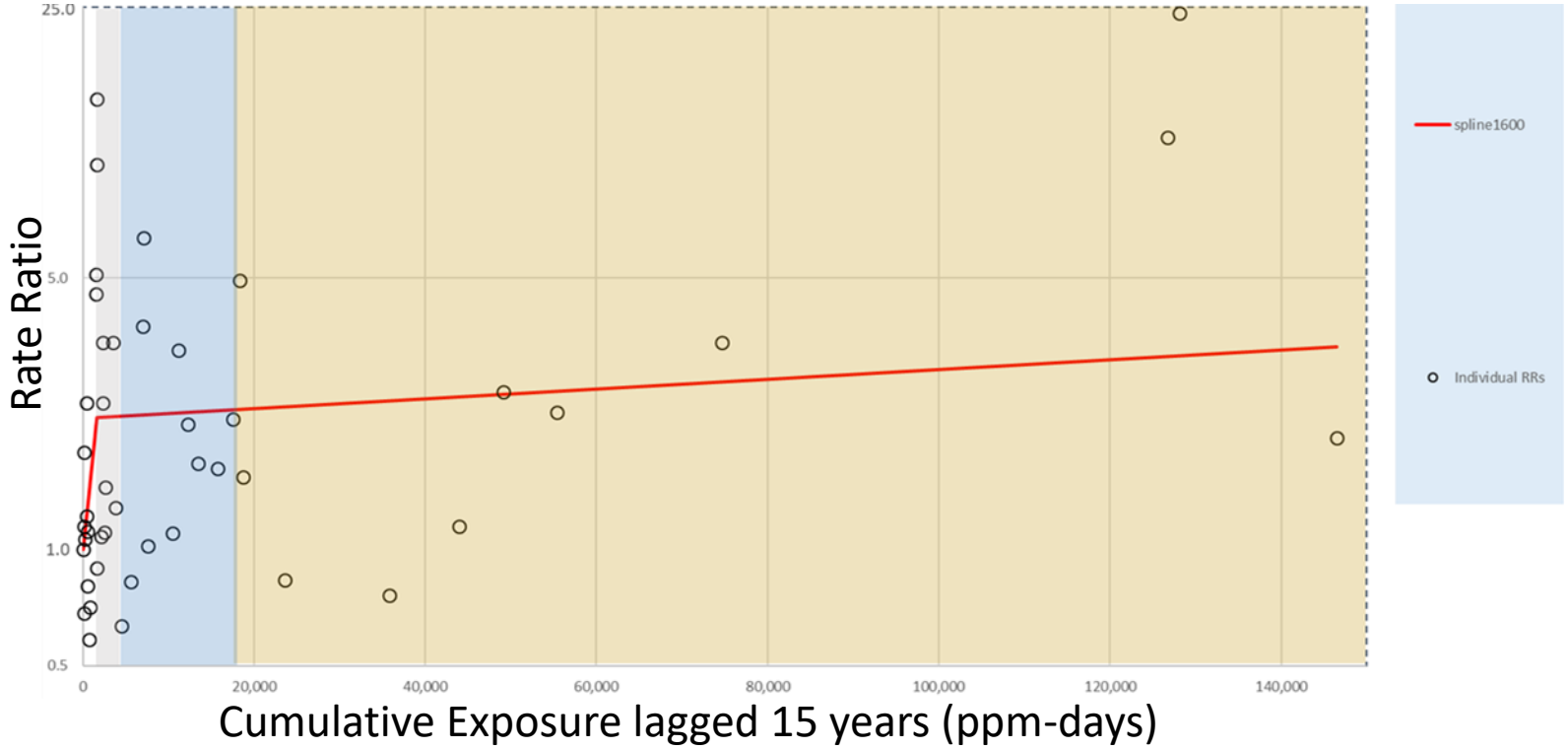


- The data points suggest no apparent dose-response pattern and less than ideal dose-response data…



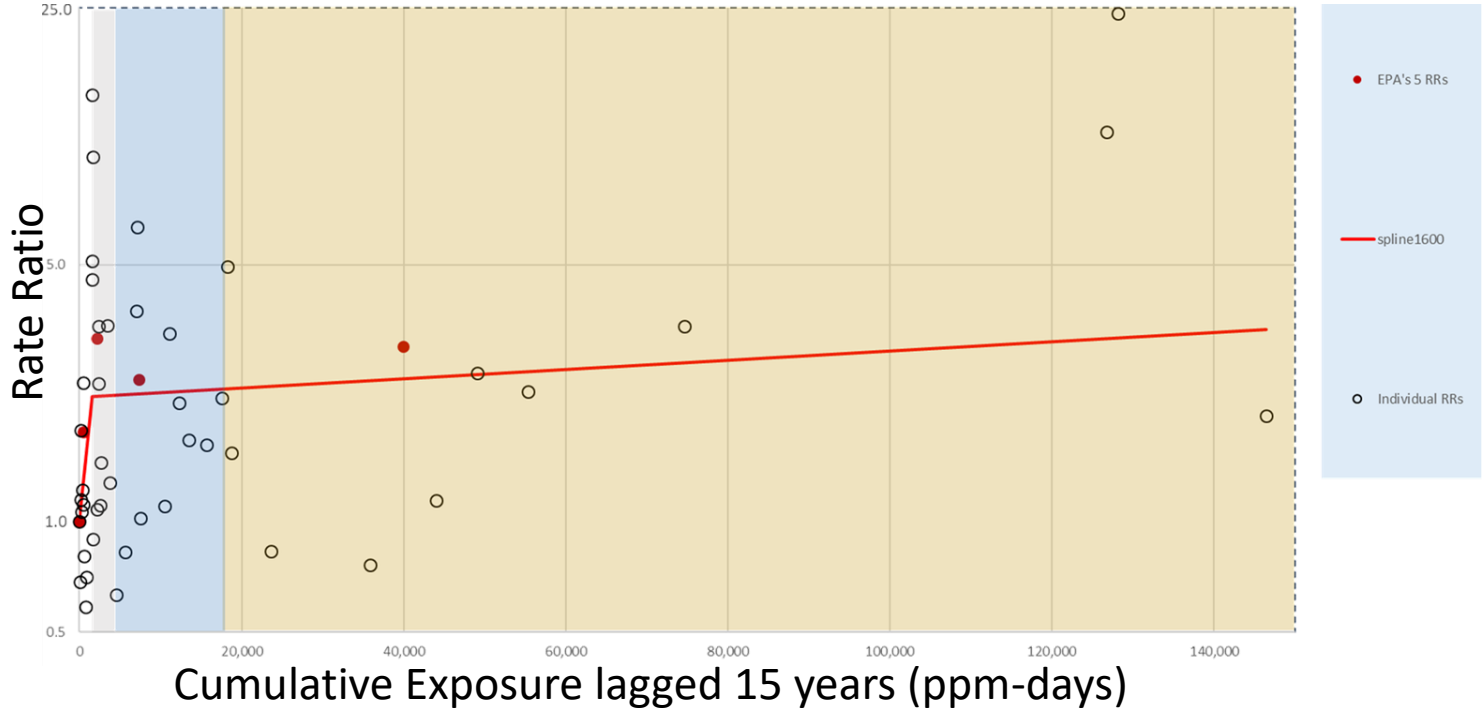
How do you in effect “connect the dots”?

- USEPA (2016) suggests that based on the SAB-reviewed assessment, the best way to connect the dots and reveal the dose-response is like this…

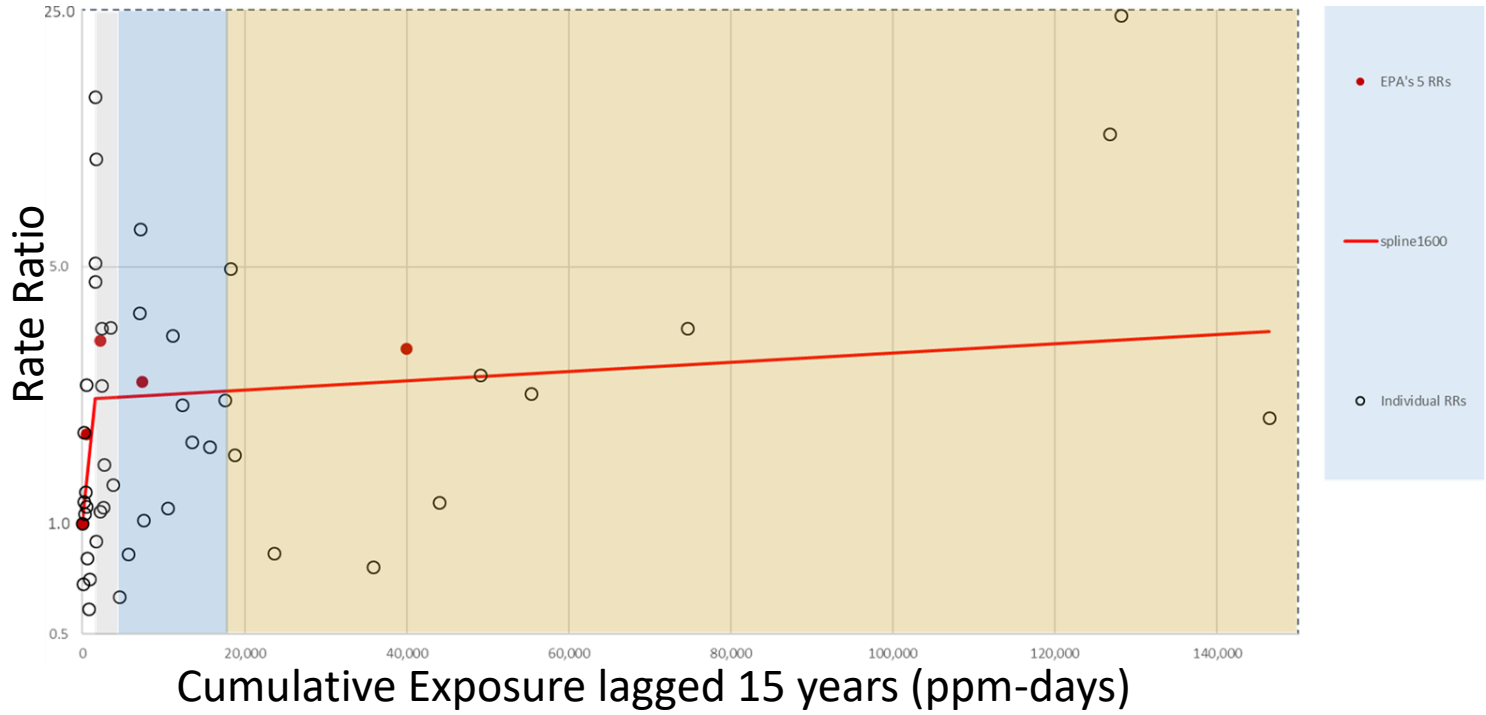


USEPA believes this because:

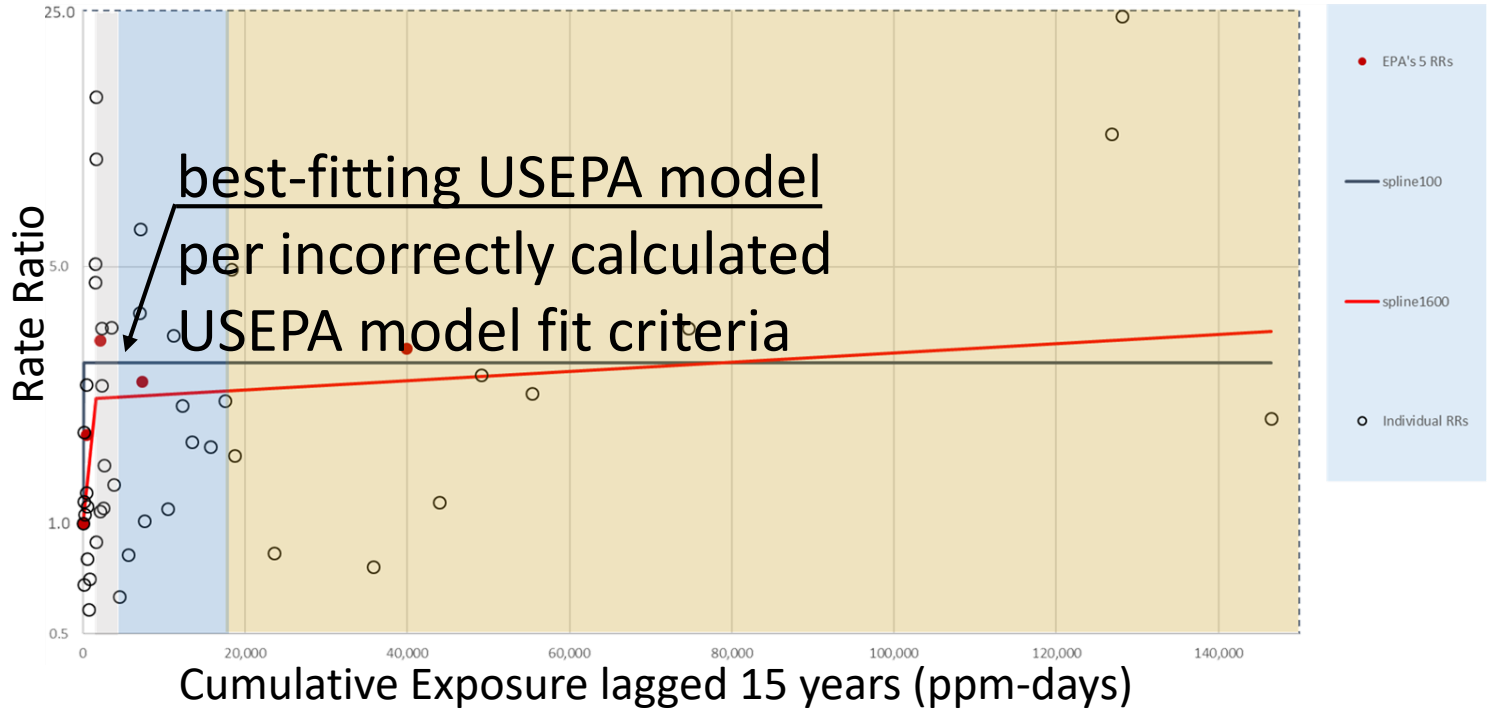
1. Arbitrarily grouping these individual data into 5 categories results in the red dots (categorical rate ratios or RRs) shown below; and
2. *Inappropriately* calculated p-values and AIC values suggest that their unconventional linear two-piece spline model fits the individual data better than standard dose-response models such as the Cox proportional hazards model used by TCEQ.



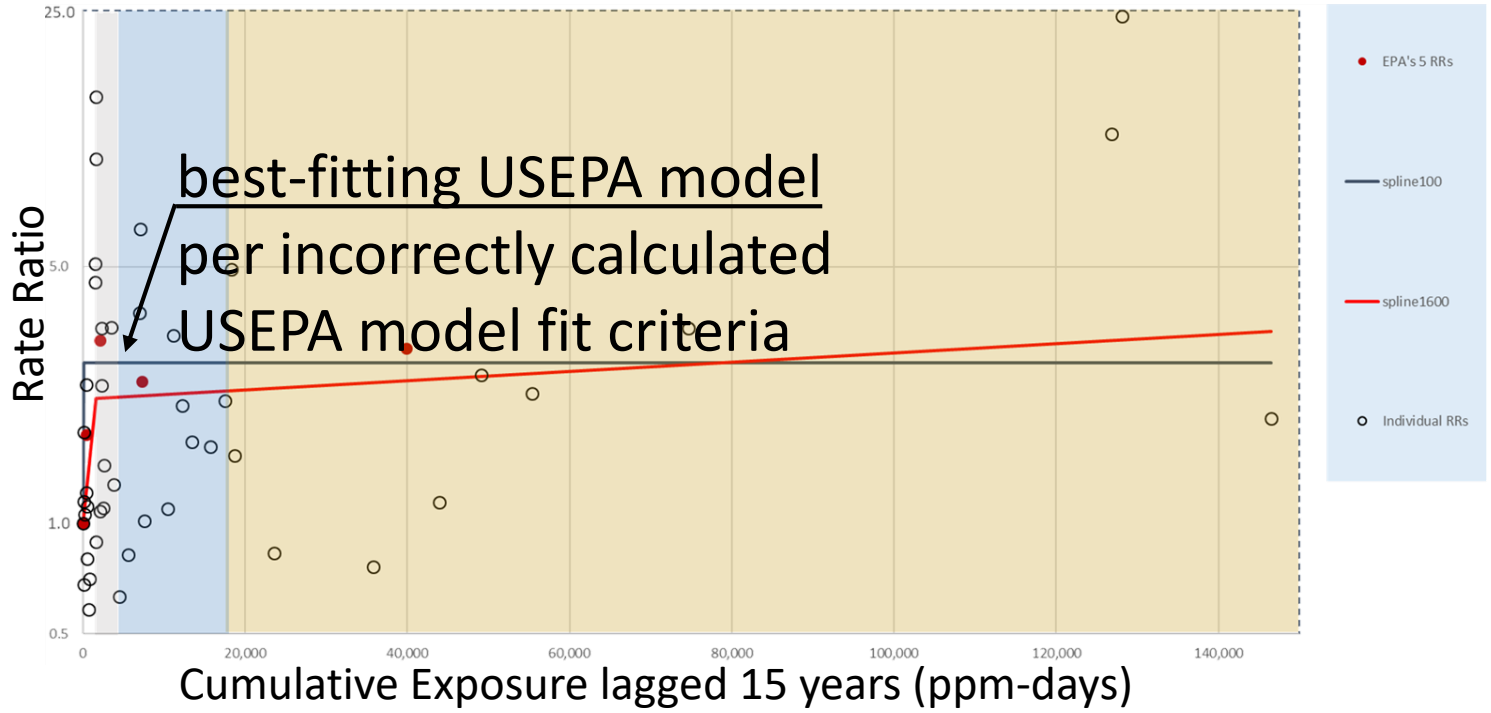
However, this was not the first time that these inappropriately calculated p-values and AIC values (and categorical RR red dots) led USEPA astray...



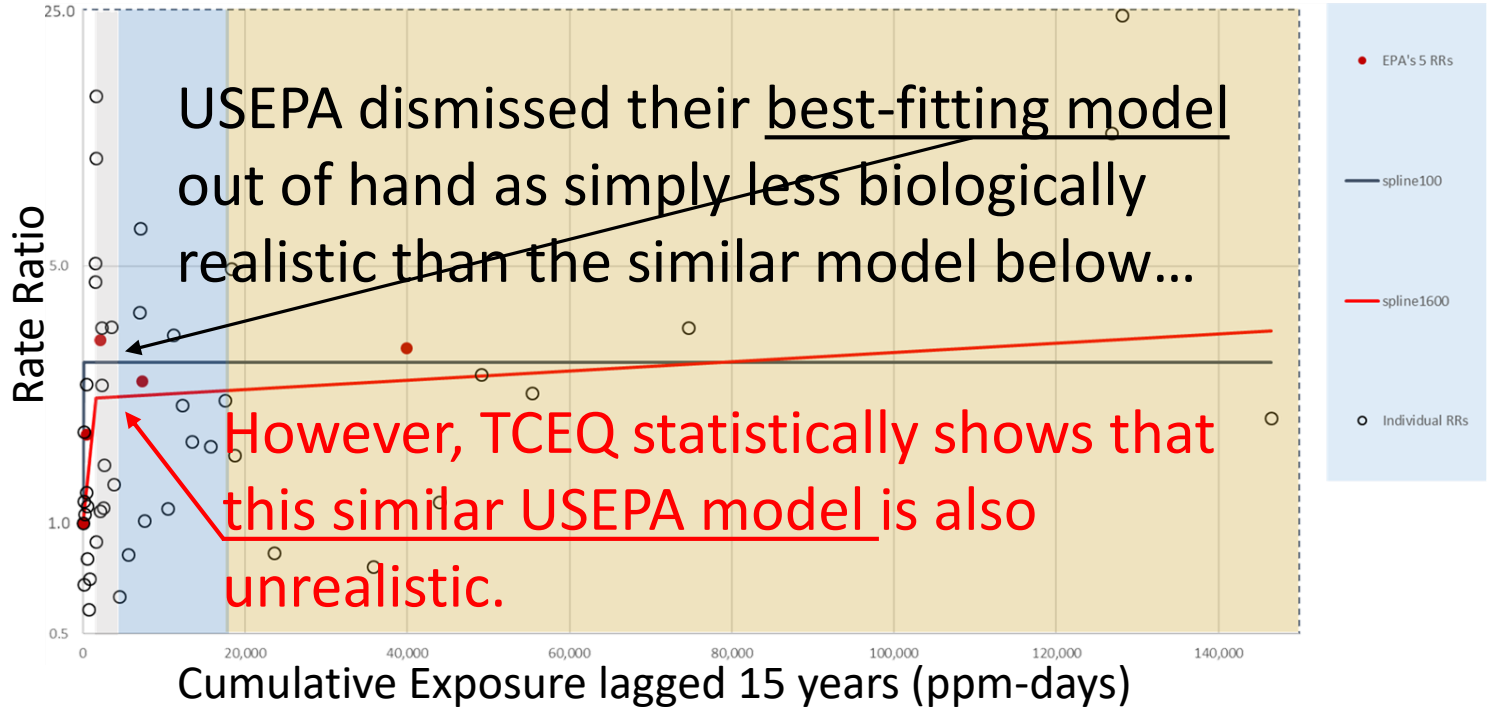
The same incorrectly calculated values suggested that a similar model (linear two-piece spline model with the knot at 100 ppm-days) fit even better…



…but USEPA dismissed their best-fitting model as less biologically realistic (relatively speaking), even in the absence of any data to put model biological plausibility into context.

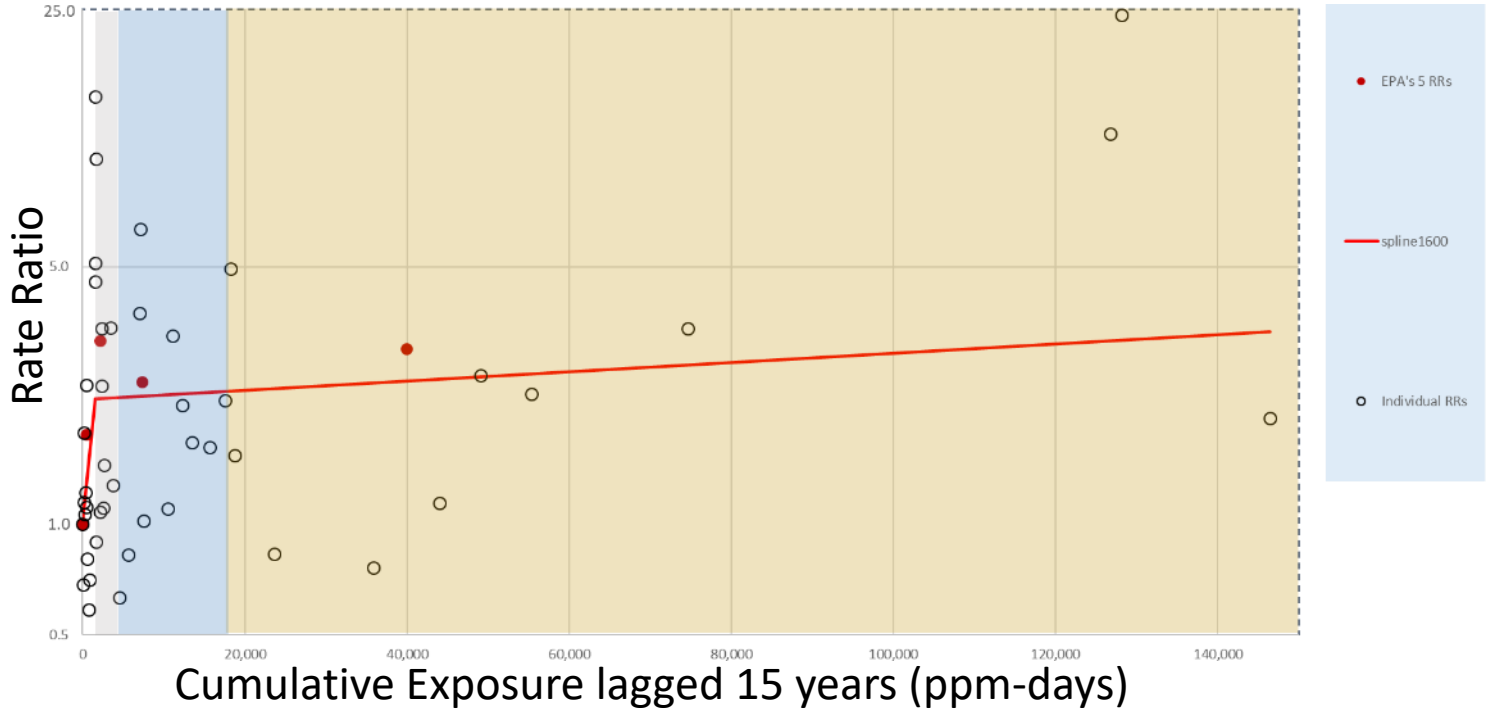


By contrast, in the context of relevant data and analyses, the TCEQ actually demonstrates that USEPA's similar, second choice model is also unrealistic.



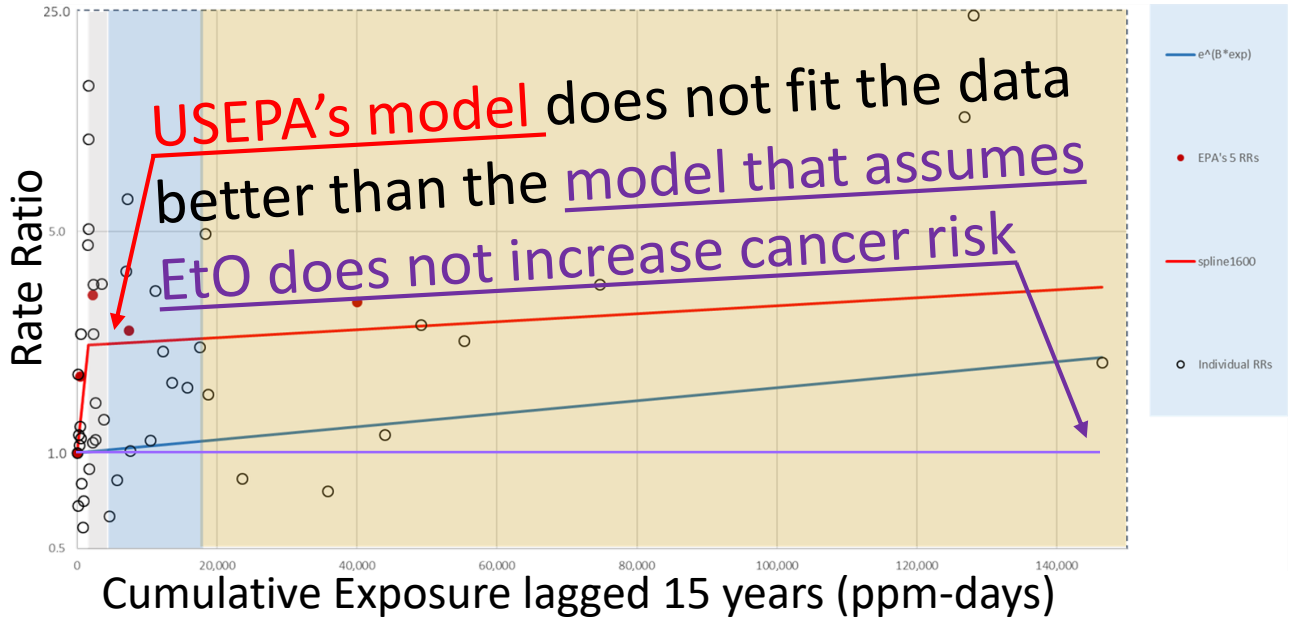
In regard to the categorical RR red dots, they…

1. Are *not* the actual observed data modeled;
2. *Hide the true variability* in the actual underlying data; and
3. Make little sense in terms of dose-response considering that there is *no mechanistic/biological explanation.*

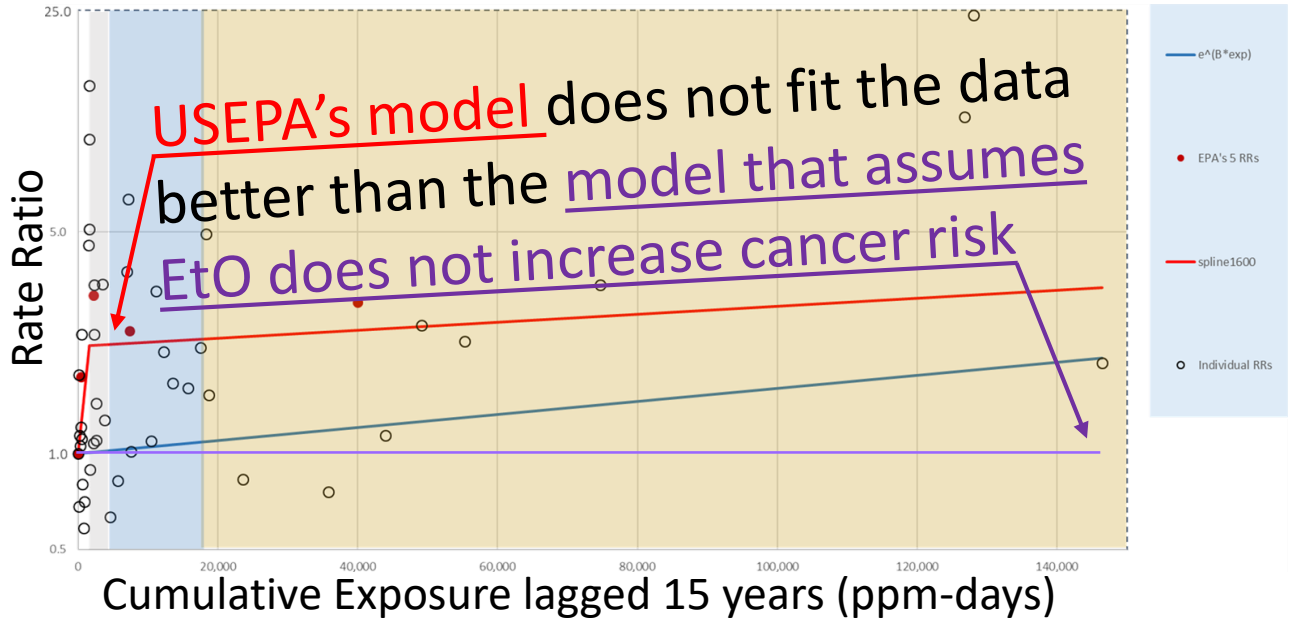


Moreover, when p-values and AIC values are *appropriately calculated* (i.e., accounting for the "knot" between splines being statistically optimized for model fit as opposed to being "fixed" *not based on the data* per SAB), TCEQ finds that the linear two-piece spline model:

1. *Does not fit the data modeled better than the standard Cox proportional hazards model*; and
2. Statistically, *does not fit the actual data better than the null model* with zero slope that assumes EtO does not increase cancer risk.

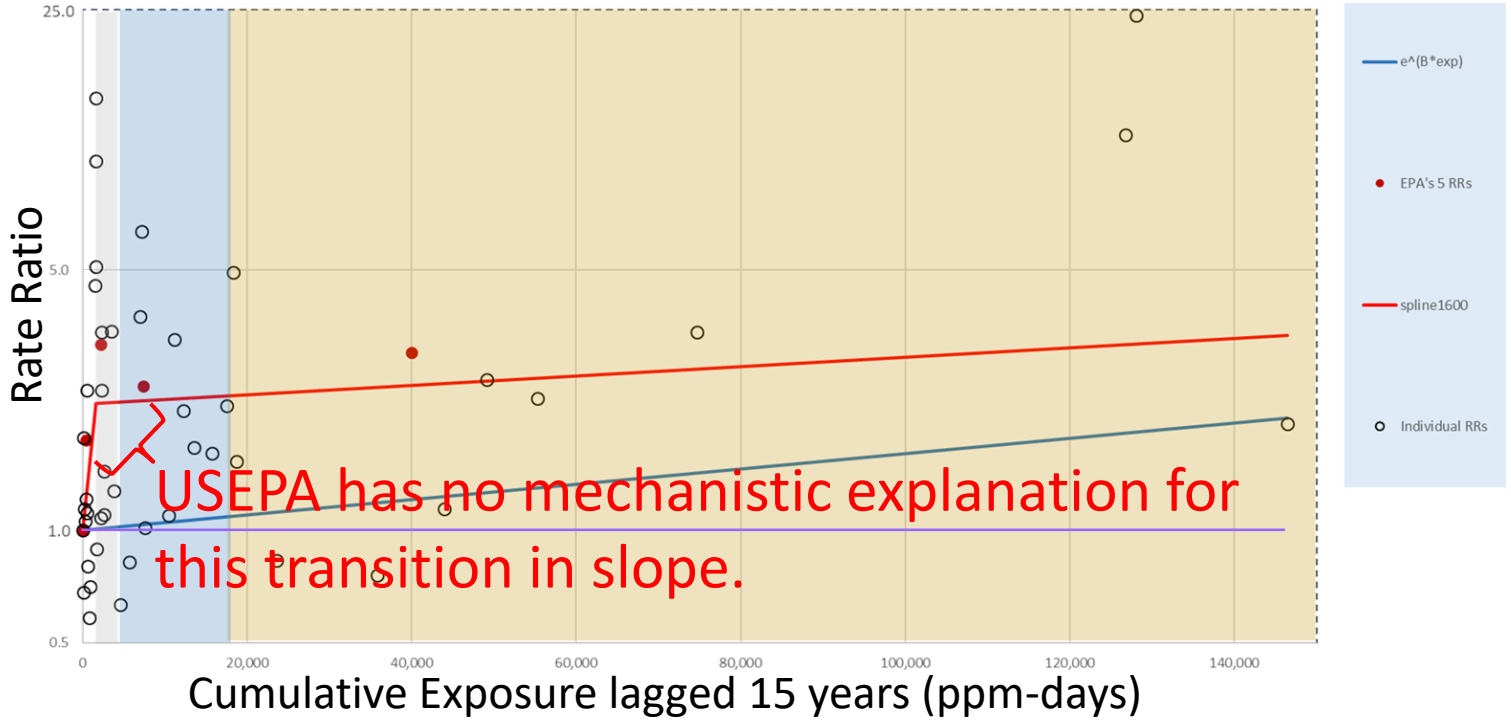


- Thus, these *appropriately calculated* model fit criteria do not suggest adopting USEPA's unconventional model over the standard Cox proportional hazards model.
- Neither do other important considerations that come into play…



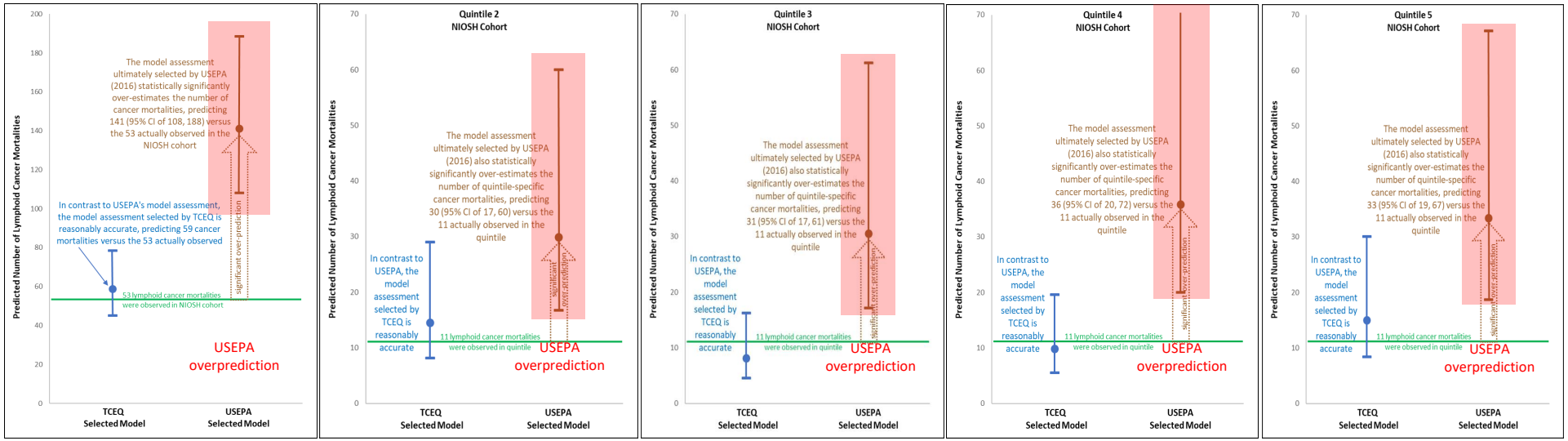
These critical considerations include TCEQ findings that…

3. USEPA (2016) acknowledges *no mechanistic support* for their overall supra-linear two-piece spline model;



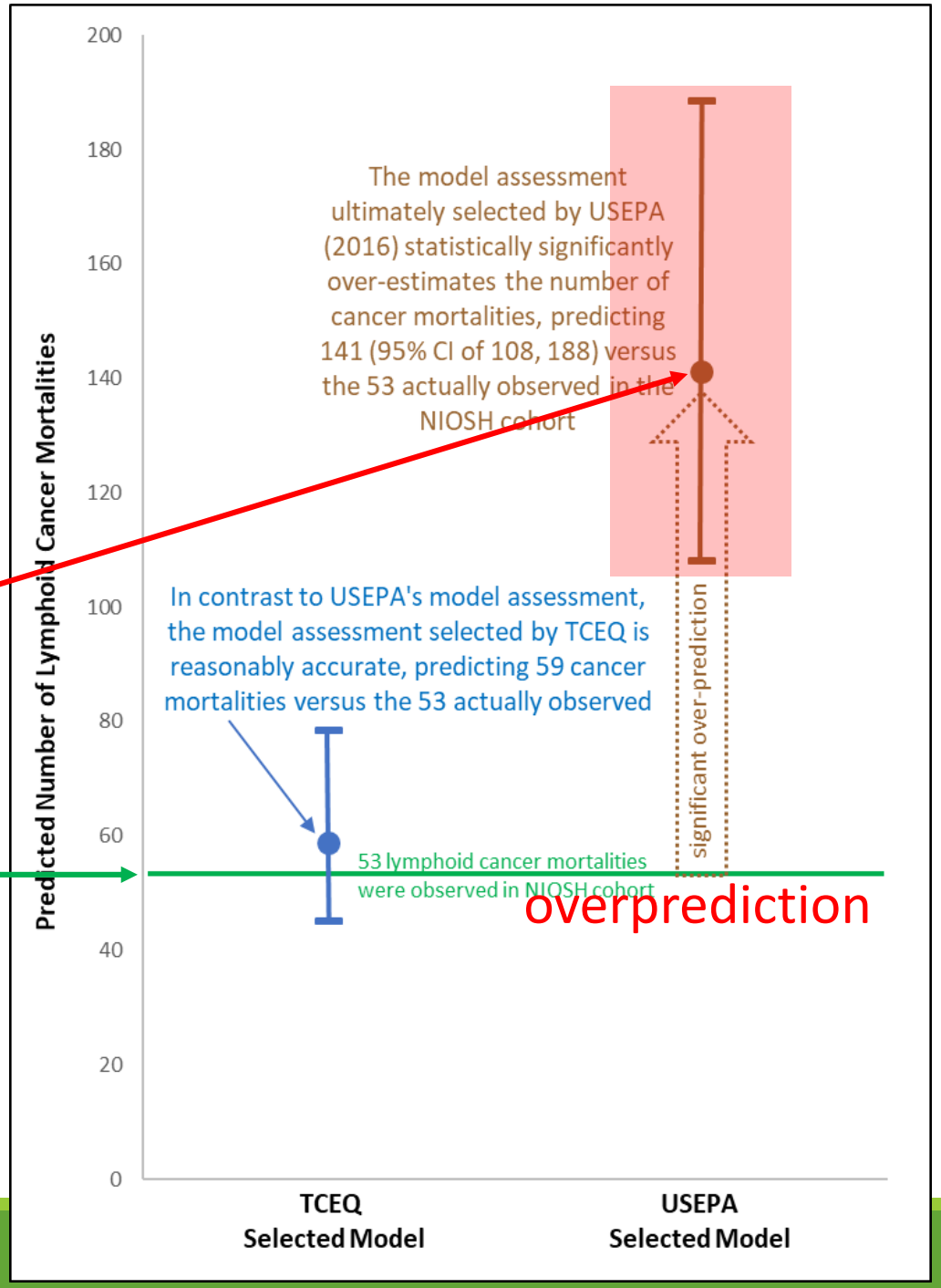
These critical considerations include TCEQ findings that…

3. USEPA (2016) acknowledges *no mechanistic support* for their unconventional, overall supra-linear two-piece spline model;
4. USEPA's model *statistically significantly overpredicts the number of lymphoid cancers* in the NIOSH cohort as a whole (both MLE and UCL), in all but one exposure quintile for the MLE, and in all quintiles for the USEPA-selected UCL…

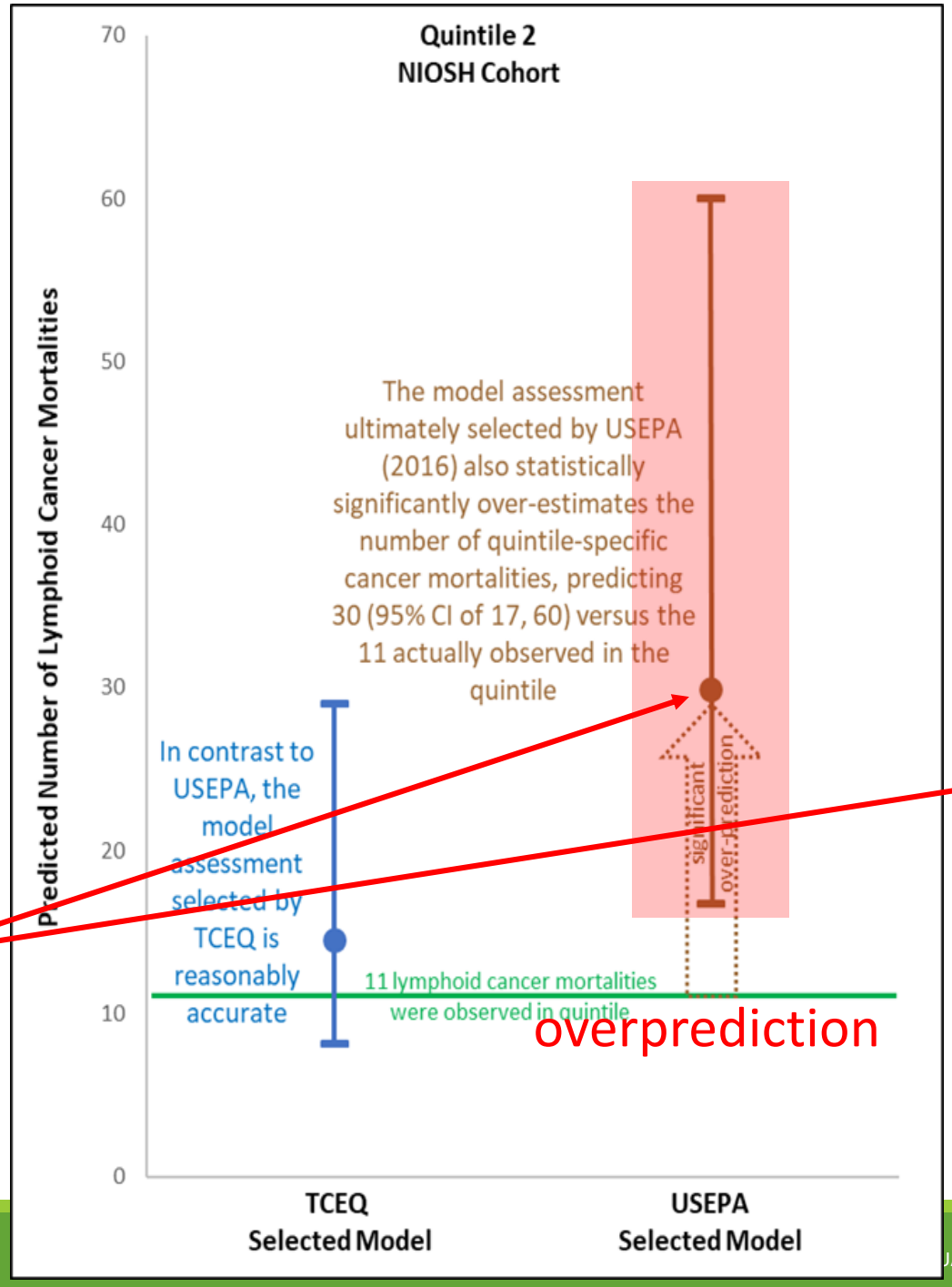


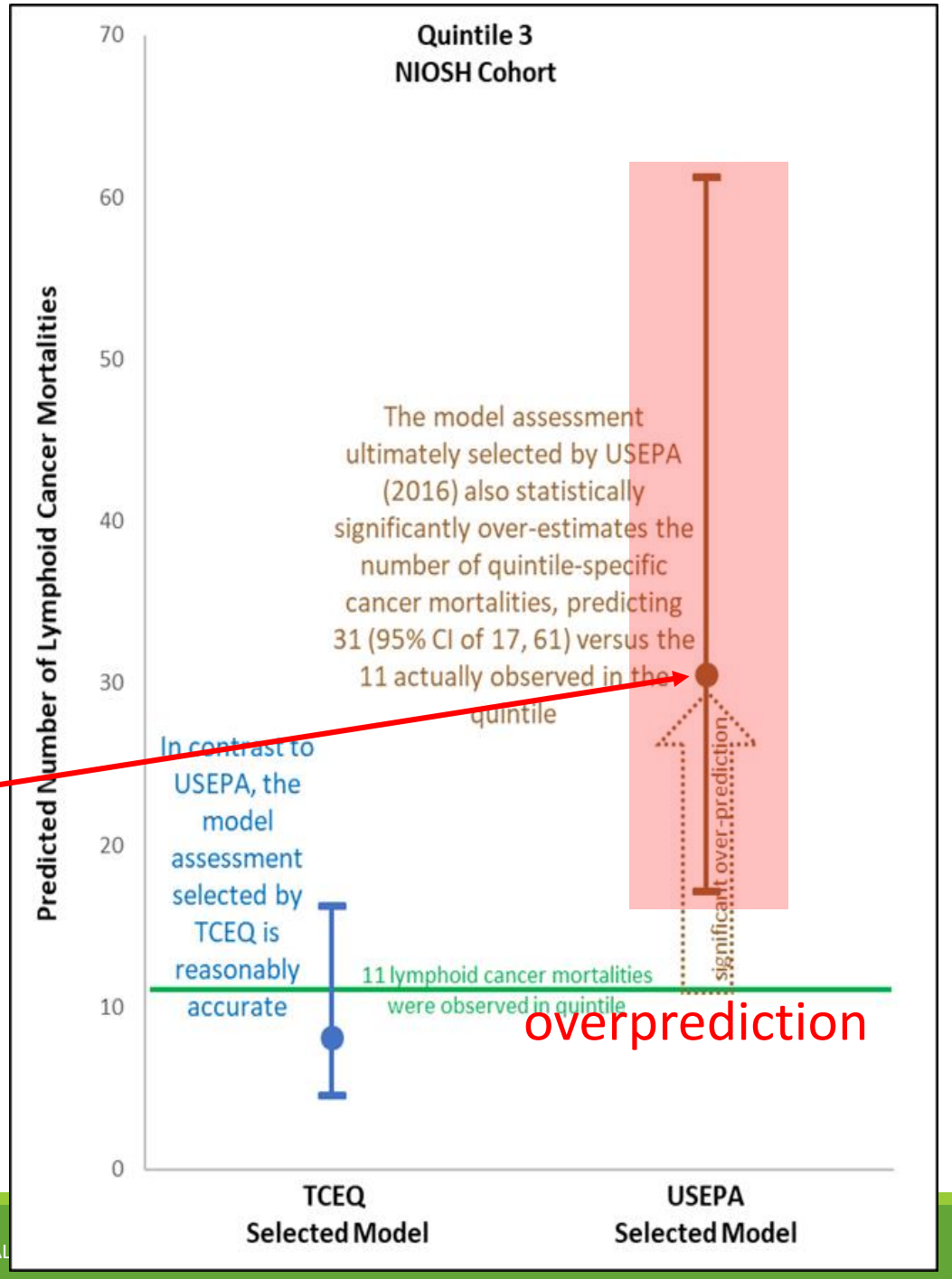
Note: Such model predictions are scientifically appropriate given that the lymphoid mortality rate in unexposed NIOSH workers was not statistically different than that in the general U.S. population. Even if a healthy worker effect for overall cancer mortality is assumed for purposes of a sensitivity analysis, cohort lymphoid cancers are still statistically significantly overpredicted by USEPA's model.

USEPA's selected model assessment predicts 141 lymphoid cancers (95% CI 108, 188) versus the 53 that actually occurred.

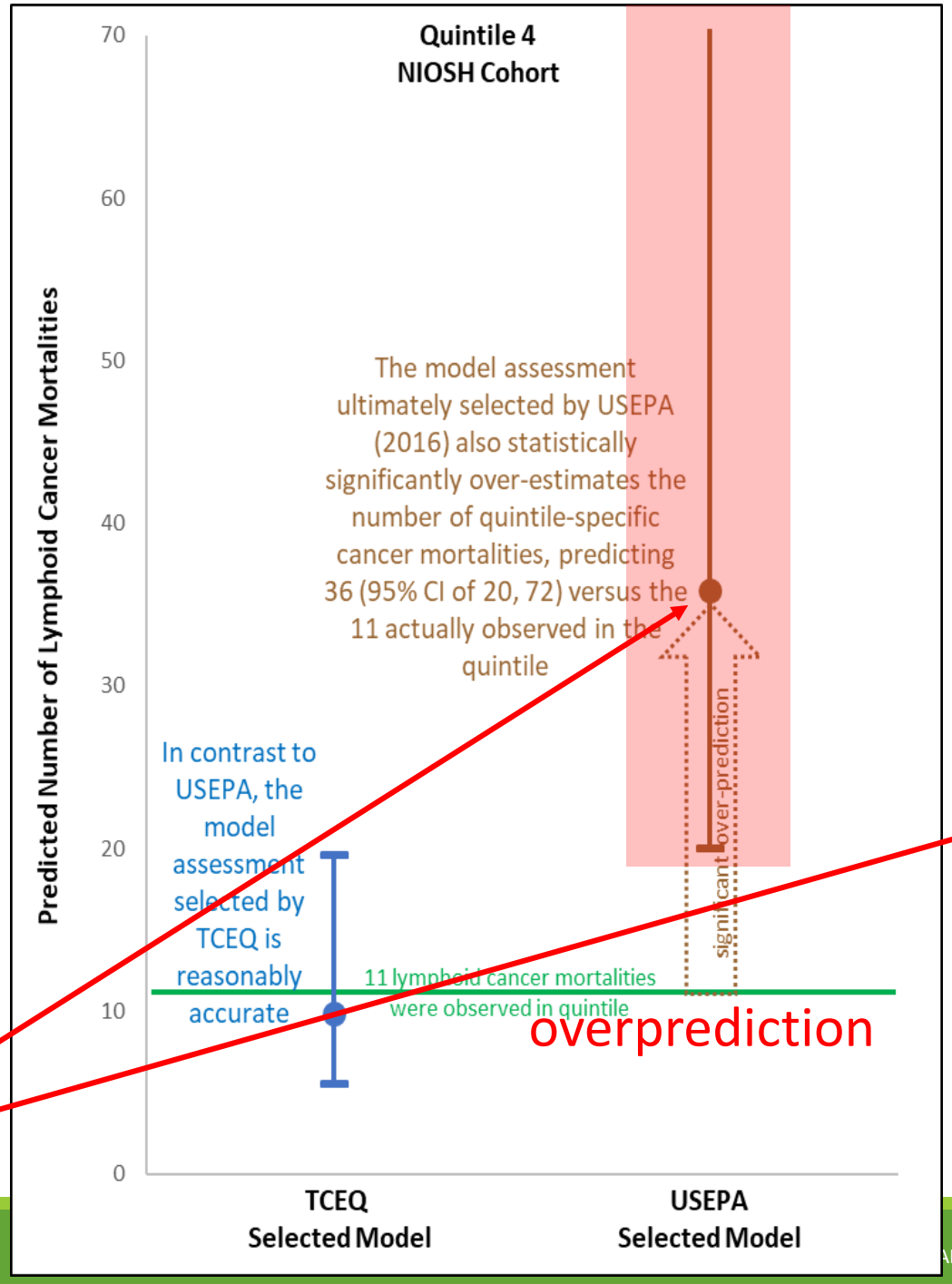


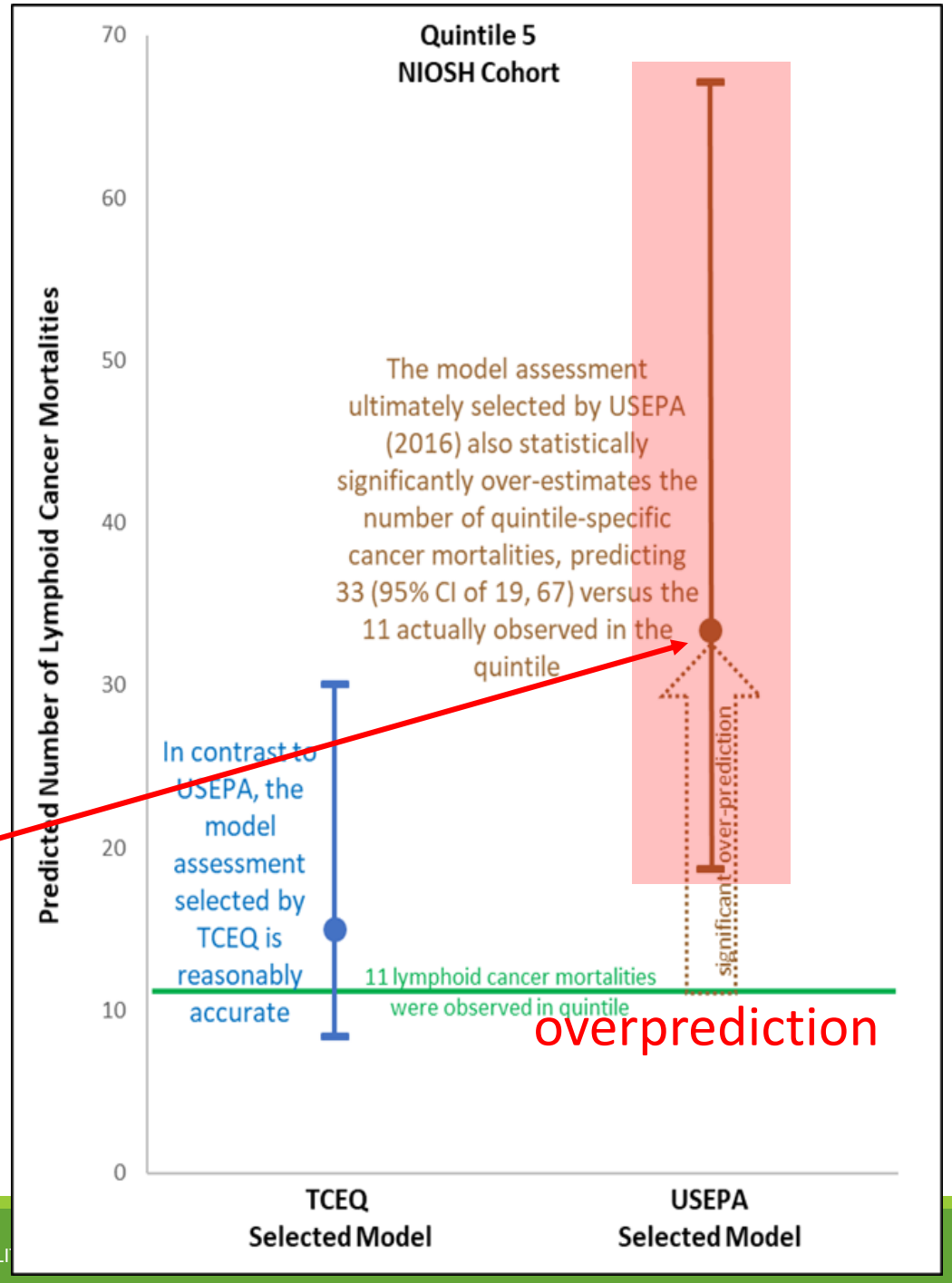
USEPA's selected model assessment also overpredicts lymphoid cancers for exposure groups…





USEPA's selected model assessment also overpredicts lymphoid cancers for exposure groups… *every exposure group*





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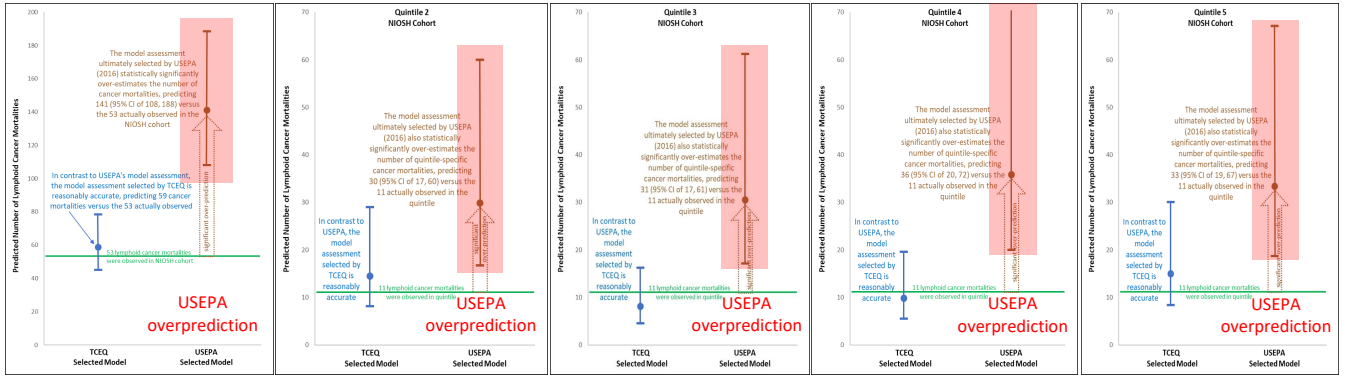
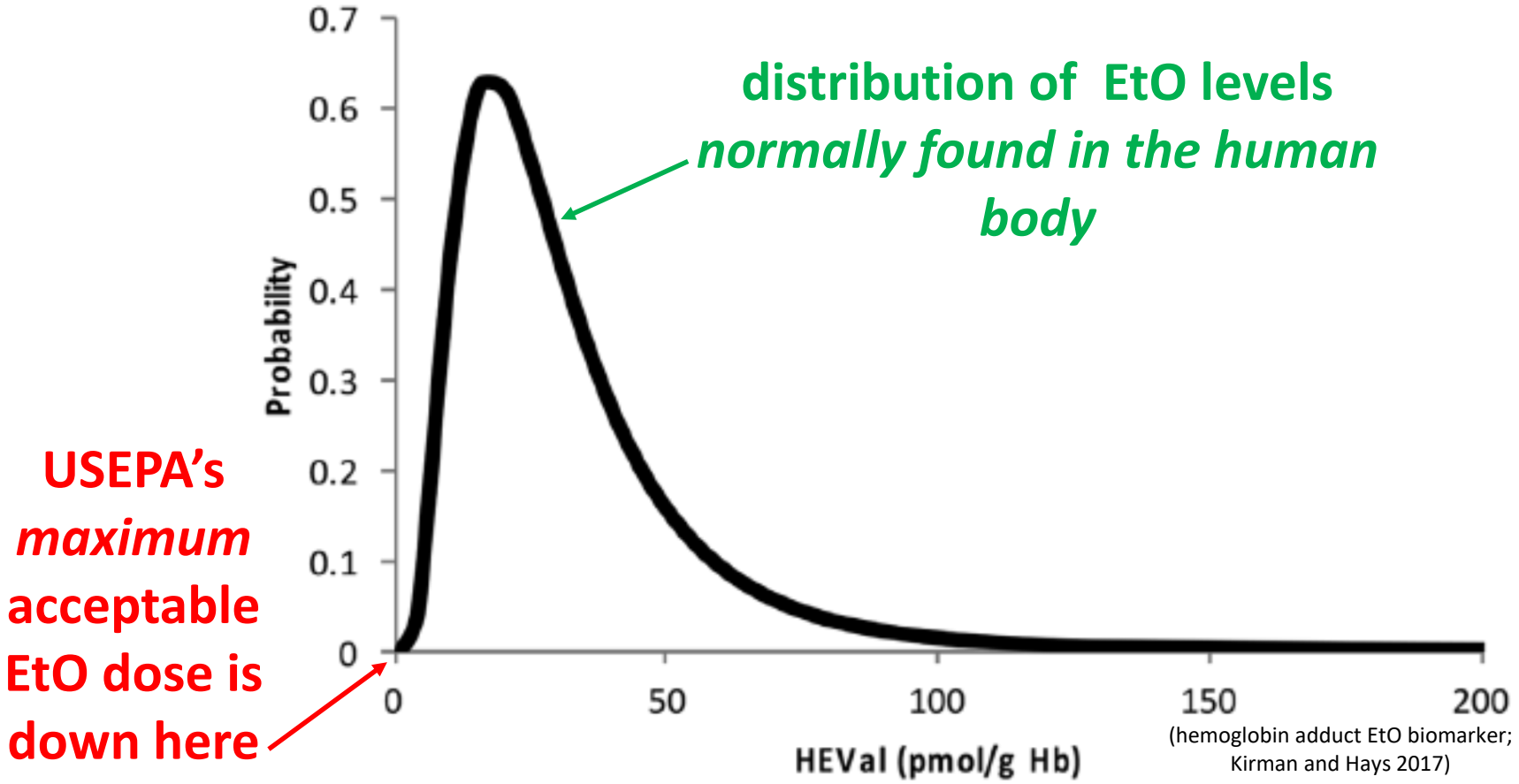


5. USEPA's model (MLE and UCL) *predicts statistically significant increased lymphoid cancers in exposure quintiles that simply were not observed*.

In addition to these important considerations, TCEQ has found:

6. USEPA's model/URF also appears to *overpredict lymphoid cancers in the general U.S. population* based on endogenous and background levels in non-smokers and smokers, respectively (population weighted; see the DSD); and
7. *USEPA's risk-based air concentrations correspond to doses orders of magnitude below even the 1st percentile of the normal endogenous range in the nonsmoking population, with such minuscule additive doses being inconsistent with doses biologically distinguishable from the range of endogenous doses normally found in the body…*

- For example, the USEPA *maximum* acceptable air concentration (0.01 ppb at 1E-04 risk) corresponds to a dose almost 40 times lower than even the *1st percentile* of the normal endogenous distribution of EtO levels in the human body.



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7. *USEPA's risk-based air concentrations correspond to doses orders of magnitude below even the 1st percentile of the normal endogenous range in the nonsmoking population, with such minuscule additive doses being inconsistent with doses biologically distinguishable from the range of normal endogenous doses that are orders-of-magnitude higher…*
8. USEPA's selected model for the NIOSH cohort *also statistically significantly overpredicts in a new TCEQ validation analysis using UCC data*.

- Despite this, USEPA's URF is still being used:
  1. To over-estimate theoretical excess cancer risk around the country (i.e., NATA);
  2. To suggest that urban background concentrations across the U.S. are unacceptably high; and
  3. As the impetus for estimating excess cancer risk around sterilizers, with over-predictive results seemingly serving as a basis for closures.
- All this stresses the importance of:
  1. TCEQ having taken a hard look at USEPA's 2016 EtO dose-response assessment; and
  2. Any URF being as risk predictive as possible (i.e., reasonably accurate/risk realistic).

Can’t TCEQ just get on board? After all, it took USEPA years to complete, is quite extensive and SAB reviewed.

Considering these scientific analyses results… No

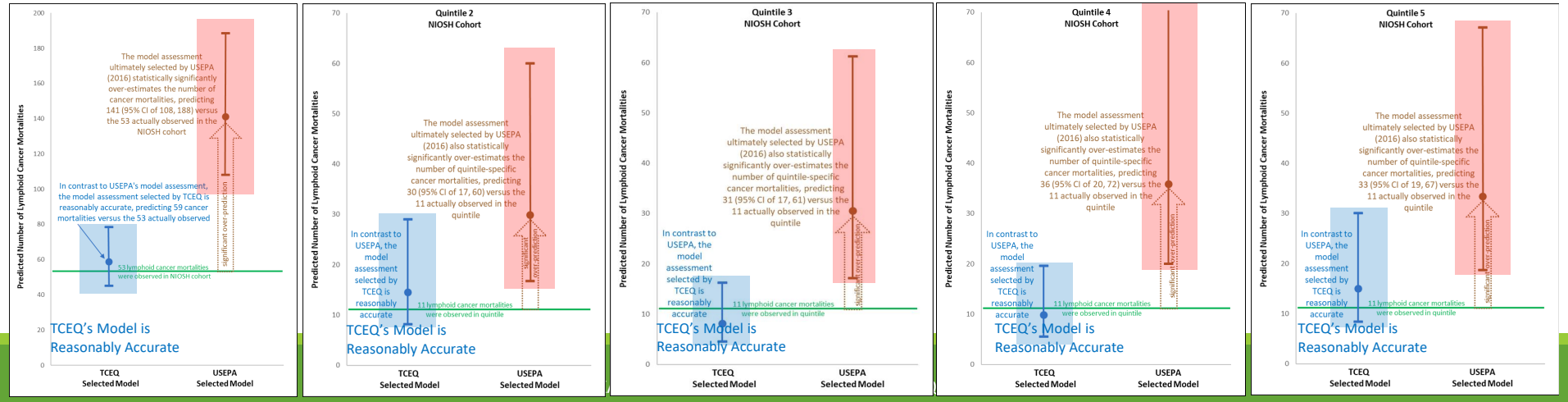
Considering the potentially dire consequences… No

For reasons discussed on previous slides, the TCEQ had a scientific and public duty to review all relevant data and conduct a dose-response assessment of its own.

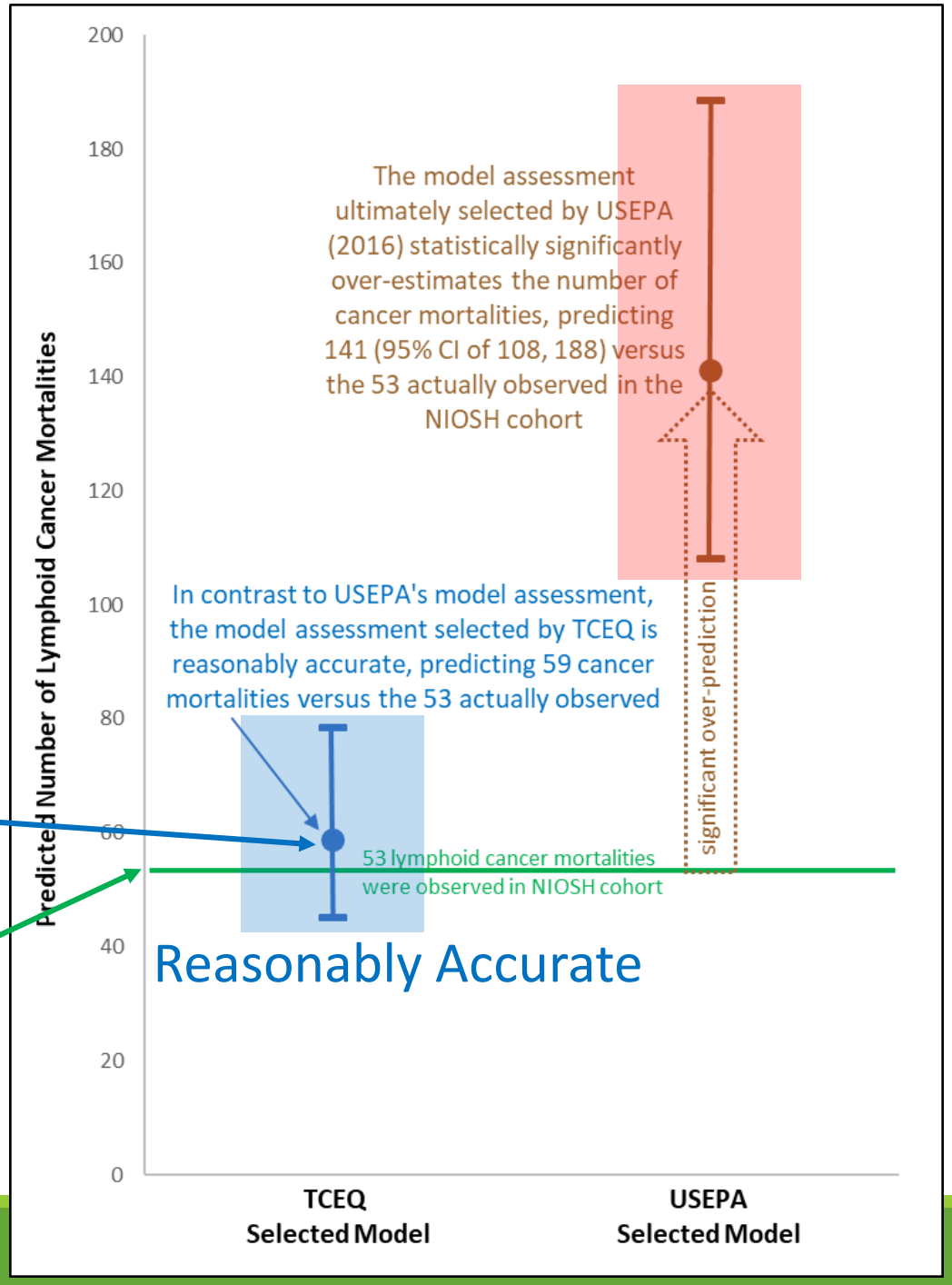
In doing so, the TCEQ was able to consider new data and/or analyses appearing in the scientific peer-reviewed literature since 2016, conduct new analyses, and address the various scientific shortcomings of the 2016 assessment (e.g., lack of MOA support, inappropriate AIC and p-value calculations, inaccuracy of model predictions for lymphoid cancer mortality, inappropriate dose-response model selection).

In contrast to findings for the linear two-piece spline model, the TCEQ has found that the standard Cox proportional hazards model…

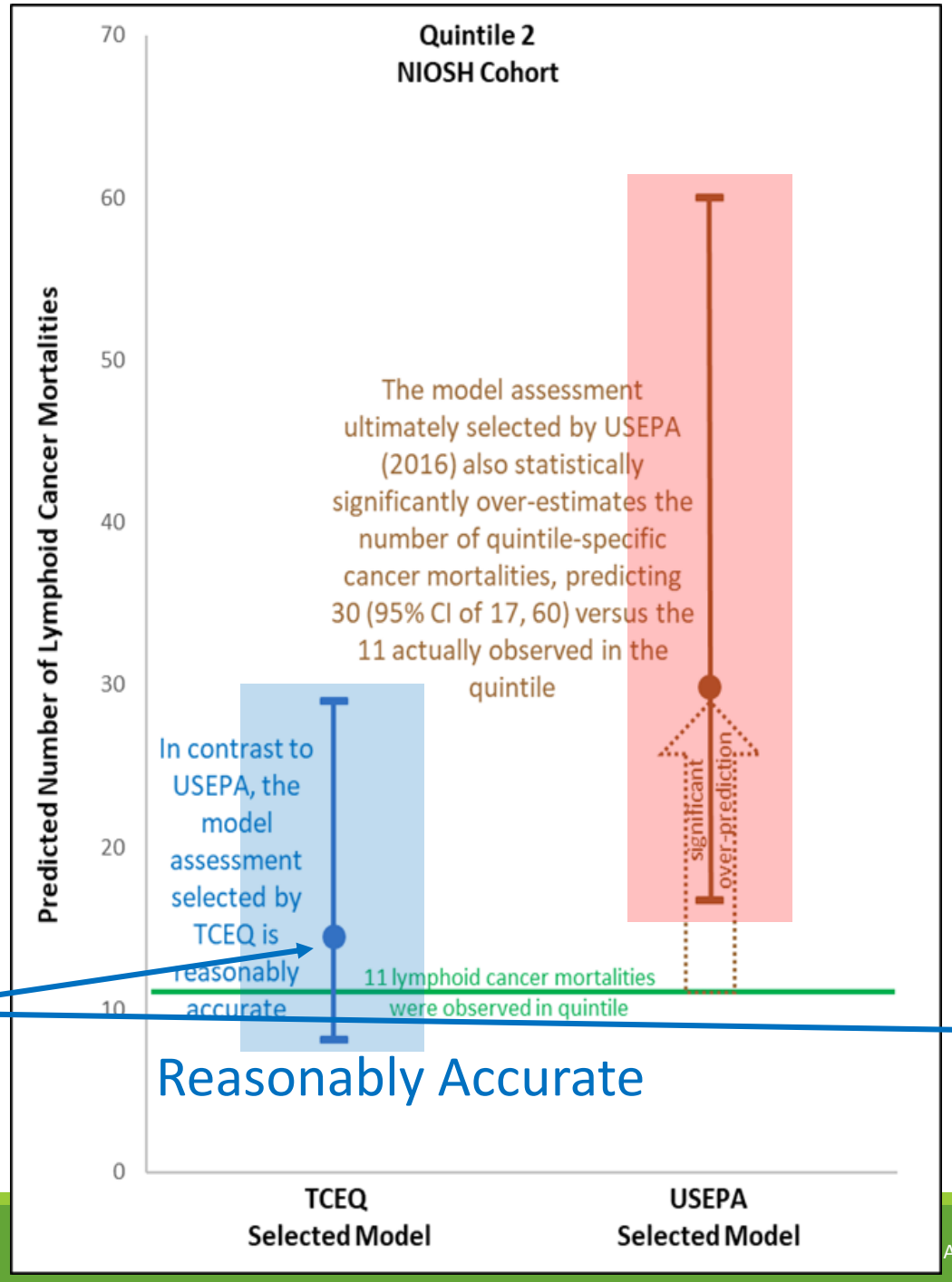
1. Is linear over the doses of interest, consistent with the mutagenic MOA (and TK considerations);
2. Does *not* statistically significantly overpredict the number of lymphoid cancers in the NIOSH cohort as a whole or in any quintile, but rather is relatively accurate; and
3. Therefore, *neither significantly overpredicts or underpredicts* lymphoid cancers in the cohort, either as a whole or for any exposure quintile…

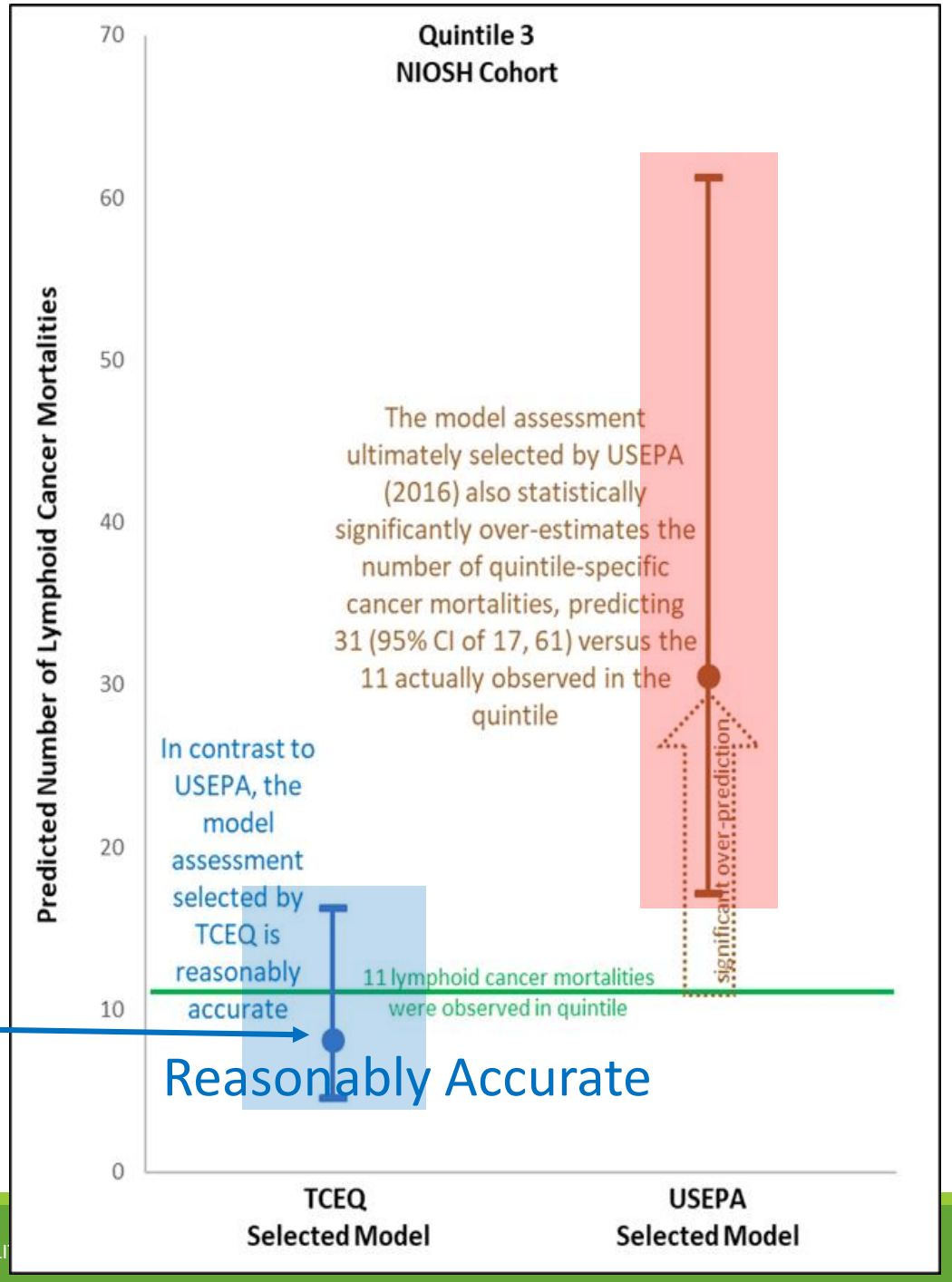


TCEQ's selected model assessment predicts 59 lymphoid cancers (95% CI 45, 78) versus the 53 that actually occurred.

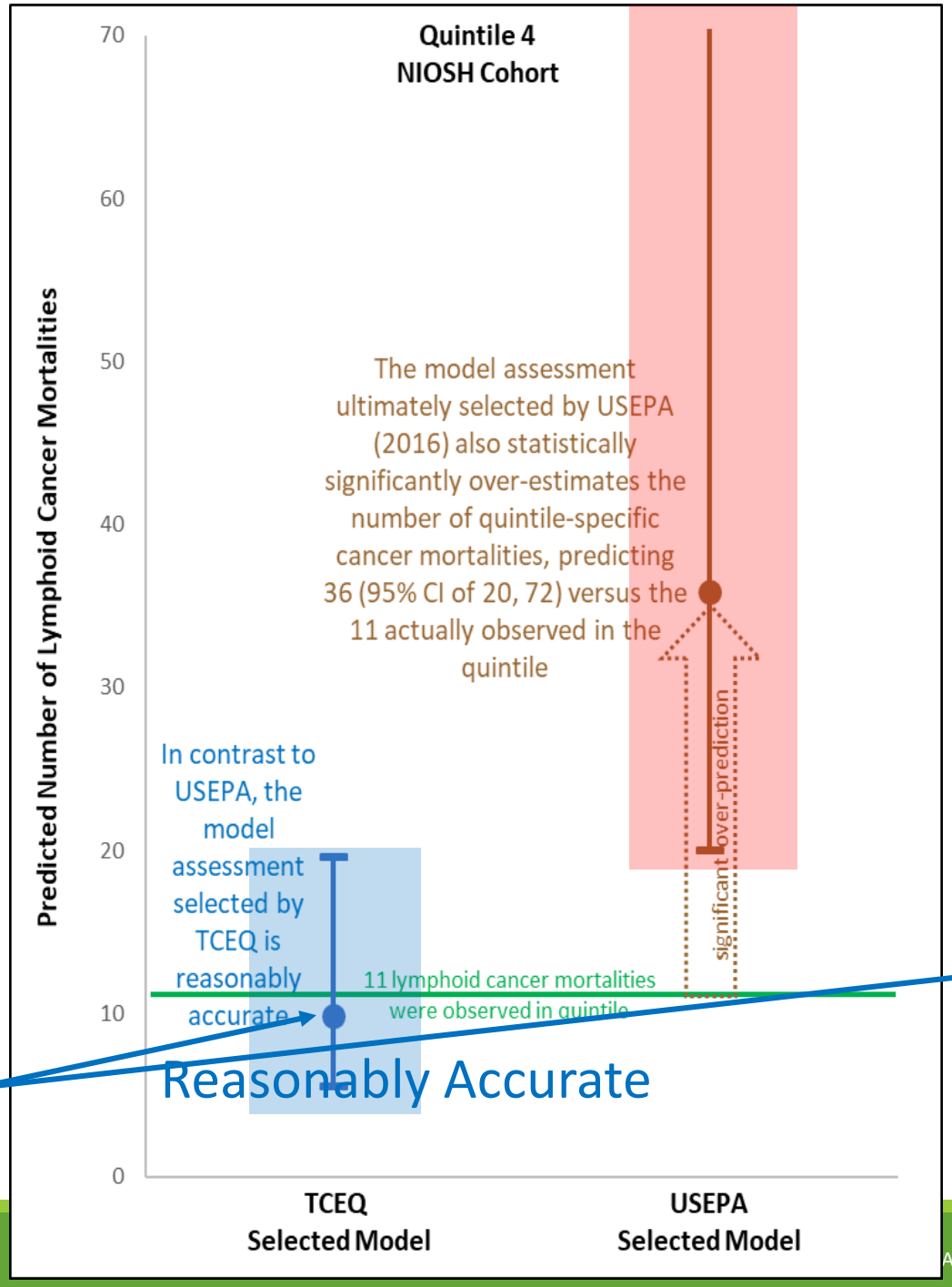


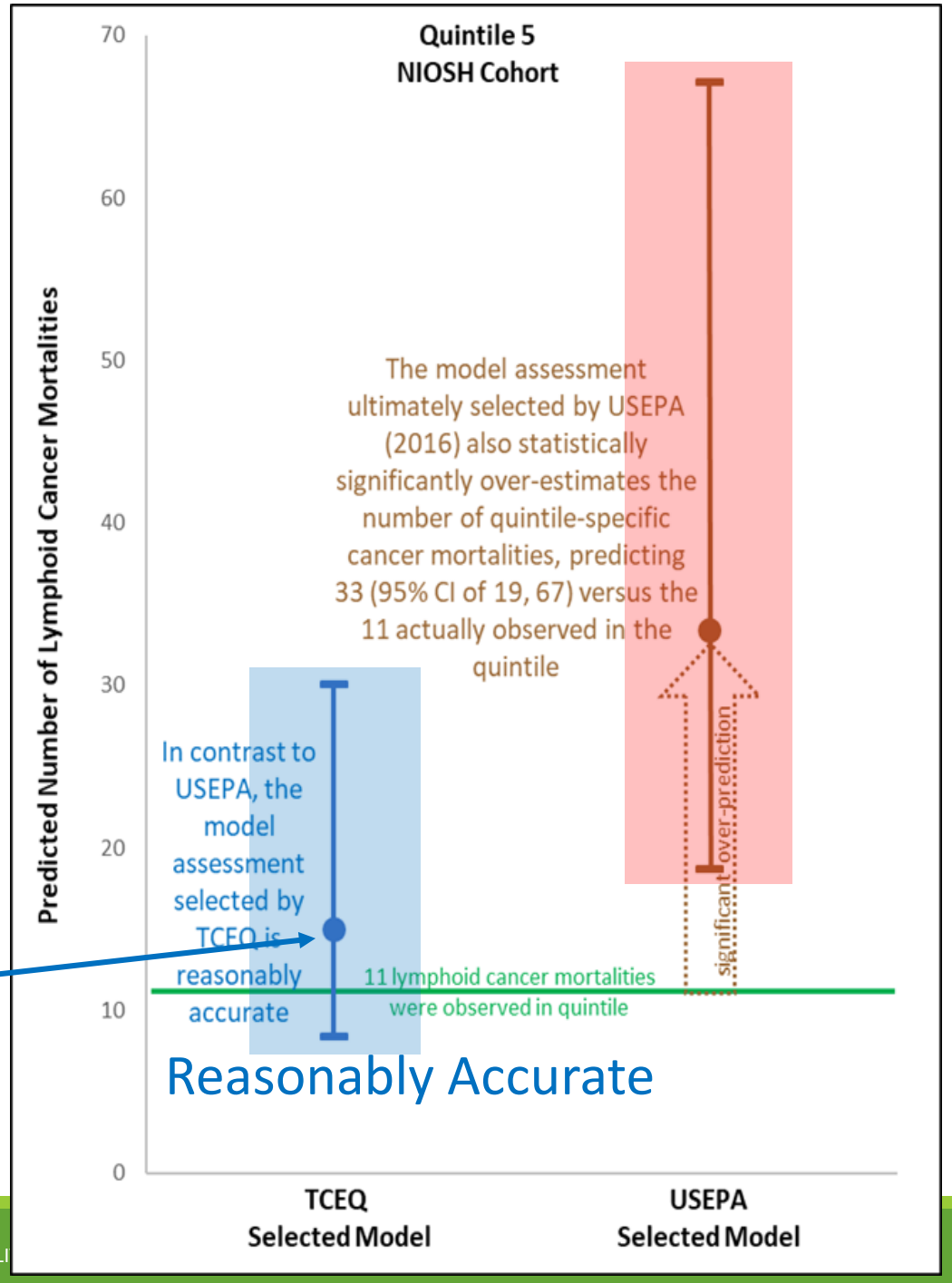
TCEQ's selected model assessment reasonably accurately predicts lymphoid cancers for exposure groups…





TCEQ's selected model assessment reasonably accurately predicts lymphoid cancers for exposure groups… *every group*





- In addition…
  4. TCEQ's selected model/URF does *not* overpredict lymphoid cancers in the general U.S. population based on endogenous and background levels in non-smokers and smokers, respectively (population weighted).
  5. TCEQ's risk-based 1E-05 air concentration (ADAF-adjusted = 2.4 ppb) corresponds to a dose within the range of normal endogenous background that is much more plausible to be biologically distinguishable (e.g., corresponds to the 75th percentile in nonsmokers).
  6. TCEQ's selected model for the NIOSH cohort also accurately predicts the number of lymphoid cancer mortalities in the UCC cohort in a new TCEQ model validation analysis.

- Bottom Line: The standard Cox proportional hazards model used by the TCEQ is scientifically demonstrated to be more realistic (e.g., risk predictive).

At the same time, keep in mind that…

7. Correctly calculated p-values and AIC values (appropriately accounting for the statistically optimized "knot" in USEPA's two-piece spline model and for the variability in the actual data) also indicate that the overall supra-linear two-piece spline model *does not* fit the data modeled better than TCEQ's more parsimonious standard Cox proportional hazards model (the SAB supported the principle of parsimony).

So the question is…

Which agency is being more scientifically reasonable given all the relevant considerations?

- The scientific weight of evidence clearly indicates that a dose-response assessment conducted using the standard Cox proportional hazards model results in more reliable and reasonable estimates of excess risk than the linear two-piece spline model used by USEPA.

In Summary:

Assessment Supported by?	TCEQ Model Assessment	USEPA Model Assessment
MOA Information	Yes ✓	No
Accurate Model Predictions: NIOSH (key) + UCC (validation)	Yes ✓	No
Reality Checks on Population Background	Yes ✓	No
Biological Plausibility	Yes ✓	No
Standard Modeling Approach	Yes ✓	No

The Weight of Evidence

In Summary:

The standard dose-response model used by TCEQ is demonstrated to be reasonably accurate, while USEPA's two-piece spline model is demonstrated to be inaccurate for the:

- Key worker lymphoid cancer data that drives the URF (NIOSH);
- A model validation dataset (UCC); and
- Background risk in the general US population.

TCEQ's dose-response model is supported by the MOA while neither agency can cite mechanistic data supportive of USEPA's overall supra-linear two-piece spline model.

In Summary:

TCEQ's model fit criteria are appropriately calculated whereas USEPA's criteria are demonstrably inappropriately calculated.

USEPA used an overall *supra-linear* dose-response model to extrapolate to doses lower than the endogenous dose range where the agency says they actually expect *sublinearity*.

As a result, USEPA's acceptable air concentrations are at doses orders of magnitude below normal levels of EtO in the body, whereas TCEQ's risk-based air concentration (2.4 ppb; ADAF-adjusted) is not.

So why is bringing all this to light important?

What difference does scientific scrutiny and using best available science make?

Consider, for example, US FDA's October 25, 2019 statement:

Sterilization facility closures could affect the availability of some sterile medical devices.

In light of the possibility of continued EtO sterilization facility closures, *FDA is again alerting the public to growing concerns about the future availability of sterile medical devices and impending medical device shortages*.

More than 20 billion devices sold in the U.S. every year are sterilized with EtO, accounting for approximately 50% of devices that require sterilization.

Without adequate availability of EtO sterilization, *FDA anticipates a national shortage of critical devices*.

In short: this method is critical to our health care system and to the continued availability of safe, effective and high-quality medical devices.

The impact resulting from closure of facilities will be difficult to reverse, and ultimately could result in years of spot or nationwide shortages of critical medical devices, which could compromise patient care.

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The impact resulting from closure of facilities will be difficult to reverse, and ultimately could result in years of spot or nationwide shortages of critical medical devices, which could compromise patient care.

All this emphasizes the critical importance of scientific scrutiny of USEPA's EtO dose-response assessment, and TCEQ's assessment, to help ensure the use of best available science for EtO risk assessment.

In Conclusion:

The TCEQ's goal is to use the *best available science* in deriving toxicity factors and making regulatory decisions.

All relevant information evaluated by the TCEQ has indicated that *USEPA's selected dose-response assessment and URF are significantly over-predictive, biologically implausible, and scientifically unsupportable*.

The same scientific information and weight of evidence fully supports the TCEQ's dose-response assessment of the carcinogenicity of EtO.

In Conclusion:

This and similar assessments have important regulatory, public health, and risk assessment/communication implications (e.g., whether typical environmental exposures and those near sterilization facilities represent realistic health concerns/hazards or not).

In Conclusion:

Consequently, other regulatory agencies or toxicology programs also have a duty to duly and objectively consider these data that inform and support the TCEQ's dose-response assessment as both biologically plausible and the most scientifically defensible available *before* using any EtO URF (from TCEQ or USEPA) to estimate excess risk or take significant regulatory action.

The TCEQ encourages you to read the agency's EtO DSD as well as all relevant studies in order to formulate your own independent and objective conclusions.

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Thank You!