IRIS Ethylene Oxide (EtO) Assessment

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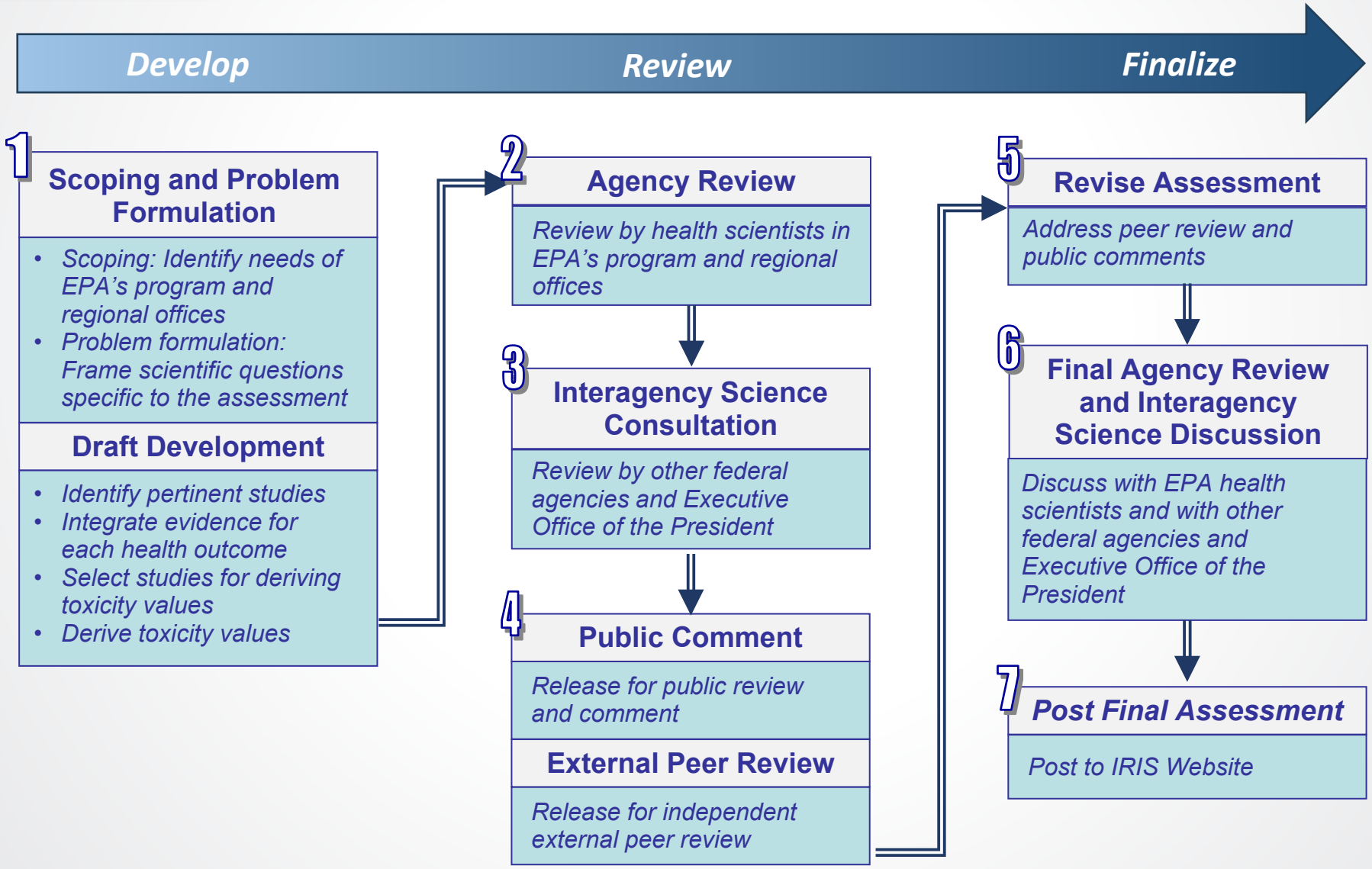
Outline

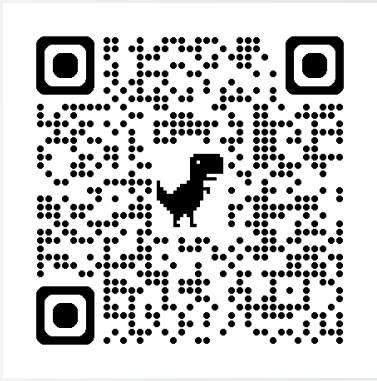
- **Overview of 2016 IRIS Evaluation of the Inhalation Carcinogenicity of EtO**
  - Scientific review process
  - Major assessment conclusions
  - Recent EPA documents addressing scientific challenges to the IRIS assessment
- **Key science considerations involved in estimating EtO cancer toxicity values**
  - Data supporting the inclusion of breast cancer
  - Model decisions made for breast and lymphoid cancer (i.e., "plateau-like", steeper at low concentrations, and biological plausibility)
  - Review of the relevance of endogenous biological sources of EtO
- **Additional resources supporting key scientific decisions in the EtO IRIS assessment**
- **Conclusions**

IRIS 7-Step Process



IRIS EtO Assessment Review

- **September 2006: EPA released external review draft for public comment and SAB expert panel review in 2007**
  - Final December 2007 report issued following approval by chartered SAB
  - Recommended EPA to undertake a *de novo* modeling analysis using individual data from the NIOSH cohort
- **July 2013: EPA released updated public comment draft**
- **August 2014: EPA released updated external review draft (revised based on public comments), which was again reviewed by the SAB in 2015)**
  - Final August 2015 SAB report provided detailed advice on the selection of preferred dose-response models for breast cancer and lymphoid cancer
  - SAB recommended against the model type model ultimately used by TCEQ
- **December 2016: EPA released final assessment**



EtO IRIS Assessment Conclusions

- **Cancer conclusion: EtO is *carcinogenic to humans* by the inhalation route of exposure**
  - *Strong evidence* of cancer in humans (lymphohematopoietic and breast)
  - *Extensive evidence* of carcinogenicity in animals, including lymphoid and mammary
  - *Clear evidence* that EtO is genotoxic and mutagenic. Weight of evidence supports a mutagenic mode of action (linear dose-response, also used by TCEQ)
  - *Strong evidence* that the key events leading to tumor progression occur in humans
  - Conclusions had consensus support of the SAB
- **Inhalation Unit Risk:** 3×10^{-3} per $\mu g/m^3$
  - High confidence in total unit risk estimate
- **Inhalation Unit Risk adjusted for early life sensitivity:** 5×10^{-3} per $\mu g/m^3$

Addressing Scientific Challenges to the IRIS Assessment

- **Responses to public comments on the IRIS/TCEQ dose-response values in EPA rulemakings**
  - National Emission Standards for Hazardous Air Pollutants (NESHAP): Miscellaneous Organic Chemical Manufacturing (MON) Risk and Technology Review (RTR)
    - Reconsideration of the 2020 MON RTR (Dec. 21, 2022 Final Action)
    - Response to Comments Document for Reconsideration of the 2020 MON RTR**
  - National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review (Sterilizers RTR)
    - Sterilizers RTR (April 5, 2024 Final Rule)
    - Response to Comments Document for Sterilizers RTR**
  - New Source Performance Standards for the Synthetic Organic Chemical Manufacturing Industry and National Emission Standards for Hazardous Air Pollutants for the Synthetic Organic Chemical Manufacturing Industry and Group I & II Polymers and Resins Industry (SOCMI NESHAP)
    - SOCMI RTR (May 16, 2024, Final Rule)
    - Response to Comments Document for SOCMI RTR
- **Litigation on EPA's MON Reconsideration Final Action**
  - Huntsman Petrochemical v. US EPA, US Court of Appeals, D.C. Circuit, Case No. 23-1045

Addressing Scientific Challenges to the IRIS Assessment

Request for Corrections (RFC) and Request for Reconsideration (RFR)

- **RFC 18003 – Ethylene Oxide**
  Subject: This RFC from Ethylene Oxide Panel of the American Chemistry Council (ACC) seeks the correction of Ethylene Oxide information disseminated in the 2014 update to the National Air Toxics Assessment (NATA), dated 09/20/2018
    - RFC 18003 - Signed Response to William Gulledge of ACC, dated12/13/2021
    - RFC 18003 - ORD review of comments on the IRIS Ethylene Oxide assessment contained in the ACC Request for Correction submitted regarding EPA's National Air Toxics Assessment, dated 08/25/2021**
    - RFC 18003 - OAR MON RTR Rulemaking; issued 08/12/2020
    - RFC 18003 - EtO EPA Response; issued 12/18/2019

RFR 18003A – Ethylene Oxide

- RFR 18003A - received 3/14/2022
    - RFR 18003A - EPA Response; issued 07/22/2022

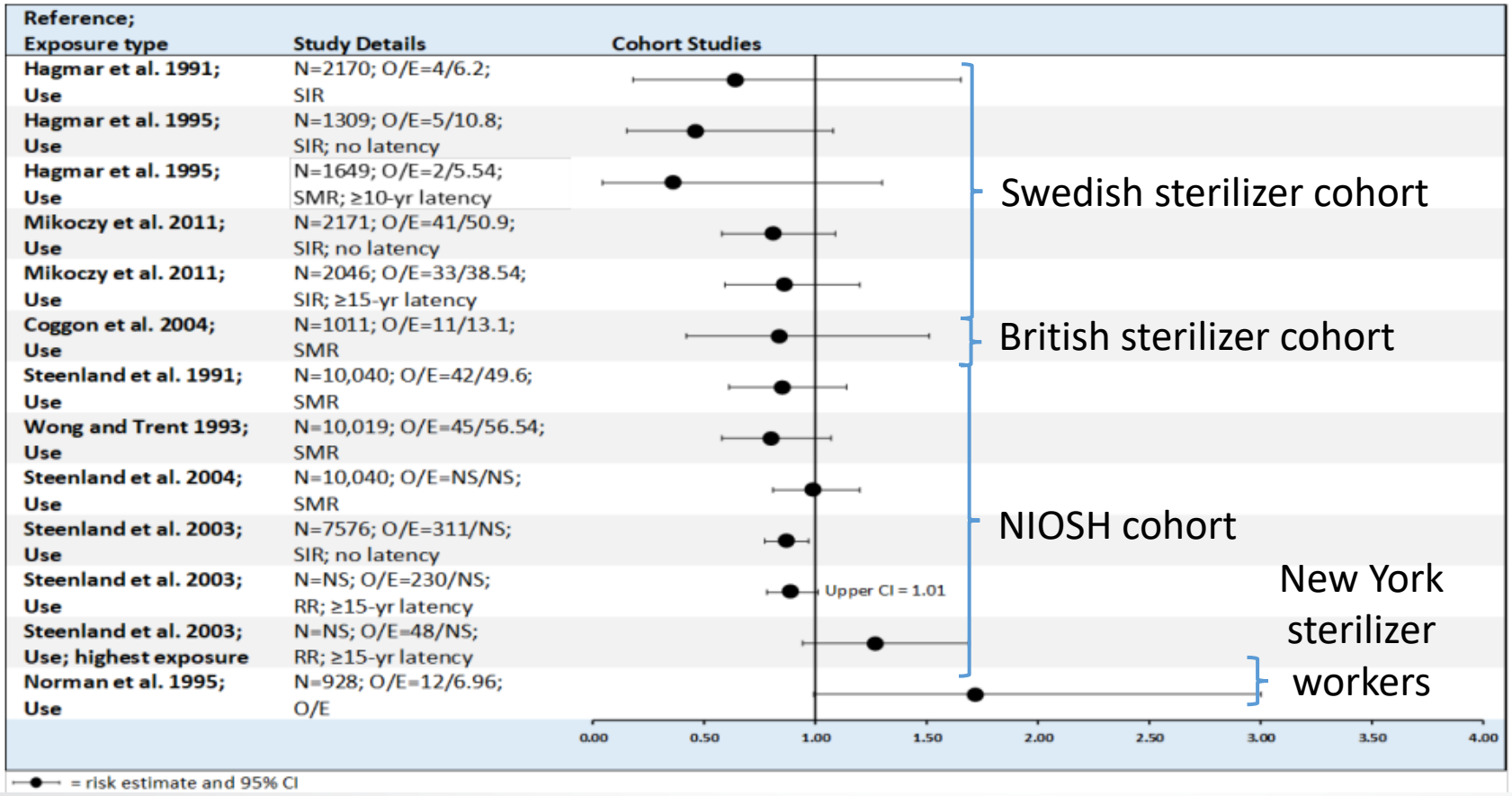
Key Science Considerations: Breast Cancer

- **Strongest cancer epidemiology evidence largely based on workers in sterilization facilities**
- **Studies of sterilization facilities are advantageous because these workers generally do not have other known chemical exposures**
- **NIOSH study of sterilizer workers (Steenland et al., 2003 and Steenland et al., 2004) demonstrates excess breast cancer risk**
  - Analyses of breast cancer incidence showed significant dose-response effects with EtO exposure using "internal" analyses in both parametric dose-response models and categorical analyses.
  - Findings further supported by breast cancer mortality analyses
- **Swedish study of sterilizer workers (Mikoczy et al., 2011) found strongly increased rates in internal analyses**
  - SAB stated this result "adds greatly" to overall breast cancer findings

See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 32-40

Breast Cancer: ATSDR Figure

Figure 2-6. Summary of Epidemiological Studies Evaluating Breast Cancer in Workers Exposed to Ethylene Oxide*



Points of consideration:

- Displays external comparisons, not internal
- Largely ignores data from the highest exposure groups
- Includes multiple estimates from the same cohort (e.g., reports on same cohort at different time periods, multiple latency periods for same cohort, same dataset analyzed by different authors)

ATSDR Toxicological Profile for Ethylene Oxide (2022), page 66

Advantages of Using Internal Reference

- **Internal reference helps account for the Healthy Worker Effect (HWE)**
  - Workers are typically healthier than the general population. If general population is used as reference group instead of employed workers, the effect of the HWE tends to produce results that are biased towards the null

- **Advantages of using an internal reference group are broader than HWE**
  - Helps account for other differences (e.g., demographic, health behaviors, medical care availability) between specific occupational groups and the general population

See 2024 Summary of Public Comments and Responses for Risk and Technology Review for Ethylene Oxide Commercial Sterilization Facilities, pages136-137

Breast Cancer Analysis in the IRIS EtO Assessment

Study	No. Outcomes	External Comparison	Internal Comparison
Mortality			
Coggon et al., 2004			
Overall	11	0.84 (0.42, 1.51)	
Steenland et al., 2004			
0 ppm–days	42	0.82	1
>0–646 ppm–days	17	1.05	1.76 (0.91, 3.43)
647–2779 ppm–days	15	1.01	1.77 (0.88, 3.56)
2780–12,321 ppm–days	15	1.15	1.97 (0.94, 4.06)
>12,321 ppm–days	13	2.07	3.13 (1.42, 6.92)
Incidence			
Norman et al., 1995			
Overall	12	1.72 (0.99, 3)	
Steenland et al., 2003			
0 ppm–days	81	0.88 (0.67, 1.04)	1
<647 ppm–days	45	0.77 (0.56, 1.04)	1.06 (0.66, 1.71)
647–2026 ppm–days	46	0.77 (0.56, 1.03)	0.99 (0.61, 1.6)
2026–4919 ppm–days	46	0.94 (0.69, 1.25)	1.24 (0.76, 2)
4919–14,620 ppm–days	45	0.83 (0.61, 1.11)	1.42 (0.88, 2.29)
>14,620 ppm–days	48	1.27 (0.94, 1.69)	1.87 (1.12, 3.1)
Mikoczy et al., 2011			
0–0.13 ppm–years	10	0.52 (0.25, 0.96)	1
0.14–0.21 ppm–years	14	1.06 (0.58, 1.78)	2.76 (1.2, 6.33)
>0.22 ppm–years	17	1.12 (0.65, 1.79)	3.55 (1.58, 7.93)

- Data more robust and consistent when using an internal comparison
- Differences noted between external and internal comparisons for most analyses
- Figure presents findings from categorical analyses, strong findings also observed from the continuous analyses

Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Table 3-2

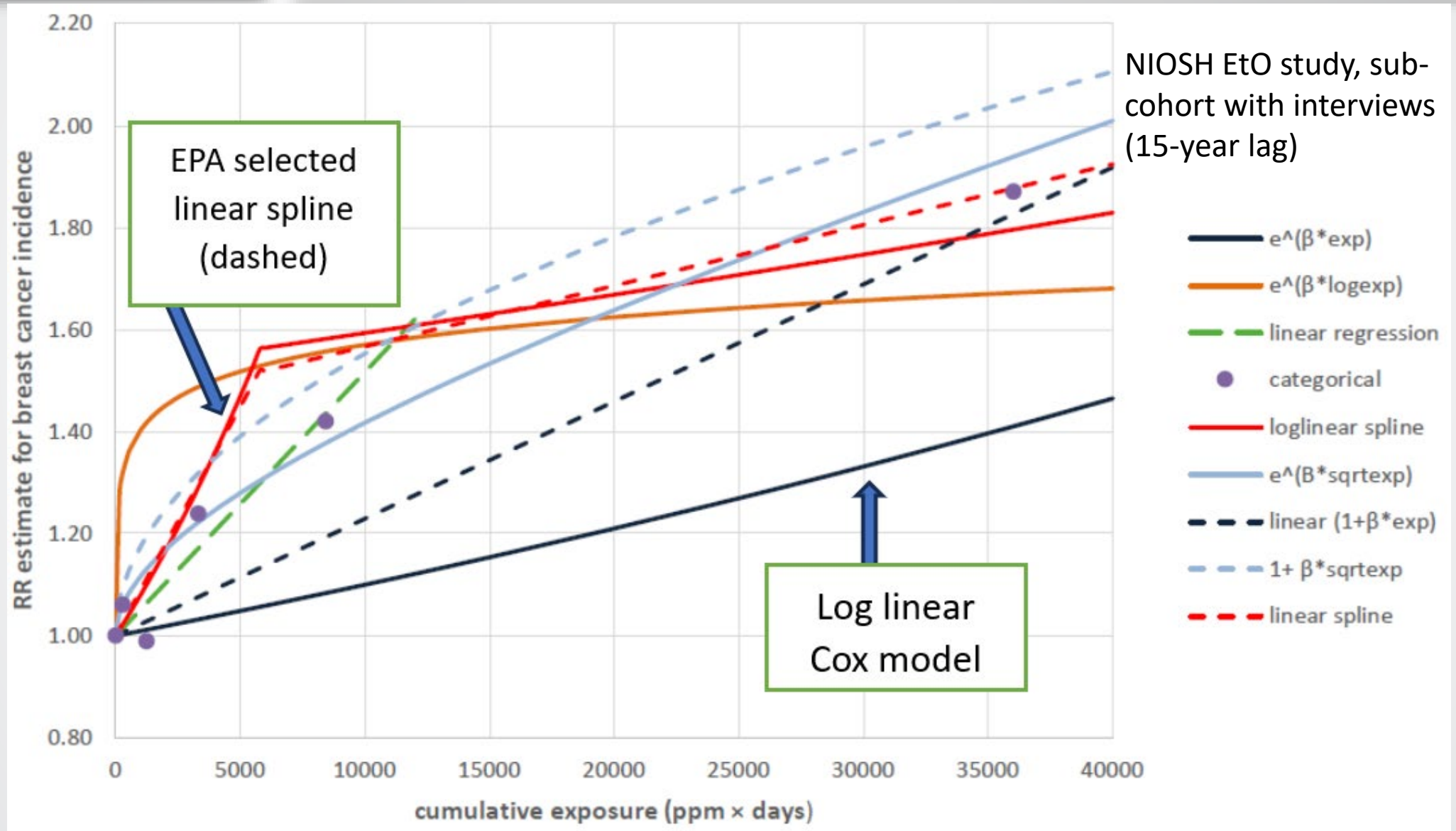
Breast Cancer Findings from NIOSH Worker Study Update

- **NIOSH has completed preparation of a study of breast cancer mortality in women in the sterilizer worker cohort previously reported by Steenland et al. (2004)**
  - Manuscript submitted for publication
  - Represents an additional 23 years of follow-up (from 1998 to 2021) and a 75% increase in the number of breast cancer deaths observed
  - Significant increases in relative risk for breast cancer mortality in each of the exposure subgroups examined ("internal" statistical analysis)
  - Best fitting dose-response models of relative risk for breast cancer mortality versus cumulative exposure show statistically significant risks increasing more steeply at lower cumulative exposure levels and less steeply at higher exposure levels

Breast Cancer Dose-Response: SAB Advice and EPA Conclusions

- **SAB recommended "prioritizing models with more local fits in the low exposure range (e.g., spline models)."** SAB prioritized models with local fits over "more global functions, such as untransformed or log-transformed cumulative exposure, that give more weight to the high exposures". SAB concurred with the selection of the two-piece spline model for breast cancer.
  - EPA prioritized the spline models as providing a local fit to the data.
- **SAB recommended less reliance on the mathematical Akaike Information Criterion (AIC) and recommended models that are "both biologically plausible and consistent with observed data"**
  - EPA found that, statistically, the best fitting models were functions using the square root of dose which showed a "plateau-like" pattern of dose response. However, EPA judged those to be less plausible, as models had increasingly steep nonlinear shape at low doses.
  - The two-piece linear spline model, while having higher AIC, showed similar plateauing form as the square root models and similar agreement with the categorical rate estimates.
  - EPA considered the linear and log-linear cumulative dose models. While plausible in shape, the linear, and particularly, log-linear models showed greater discrepancy with the categorical rate estimates.

Breast Cancer: Relative Risk Incidence Estimates



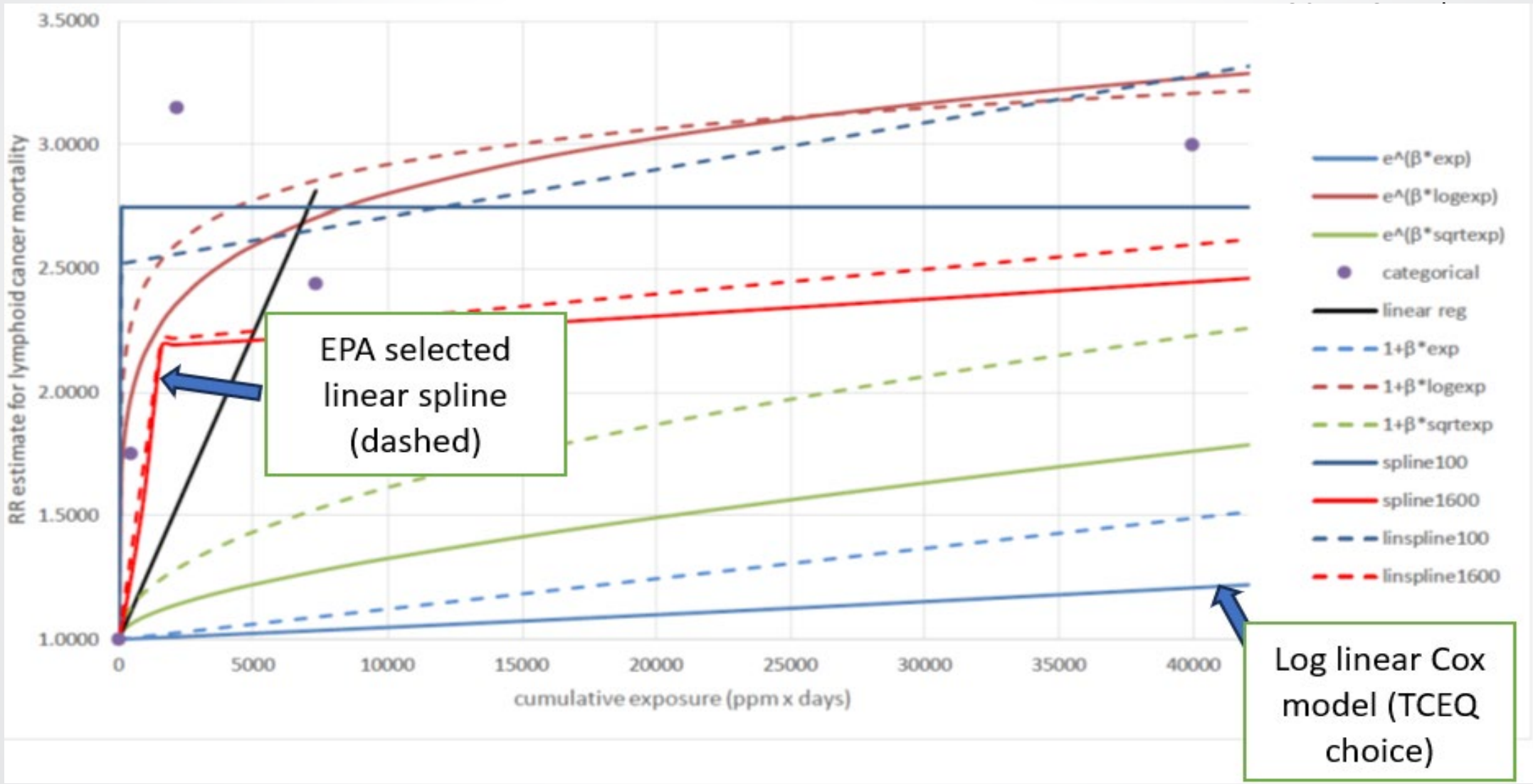
NIOSH EtO study, sub-cohort with interviews (15-year lag)

Lymphoid Cancer Dose-Response: SAB Advice and EPA Conclusions

- **SAB recommended that dose-response assessment for lymphoid cancer follow their advice for breast cancer.** This includes emphasis on models with a local fit to data, deemphasis on global fit statistics, and consideration of plausibility.
  - EPA again prioritized spline models as providing a local fit to the data
- **SAB stated that "the cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures."**
  - *Statistically,* the best fitting models were functions using the log of exposure. EPA judged these models to be less plausible, as they had increasingly steep nonlinear shape at low doses.
  - The two-piece linear spline model, while having higher AIC, showed similar plateauing form as the log-exposure models and provided agreement with the categorical rate estimates.
  - EPA considered linear and log-linear cumulative dose models [the latter also termed the "standard Cox model" preferred by TCEQ] which provided the lowest relative risk estimates among models fit. The linear and, particularly, the log-linear models showed much greater discrepancy with the dose-response pattern seen with the categorical rates well as the plateauing shapes of the best fitting models.

See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 47-61

Lymphoid Cancer: Relative Risk Estimates



Biological Plausibility for Cancer Dose Response Shapes

- **EtO is a direct acting genotoxic carcinogen, dose response functions that are linear at low dose are judged most plausible**
  - EPA deemphasized functions where responses have an increasingly steep nonlinear shape at low dose
- **Dose-response curves that begin steeply but are attenuated at higher dose have been seen for many occupational carcinogens**
  - "Plateau-like" patterns may occur due to the depletion of susceptible subpopulations, mismeasurement at high exposure, and the healthy worker survivor effect
  - Mechanistically, plateaus can arise when, at higher doses, risk protective responses are induced – or risk associated responses are inhibited
- EPA reviewed dose-response patterns in experimental studies on EtO mutagenesis and carcinogenesis. A variety of shapes were seen including plateau-like and as well as more steeply increasing shapes.

See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 77-85 & Response to Comments for the Sterilizers RTR, pages 77–181

Summary of Dose-Response Choices

EPA selected the two-piece linear spline models as being appropriate for both breast and lymphoid cancers. These models:

- Follow dose-response methodology for local fit, especially for low-concentration data.
- Provided appropriate overall statistical fit to the data.
- Showed consistency with the plateau-like pattern of response seen in the categorical rates and statistically best-fitting models.
- Were judged biologically and epidemiologically plausible, being low dose linear and having a plateau-like dose-response shape.

Consideration of Endogenous Biological Sources of EtO

- **The IRIS cancer risk estimate for environmental EtO exposure represents the increased cancer risk above and beyond any risk from endogenous EtO exposure**
  - The assessment modeled increased cancer risks from workplace exposure - however these workers would also have endogenous and background exposures to EtO.

See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 63-69 & Response to Comments Document for Sterilizers RTR, pages 192-205

Consideration of Hemoglobin Adducts

- **Hemoglobin adducts [N-(2-hydroxyethyl valine or HEV] have been used in occupational hygiene as a biomarker of high-level workplace exposure to EtO**
- **Kirman et al. (2017) re-purposed the industrial hygiene slope factor for HEV and applied it to background HEV levels - for individuals without known EtO exposures**
  - They termed these calculations as "endogenous equivalent" EtO air concentrations
  - EPA considers this an unvalidated usage of industrial hygiene data and not supported by any direct measurements of endogenous EtO
  - Subsequent analyses from Kirman and coworkers use this same unvalidated assumption

See Response to Comments Document for Reconsideration of the 2020 MON RTR, page 63-69 & Response to Comments Document for Sterilizers RTR, pages 192 – 205

EPA Analysis of Endogenous Biological Sources of EtO

- **Internal formation of ethylene believed to be major source of endogenous EtO**
- **Studies of ethylene in breath can be informative about internal exposures**
- **Recent EPA presentation on this topic at 2024 International Congress for Breath Research**
  - Literature review of ~25 ethylene breath studies reported a wide range of results, but studies judged as most informative found mean breath ethylene ~0.5 ppb.
  - Examination of pharmacokinetic (PK) models estimating formation of endogenous ethylene showed that models, while variable, also predicted breath ethylene levels in the low ppb or sub-ppb range.
  - Some PK models also allow prediction of hemoglobin adducts resulting from metabolism of endogenous ethylene to EtO. More recent PK analyses predict resulting hemoglobin adducts well below levels reported in population studies.
- **EPA analyses do not support the hypothesis that background levels of hemoglobin adducts can be used to infer endogenous EtO exposures resulting from ethylene**

Additional Resources Supporting Key Scientific Decisions in the EtO IRIS Assessment

Covered Topics

- Breast cancer: Response to Comments for Reconsideration of the 2020 MON RTR page 33
- Advantages of using an internal reference group: 2024 Summary of Public Comments and Responses for Risk and Technology Review for Ethylene Oxide Commercial Sterilization Facilities pages 136-137
- Lymphoid cancer dose response: Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 47-61
- Biological plausibility for cancer dose response shapes: Response to Comments Document for Reconsideration of the 2020 MON RTR pages 77-85 & Response to Comments for the Sterilizers RTR pages 77–181
- Consideration of Endogenous Biological Sources of EtO: Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 63-69 & Response to Comments Document for Sterilizers RTR, pages 192-205

Other Topics

- Estimating historical exposures: Response to Comments for the Sterilizers RTR pages 163-167
- Strength of the lymphoid cancer signal: Response to Comments for the Sterilizers RTR pages 143-153
- Categorical estimates of cancer risk: Response to Comments for the Sterilizers RTR pages 171-176
- Human-animal site concordance: Response to Comments for the Sterilizers RTR pages 139-141

Additional Resources Supporting Key Scientific Decisions in the EtO IRIS Assessment

Other Topics, continued

- Response to TCEQ "reality-check" calculations that are stated to show that the linear spline model "significantly overestimates risk": Response to Comments for the Sterilizers RTR pages 220-226
- Response to TCEQ statements about errors in AIC calculations: Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 59-61
- Response to TCEQ statements that categorical and continuous dose-response modeling estimates should not be compared: Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 52-56 & Response to Comments for the Sterilizers RTR, pages 171-176

Conclusions

- **IRIS 2016 EtO assessment was rigorously developed and extensively reviewed**
  - Underwent the IRIS 7-step process with multiple opportunities for public comment, Agency review, Interagency review, and public external peer review
  - Process included two rounds of SAB review, with a focus on dose-response analysis
- **EPA's monitoring of the evidence and related activities shows the 2016 assessment continues to reflect best available evidence**
  - Response to comments as part of rule-making (2020-2024)
  - Litigation challenges (2024)
  - Request for Correction and Request for Reconsideration challenges (2018-2022)

Reference Slides

Models for breast cancer incidence, sub-cohort with interviews. Consolidated results from EtO IRIS Assessment

model name	-2*LL (deviance)	AIC	p-value	local low dose fit	low dose shape	Plateau-like	Unit risk/ppm (low dose)	Considerations
Two-piece linear spline (knot 5750)	1940.4	1954.4/ *1956.4	0.01/ *0.04	yes	linear	yes	1.5	**Selected model.** Good statistical and visual fit, including low dose range. Uses a local fit of data.
Two-piece log linear spline (knot 5800)	1940.5	1954.5/ *1956.4	0.01/ --	yes	linear	yes	1.1	Comparable to linear spline
linear using square root exposure	1940.5	1952.5	0.004	no	supralinear	yes	13	Good statistical and visual fit; lowest AIC. Increasingly steep at low dose and concern that unreliable risk estimates may result. Preference given to models with local fits. Note deviance equivalent to spline models.
log linear using square root exposure	1941.0	1953.0	0.006	no	supralinear	yes	3.7	Similar to linear, square root exposure model.
log linear using log exposure	1944.2	1956.2	0.03	no	supralinear	yes	nc, high	Poor local fit in low dose exposure range, preference given to models using local fits.
linear, cumulative exposure	1942.5	1954.5	0.01	no	linear	no	0.38	Poorer fit in low exposure range, preference given to models using local fit
log linear, cumulative exposure	1944.7	1956.7	0.04	no	linear	no	0.14	Highest deviance statistic amongst models and poor local fit to data. Not a health protective choice.

Linear models: RR = β*function(exposure); Log linear models: RR = exp(β*function(exposure)), i.e., log(RR)= β*function(exposure)

*Following SAB advice, spline knots values were determined in prior analyses and not varied in determining confidence limits. Given this approach IRIS treats as these models as penalized for one parameter in AIC/p-value, but as knot was set at maximum likelihood value for breast cancer also show here statistics as penalized for two parameters.

nc, high: Not calculated (technical problem). Curve shape implies low dose risk well above estimates from spline 1600 models.

Models for lymphoid cancer mortality. Consolidated results from EtO IRIS Assessment

model name	-2*log likelihood (deviance)	AIC	p-value	local low dose fit	low dose shape	Plateau-like shape	Unit risk/ppm (low dose)	Considerations
Two-piece linear spline (knot 1600 ppm-days)	458.1	462.1*	0.07*	yes	linear	yes	5.3	**Selected model.** Adequate statistical and visual fit, including in low exposure range. Used local fit of data. Deviance as low as best fitting models, AIC within 2 units.
Two-piece log linear spline (knot 1600)	458.1	462.6*	0.07*	yes	linear	yes	1.9	Characteristics similar to linear spline model, but that linear model was preferred.
linear, square root exposure	459.8	461.8	0.05	no	supralinear	yes	nc	Adequate statistical fit, but poor local fit at low dose.
log linear, square root exposure	460.0	462.8	0.08	no	supralinear	yes	0.20	Similar to linear, square root exposure model, less good global fit
linear, log exposure	458.2	460.2	0.02	no	supralinear	yes	nc, high	Good overall statistical fit, but very steep in low dose region
log linear using log exposure	458.4	460.4	0.02	no	supralinear	yes	nc, high	Good overall fit, lowest AIC among models. Becomes increasingly steep as exposures decrease. Preference for models with local fit.
linear, cumulative exposure	461.2	463.2	0.13	no	linear	no	0.083	Poorer fit in low exposure range, preference given to models using local fit
log linear, cumulative exposure	462.8	464.4	0.16	no	linear	no	nc, low	Poor fit: Highest deviance and AIC amongst models, 4 units above best fitting (plateau-like) models. Poor local fit to all categorical points. Not a health protective choice.

Linear models: RR = β*function(exposure); Log linear models: RR = exp(β*function(exposure)), i.e., log(RR)= β*function(exposure)

*Following SAB advice, knots were fixed in prior analyses, and not varied in determining confidence limits. As the 1600 ppm-day knot was not maximum likelihood value, it was not penalized as if it were a MLE fit.

nc: Not calculated.

nc, high: Not calculated (technical problem). Curve shape implies low dose risk well above estimates from spline 1600 models.

nc, low: Not calculated. Curve well below linear cumulative dose model. Upper bound on low dose slope` (used for unit risk calculations) is approx. 5 x lower than for linear cumulative exposure model (IRIS Appendices)

Consideration of TCEQ "Reality Check" Calculations

- TCEQ interpreted their "reality-check" calculations as showing that the EPA linear spline model "significantly over-estimates the observed risk" in the NIOSH cohort. However,
  - TCEQ confidence intervals (CIs) for "predicted" cancer deaths are statistically incorrect. The calculation modifies a formula for a CI on SMRs, however predicted deaths isn't a random estimator in this formula - and shouldn't be represented with a CI
  - Instead, these calculations are consistent with original NIOSH reporting that exposure category SMRs (external comparisons) are lower than exposure category relative risk (RR) estimates (internal comparisons using Cox model).
  - EPA has shown that RR risk estimates from the two-piece spline model are similar to categorical RR estimates - and higher than SMR values. Predictions from the log-linear Cox model (TCEQ choice) are well below category RR estimates and below the SMR estimates.
  - See: Response to Comments for the Sterilizers RTR pages 220-226 & next reference slide

Comparison of rate ratio calculations for NIOSH lymphoid cancer mortality results by exposure quartiles

	Unexposed	Quartile 1	Quartile 2	Quartile 3	Quartile 4
External comparison: SMR [95% CI] (obs. tumors deaths)	0.78 [0.36-1.49] (9 obs.)	0.76 [0.38-1.35] (11 obs.)	1.39 [0.69-2.50] (11 obs.)	1.21 [0.60-2.16] (11 obs.)	1.49 [0.74-2.6] (11 obs.)
Internal comparison: Relative Risk (RR) [95% CI]	1.00	1.75 [0.59−5.25]	3.15 [1.04−9.49]	2.44 [0.80−7.50]	3.00 [1.02−8.45]
Theoretical risk ratios using TCEQ's calculations of model predicted cancer deaths, obtained by applying US population mortality rates to the NIOSH study population.					
TCEQ log linear Cox relative risk, MLE and [UCL]	1.00 [1.00]	1.00 [1.01]	1.01 [1.03]	1.03 [1.08]	1.23 [2.03]
EPA linear spline relative risk, MLE and [UCL]	1.00 [1.00]	1.45 [2.08]	2.23 [3.86]	2.29 [3.93]	2.82 [4.51]

[Calculation notes: The SMRs and their CIs are calculated from values and "CIs" shown expected values in TCEQ Table 7 (footnote) and Table 30 and using CI formula, page 100.

Internal comparison ranges and relative risk estimates are from IRIS Appendix D, Tables D-26 and D-28. The exposure ranges for external and internal comparisons are similar, not identical, as noted by TCEQ.

The theoretical risk ratios shown are simply the model predicted cancer deaths divided by the background "no model" predicted cancer deaths, by exposure category, from TCEQ table 30. EPA has not verified TCEQ predicted values.

Statements about Errors in EPA's AIC Calculations

- **EPA used a two-step process in fitting linear spline models to the NIOSH cancer data. First, a knot value was selected. The knot value was then held fixed in applying the model and calculating bounds on model risk estimates. In this process the knot was not counted as an adjustable parameter.**
  - This approach specifically followed SAB advice (p. 12, SAB, 2015) and these calculations were presented in the public comment drafts of the assessment
  - It has been claimed that the knot should have been counted as an adjustable parameter and they presented a recalculation of AIC and p-values for the lymphoid cancer linear spline model
  - EPA does not agree. The knot (1600 ppm-days) for the lymphoid cancer spline model was not the maximum likelihood estimate (which would have been lower) but was preferred as having more case data for estimating the low-dose slope. The AIC procedure penalizes for parameters optimized as maximum likelihood estimates
  - EPA, following SAB advice, deemphasized the role of AIC in model selection so this question would not have affected EPA's bottom line model choice
  - See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 59-61

Statements that Categorical and Continuous Model Risk Estimates Should Not be Compared

- **Some commenters to EPA disagreed with comparing categorical and continuous dose-response estimates (dose-response slides above).**
  - Plotting of fits of continuous models in comparison with categorical breakouts of the data is a very useful and commonly used tool in epidemiology
  - In the NIOSH study, the categorical RR estimates and continuous model fits were developed from the same individual level data using proportional hazard methodology for internal comparisons.
  - The categorical and continuous results use the same comparison – to workers having no estimated exposure after taking into account the lag period used in the modeling
  - Relative risk of cancer in exposed versus non-exposed workers is a well-defined quantity. Thus, categorical results and the predictions of appropriate continuous models should be in general agreement.
  - EPA notes that the TCEQ graph (Fig. 14) which shifts the curve for the preferred model upwards to be more consistent with categorical results is not appropriate. By basic logic, for internal comparisons the relative risk at zero exposure needs to be 1.0
  - See Response to Comments Document for Reconsideration of the 2020 MON RTR, pages 52-56