

Oral Comments to the Chemical Assessment Advisory Committee (CAAC) Augmented for the Ethylene Oxide Review



Overview:

- Charge Question #5: Transparency
- Charge Question #7: Previous Comments

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Charge Question #5: Transparency

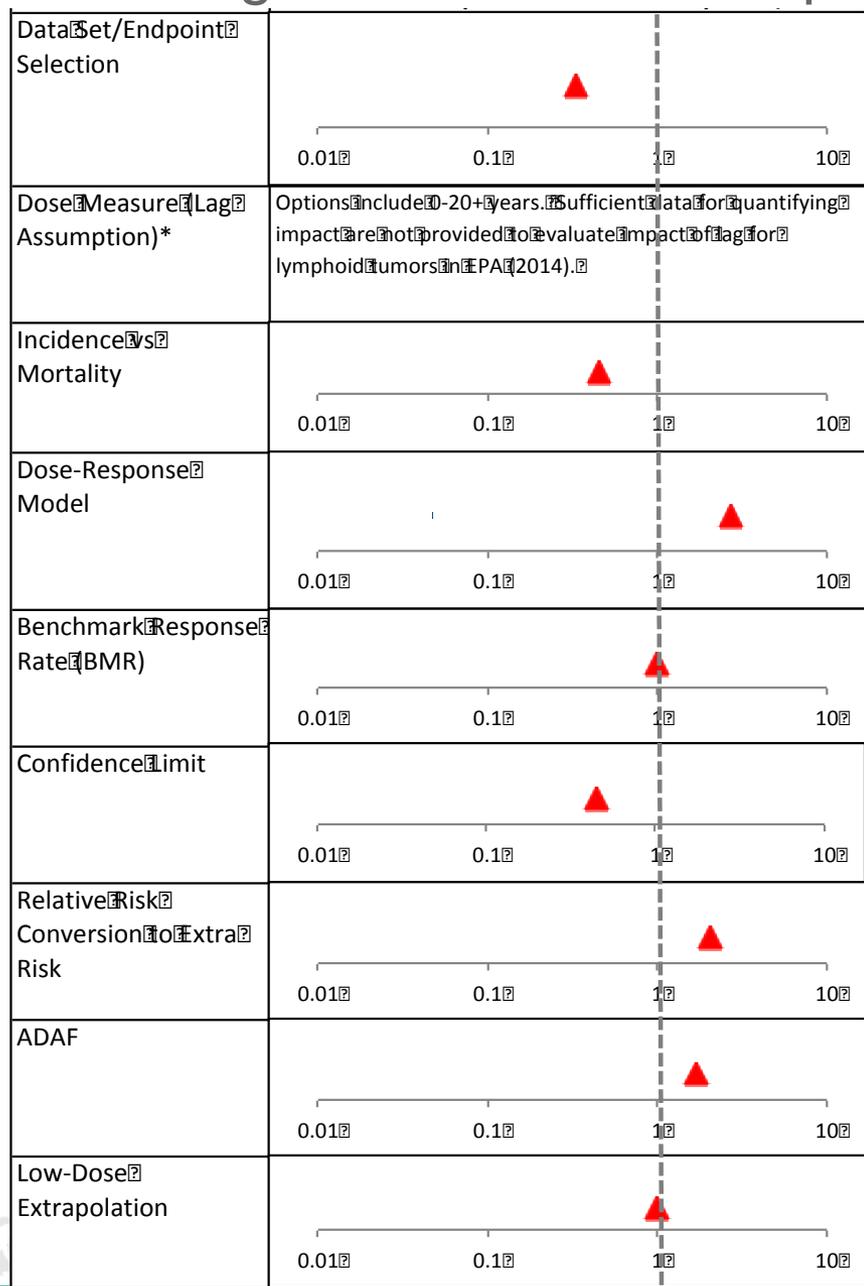
- ~10 decisions embedded in EO unit risk calculation:
 - *Many appear to be driven by statistical/ empirical bases, without consideration of biology.*
 - » MOA needs to be considered for each decision
 - *Key Questions:*
 - » Are there viable alternatives?
 - » What are quantitative impacts of alternative options on resulting unit risk value?
 - *The following table illustrates a tool developed at ARASP workshop to:*
 - » Help answer questions above, improving transparency in IRIS assessments
 - » Identify key sources of uncertainty and variability
 - » Prioritize data needs

Charge Question #5: Transparency

Example Summary Format for Lymphoid Cancer Unit Risk

Decision Point	Range of Options Fraction of Central Tendency Value (indicated by dashed line for quantitative decision points)	Range Reflects Uncertainty or Variability	Basis for Normalizing Values (e.g., Central tendency or highest confidence value)	Decided Option	Confidence in Decision (Science- or Policy-based); [Note]
Data Set/Endpoint Selection		Sufficient data are not available in EPA (2014). Variation in data set and endpoint based on EC values reported in Valdez-Flores et al. (2010, Table 6)	Mean of EC values using different data sets and endpoints	Lymphoid cancers in men and women (NIOSH)	EPA places high confidence in key study since it is large, high-quality epidemiology study with individual worker exposure estimates (EPA, 2014; Section 5)
Dose Measure (Lag Assumption)*	Options include 0-20 years. Sufficient data for quantifying impact are not provided to evaluate impact of lag for lymphoid tumors in EPA (2014).	--	--	Lymphoid (15-year lag)	[Impact of lag assumption on the unit risk value is not transparent. It is also unclear if lag assumption contributes to supralinearity observed in dose-response data]
Incidence vs Mortality		Uncertainty associated with the most appropriate response measure, based on EC1 values provided in EPA (2014) Table 5	Mortality-based value was selected based on consideration of RIS precedent assessments	Incidence	
Dose-Response Model		Uncertainty associated with the dose-response model, based on EC1 values provided in EPA (2014) Table 5	Arithmetic mean EC1 calculated for competing models	Linear regression of categorical results	Although not explicitly stated, confidence is presumed low since 2 models were considered unsuitable for deriving unit risk values (EPA, 2014; Table 5)
Benchmark Response Rate (BMR)		Reflects uncertainty in potency estimate considering alternative PODs (0.0001-0.1).	BMR = 0.1 (default)	BMR = 0.01	[Linear dose-response model is expected to yield the same potency estimate when near extrapolation is assumed; however, different values are expected when nonlinear extrapolation is used]
Confidence Limit		Reflects uncertainty in the dose-response model parameters, based on LCL, UCL & central tendency estimates for the best fitting model (EPA, 2014;)	Central tendency value	95% Lower confidence limit	
Relative Risk Conversion to Extra Risk		Reflects uncertainty in potency estimate alternative definitions of lifetime (70-85 years) in the lifetime analysis (EPA, 2014; Table 1)	70 years, since this is considered the default definition of lifetime for RIS calculations	85 years	
ADAF		Reflects variation in the potency estimate when extrapolated across lifetimes, based on potencies with and without ADAF application	1, no adjustment needed	~1.7, based upon ADAF applied to 70 year lifetime	
Low-Dose Extrapolation		Uncertainty in low dose extrapolation (linear extrapolation from EC1 to LEC1E-6 vs. nonlinear extrapolation using UF of 100)	Linear extrapolation (default)	Linear extrapolation	EPA places high confidence in the low-dose linearity assumption since the mutagenic model reactions are strongly supported (EPA, 2014; Section 5)
Results			Central Tendency Estimate: 0.000095 per ug/m3	Unit Risk = 0.0018 per ug/m3	High confidence in Unit Risk

Charge Question #5: Transparency



Key conclusions:

- Decisions having greatest impact (widest bars); warrant most attention
 - *Data set selection*
 - *Dose-response model*
 - *Low-dose extrapolation*
- Impact of lag assumption is unclear
 - *Quantitative Impact on unit risk value?*
 - *Contribution to apparent supralinear dose-response?*
- Adopting alternative decisions, Valdez-Flores et al. (2010) derived unit risk value ~1,500 fold lower than derived by EPA

Charge Question #7: Previous Comments (Risk Comparisons)

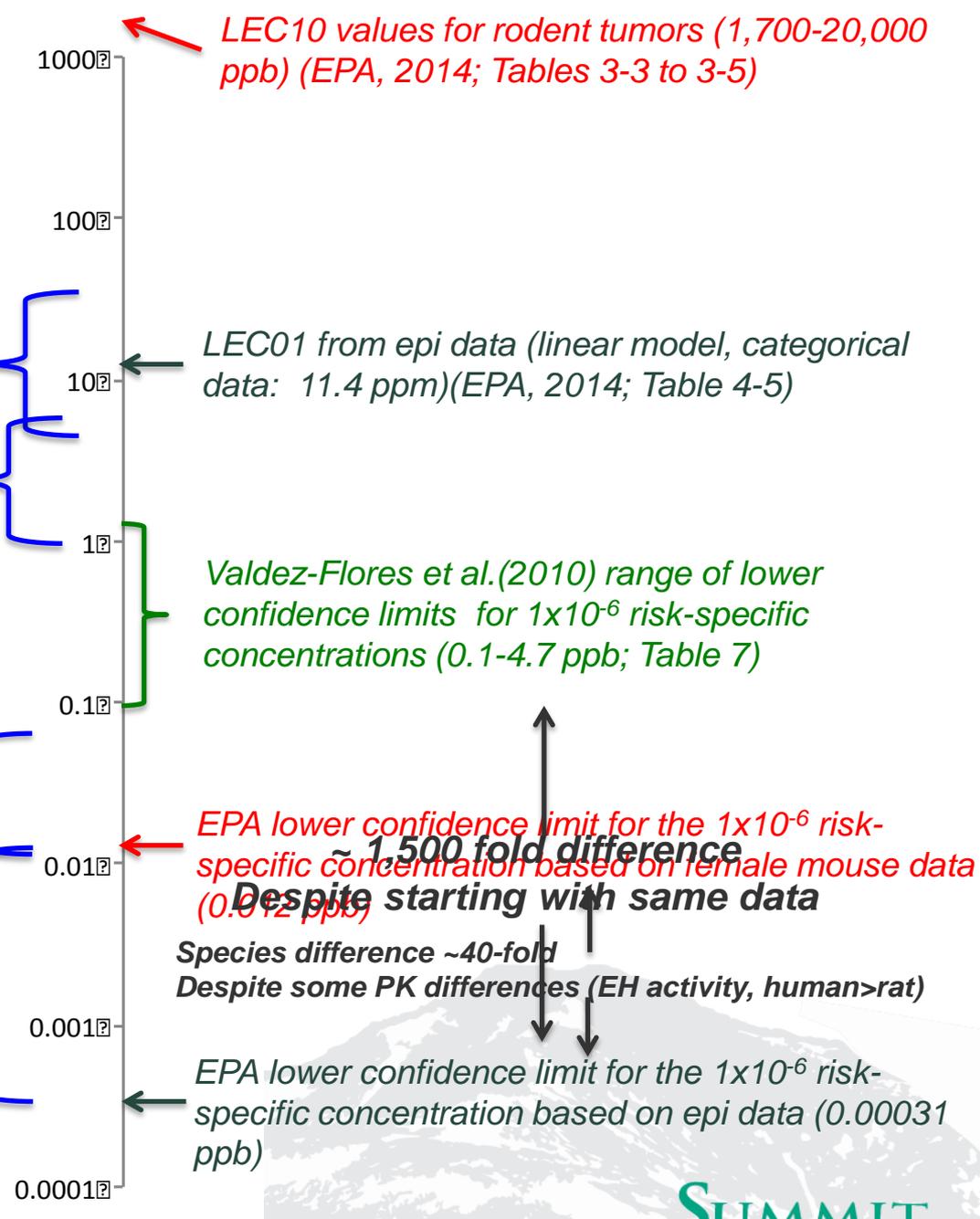
EO in Air (lifetime continuous, ppb)

Smoker Equivalent EO exposure based upon range of mean HEVal: ~60-400 pmol/g Hb, which corresponds to ~5-35 ppb EO in air

Nonsmoker Equivalent EO exposure based upon range of mean HEVal: ~13-63 pmol/g Hb, which corresponds to ~1-6 ppb EO in air

EO estimated in exhaled breath from endogenous ethylene 0.01-0.05 ppb

EO estimated in ambient US Air : 0.0003-0.01 ppb (EPA National Scale Air Toxics Assessment, 2005)



Charge Question #7: Risk Comparison Conclusions

Potency estimate is not consistent with the relative toxic and mutagenic potencies

- 1×10^{-6} risk-specific concentrations calculated for EO using EPA's unit risk value are up to orders of magnitude lower than:
 - Risk-specific concentrations calculated by Valdez-Flores et al. (2010)
 - Ambient EO concentrations
 - EO in exhaled breath
 - Endogenous EO concentrations
- When several plausibility checks are made and none of the outcomes are determined reasonable, it suggests that there is something incorrect with the risk determination assumptions, calculations, and/or modeling, and alternatives must be examined.