NAS Science and Decisions Report: Implications for Toxic Reductions Benefits Assessment

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Presentation to EPA Workshop on Estimating the Benefits of Reducing Hazardous Air Pollutants
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Committee

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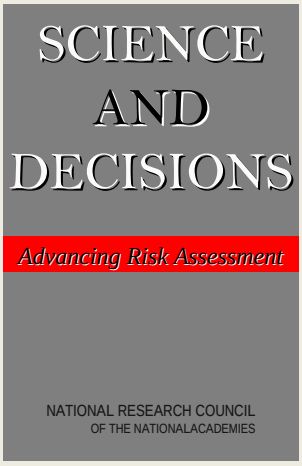
Charge: Recommend Practical Improvements to EPA Risk Assessment



Topics recommendations covered:

- Design of risk assessment
- Dose response assessment
- Uncertainty and variability
- Default selection and use
- Cumulative risk assessment
- Improving risk assessment utility
- Stakeholder involvement
- Capacity building

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Current EPA Dose Response Framework Committee Observations

Non-Cancer

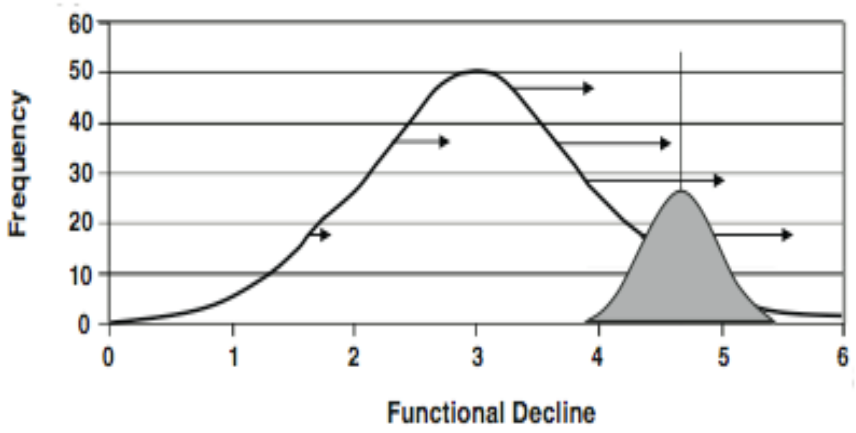
- No risk measure produced
  - HI, RfD, MOE limited for risk/benefit assessment
- Possible low dose linearity not assessed
- Uncertainty not distinguished from variability or other adjustments

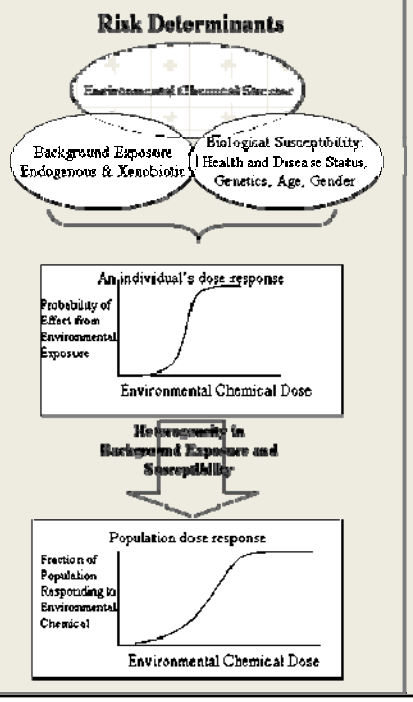
Cancer

- Inter-human variability
  - Not addressed (animal data based) or
  - Incomplete (epidemiologic data based)
- "Low dose nonlinear" carcinogens
  - No risk measure
- Uncertainty not characterized

Impacts of Background and Vulnerability on Risk

- Background
  - Biological
  - Exposure
- Vulnerability
  - Age, genetics, health disease status
  - Interactions with SES and other community factors





Dose-response relationship is dependent on heterogeneity in:

- Background exposure (endogenous and xenobiotic)
- Biological susceptibility

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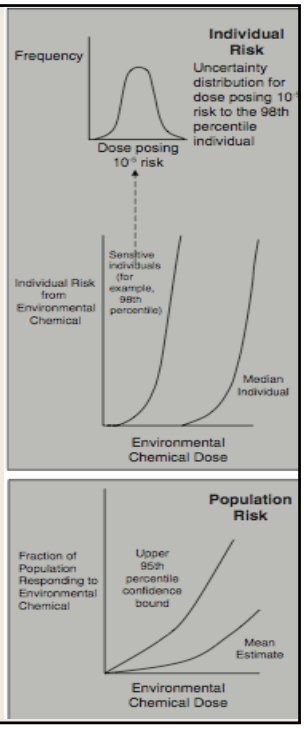
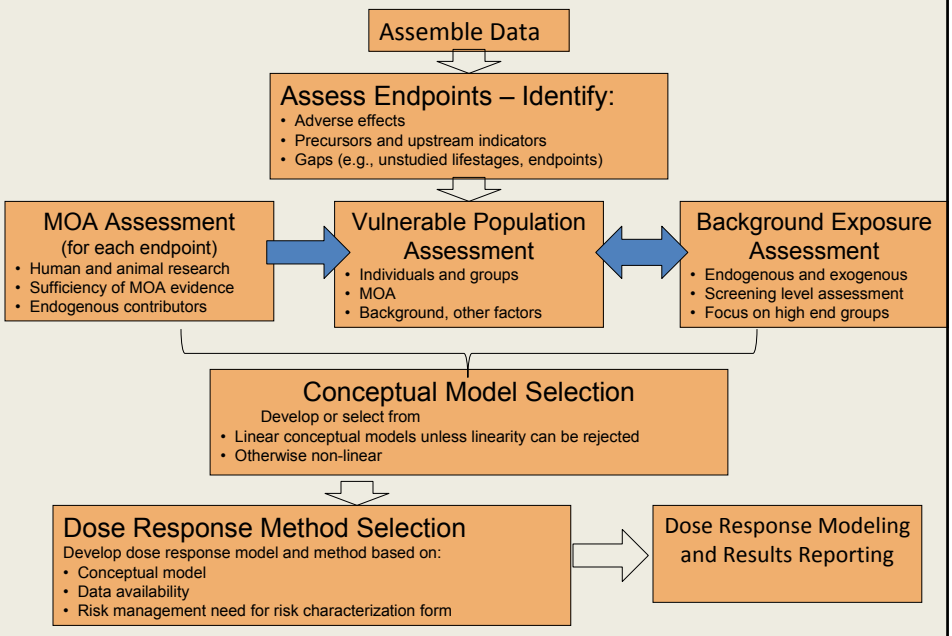
Desirable Features of Dose Response Framework

Dose response is probabilistically characterized:

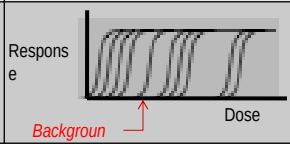
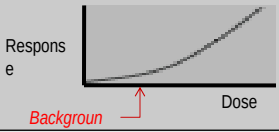
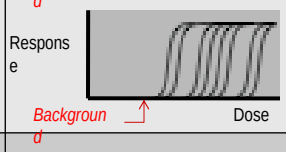
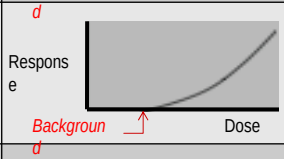
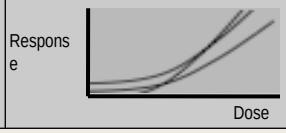
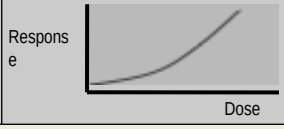
- explicitly considers human heterogeneity
  - describes sensitive individuals and populations
- characterizes most important uncertainties
  - uses distributions not "uncertainty factors"
- accounts for background exposure and susceptibility
- is based on spectrum of evidence (human, animal, other)
- methods and assessments are



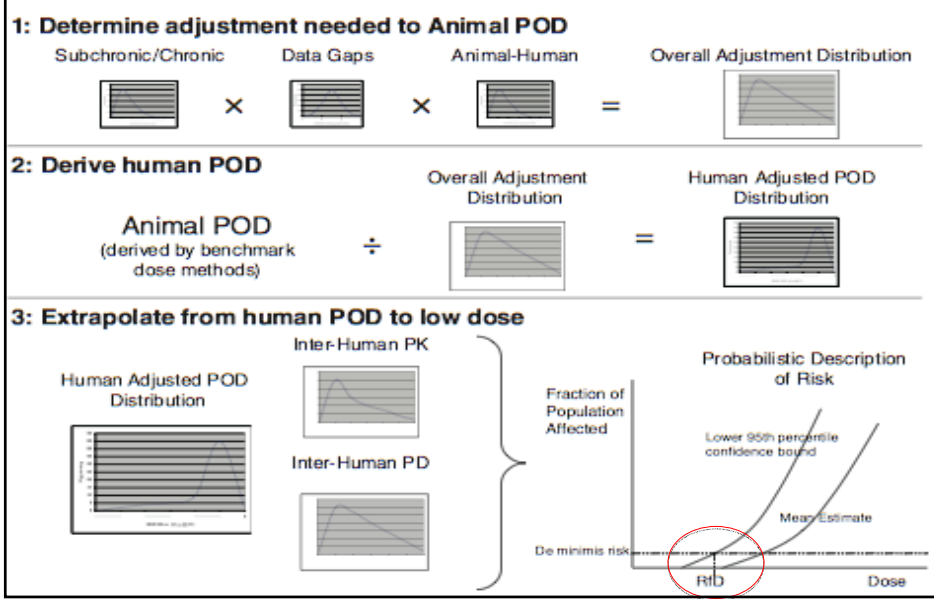
Unified Approach to Dose-Response Assessment



Conceptual Dose-Response Model – From MOA, Background Exposure and Disease Processes

Low Dose Conceptual Model	Individual Dose Response	Population Dose Response
Individual's: Nonlinear Population's Linear		
Individual's: Nonlinear Population's: Nonlinear		
Individual's: Linear Population's: Nonlinear		

Conceptual Models and Methods Example: Individual and Population Nonlinear DR



Example Mathematics for Linear Framework

Low Dose Risk for y^{th} Percentile Person

$$= \text{Dose} \times \text{Slope}_{\text{LowD Human}} \times V_{yth}$$

$$= \text{Dose} \times \text{Slope}_{\text{Animal}} \times F_{H\text{-}A} \times M_S \times F_{Other} \times V_{yth}$$

Adjustment Factors

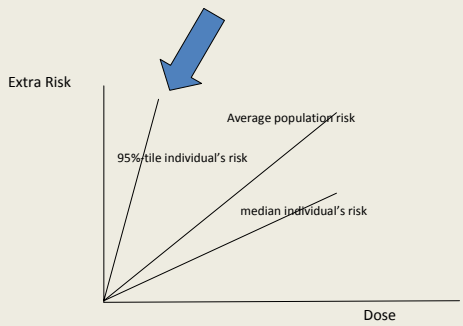
- $F_{A\text{-}H}$ Cross species
- M_S **Slope adjustment**
  - » Sensitive subpopulations (threshold individual effects)
  - » mixed modes of action (non-threshold individual effects)
- F_{Other} Other Adjustments (e.g., route, duration)
- Factors are random variables to account for uncertainty
- V_{yth} **Ratio of Risk of the yth percentile to median person**

Linear example cont'd: Individual and population risk and uncertainty

$$\text{Risk} = \text{Dose} \times \text{Slope}_{\text{LowD Human}} \times V_{yth}$$

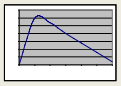
$$= \text{Dose} \times \text{Slope}_{\text{Animal}} \times AF_{A\text{-}H} \times M_{\text{Slope}} \times V_{yth}$$

Median AFs, $\text{Slope}_{\text{animal}}$, and 95th percentile of V



Uncertainties in AFs, $\text{Slope}_{\text{animal}}$

Uncertainty in 95%-tile individual's risk specific dose



Main Dose Response Recommendations

- Formal, systematic assessment of human status
  - background disease processes and exposures
  - vulnerable populations
  - use of modes of action in the assessment.
- Probabilistic risk estimation for "threshold" (nonlinear) endpoints
  - Redefine the RfD and RfC as risk-specific dose
  - Characterize fraction of the population affected vs dose
  - Describe uncertainty in that characterization
- Formal introduction of variability into cancer dose-response modeling
- For implementation and development:
  - Develop default distributions
    - Quantitatively characterize adjustments and key uncertainties
    - Develop accurate labels for them to avoid confusion
  - Of test cases to explore new framework.

Defaults: Main Conclusions and Recommendations

- Defaults need to be maintained
  - Continue and expand use of best, most current science to support and revise defaults.
  - Develop clear, general standards for level of evidence needed for using default alternatives
- A number of missing or implicit defaults are engrained in EPA practice
  - e.g., chemicals not toxicologically characterized carry no weight in the final characterization
  - work toward replacing implicit "missing" defaults with explicit ones
- To the extent feasible, make quantitative the uncertainty characterization when using defaults

Cumulative Risk Assessment
Some Key Recommendations

- There is a need for CRA that include, e.g.,
  - exposure to multiple stressor including their pathways, sources
  - chemical, biologic, radiologic, physical, psychologic stressors.
- EPA should draw on other approaches to include chemical and non-chemical stressors interactions in assessments
  - including those from ecologic risk assessment and social epidemiology
- EPA should develop guidelines and methods for simpler analytical tools
  - to support CRA and greater involvement of stakeholders.
- Short-term, EPA should develop databases and default approaches for key non-chemical stressors (absent population-specific data), considering
  - exposure patterns, contributions to relevant background processes, interactions with chemical stressors.