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Characterizing Uncertainty for Better Decisions

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Risk Means Uncertainty

- Causal relationships
- Likelihood of occurrence
- Consequences

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The Role of Risk Assessment is Changing

- Used to be focused on standard setting

- Now emphasizes comparisons
  - Alternatives Analysis
  - Sustainability
  - BCA

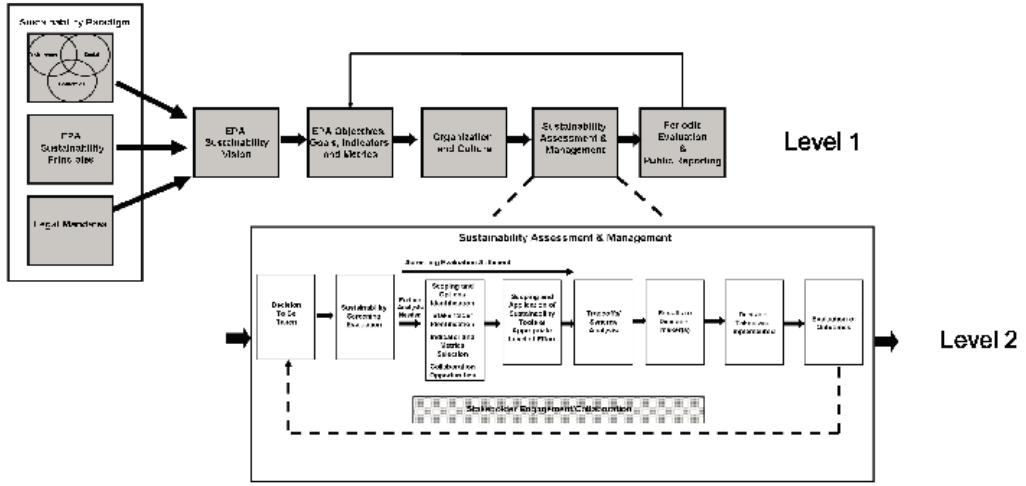

FIGURE 3-1 A framework for EPA sustainability decisions

Source:NRC (2011) Sustainability and the U.S. EPA

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A Critical Point: Protective vs Predictive Assessments

- Many uses of risk assessments involve “protective” decisions aimed at minimizing risks
  - Water standards
  - Pesticide tolerances
  - *etc*.
- Making comparisons (e.g., which choice is more sustainable?) requires predictive assessments
- A good job characterizing uncertainty will allow IRIS to serve both needs

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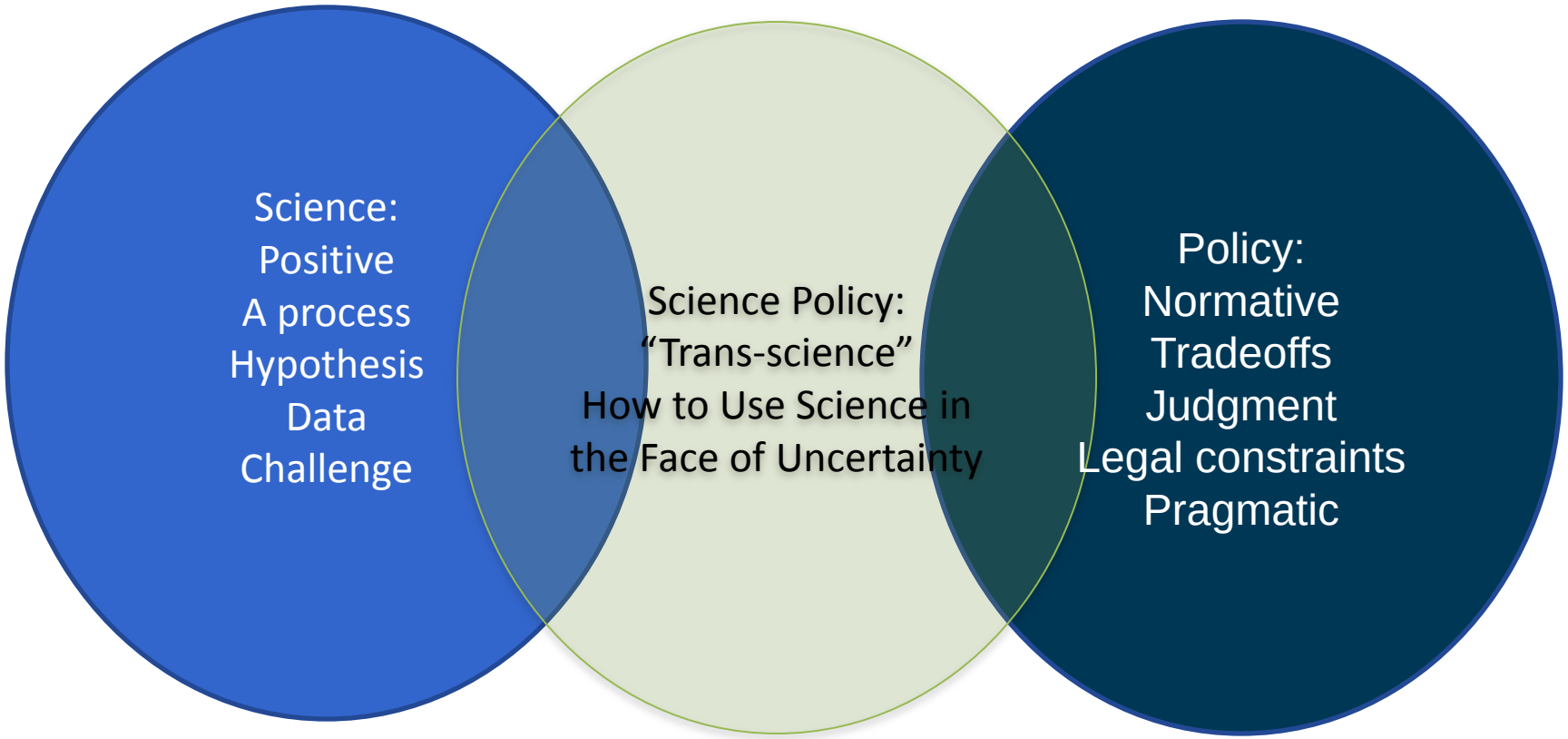
Science, Science Policy, and Policy



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Science Policy Choices

- Standard assumptions and defaults of risk assessment are more scientifically plausible for some chemicals than for others
- Some chemicals have more data or higher quality data
- Degree of conservatism in risk estimates varies between chemicals

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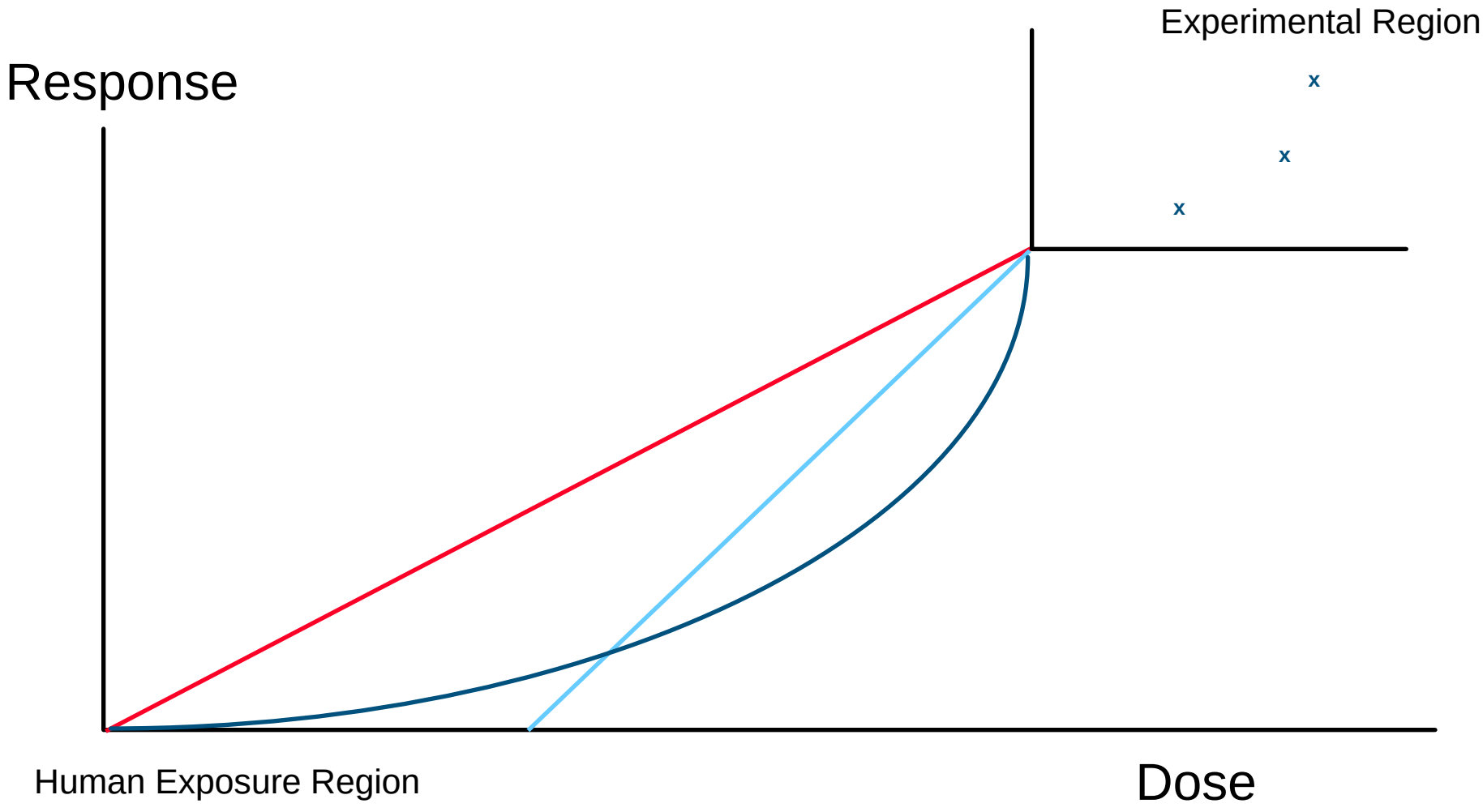
Model Uncertainty



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The Same Dose-Response Relationship for All Carcinogens?

"Evidence concerning the modes of action of different classes of carcinogens suggests that a linear non-threshold model may be appropriate only for initiating agents and complete carcinogens, whereas models yielding smaller estimates of risk at low doses might represent more accurately the dose-response relationship for other classes of carcinogens. For some types of carcinogens, thresholds might even be envisioned to exist...."

Arthur C. Upton (1988) *Are There Thresholds for Carcinogens? The Thorny Problem of Low-Level Exposure*. Annals of the New York Academy of Sciences **534**:863-883

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Why Not Use Linear for All?

- Ignoring scientific information makes risk characterization potentially misleading – distorts comparisons to inform decisions
- Example: cancer risk from outdoor exposure to carbon tetrachloride or ethylene dibromide
  - Carbon Tetrachloride Nationwide Cancer Risk 2.9 x 10^{-6} (870/yr)
  - EDB - Nationwide Cancer Risk 2.2 x 10^{-7} (66/yr)

Source: U.S. EPA (2005) National Air Toxics Assessment (http://www.epa.gov/ttn/atw/nata2005/index.html)

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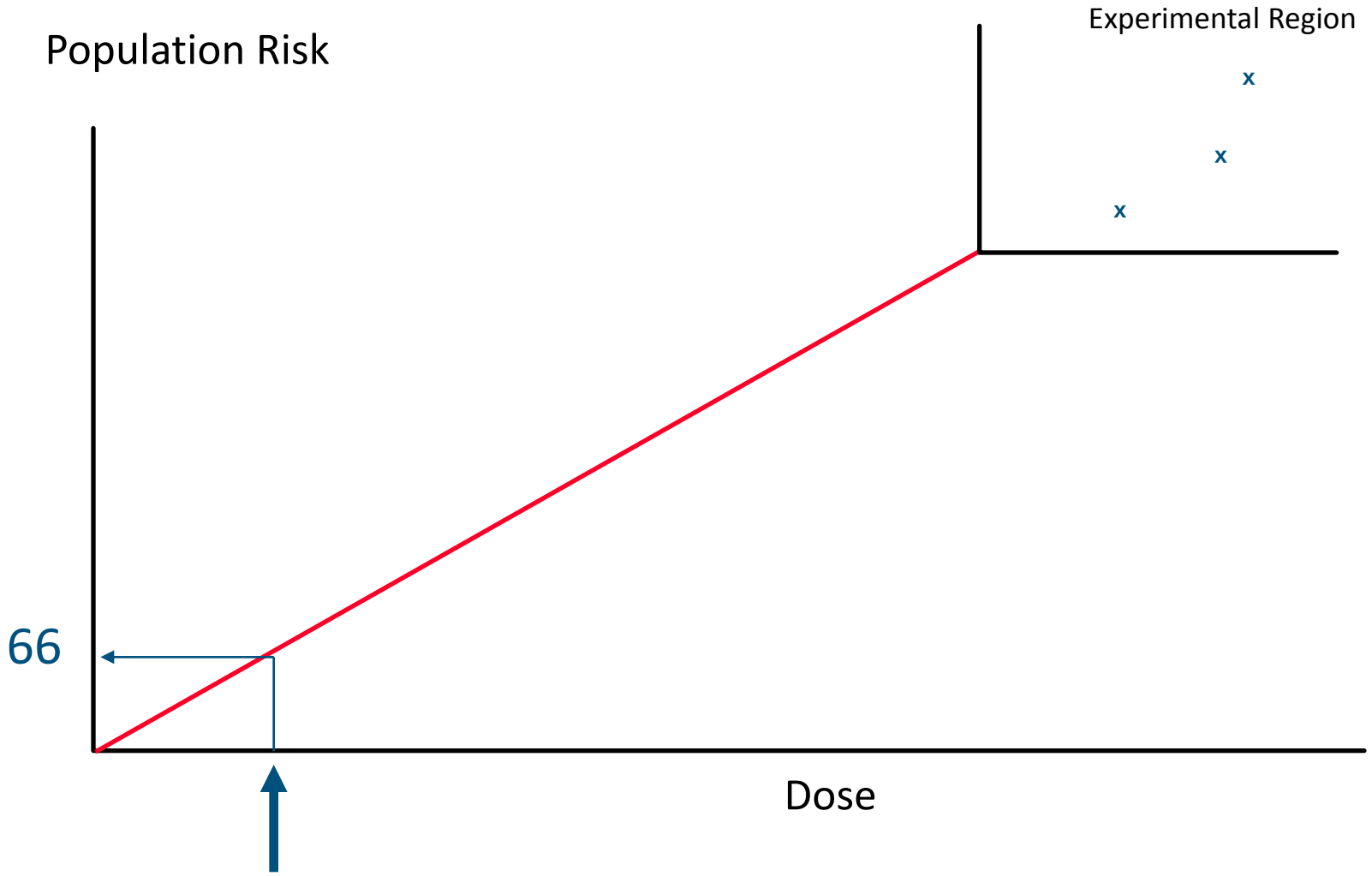
Low-Dose Extrapolation for EDB



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Carbon Tet at Low Dose

- International Program on Chemical Safety
  - "It is likely the carcinogenicity of carbon tetrachloride is secondary to its hepatotoxic effects"
  - "A quantitative risk assessment for threshold effects… was therefore adopted"

Source: IPCS Environmental Health Criteria 208

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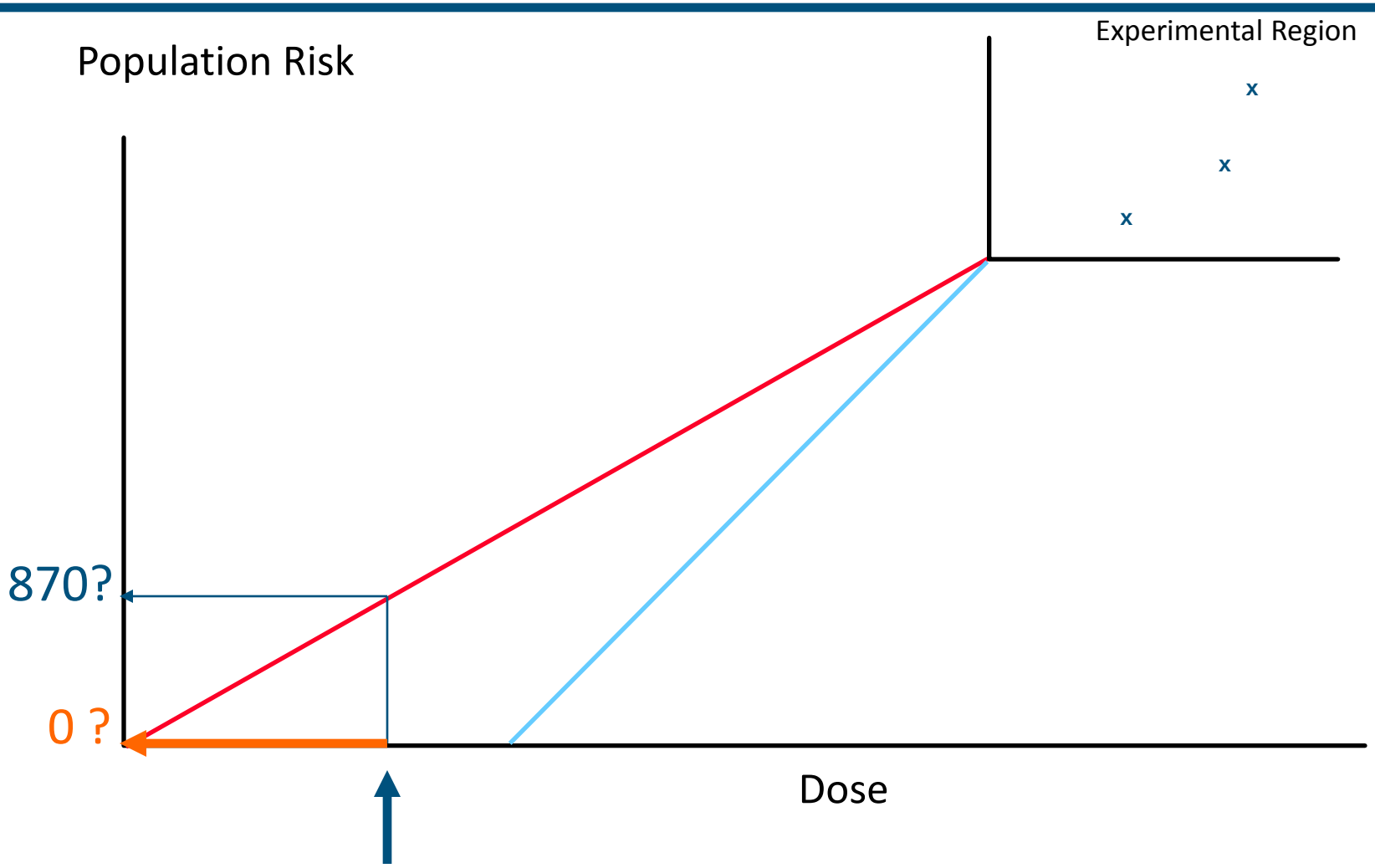
Low-Dose Extrapolation for Carbon Tetrachloride



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Moving Forward?

- Multiple estimates based on plausible models/data/assumptions

  Characterizing the empirical-variation range of the overall uncertainty that is due to differences between studies or end points is useful in elucidating the totality of uncertainty (NRC Review of EPA's Integrated Risk Information System (IRIS) Process, page 127)

  The present committee agrees with the previous NRC committee and recommends that analysis and communication of uncertainty be an integrated component of IRIS assessments even when a default used in the assessment is consistent with EPA's own guidelines. At a minimum, that approach would include a demonstration of variation in the final toxicity- value estimates under different assumptions, options, models, and methods. (NRC Review of EPA's Integrated Risk Information System (IRIS) Process, page 125)

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Moving Forward?

- *Another short-term strategy that EPA could adopt to improve uncertainty communication is to present clearly two dose-response values in each future toxicity assessment: a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower bound estimate for a POD from which a final toxicity value is derived*. (NRC Review of EPA's Integrated Risk Information System (IRIS) Process, pages 127-128)

- CAREFUL! – May give false sense that value is true central estimate when it may only reflect stochastic uncertainty in the parameters of the dose-response model

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Danger – Characterizing Some Uncertainty May Hide the Fact that Other Sources are Not Considered

- Causality
- Magnitude
  - Model uncertainty
  - Parameter uncertainty
- Consequences
  - Concordance?
  - Match to identifiable human outcome?
- Which sources matter most?

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Moving Forward?

- Integration of available data along with model and parameter uncertainty – developing probability distributions for risk values

> *As the IRIS program evolves, EPA should develop and expand its use of Bayesian or other formal quantitative methods in data integration for dose-response assessment and derivation of toxicity values.* (NRC Review of EPA's Integrated Risk Information System (IRIS) Process, page 130)

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Moving Forward: A Provocative Idea

- Drop attempts to comprehensively characterize uncertainty – instead present multiple quantitative values to empirically reflect plausible alternatives
- Make IRIS a compendium of ED_{50}, E_{90} and ED_{10} values for multiple endpoints in multiple species
- Question of which species, which endpoint, UFs, *etc*. made in risk management
- Advocate MOE approach to decision making

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The Margin of Exposure (MOE)

$$\frac{\text{RfV}}{\text{Exposure}} = \text{MOE}$$

- Reference Value (RfV) is a point of departure (POD) from toxicologic or epidemiologic data
  - No Observed Adverse Effect Level
  - Benchmark Dose (or bound)
  - ED_{50}?
- Exposure can be measured or modeled – reflect variability

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Using MOE

- Health Canada – "*The "margin of exposure" is the magnitude of the ratio between the level (dose) at which the critical effect is observed in studies conducted in animals or, in some cases, humans and the upper-bound estimated (or measured) level of human exposure to a substance. Recommendations are based on the adequacy of this margin of exposure, ……..*"

- European Food Safety Authority – "*The MOE is a ratio of two factors which assesses for a given population the dose at which a small but measurable adverse effect is first observed and the level of exposure to the substance considered.*"

- Also European Chemicals Agency, Norwegian Scientific Committee for Food Safety, Australian Department of Health and Aging, US EPA Office of Pesticide Programs, *etc*.

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IRIS As a Collection of RfVs?

- Present Reference Values for endpoints of concern for each chemical
- Straightforward calculation, no need to identify and justify particular approaches, models or UFs
- Enhance transparency

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Advantages of RfV/MOE Approach

- Faster – more chemical coverage
- More transparent – science policy choices made in risk management phase
- Readily applied to different settings/uses (*i.e.*, fit for purpose (NAS and EPA))

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Concerns About RfV/MOE Approach

- How to calculate RfV?
- Which endpoints?
  - sex/species/strain
  - Concordance?
- How to judge adequacy of MOE (>100? >1000? >233?) – are we putting science judgments in the wrong hands?
- Does use imply linearity (*e.g.*, MOE of 500 is 5X better than 100?)
- Can it be used in benefit/cost analysis and other important uses of risk assessment?

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Thank You!