United States Environmental Protection Agency

DOSE-RESPONSE ANALYSIS

Steps 4 & 5: Selection of Studies and Derivation of Toxicity Values

Weihsueh A. Chiu, PhD
Chief, Toxic Pathways Branch/IRIS Division
Project Area Lead, Advancing Dose-Response Assessment/
Human Health Risk Assessment Research Program

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington DC

Development of IRIS Health Assessments: Dose-Response Analysis

Steps Outlined by NAS (2011)

1. Identify Evidence → 2. Evaluate Evidence → 3. Synthesize and Integrate Evidence → 4. Select Studies to Derive Toxicity Values → 5. Derive Toxicity Values

Dose-Response Analysis

- Overview of toxicity values in IRIS assessments
- Selection of studies for derivation of toxicity values
- Deriving toxicity values
- Summary

What Kinds of Toxicity Values Are Typically Developed in IRIS?

- Oral Slope Factor (OSF) and Inhalation Unit Risk (IUR)
  - Derived for cancer effects with linear mode of action or with inadequate data to support a mode of action
  - Historically, have been based on a <u>single cancer bioassay</u>
- Reference Dose (RfD) and Reference Concentration (RfC)
  - Derived for non-cancer effects or cancer effects with non-linear mode of action
  - Historically, have been based on a <u>single critical effect from a single study</u>

Definitions of Toxicity Values Typically Developed in IRIS

- **Oral Slope Factor.** An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

- **Inhalation Unit Risk.** The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2×10^{-6} per $\mu g/m^3$, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per m^3 of air.

- **Reference Dose.** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

- **Reference Concentration.** An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Selection of Studies for Derivation of Toxicity Values

- For each health effect for which there is credible evidence of a hazard, toxicity values are derived if there are suitable epidemiologic or experimental data.

- For each hazard, a study or group of studies has been identified and evaluated for hazard identification. These studies are evaluated for consideration for dose-response analysis.

- Quantitative exposure and response data must be available to compute a point of departure (i.e., no observed adverse effect level [NOAEL], lowest observed adverse effect level [LOAEL], 95% lower confidence limit on the benchmark dose [BMDL]).

- Building on the initial individual study quality evaluations that identified strengths and weaknesses of the individual studies, additional attributes (aspects of the study and data characteristics) pertinent to derivation of toxicity values are considered to evaluate the studies for dose-response analysis:
    - Species studied
    - Relevance of exposure paradigm
    - Potential selection bias
    - Potential confounding
    - Measurement of exposure
    - Measurement of health outcome
    - Power and precision

Selection of Studies for Derivation of Toxicity Values

- Epidemiologic studies are preferred over animal studies, if quantitative measures of exposure are available and effects can be attributed to the agent.
- Among experimental animal models, those that respond most like humans are preferred, if the comparability of response can be determined.
- Studies by a route of human environmental exposure are preferred, although a validated toxicokinetic model can be used to extrapolate across exposure routes.
- Studies of longer exposure duration and follow-up are preferred, to minimize uncertainty about whether effects are representative of lifetime exposure.
- Studies with multiple exposure levels are preferred for their ability to provide information about the shape of the exposure-response curve.
- Studies with adequate power to detect effects at lower exposure levels are preferred, to minimize the extent of extrapolation to levels found in the environment.
- The most relevant, informative studies, a subset of the studies used in hazard identification, are selected to move forward for derivation of toxicity values.

EPA Derives Toxicity Values Using a Two-Step Approach

1. Analysis of observed dose-response data, resulting in a **point of departure (POD).**

2. Inferences at lower doses, resulting in a **toxicity value.**

Step 1: Analysis of Observed Dose-Response Data, Resulting in a POD

Dose-response data considerations: modeling dose to sites of biologic effects.

- Where data allow, physiologically-based pharmacokinetic (PBPK) models are used to model dose to sites of biologic effects.
- Because PBPK models can require many parameters and more data than are typically available, EPA has developed standard approaches that can be applied to typical data sets.
  - Intermittent study exposures are standardized to a daily average over the duration of exposure (facilitates comparison across exposure patterns and species).
  - Doses are standardized to equivalent human terms to facilitate comparison of results from different species.

Step 1: Analysis of Observed Dose-Response Data, Resulting in a POD

Dose-response data considerations: modeling the response in the range of observation.

- The POD is an estimated dose near the lower end of the observed range of effects.
- This estimation considers biological and statistical factors.
- Modeling is the preferred approach because it incorporates a wide range of data into the analysis.
- EPA has developed a standard set of empirical ("curve-fitting") models (http://www.epa.gov/ncea/bmds/) that can be applied to typical data sets, including those that are nonlinear to derive a benchmark dose (BMD).
- The POD derived by modeling is the 95% lower bound on the benchmark dose (i.e., BMDL) associated with a selected response level.
- If the POD cannot be derived by modeling, a NOAEL or a LOAEL is used instead.

Step 2: Inferences at Lower Doses, Resulting in a Toxicity Value: Application of Uncertainty Factors Applied to Threshold PODs (Noncancer and Cancer)

- **Human variation UF.** The assessment accounts for variation in susceptibility across the human population and the possibility that the available data may not be representative of individuals who are most susceptible to the effect.
- **Animal-to-human extrapolation UF.** If animal results are used to make inferences about humans, the assessment adjusts for cross-species differences. These may arise from differences in toxicokinetics or toxicodynamics.
- **LOAEL to NOAEL UF.** If a POD is based on a LOAEL, the assessment must infer a dose where such effects are not expected.
- **Subchronic-to-chronic exposure UF**. If a POD is based on subchronic studies, the assessment considers whether lifetime exposure could have effects at lower levels of exposure.
- **Incomplete database UF.** If an incomplete database raises concern that further studies might identify a more sensitive effect, organ system, or lifestage, the assessment may apply a database uncertainty factor.

Step 2: Inferences at Lower Doses, Resulting in a Toxicity Value

- The purpose of extrapolating to lower doses is to estimate responses at exposures below the observed data.
- Low-dose extrapolation is typically used for cancer data and considers what is known about the modes of action.
  - Biologically-based models - If a biologically based model has been developed and validated for the chemical, extrapolation may use the fitted model below the observed range.
  - Linear extrapolation - Linear extrapolation is used if the dose-response curve is expected to have a linear component below the POD or if there is an absence of sufficient information on modes of action (i.e., derive cancer OSF and IUR).

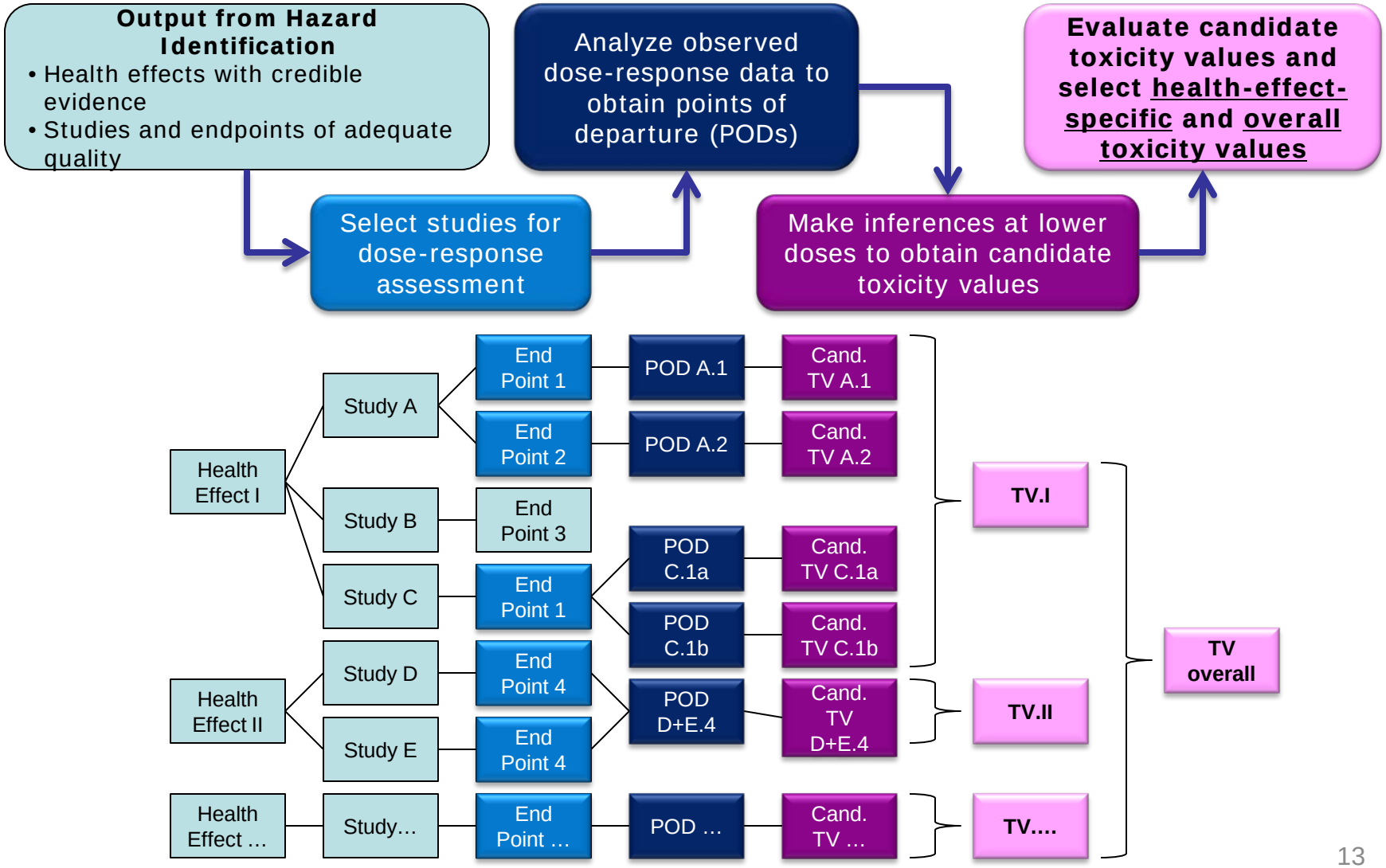
    Straight line from the POD representing an upper bound on risk per increment of dose or exposure.

    OSF $(mg/kg\text{-}day)^{-1}$ = Risk/dose (mg/kg-day)

Step 2: Inferences at Lower Doses, Resulting in a Toxicity Value

- Nonlinear modeling - Nonlinear models are used for extrapolation if there are sufficient data to ascertain the mode of action and to conclude that it is not linear at lower doses, and the agent does not demonstrate mutagenic or other activity consistent with linearity at lower doses.
- Nonlinear threshold - If nonlinear extrapolation is appropriate but no model is developed, an alternative is to calculate reference values (derive RfD and RfC) by applying a series of *uncertainty factors (UF)* to the POD to account for uncertainty and variability in the derivation of a lifetime human exposure where adverse effects are not anticipated to occur, i.e., RfD (mg/kg-day) = POD (mg/kg-day)/UF.

Systematically Moving from Hazard Identification to Toxicity Values

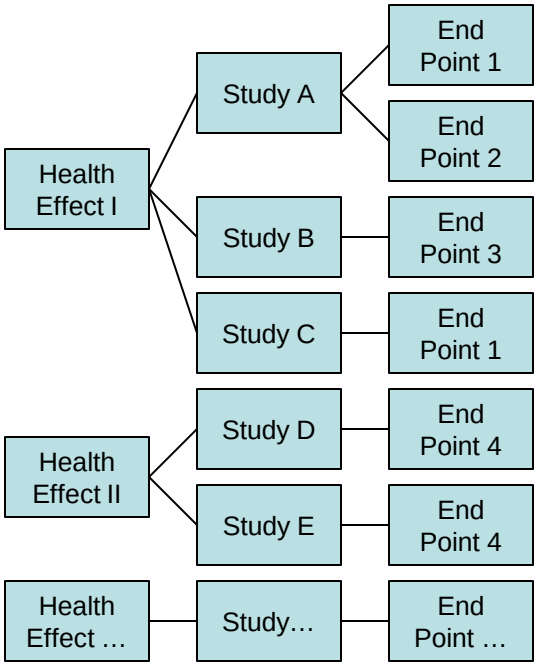


Adapted from NRC (2011) Figure S-1

Selecting Health-Effect-Specific and Overall Toxicity Values

Output from Hazard Identification

- Health effects with credible evidence
- Studies and endpoints of adequate quality



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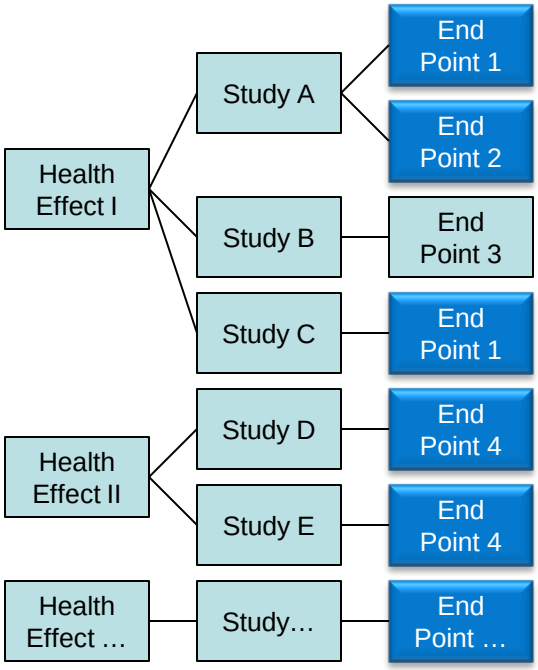
Selecting Health-Effect-Specific and Overall Toxicity Values

Output from Hazard Identification

- Health effects with credible evidence
- Studies and endpoints of adequate quality

Select studies for dose-response assessment



- Suitable for deriving BMD, NOAEL, or LOAEL
- Other considerations evaluated include:
  - Species/population studied
  - Exposure route
  - Exposure duration or during critical window, and duration of follow-up
  - Exposure levels and statistical power
  - Study design attributes

Adapted from NRC (2011) Figure S-1

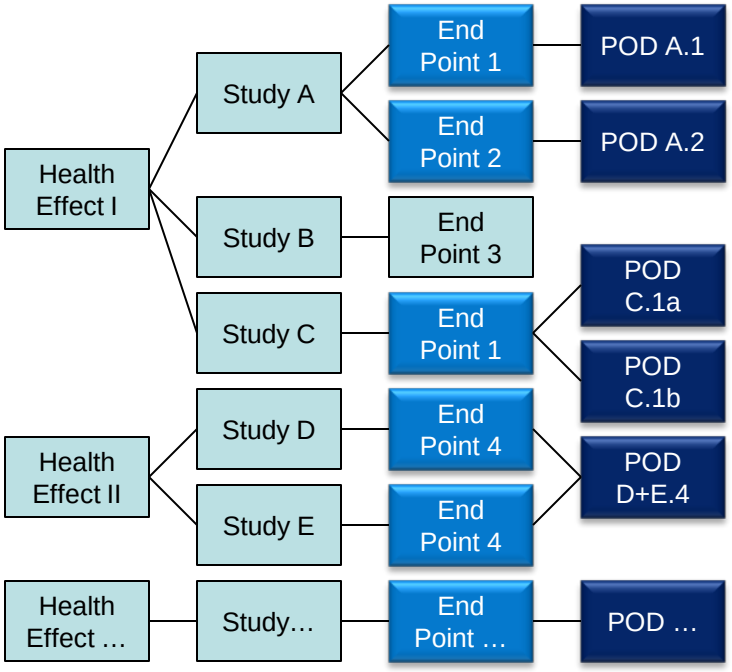
Selecting Health-Effect-Specific and Overall Toxicity Values

Output from Hazard Identification

- Health effects with credible evidence
- Studies and endpoints of adequate quality

Select studies for dose-response assessment

Analyze observed dose-response data to obtain points of departure (PODs)



- Adjust doses to standardize intermittent exposures and to derive human equivalent doses/concentrations
- Analyze dose-response in the observed range of effects to derive a Point of Departure (POD) (BMDL, NOAEL, LOAEL)

Adapted from NRC (2011) Figure S-1

Selecting Health-Effect-Specific and Overall Toxicity Values

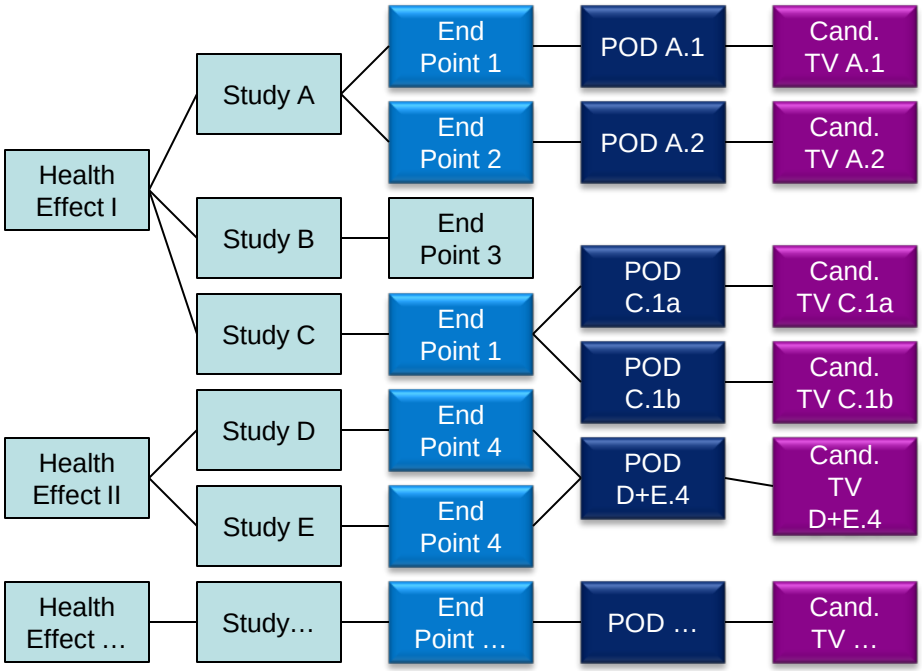
Output from Hazard Identification

- Health effects with credible evidence
- Studies and endpoints of adequate quality

Select studies for dose-response assessment

Analyze observed dose-response data to obtain points of departure (PODs).

Make inferences at lower doses to obtain candidate toxicity values



For candidate OSFs and IURs:

- Estimate based on adequate biological model
- Straight line from the POD representing an upper bound on risk per increment of dose or exposure

Adapted from NRC (2011) Figure S-1

Selecting Health-Effect-Specific and Overall Toxicity Values

Output from Hazard Identification
- Health effects with credible evidence
- Studies and endpoints of adequate quality

Select studies for dose-response assessment

Analyze observed dose-response data to obtain points of departure (PODs).

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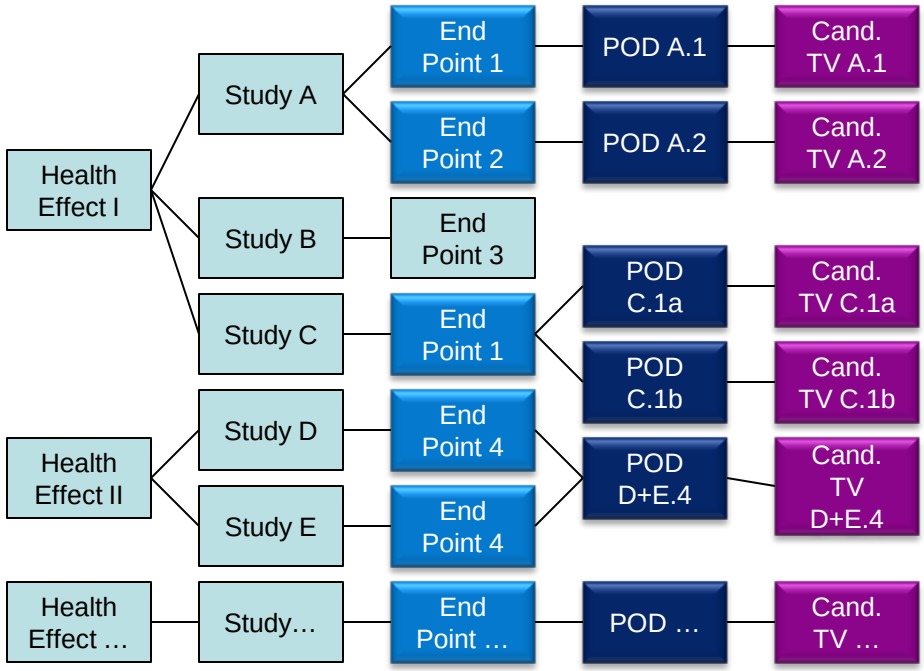


For candidate RfDs and RfCs

The POD is divided by:
- Default Uncertainty Factors, or
- Data-Derived Extrapolation Factors

to make extrapolations for:
- Human variability
- Animal-to-human differences
- LOAEL to NOAEL
- Subchronic-to-chronic exposure
- Incomplete database

These "Factors" address more than just uncertainty

Adapted from NRC (2011) Figure S-1

Selecting Health-Effect-Specific and Overall Toxicity Values

Output from Hazard Identification
- Health effects with credible evidence
- Studies and endpoints of adequate quality

Select studies for dose-response assessment

Analyze observed dose-response data to obtain points of departure (PODs)

Make inferences at lower doses to obtain candidate toxicity values

Evaluate candidate toxicity values and select <u>health-effect-specific</u> and <u>overall</u> toxicity values

Health Effect I
- Cand. TV A.1
- Cand. TV A.2
- Cand. TV C.1a
- Cand. TV C.1b

→ **TV.I**

Health Effect II
- Cand. TV D+E.4

→ **TV.II**

Health Effect …
- Cand. TV …

→ **TV….**

→ **TV overall**

Options are:
- Selecting a <u>single candidate toxicity value</u> as most appropriate
- Deriving a <u>composite toxicity value</u> based on multiple candidate values

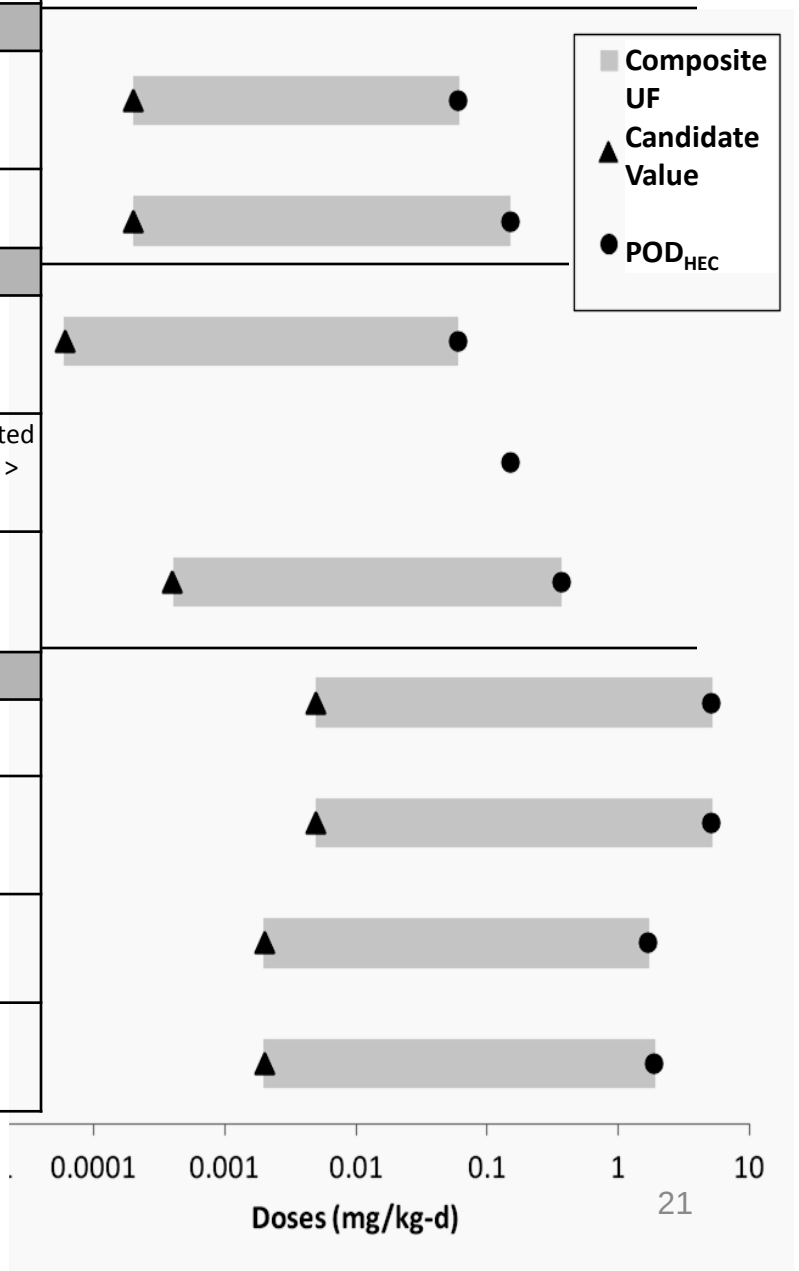
Evaluation considerations include:
- Previous considerations used in study selection
- Uncertainty in POD estimate
- Uncertainty in extrapolation(s)

Adapted from NRC (2011) Figure S-1

Example from Benzo[a]pyrene Draft Assessment

- Three health effects
  - Developmental
  - Reproductive
  - Immunologic
- Multiple candidate toxicity values for each health effect
  - Different studies/endpoints
  - Different points of departure
  - Different uncertainty factors

Endpoint and Reference	POD_{HED}[a]	POD type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF	Candidate value (mg/kg-d)
DEVELOPMENTAL									
Neurodevelopmental impairments in rats (Chen et al., 2012)	0.06	$BMDL_{1SD}$	10	10	1	1	3	300	2×10^{-4}
Cardiovascular effects (Jules et al., 2012)	0.15	LOAEL	3	10	10	1	3	1000	2×10^{-4}
REPRODUCTIVE									
Cervical epithelial hyperplasia (Gao et al., 2011)	0.06	$BMDL_{10}$	3	10	1	10	3	1000	6×10^{-5}
Decreased sperm count in mice (Mohamed et al., 2010)	0.15	LOAEL	3	10	10	10	3	10000	Not calculated due to UF > 3000
Decreased ovary weight and ovarian follicles in rats (Xu et al., 2010)	0.37	$BMDL_{1SD}$	3	10	1	10	3	1000	4×10^{-4}
IMMUNOLOGICAL									
Decreased serum IgA in rats (De Jong et al., 1999)	5.2	NOAEL	3	10	1	10	3	1000	5×10^{-3}
Decreased number of B cells in rats (De Jong et al., 1999)	5.2	NOAEL	3	10	1	10	3	1000	5×10^{-3}
Decreased thymus weights (Kroese et al., 2001)	1.9	$BMDL_{1SD}$	3	10	1	10	3	1000	2×10^{-3}
Decreased serum IgM in rats (De Jong et al., 1999)	1.7	NOAEL	3	10	1	10	3	1000	2×10^{-3}



Dose-Response Analysis: Summary

- Dose-response analysis involves a process of evaluating and selecting studies for derivation of toxicity values, consideration of MOA, analysis of observed dose-response data in these studies, estimating a point of departure, and applying inferences at lower doses to derive a toxicity value.

- This process results in development of health-effect-specific toxicity values and overall toxicity values for cancer and noncancer effects.

- In IRIS assessments, Dose-Response Analysis includes:
  - A chapter in the new document template, with a subsection provided to explain the rationale used to select and advance studies for consideration in deriving toxicity values based on conclusions regarding potential hazards associated with chemical exposure.
  - Key data supporting dose-response analysis reported, and the methodology and derivation of toxicity values described.
  - Tables and figures show candidate toxicity values for comparison across studies and endpoints.
  - Clear documentation of the conclusions and selections of the health-effect-specific and overall toxicity values provided.

Newer Developments in Response to the NRC Recommendations

- A comprehensive, transparent review and documentation process for selecting studies and deriving toxicity values.
- New document structure focuses on Dose-Response Analysis; separated from Hazard Identification.
- Identified evaluation considerations for selecting studies for deriving toxicity values.
- In analysis of dose-response data:
  - Consider whether combining studies/datasets is warranted (e.g., averaging, meta-analysis).
  - Document assumptions, modeling, and risk-estimation approaches.
- In deriving toxicity values:
  - Evaluation includes sensitivity to model assumptions and endpoints selected.
  - Consider selecting a composite toxicity value based on multiple candidate values.
  - Look across effects, studies, and endpoints to develop candidate toxicity values for each health effect associated with exposure to the chemical, and selecting overall toxicity values.