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Risk Assessment and Hazard Identification for Metals

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Risk Assessment and Hazard Identification for Metals

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Risk Assessment
(organizing & analyzing to set priorities & guide management)

- Hazard identification/
- characterization
- Dose-response
- Exposure estimation
- Risk characterization

Risk Management
(decision & action)

- Political
- Social
- Economic
- Engineering

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Risk Assessment/Management Components

- **Hazard identification:** Is this toxic to humans?
- **Dose-response assessment:** How toxic is it?
- **Exposure assessment:** Who is exposed, how much, how often, and for how long each time?
- **Risk characterization:** So what?
- **Risk management:** So what will be done about it?

SOURCE: Don Barnes, 1993

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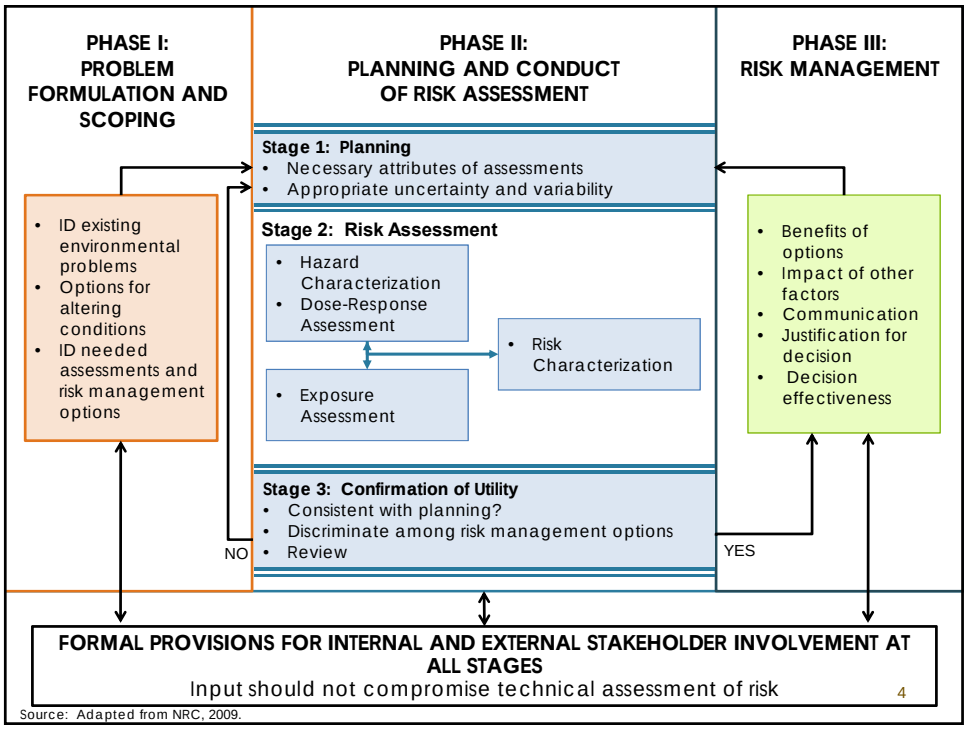

Source: Adapted from NRC, 2009.

Examples of Risk Assessments

- **All involve evaluation of all relevant and important information on toxicity, kinetics, mode of action, and exposure…**
  - Identification of a "safe dose" for a methyl mercury found in fish
  - Determination of a margin of exposure (MOE) for chromium VI in drinking water
  - Identification of a cancer classification or descriptor for arsenic found in soil

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Hazard Indentificaion

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Hazard Identification

- **Purpose is to make a qualitative judgment of the effect caused by the agent under consideration**
- **Questions to be answered:**
  - Is the database sufficient to proceed with an assessment?
  - What is the critical effect?
  - What is the appropriate study?
- **Generally considers toxicity from one route of exposure relevant to other routes**
- **Culminates in discussion of the weight-of-evidence supporting a conclusion of toxicity**

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Evaluating the Evidence

- **Strength of evidence (the "comfort" zone)**
  - Judgment on the reliability of a given data set supporting a toxicological effect
    - Quality of the studies and methodology
- **Weight of evidence (WOE) (early, systematic assimilation)**
  - Comprehensive, integrated judgment of all relevant information supporting conclusions regarding a toxicological effect, including MOA
    - Dose/response and temporality
    - Consistency and specificity
    - Biological plausibility and coherence

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Hazard Identification

- **Discussion of the weight-of-evidence for critical hazard(s) and human relevance, based on:**
  - Consistency, specificity, biological plausibility
- **Which critical effect(s)?**
- **How they're induced**
- **Critical studies for dose-response analysis**

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Hazard Characterization

- **Considers:**
  - Data on toxicity
    - Various endpoints
  - Mechanistic data/mode of action
    - How a chemical induces an effect
      - Kinetics
      - Dynamics

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Mechanistic Data

- **Toxicokinetics:** Uptake by the body, biotransformation and distribution and elimination of the substance and metabolites from the body (absorption, distribution, metabolism, excretion—ADME)
- **Toxicodynamics:** Interaction with target sites and the subsequent reactions leading to adverse effects (e.g., biochemical, tissue effects)

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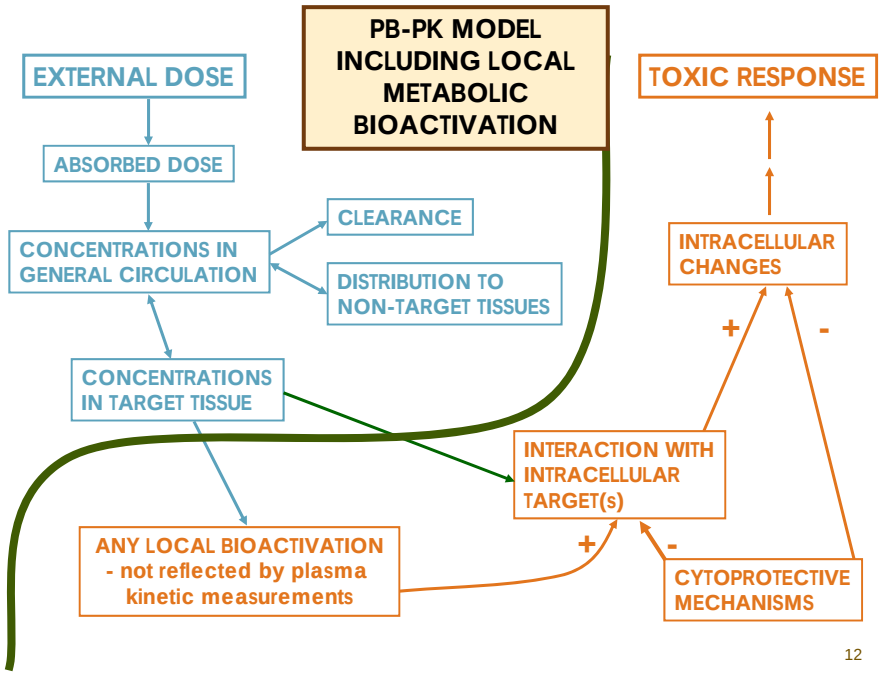

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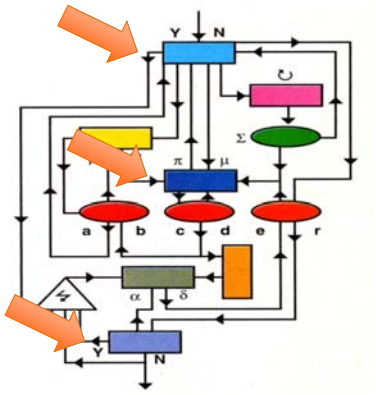
Mode versus Mechanism

Plausible Hypothesis

Key event:

- Critical
- Quantifiable
- Repeatable

Detailed Molecular Description



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Key Event

- **An empirically *observable*, precursor step that is a *necessary* element of the mode of action, or is a marker for such an element**
  - Key events are ***necessary*** but not always ***sufficient***
- **Examples:**
  - Specific metabolic transformation
  - Receptor-ligand changes
  - Increased cell growth and organ weight
  - Hormonal or other physiological perturbations

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Common Modes of Action

- There are many toxicological modes of action and several may apply for a single chemical
- Direct covalent interactions with macromolecules (e.g., protein or DNA adducts or lipid membrane disruption)
- Interactions of secondary reaction products (e.g., reactive oxygen) with macromolecules
- Disruption of vital cell functions, such as cell energetics or cell division processes
- Receptor binding or altered hormone responses that control cell growth or function

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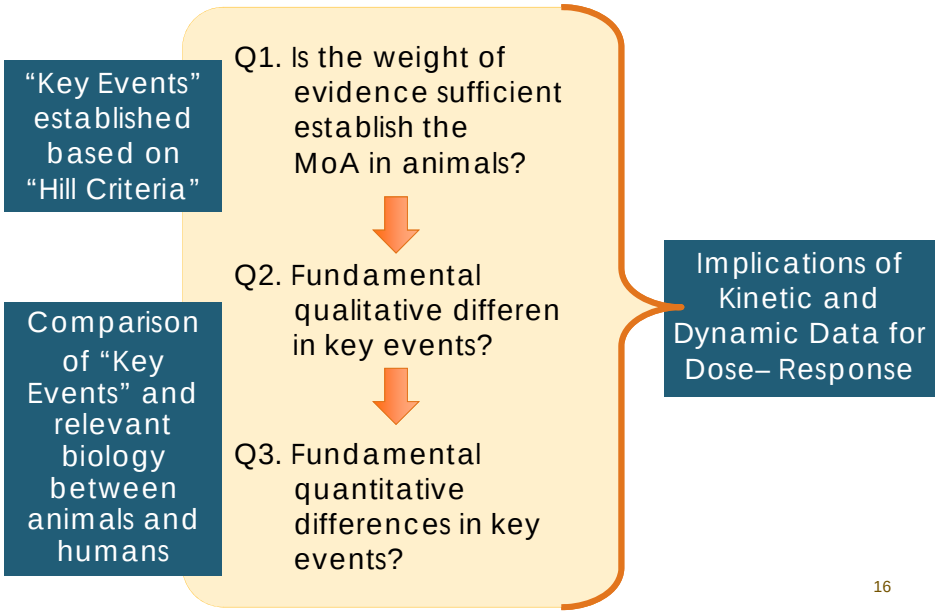
IPCS/ILSI MOA/HR (WOE) Framework



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Trends in Hazard Identification

- **Early and structured consideration of weight of evidence, based on framework analysis, taking into consideration**
  - e.g., consistency, specificity, biological plausibility
- **Earlier consideration of mode of action to more meaningfully inform "risk characterization"**
- **Less reliance on structured classification systems and more on narrative descriptions of the weight of evidence**

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Issues Associated with the Hazard Identification of Metals

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Dose-Response Assessment

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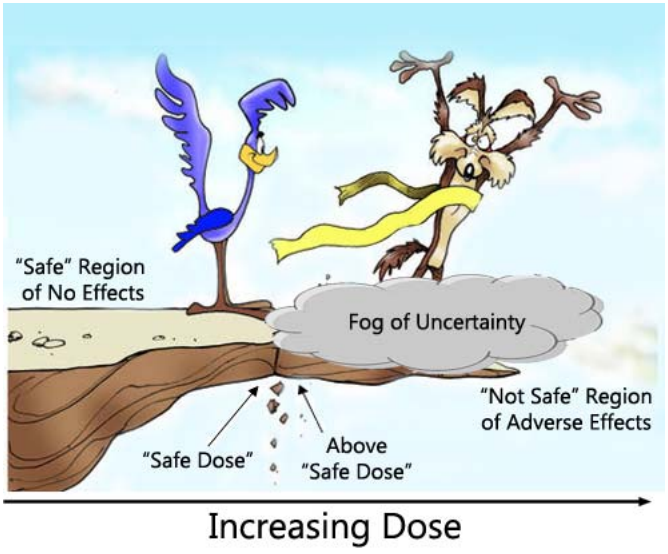
The Risk Value Concept



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Dose-Response Assessment

- **Dose-response assessments are estimates of the quantitative relationship between the amount of exposure and the likelihood of health effects**
  - Both in the range of observation,
  - And inference/extrapolation
    - Requires consideration of how effects are induced
- **Require consideration of animal-human differences and human variability**

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Considering Dose Response

- **What is the shape of the dose-response curve in the range of both observation and inference for the rate limiting key events, based on an understanding of MOA?**
- **Meaningfully combining that information**
- **Are kinetic and dynamic data sufficient to quantitatively inform interspecies differences and human variability?**

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Key Events Dose-Response Framework

- *Systematic* analytical approach to examining in detail the *fundamental* determinants of dose-response relationships, including determinants of *variability* in such relationships
- Pathway as a series of conditional events
- Some events are *control points* – engage mechanisms (e.g. homeostatic, repair, etc.) to control or maintain physiology – need to be overwhelmed to reach endpoint of concern

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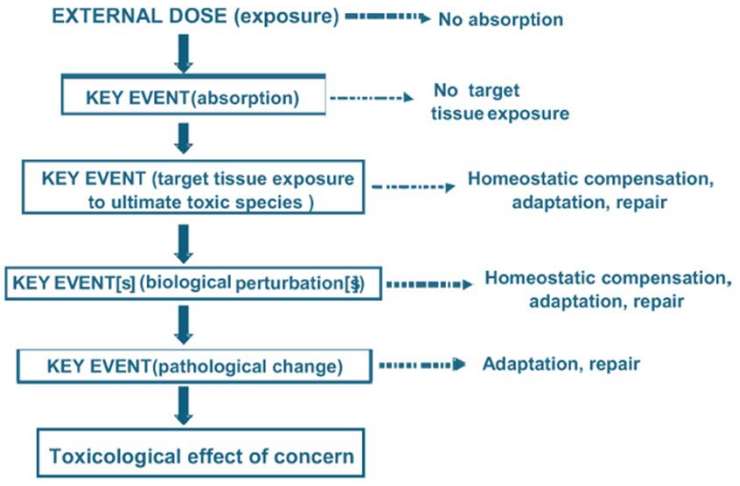
Key Events Dose-Response Framework



Source: Boobis et al. 2009.

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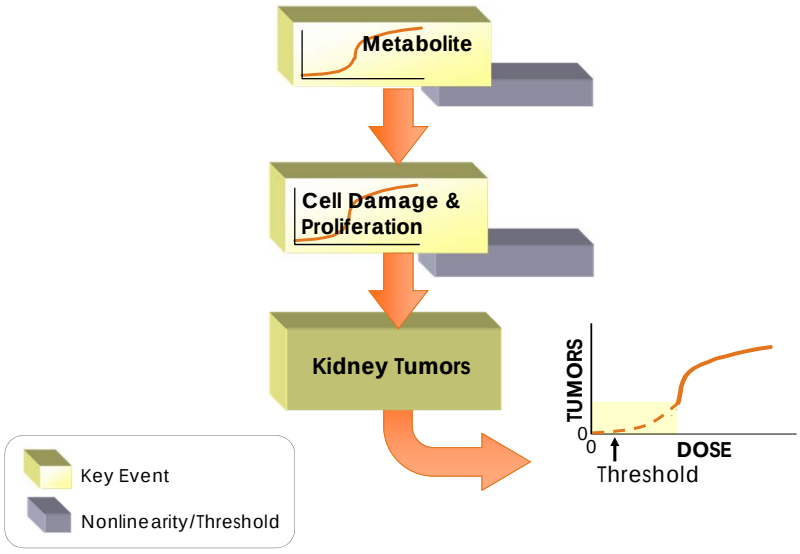
Hypothesized Mode of Action for Rat Kidney Tumors



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Dose-Response Approaches
(continued)

- **Low dose linear extrapolation from a point of departure in the experimental range**
  - Restricted principally to cancer in U.S. context
- **More biologically based approaches to address interspecies differences and human variability incorporating information on:**
  - Kinetics: Physiologically Based Pharmacokinetics (PBPK)
  - Dynamics: Biologically Based Dose Response (BBDR)

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Physiologically Based Pharmacokinetic (PBPK) Models in Risk Assessment

- **Increasing precision of risk estimates and understanding of uncertainty and variability**
  - Estimating internal dose measures for extrapolation across species, groups, routes, doses, time and age
    - Physiology (weights of organs and tissues and blood flows)
    - Physical-chemical and biochemical constants of compound
- **Reducing reliance on animal testing**
  - Biologically meaningful quantitative framework in which *in vitro* data can be more effectively utilized

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Dose-Response Approaches

Depending on purpose of assessment and mode of action:

Tolerable or reference doses/concentrations:

$$\frac{\text{Measure of dose-response}}{\text{Uncertainty factor}}$$

- **Margins of exposure:**

$$\frac{\text{Measure of dose-response}}{\text{Exposure}}$$

- **Exposure potency indices:**

$$\frac{\text{Exposure}}{\text{Measure of dose-response}}$$

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As Defined by EPA

RfD or RfC is …

- an estimate (with uncertainty spanning perhaps ***an order of magnitude***) of
- a ***daily*** (for RfD) or ***continuous*** (for RfC) exposure to the human population (including ***sensitive subgroups***)
- that is ***likely to be without*** an appreciable risk of deleterious effects during a lifetime.

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Reference Dose/Reference Concentration

$$\text{RfD or RfC} = \frac{\text{NOAEL, LOAEL or BMD}}{\text{UF x MF}}$$

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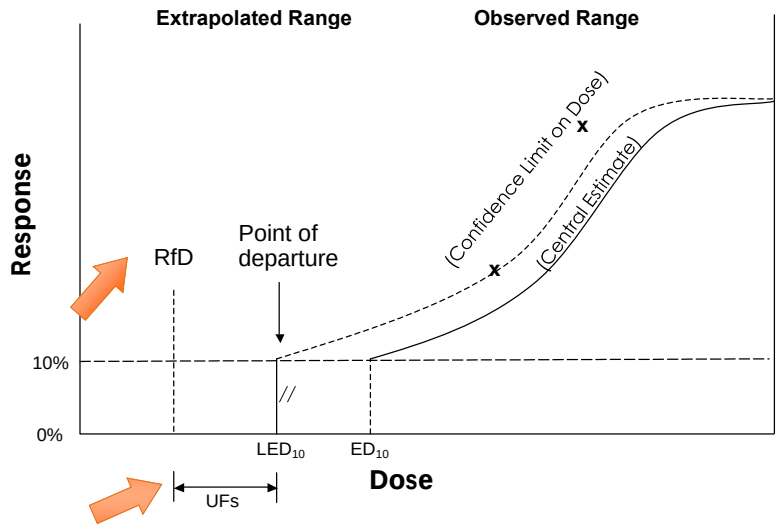
Curve Fitting: RfDs/RfCs



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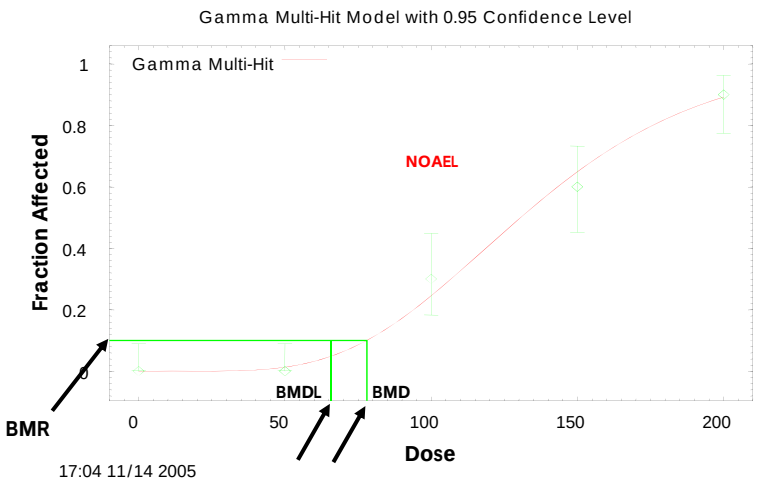
Example of Calculation of a BMD



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Reference Dose/Concentration

$$\text{RfD or RfC} = \frac{\text{N/LO(A)EL or BMC/D}}{\text{UF}}$$

- **BMC/D =** Benchmark Concentrations or Doses
- **N/LO(A)EL =** No or Lowest Observed (Adverse) Effect Level
- **Uncertainty Factor:**
  - Interspecies differences (x10)
  - Human variability (x10)
    - Interindividual or intraspecies variation
  - Other
    - Adequacy of database (x1–100)

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U.S. EPA Uncertainty Factors

Factor*	Extrapolation
H	Average human to sensitive human
A	Animal to human
S	Sub-chronic to long-term exposure
L	LOAEL to NOAEL
D	Minimum to complete database

* These factors are as used by the U.S. EPA. Other health organizations use similar factors.

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The Continuum
Default Data-Informed

- **Default:** 10 x 10
- **Database-derived:** Databases of information, not group or chemical-specific
- **Categorical:** Applies to categories of substances/species based on their characteristics (BSA correction; RfC - gases/particles)
- **Chemical Specific Adjustment Factors:** Addressing kinetic or dynamic aspects with chemical specific or compound-related information (e.g., PBPK)
- **Fully Data-derived:** Biologically-based dose-response modeling addressing kinetic and dynamic aspects (BBDR)

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Data First, Defaults Last

- **These 10 fold values are "defaults"**
- **Use data first; "defaults" are a last resort**
  - We don't aspire to use "defaults"
- **Data must be available to drive chemical- or group-specific adjustments**
- **Part of the reason we rely on "defaults" so often is lack of emphasis on mode of action in both risk assessment and design of tox testing**
- **Be aware that points of departure (PODs) and UFs are interdependent**

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Uncertainty and Variability

- **Variability = heterogeneity in time, space (pharmacokinetics, pharmacodynamics)**
  - Variability is inherent to the population
  - Can quantify variability, but more data doesn't decrease variability
  - Interspecies differences (UFA)
  - Interindividual (human) variability (UFH)
- **Uncertainty = lack of knowledge, can be decreased by additional data**
- **Examples for adequacy of database**
  - Lack of testing of potentially important endpoint(s) (UFD) or duration (s) (UFS)
  - Lack of adequate characterization of dose-response (UFL)

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What About Sensitive Populations and Children?

- **These groups are considered in human variability**
- **Children may be more or less sensitive, depending on how a chemical acts**
- **Hypersensitive populations are not necessarily protected**

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Dose-Response Approaches

Depending on purpose of assessment and mode of action:

Tolerable or reference doses/concentrations:

$$\frac{\text{Measure of dose-response}}{\text{Uncertainty factor}}$$

- **Margins of exposure:**

$$\frac{\text{Measure of dose-response}}{\text{Exposure}}$$

- **Exposure potency indices:**

$$\frac{\text{Exposure}}{\text{Measure of dose-response}}$$

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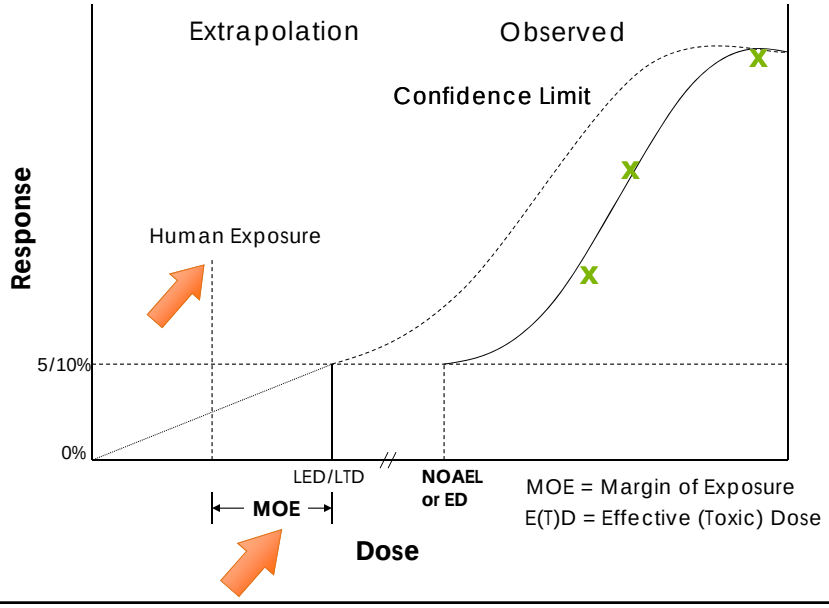
Curve Fitting: Margins of Exposure



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Cancer Classification

- **The hazard identification step results in a cancer classification (or more recently a weight of evidence descriptor with supporting narrative)**
- **Numerous agencies have schemes that are conceptually similar – but vary in the specific descriptors and criteria used**
  - U.S. EPA (1986 and 2005)
  - Health Canada
  - IARC
  - NTP
  - And many others

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Cancer Dose Response Threshold vs. Nonthreshold

- **Noncancer effects traditionally considered to have threshold**
- **Cancer effects traditionally considered to have no threshold; that is any exposure is associated with some risk. Newer thinking emphasizes Mode of Action.**
  - Health Canada notes the potential for a "practical" threshold for genotoxic effects, due to the interplay between the genotoxicity and cellular DNA-repair mechanisms, but it is assumed that all exposure levels have some risk
  - Mode of action determines quantification approach
    - DNA-reactive = linear extrapolation
    - Other MOA – UF approach

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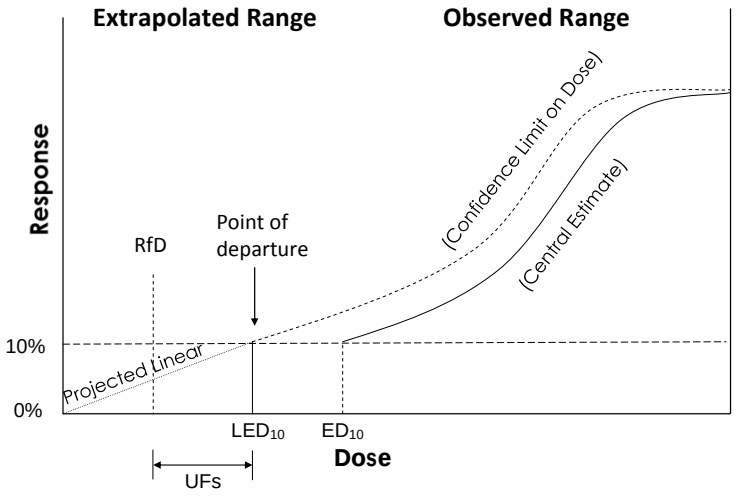
Graphical Representation of Data and Extrapolation



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Trends in Dose Response Assessment

- **Approaches to dose-response assessment will be mode of action rather than endpoint-based**
  - i.e., Increasingly less distinction between cancer and non-cancer endpoints
- **Earlier and more meaningful assimilation of all of the empirical dose-response data**
  - Avoid collapsing to a POD from a single study
    - Lose valuable information

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Trends in Dose Response Assessment *(continued)*

- **Better linkage to hazard characterization through mode of action (MOA)**
  - Kinetic/dynamic data
- **Development of frameworks to have risk assessors thinking in the context of data to replace default assumptions based on MOA**
  - "Default" is not well informed

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Issues Associated with the Dose Response Assessment of Metals

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Risk Characterization

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Risk Characterization

- Integrates exposure data and dose-response (informed by hazard characterization) to obtain risk estimates
- Provides risk managers with information regarding the probable nature and distribution of health risks
- Has both quantitative and qualitative components
- Clearly delineates uncertainty and data gaps

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Range of the "Safe" Dose

- **The resulting range of the safe dose, such as an RfD or RfC has been defined as "perhaps an order of magnitude." This range is expected to differ among RfDs or RfCs, in part because of the use of different UFs**
- **What this means in general is that environmental exposures falling into the range of the subthreshold estimate cannot be scientifically distinguished from the estimate**

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Key Components of Risk Characterization

- **Transparency: Is the rationale for all judgments clear?**
  - Logical steps, key assumptions
- **Clarity: Easy to understand**
- **Consistency**
  - Consistent with guidelines and precedent; comparison with other assessments
- **Reasonableness**
  - In context of state-of-science, default assumptions, science policy decisions

Source: U.S. EPA. 2000. Science Policy Council Handbook: Risk Characterization. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-002.

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Trends in Risk Characterization

- **Provision to risk managers of a range of options with predicted risks, wherever possible, and clearly delineated associated uncertainties as a basis for decision-making**
- **The challenge:**
  - Requires transparent delineation of decision-making criteria on science policy and other factors beyond risk assessment

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Issues Associated with the Risk Characterization of Metals

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Any Questions?

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