The Dose: Toxicokinetics for Human Health Risk Assessment

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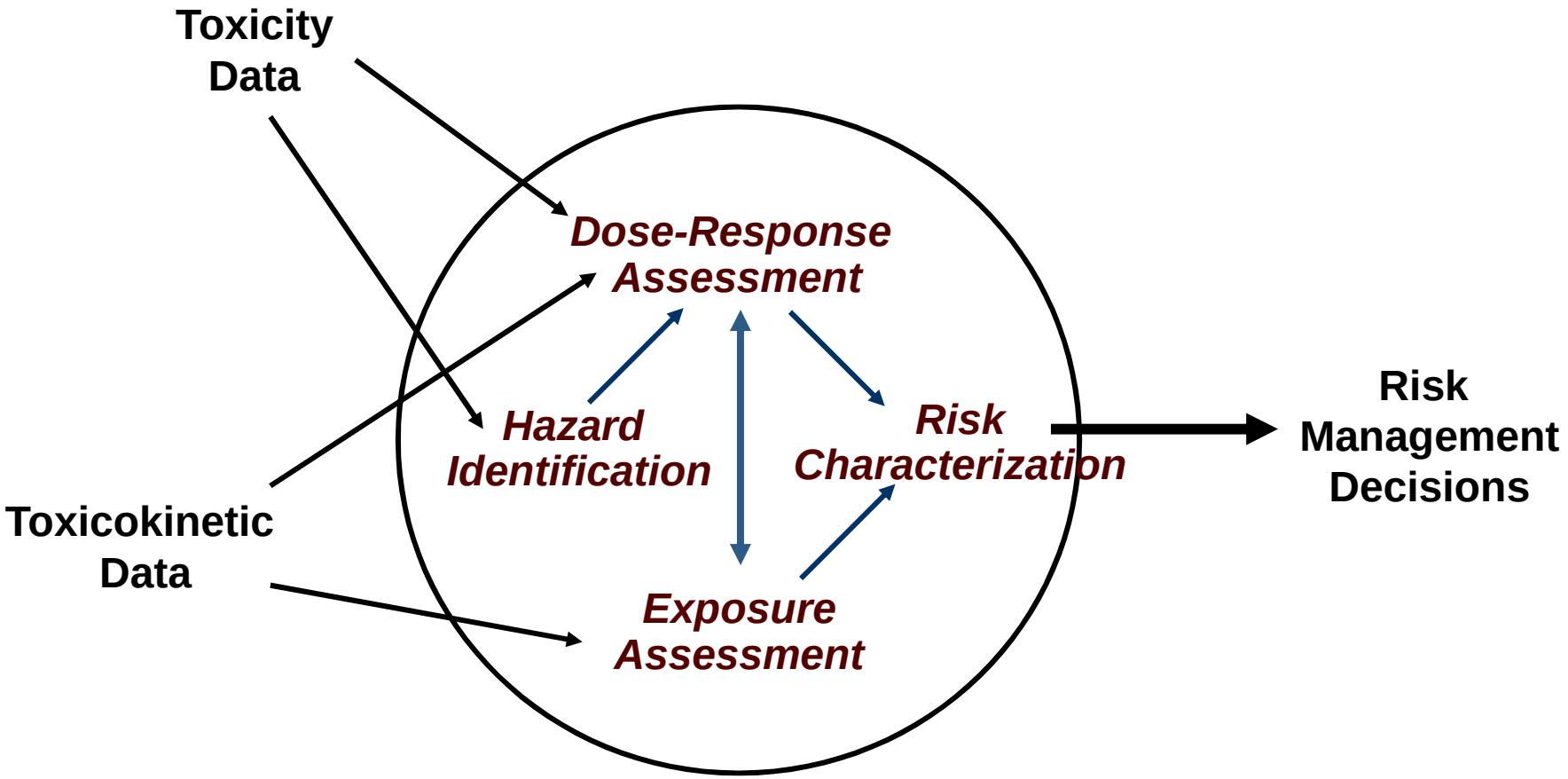
Abbreviations

BMDL	Benchmark Dose Lower Confidence limit
DM	Dose Metric
IPCS	International Programme on Chemical Safety
IRIS	U.S. EPA's Integrated Risk Information System
LOAEL	Lowest Observed Adverse Effect Level
MOA	Mode of Action
NOAEL	No Observed Adverse Effect Level
POD	Point of Departure, NOAEL, LOAEL, BMDL
RfV	Reference Value
TK	Toxicokinetics
UF	Uncertainty factor
WHO	World Health Organization
WOE	Weight of Evidence

Learning Objectives/Goal

- Appreciate the usefulness of Toxicokinetic models to simulate tissue dosimetry
- Understand the need to verify the biological basis for toxicity and for the developed TK models
- Accept that these models are frameworks for decreasing the uncertainty in health risk assessment

Risk Assessment



NAS paradigm (adapted from NRC, 1983)

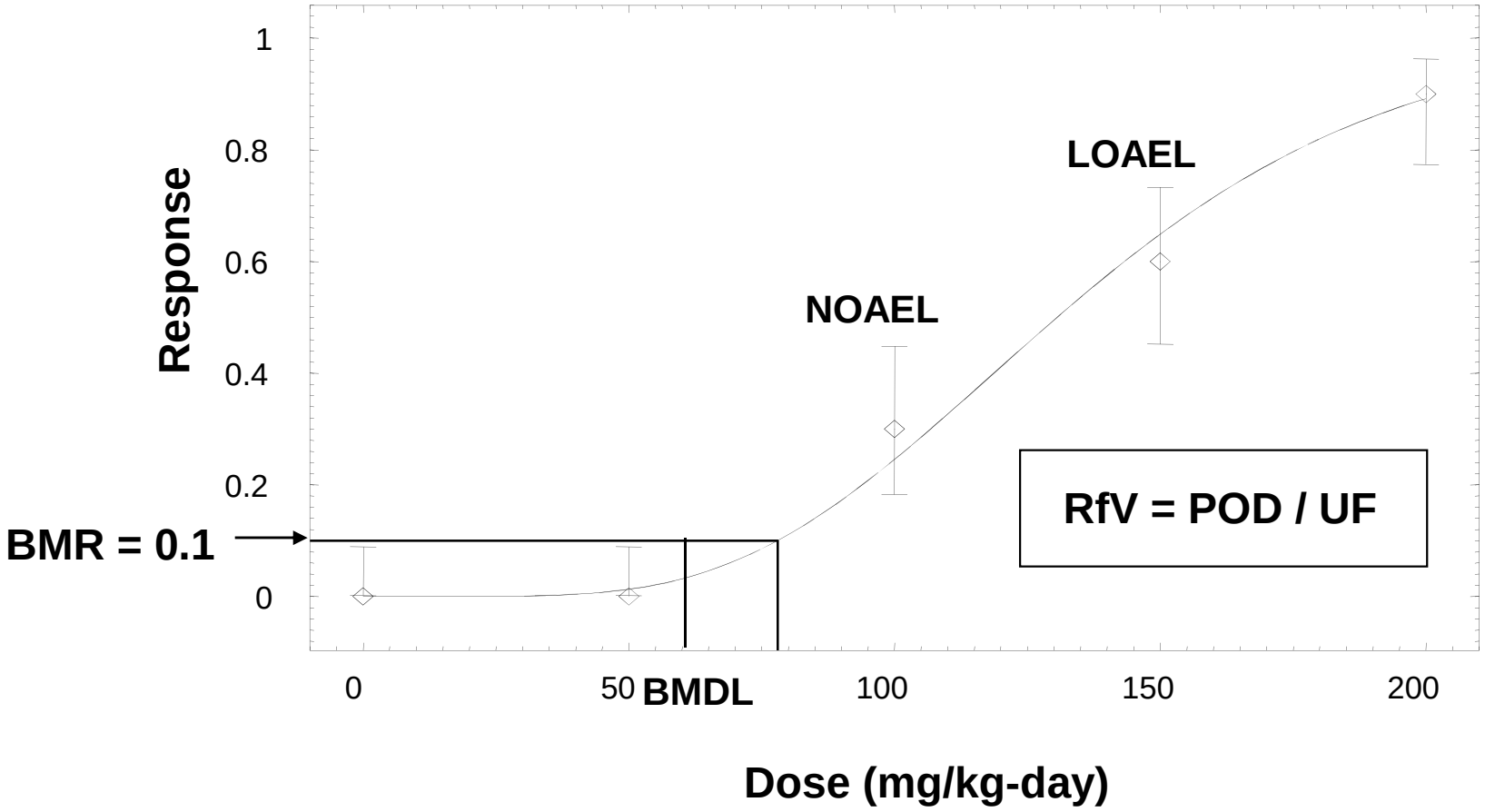
United States Environmental Protection Agency

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

-Paracelsus

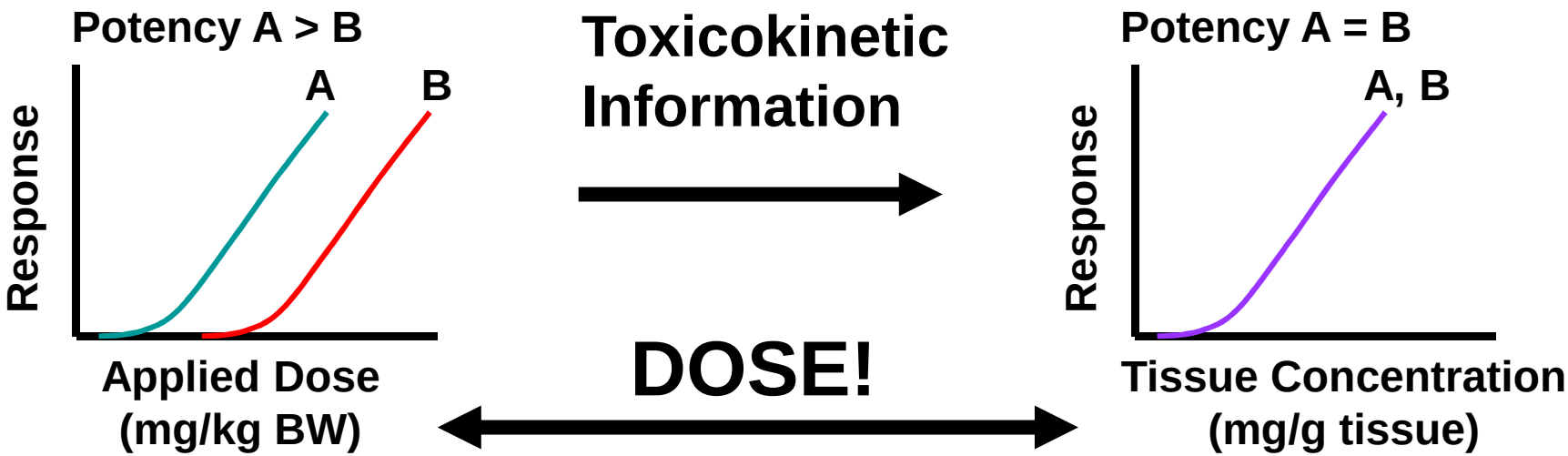
Observable adverse responses begin when the toxicologically active chemical species comes into contact with the biological receptor; the likelihood and severity of the response is determined by the tissue concentration of the toxicologically active chemical species.

Dose Response, Point of Departure (POD), & Reference Values (RfV)

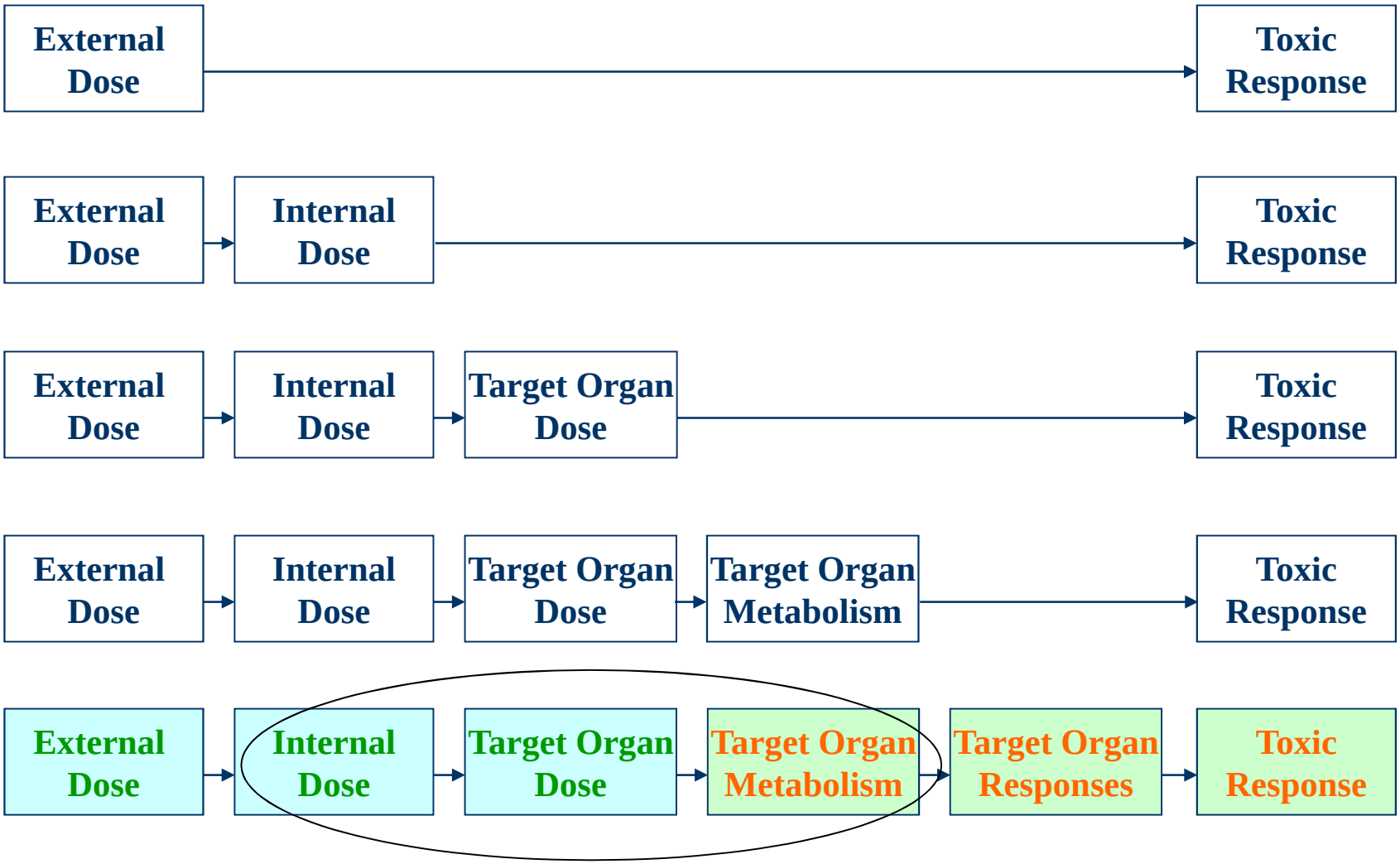


Modulation of Response

- Dose at Target (Toxicokinetics)
- Responsiveness of Target (Toxicodynamics)

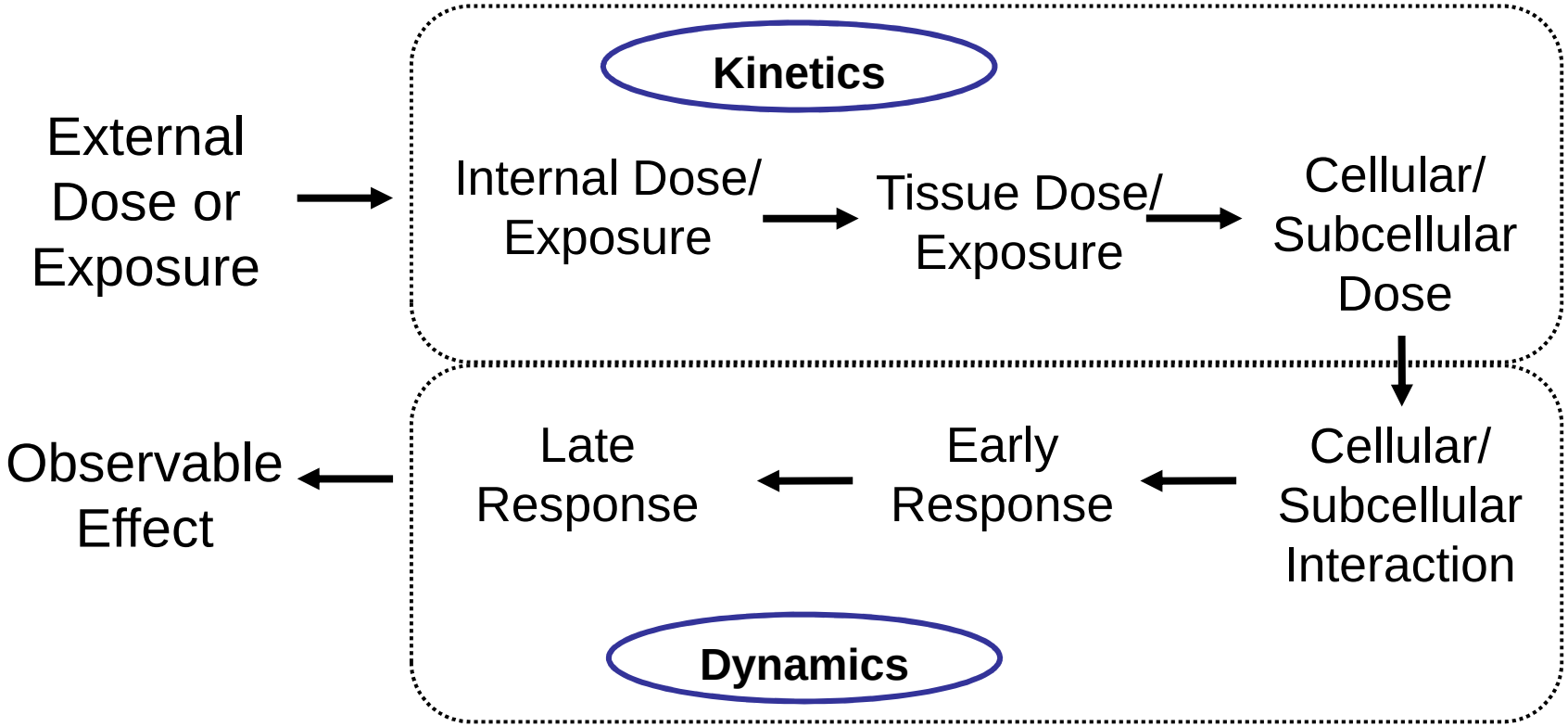


Expression of Dose



Potential Dose Metrics

Schematic of the processes involved in the expression of toxic responses placed in a risk assessment context



(IPCS, 2010)

Risk Assessment for Noncancer Toxicities

$$\text{Reference Value (RfV)} = \frac{\text{POD}}{\text{UF}}$$

Interspecies Extrapolation, UF_A, *default* value 10

Intraspecies Extrapolation, UF_H, *default* value 10

Dosimetry and Application in Risk Assessment

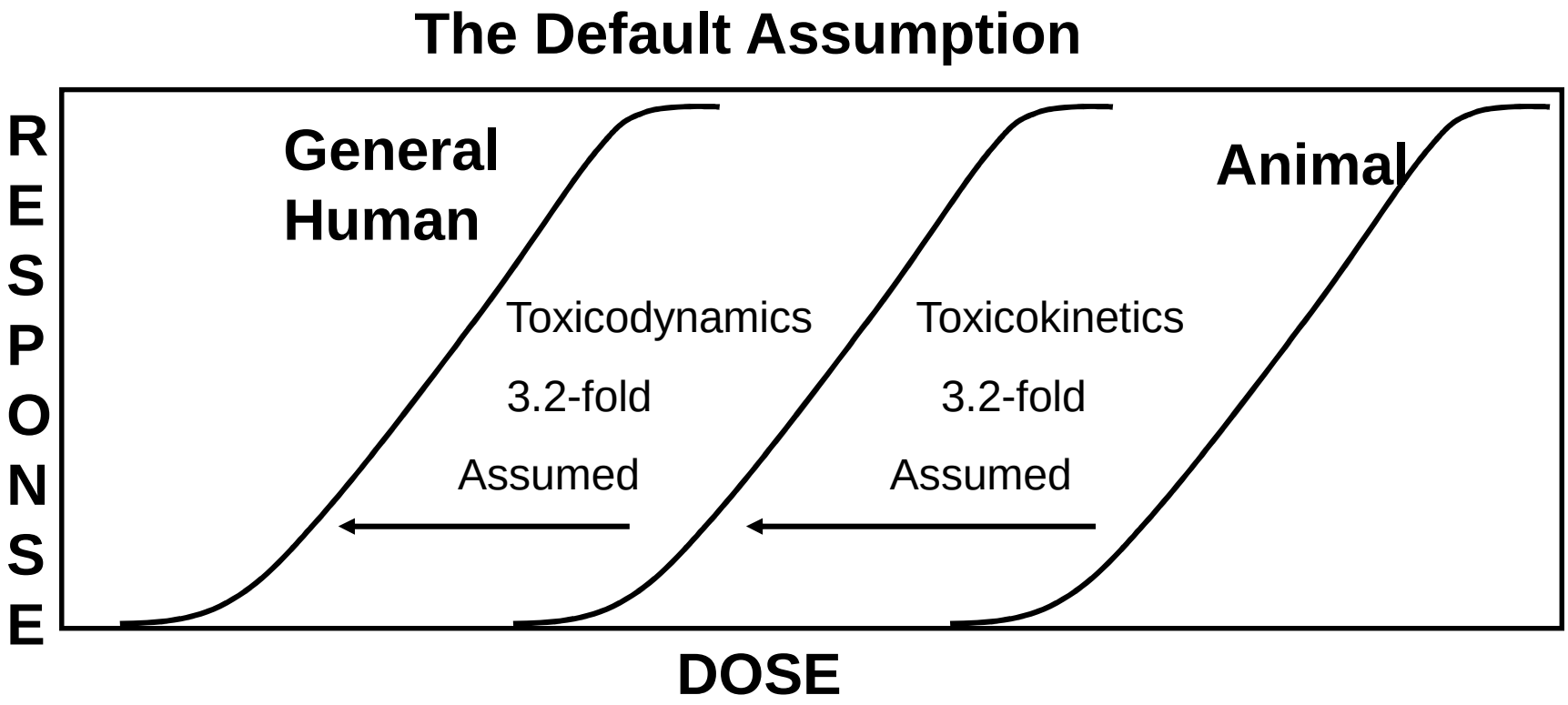
Toxicokinetics: TK, how the chemical travels through the body

Humans are assumed to be more sensitive than animals

Toxicokinetics—Relative to animals, humans are assumed to attain a higher tissue concentration at equivalent doses; and to attain the same tissue concentrations at lower doses.

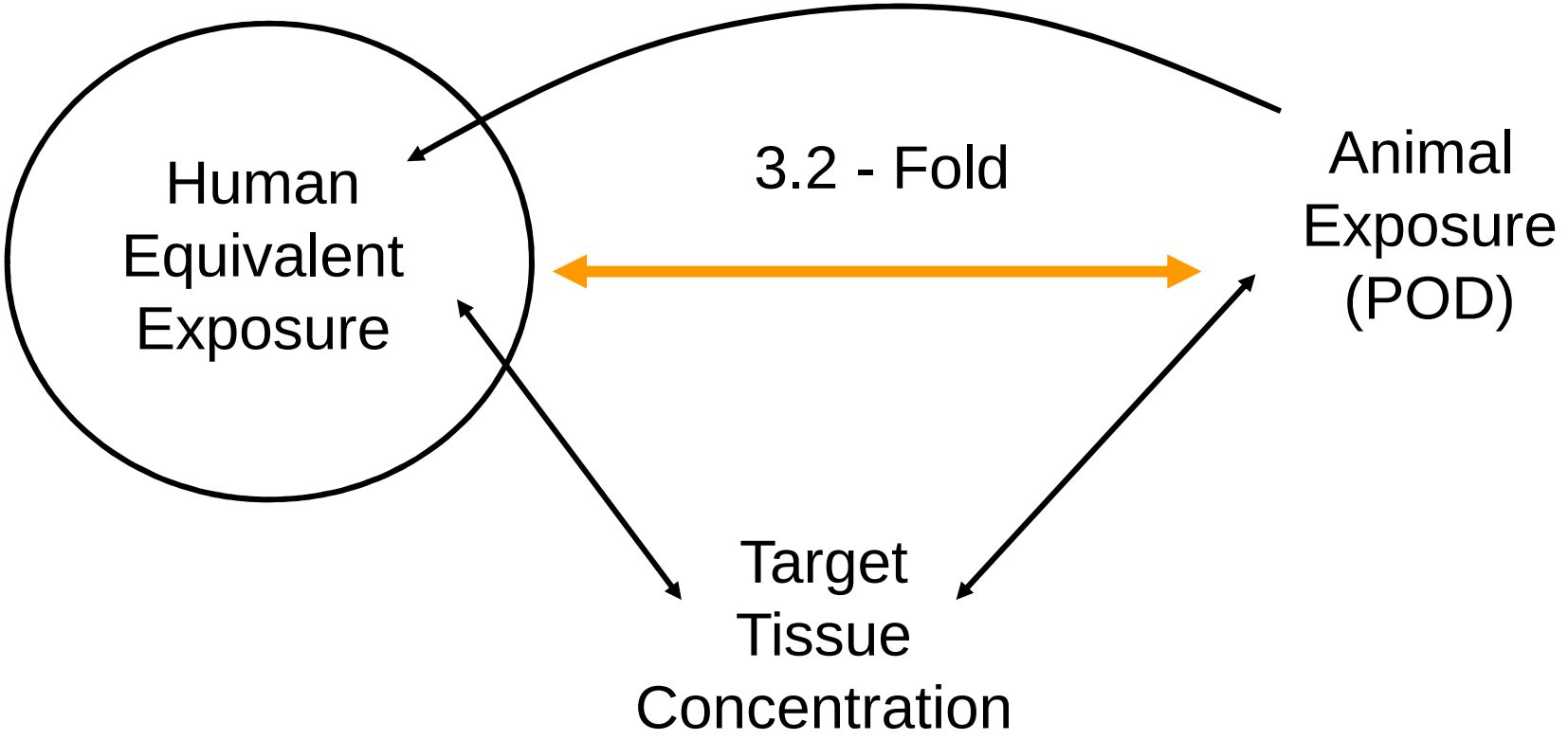
Interspecies Extrapolation (UFA)

- Consider all relevant data before retreating to default options
- Animal to human variability, *default* value = 10
- Toxicokinetic and toxicodynamic components



(U.S. EPA, 2005; U.S. EPA, 1994)

The Default Toxicokinetic Assumption for Interspecies Extrapolation



Nondefault UF Values

- Approach developed and adopted internationally
- Necessary framework for inclusion of relevant data
- Increase application of quantitative data in risk assessment
- Increase transparency of extrapolations
- Mode-of-action data critical in supporting choices
- Stimulate development of targeted data sets

Chemical-Specific Adjustment Factors

- WHO / IPCS, 2005
- Active chemical Species
- Target Tissue (or central Compartment)
- Time-normalize the expression of dose?
- Guidance Document
- Case study examples
- The CSAF approach does not require consensus on Mode of Action, neither does it require full elucidation of Mode or Mechanism of action

http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf *(IPCS, 2005)*

Mode of Action

- A sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation
- A *"key event"* is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element
- Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode of action as the term is used here

(U.S. EPA, 2005) Cancer Guidelines

Mode of Action and Tissue Dosimetry

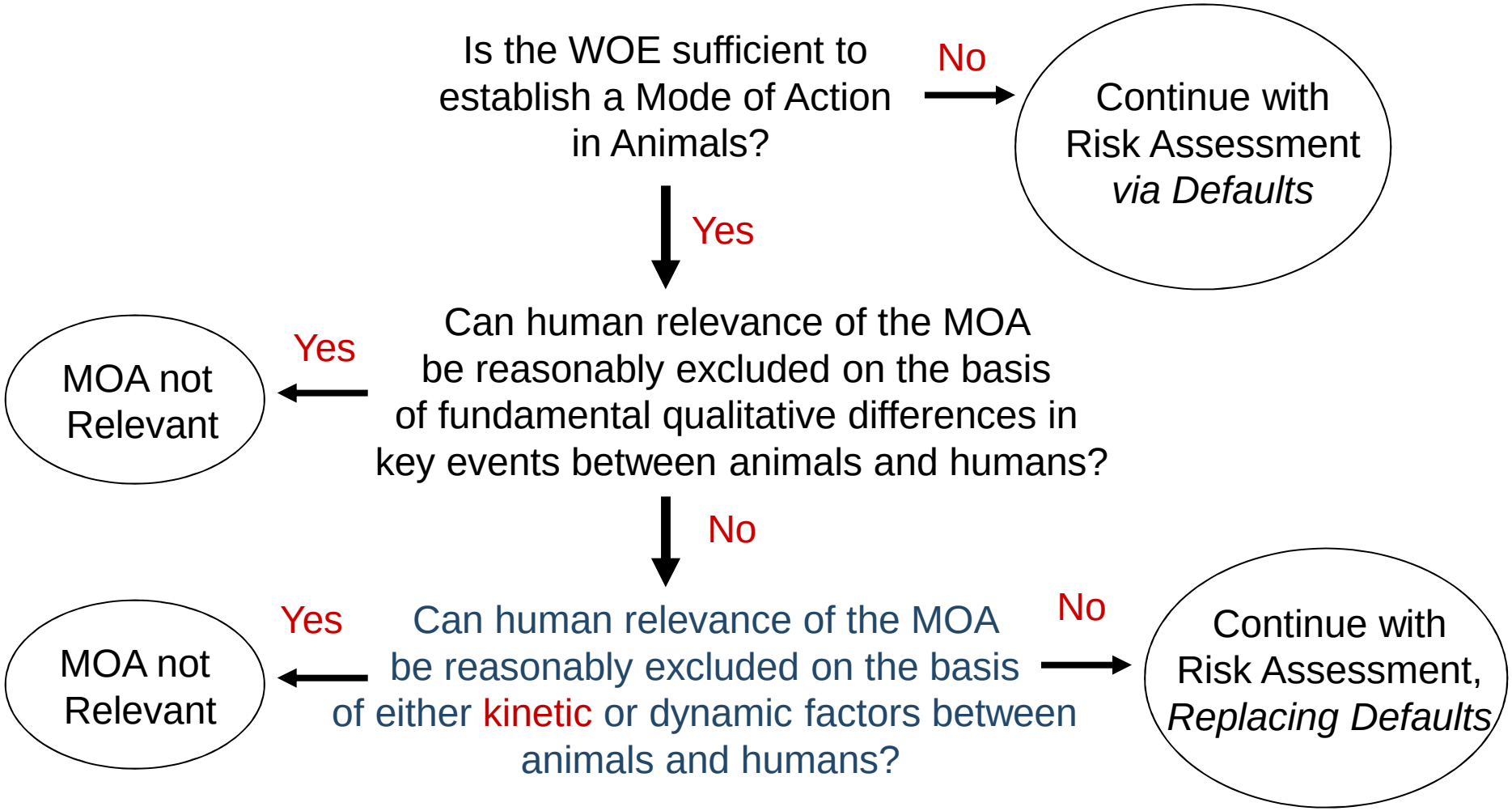
- Consider the toxicology of the chemical insult
- Consider the biology of the system
- Think about molecular interactions
- Leading to a cascade of effects

- Where to start?

Example Toxicity: Dichloromethane

- Acute Toxicity: Central Nervous System Depression
  - Parent compound absorbed, metabolized, distributed
  - Brain is target tissue
  - Consider potential Mode(s) of action:
    1. CNS depression via parent
    2. Metabolite-induced carboxyhemoglobin formation, leading to hypoxia
- How likely are these effects in humans?
- Can a dose metric be identified?
- Can the dose metric be modeled?

IPCS' Human Relevance Framework



(Boobis et al., 2008)

Expression of Dose: The Dose Metric

DOSE METRIC—The measure of “dose” causally related to toxic outcome.

- Optimally, the Dose Metric will be well-integrated in the MOA.
- Evaluate toxicity data
- Identify the target organ—In the absence of data to the contrary,
  - Assume the response is mediated by exposure of the responding organ
- Determine whether parent or metabolite(s) exert toxicity
- Decide whether to use a maximal concentration or AUC values
- Consider the biological basis for the Model and the Dose Metric

PBPK Modeling at First Mention

- Mathematical structure of the organism
- Portals of entry
- Routes of elimination
- Targets of toxicity
- Important determinants of dosimetry
- Parameters and values
- Parsimony

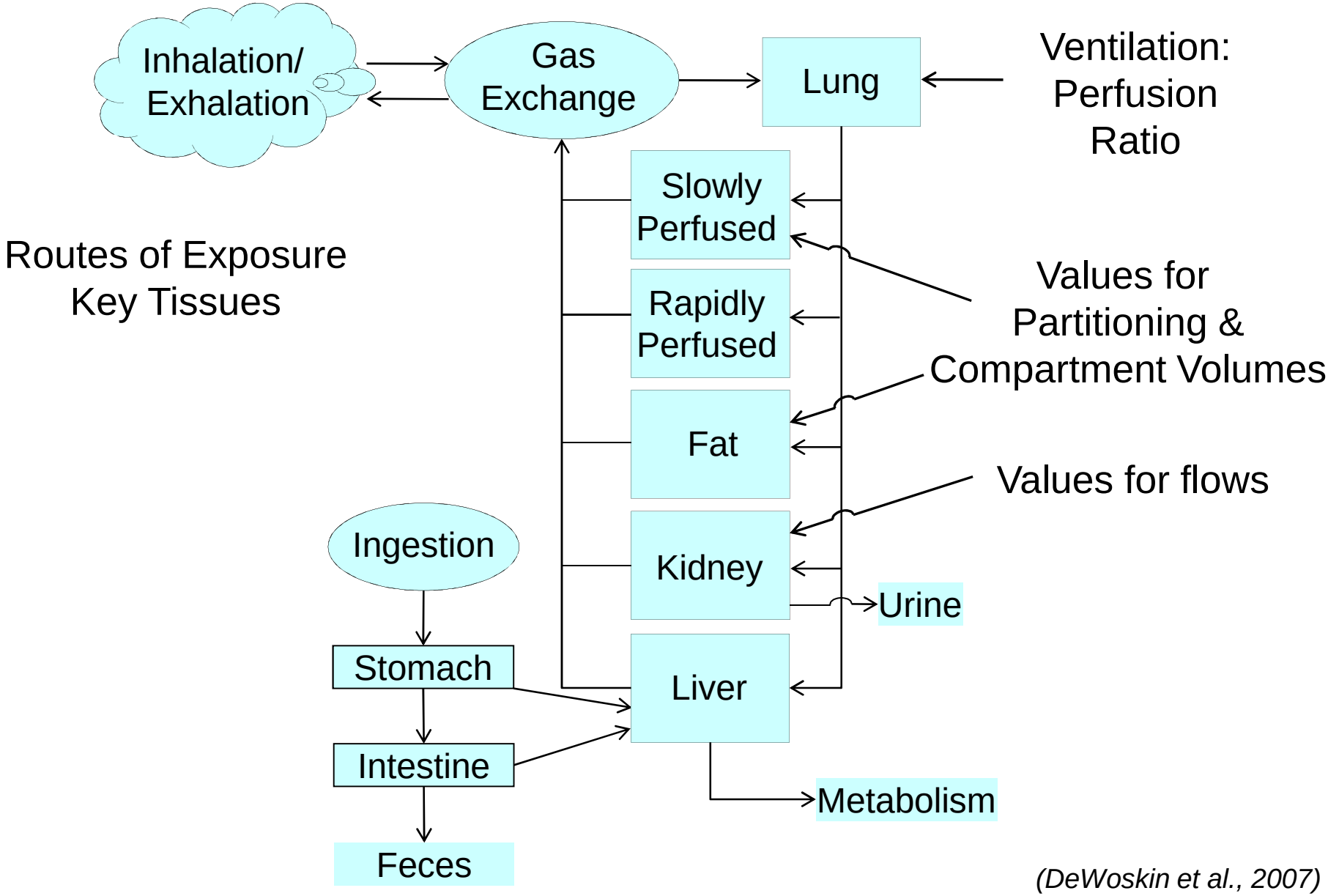
THE PBPK MODELING GOAL

- PBPK Models can extrapolate dosimetry across ranges of doses, routes of exposures, species and lifestages
- PBPK modeling approaches are the gold standard in dosimetric adjustments in Human Health Risk Assessment per the U.S. EPA's 1994 RfC guidance, the IPCS' 2005 CSAF guidance and the U.S. EPA's 2005 Cancer Risk Assessment guidance
- In the context of this talk, the goal of PBPK modeling studies is to decrease the uncertainty in Human Health Risk Assessment

- Reliability
- Performance
- Biological basis

(U.S. EPA, 2007; IPCS, 2010)

PBPK Models- Parameters, Structure, Assumptions



(DeWoskin et al., 2007)

Minimum Data Requirements

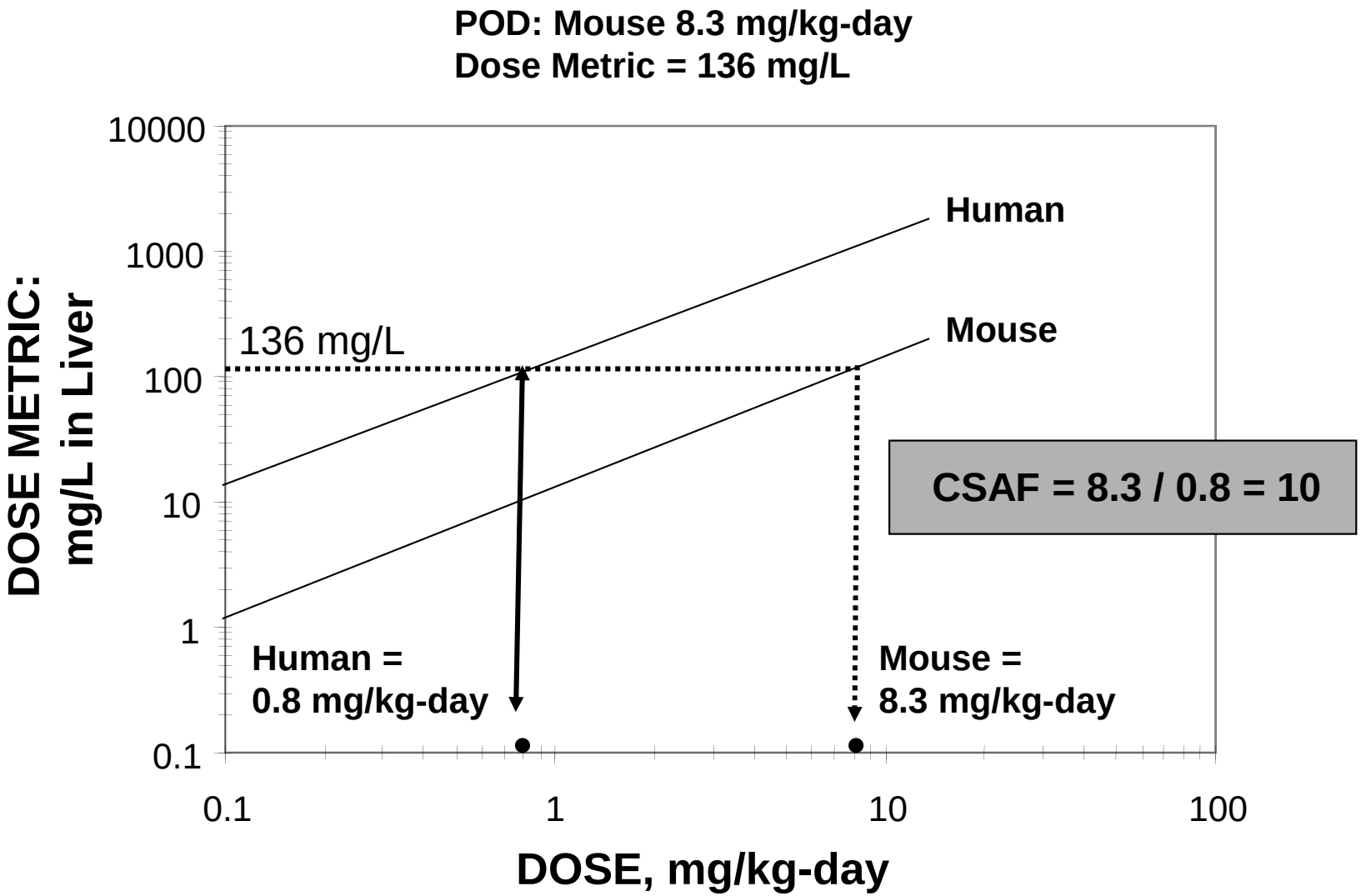
- What are the sensitive target tissues?*
  - These must be contained in the PBPK model
  - Parameter values must be fairly certain
- What is the active chemical species?*
  - Is it the parent or a metabolite?
  - Which metabolite is active?
- What time-normalization should be performed for dose?*
- Is toxicity related to peak or averaged tissue concentrations?
- What is the POD from toxicity studies?
- Use the model to relate dose @ POD to target tissue concentration (dose metric)

*Minimum requirements for MOA (IPCS, 2005)

PBPK Model Parameters

- Physiological—Organism-specific compartment volumes and flows (See Arms and Travis, 1988; Brown et al., 1997) See NCEA-Sponsored Physiological Parameters Database for rodents – (Gentry et al., 2004); http://www.epa.gov/comptox/parameters.html
- Physicochemical—Chemical-specific, e.g., values for partitioning. Measure in vitro, predict in silico (e.g., Poulin & Krishnan, 1995), determine value via model optimization
- Biochemical—Mainly metabolism, receptor binding. Often measured in vitro and extrapolated (Lipscomb et al., 2003), also predicted by optimization

Animal to Human Extrapolation



Confidence in PBPK Models: Model Characterization

- Purpose
- Structure
- Parameterization
- Mathematics
- Evaluation
- Uncertainty and variability—can reduce uncertainty by collecting additional data; not so for variability
- Sensitivity analysis—not all parameters really determine output

Determinants of Model Usefulness

- Model credibility
- Model reliability and
- Model applicability
- To be credible, a PBPK model should possess certain characteristics in terms of its structure and parameters as well as documented evaluation of these aspects. A credible model may, however, not be reliable or applicable for risk assessment
- To be reliable for risk assessment application, the model should be able to simulate the dose metrics of relevance to the MOA of the chemical
- Finally, to be applicable in a risk assessment, it should have the essential features consistent with the intended use in risk assessment

Some Examples of PBPK Application in Risk Assessment

- Dichloromethane: (U.S. EPA, IRIS)
  - Interspecies and route to route extrapolation, GST-derived metabolite for liver toxicity
- EGBE: (U.S. EPA, IRIS)
  - Interspecies extrapolation of blood concentration, precursor events for hematological effects
- Iodomethane: (U.S. EPA, Pesticide reregistration)
  - Interspecies extrapolation of:
    1. Fetal plasma iodide concentration for developmental toxicity
    2. CNS methyl iodide concentration for neurotoxicity
    3. Nasal tract dosimetry and GSH depletion for nasal toxicity

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