

# Project Proposal: Using PBPK Models to Estimate Adjustment Factors for Probabilistic Reference Doses

**Dustin Kapraun**  
(ORCID 0000-0001-5570-6383)

**Paul Schlosser**  
(ORCID 0000-0002-9699-9108)

**National Center for Environmental Assessment  
US Environmental Protection Agency**

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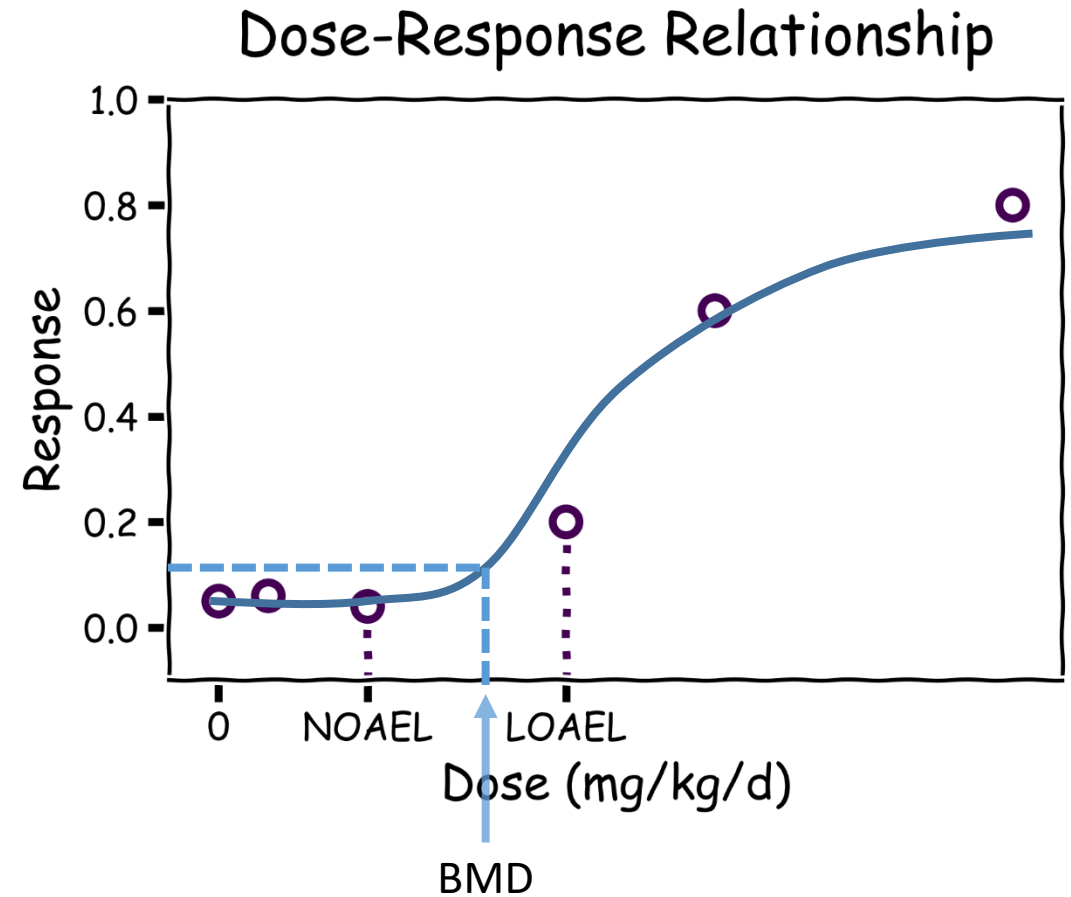
# Outline

- Background and motivation
- Use of PBPK models in chemical risk assessment
- Quantifying uncertainty in PBPK model predictions
- Moving beyond default “uncertainty factors”
- Project specifications

# Traditional Chemical Risk Assessment

- Collect data from a **toxicological study** and examine the **dose-response relationship**.
- Determine a **point of departure (POD)**:
  - NOAEL = no observed adverse effect level
  - LOAEL = lowest observed adverse effect level
  - BMD = benchmark dose
- Divide by **uncertainty factors (UFs)** to obtain a **reference dose (RfD)**:

$$RfD = \frac{POD}{UF_1 \times UF_2 \times \dots}$$



# Reference Dose

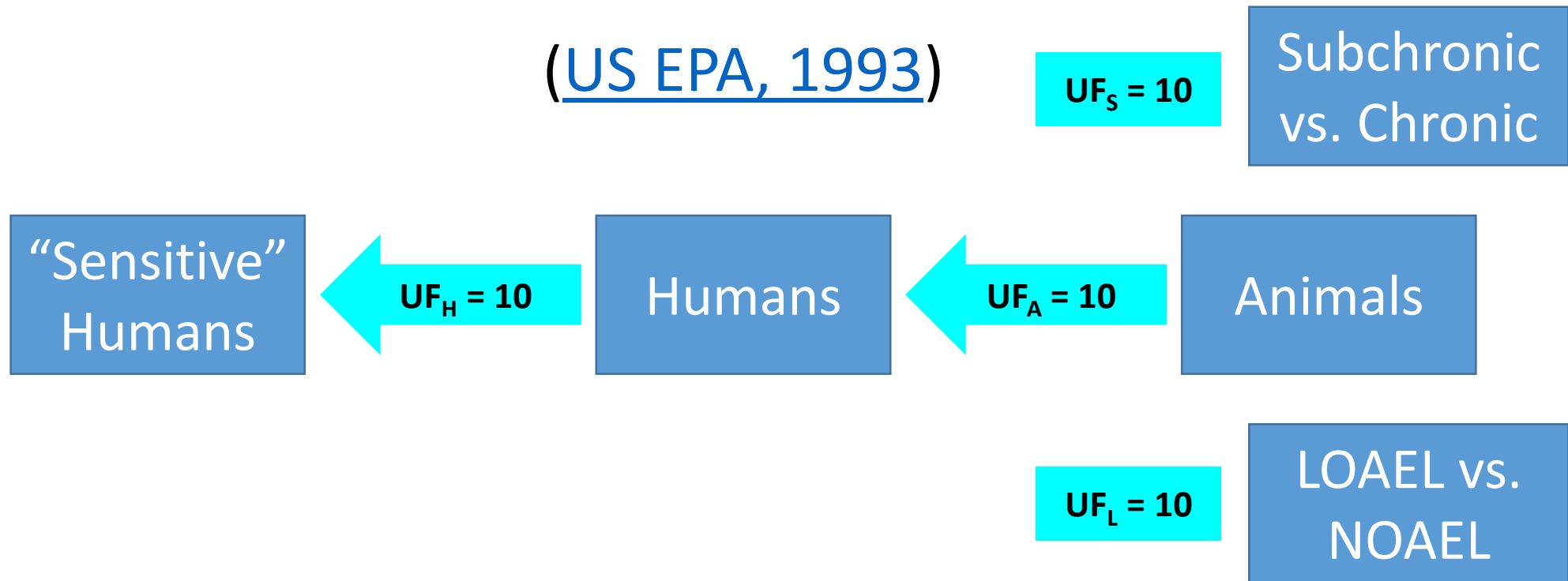
“In general, the **RfD is an estimate** (with uncertainty spanning perhaps an order of magnitude) **of a daily exposure** to the human population (including sensitive subgroups) **that is likely to be without** an appreciable **risk of deleterious effects** during a lifetime.”

([US EPA, 1993](#))

# Uncertainty Factors

“The RfD is a benchmark dose operationally derived from the NOAEL by consistent application of generally order-of-magnitude **uncertainty factors** (UFs) that **reflect various types of data sets** used to estimate RfDs.”

([US EPA, 1993](#))

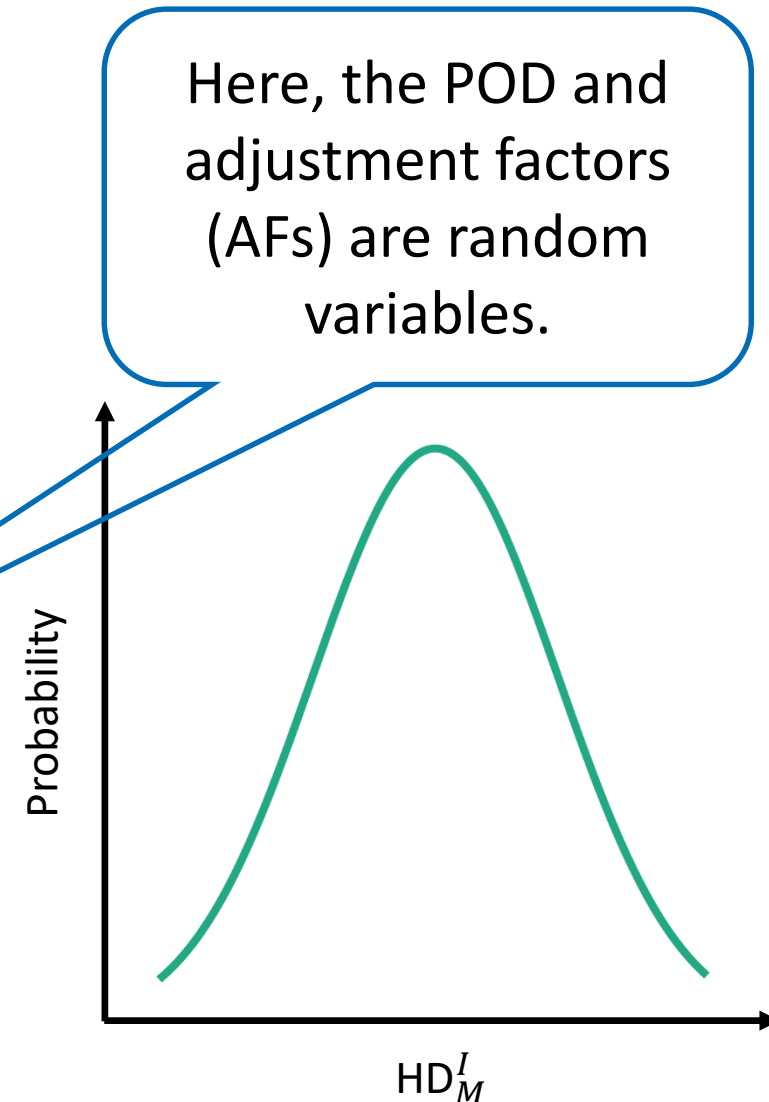


# Probabilistic Reference Dose

- WHO\* IPCS† ([2017](#)) provides a **framework** for computing a “**probabilistic**” reference dose.
- The **human dose** at which a fraction  $I$  of the population shows an effect of magnitude (or severity)  $M$  or greater (for the critical endpoint considered) is

$$HD_M^I = \frac{POD}{AF_A \times AF_S \times AF_L \times AF_H}.$$

- The  $HD_M^I$  is a **random variable** (represented by a distribution) rather than a scalar.



# Probabilistic Reference Dose

Note the similarities and differences between the  $HD_M^I$  and the RfD...

$$HD_M^I = \frac{POD}{AF_A \times AF_S \times AF_L \times AF_H}$$

- Random variable
- Calculated by multiplying/dividing random variables
- Represented by a probability distribution for a well-defined quantity

$$RfD = \frac{POD}{UF_A \times UF_S \times UF_L \times UF_H}$$

- Scalar
- Calculated by multiplying/dividing scalars
- Represents a “lower bound” estimate of a vaguely-defined quantity

# Motivation

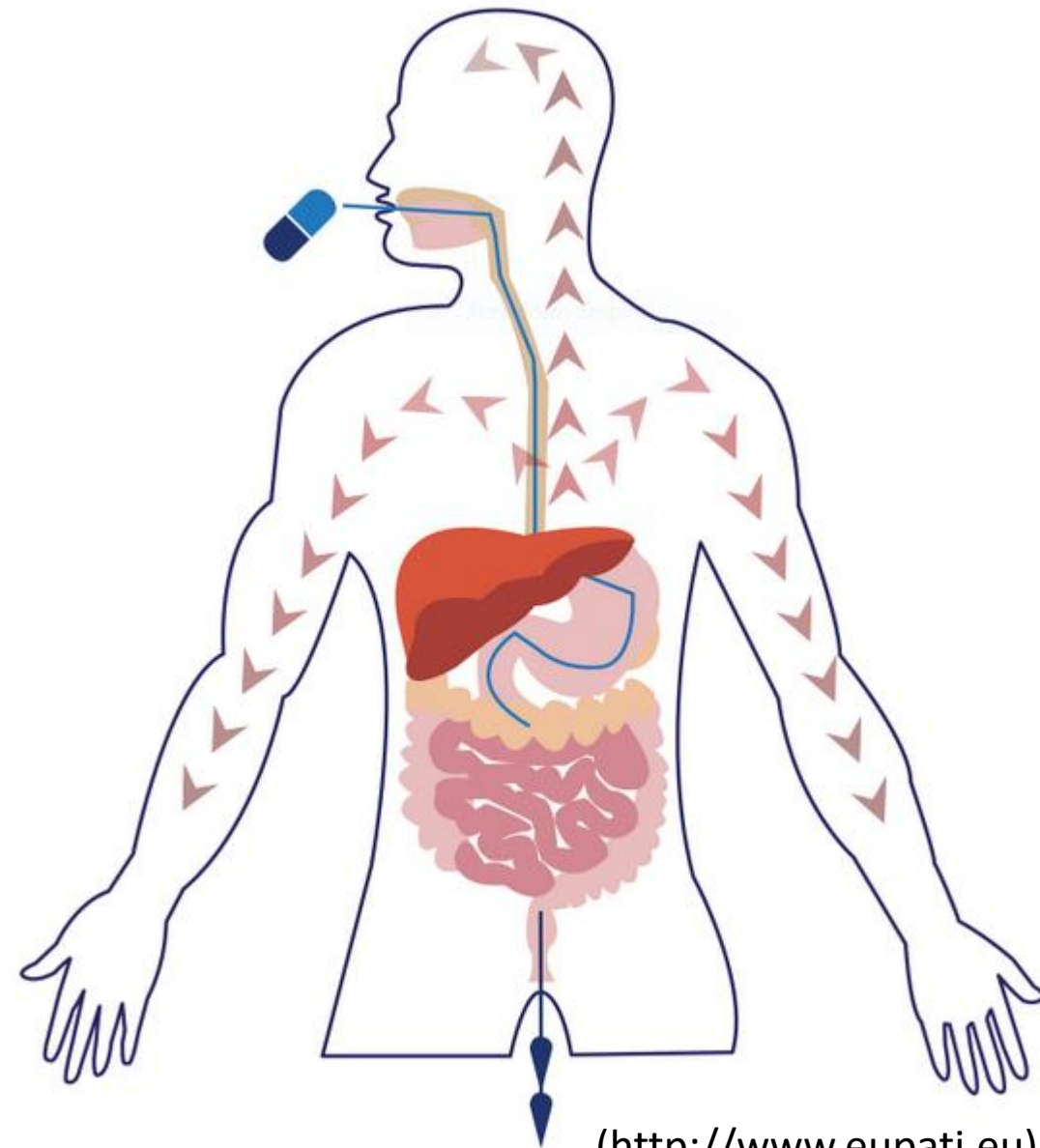
Toxicological studies are mostly performed in *animals* (such as rats and mice) to reveal possible toxicity points of departure, so...

How can results from *animal* toxicological studies be used to identify RfDs for *humans*?

One answer is to apply an “interspecies” UF or AF, but another approach is...

# Pharmacokinetics!

- Branch of pharmacology that deals with **fate and transport** of a drug (or other substance) within an organism.
- *What the body does to the substance.*
- Different from **pharmacodynamics** (*what the substance does to the body*).
- PK\* accounts for **absorption, distribution, metabolism, and excretion (ADME).**



\*PK = pharmacokinetic(s)

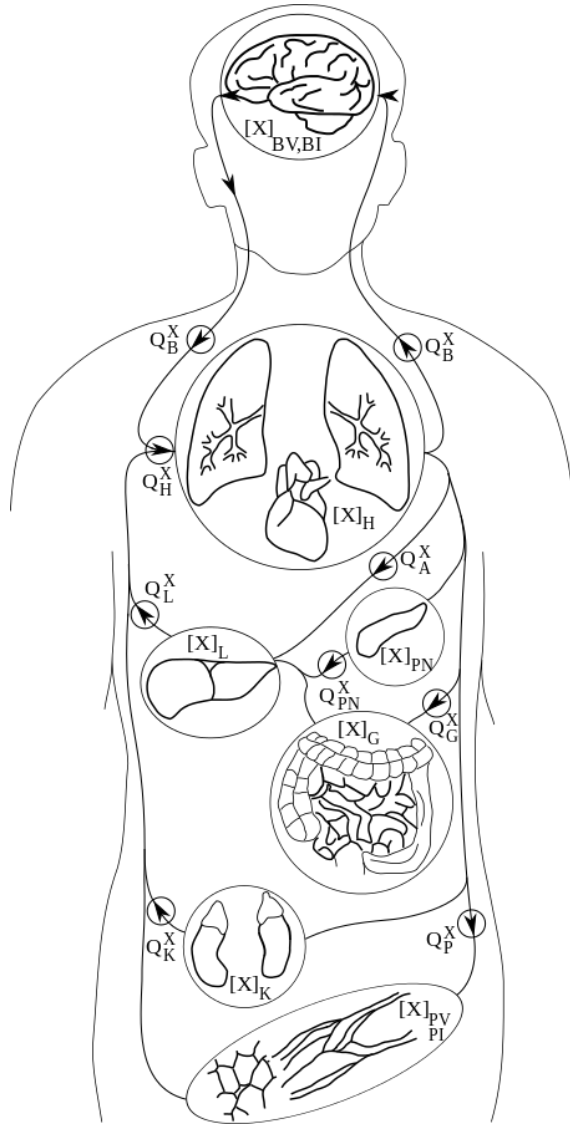
# What is a Pharmacokinetic Model?

- A **quantitative statement** of a **set of hypotheses** regarding ADME.
- A **set of equations** (often ODEs<sup>\*</sup>) that describe the **amount** of a substance in one or more **compartments** of an organism's body.
- Motivated by the expectation that **observed effects** are more **directly related** to **internal dose** than administered (or exposure) dose.
- Classical PK<sup>†</sup> models are sometimes used, but we focus here on physiologically based PK (or PBPK) models...

<sup>\*</sup>ODE = ordinary differential equation

<sup>†</sup>PK = pharmacokinetic

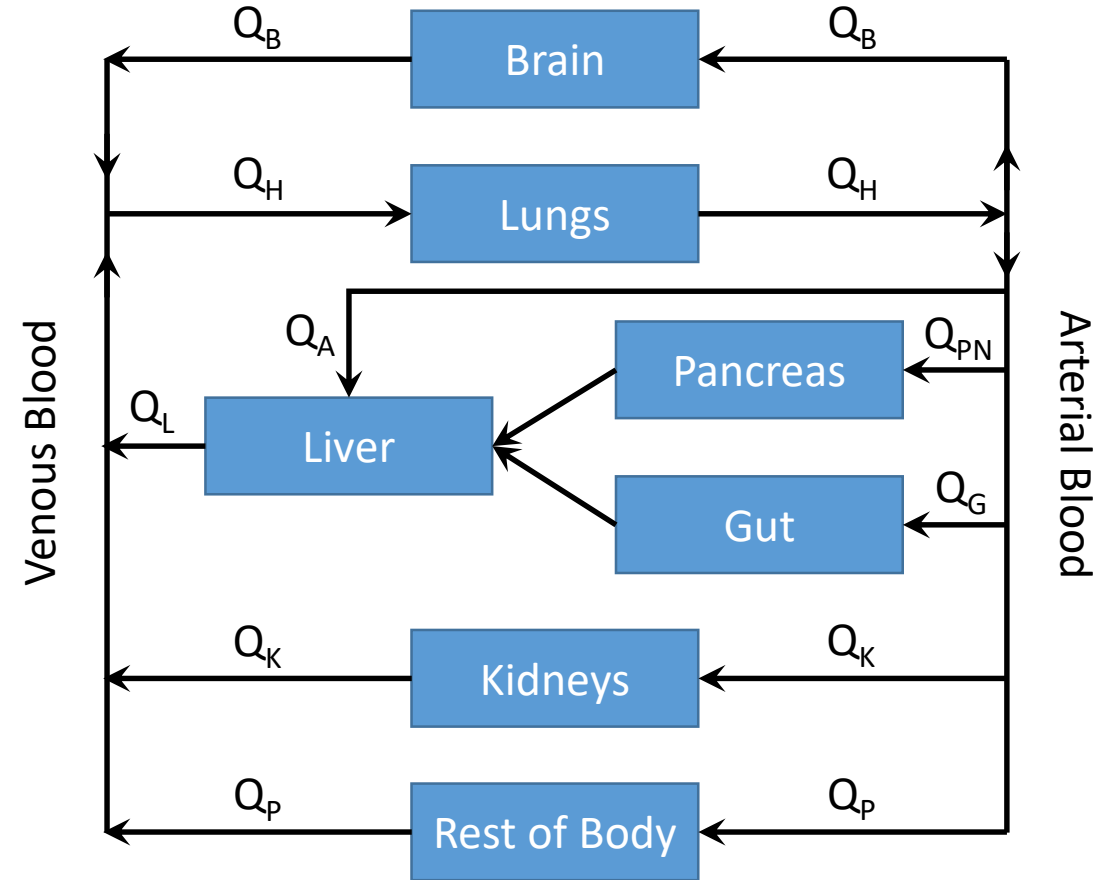
# PBPK Model



**Chemical engineering**  
applied to a  
**biological organism**



**Model parameters** are  
based on **anatomy**,  
**physiology**, and  
**biochemical properties**.



# PBPK Model Features

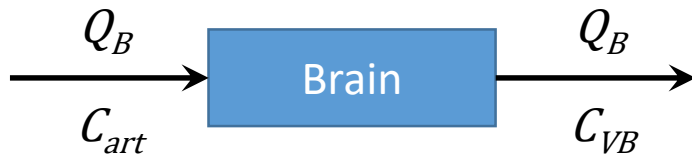
- Based on the **actual anatomy and physiology** of a given organism:
  - Body mass
  - Organ and tissue volumes
  - Respiration rates
  - Cardiac output
  - Fractional blood flows
- Allow for various types of extrapolations:
  - Between **species** (e.g., rat vs. human)
  - Between **exposure routes** (e.g., oral ingestion vs. inhalation)
  - Between **exposure scenarios** (e.g., continuous exposure vs. bolus dosing)
  - **Intraspecies** extrapolation (e.g., “average” to “sensitive” humans)

# PBPK Model Equations

## General Form

$$\frac{d}{dt} [\text{Amount}] = [\text{Rate In}] - [\text{Rate Out}]$$

## Example



$$\frac{d}{dt} A_B = \overbrace{Q_B \cdot C_{art}}^{[\text{Rate In}]} - \overbrace{Q_B \cdot C_{VB}}^{[\text{Rate Out}]}$$

$Q_B$  = Blood flow rate to brain (L/h)

$C_{art}$  = Concentration in arteries (mg/L)

$C_{VB}$  = Concentration in veins leaving brain (mg/L)

$A_B$  = Amount in brain (mg)

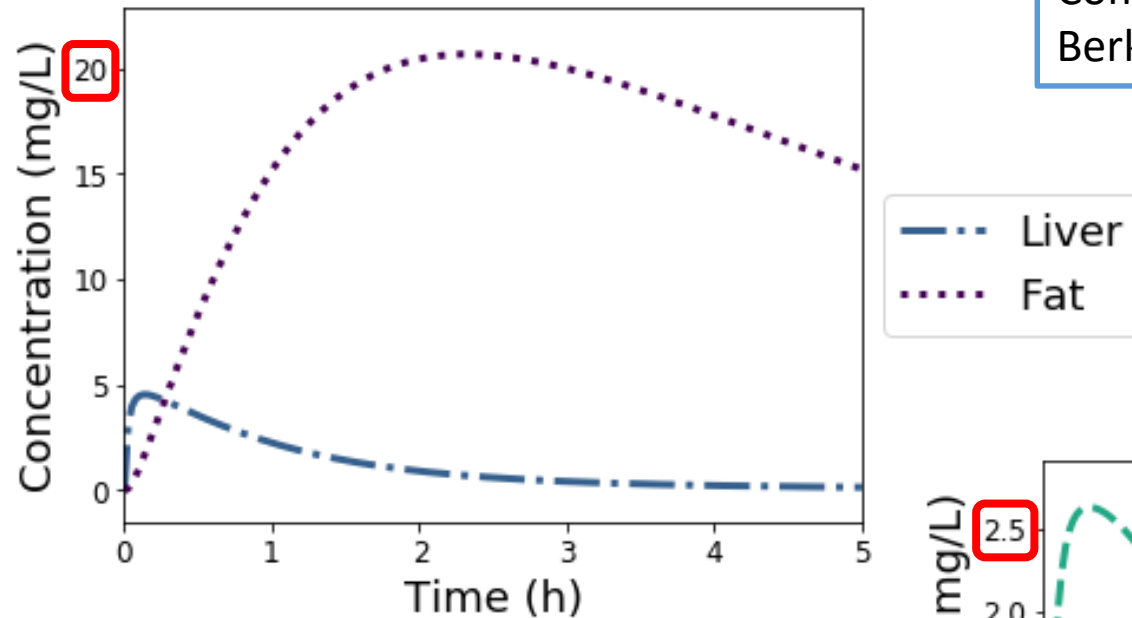
- Units agree:  
 $(\text{mg/h}) = (\text{L/h}) \cdot (\text{mg/L}) - (\text{L/h}) \cdot (\text{mg/L})$
- **Conservation of mass**
- In general, there can also be terms for metabolism or excretion (out) or absorption or uptake (in).

# PBPK Model Simulations

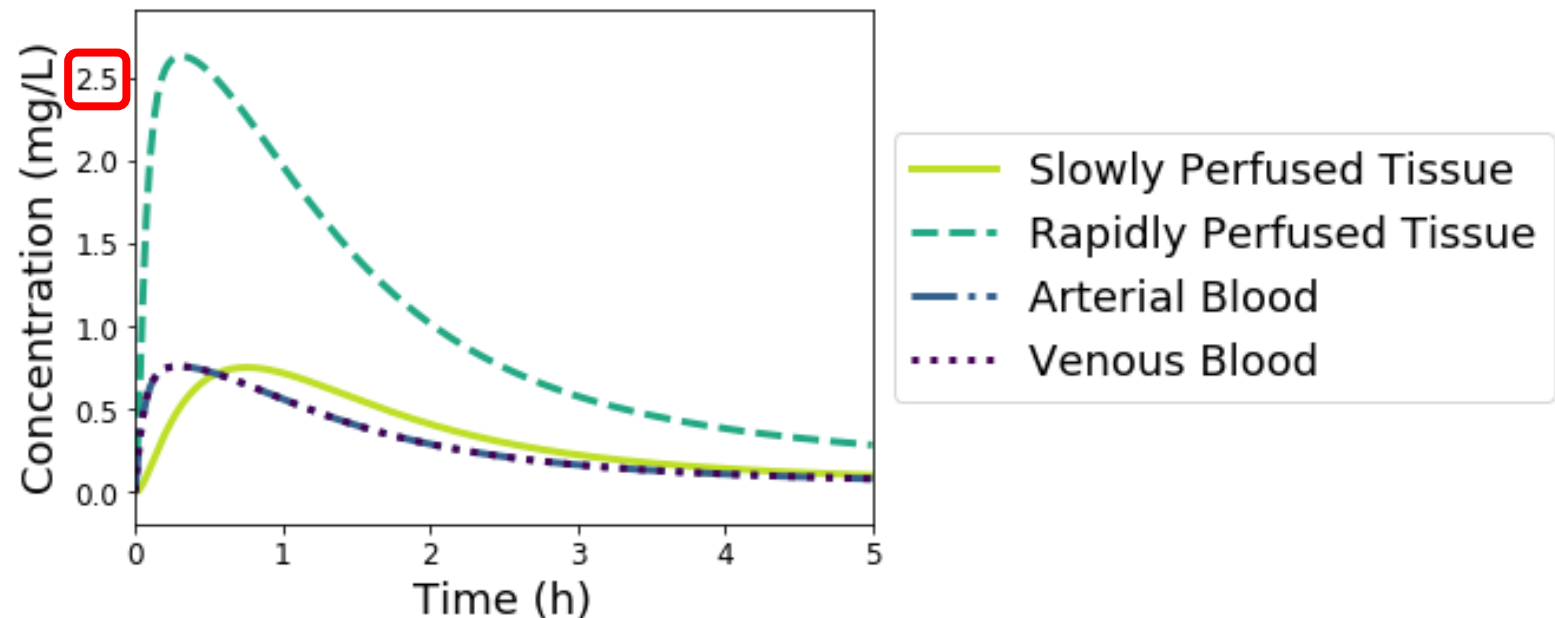
PBPK models are implemented as **computer programs**.  
Commonly used software/languages include: acslX,  
Berkeley Madonna, MCSim, Matlab, and R.

Once implemented, **simulations** can be performed.

**Output** includes **time course** information describing  
**concentrations** in various compartments.



**Concentrations** in different parts of the  
body can **differ by orders of magnitude!**

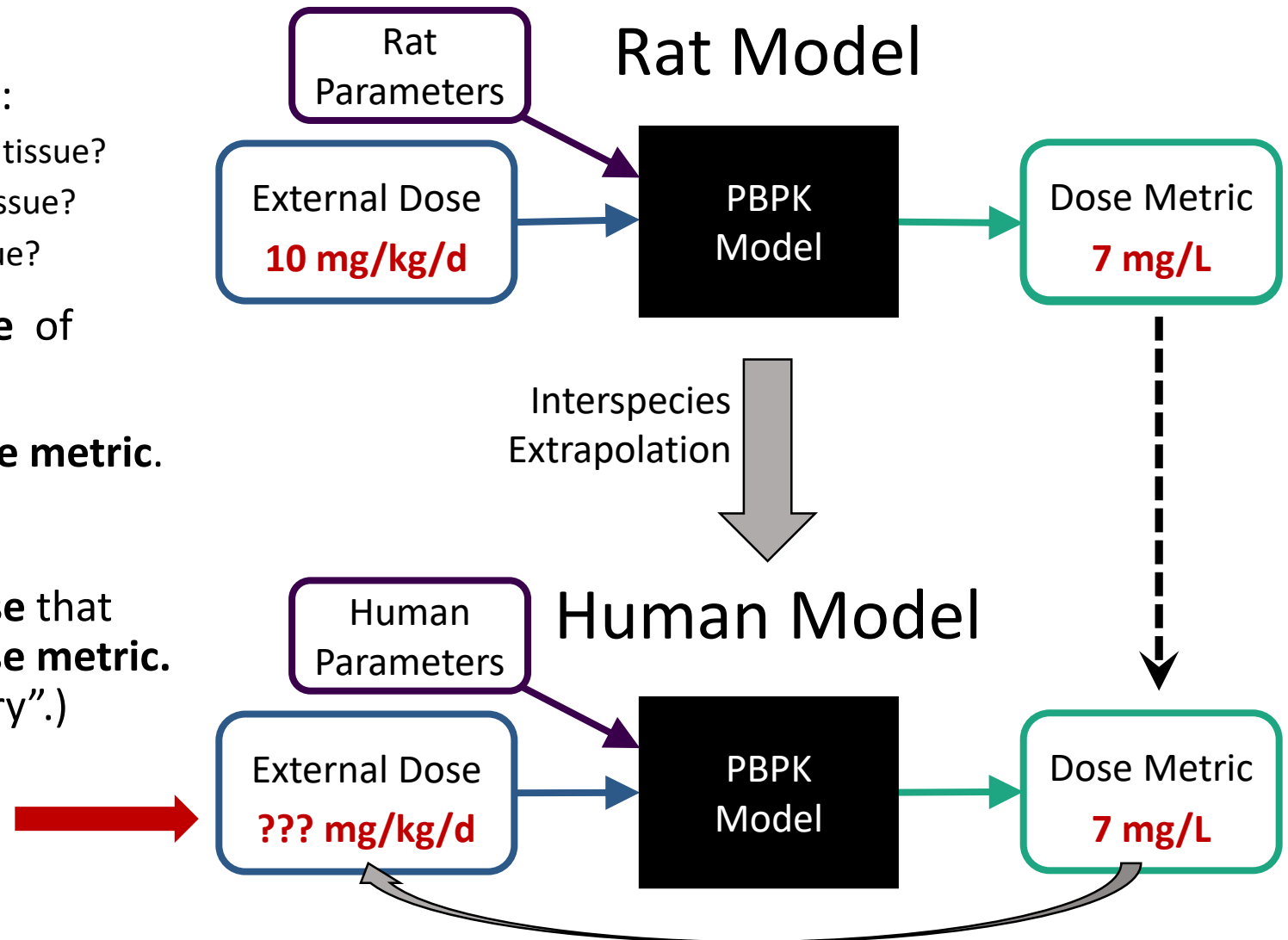


“The primary advantage gained by using PBPK models in risk assessment is their ability to relate toxicity responses in a test species to humans and outcomes observed in smaller populations to likely outcomes in the general population. Thus, foremost among the extrapolations afforded by PBPK models are inter- and intra-species extrapolations.”

([US EPA, 2006](#))

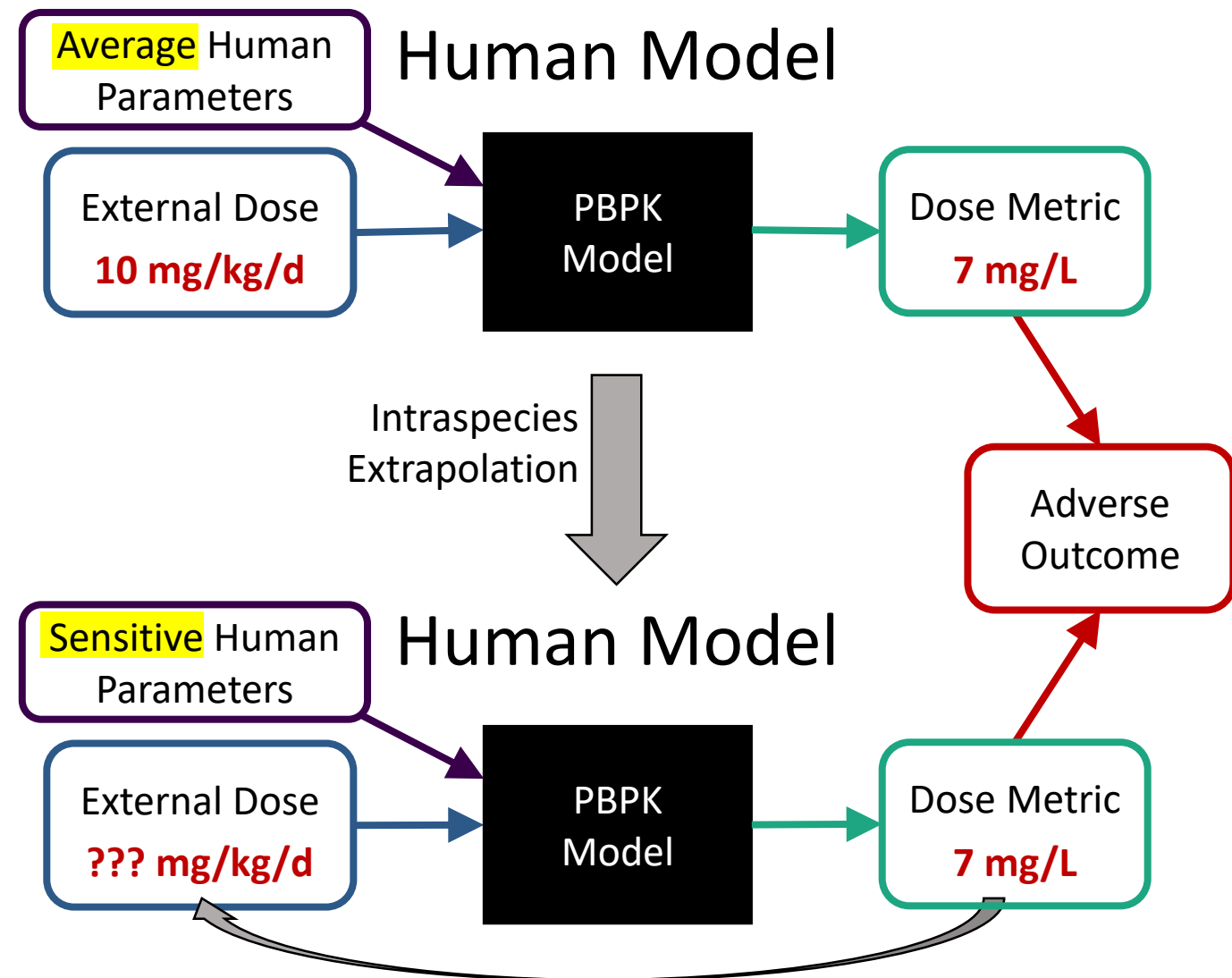
# Application: Interspecies Extrapolation

- Parameterize **animal model**.
- Choose an **internal dose metric**:
  - Maximum concentration in target tissue?
  - Average concentration in target tissue?
  - Steady state concentration in tissue?
- Choose an *animal* **external dose** of interest (e.g., a POD).
- Run simulation to calculate **dose metric**.
- Parameterize **human model**.
- Compute a *human* **external dose** that results in the same **internal dose metric**. (This is called “reverse dosimetry”).
- The result is called the **human equivalent dose (HED)**.



# Application: Intraspecies Extrapolation

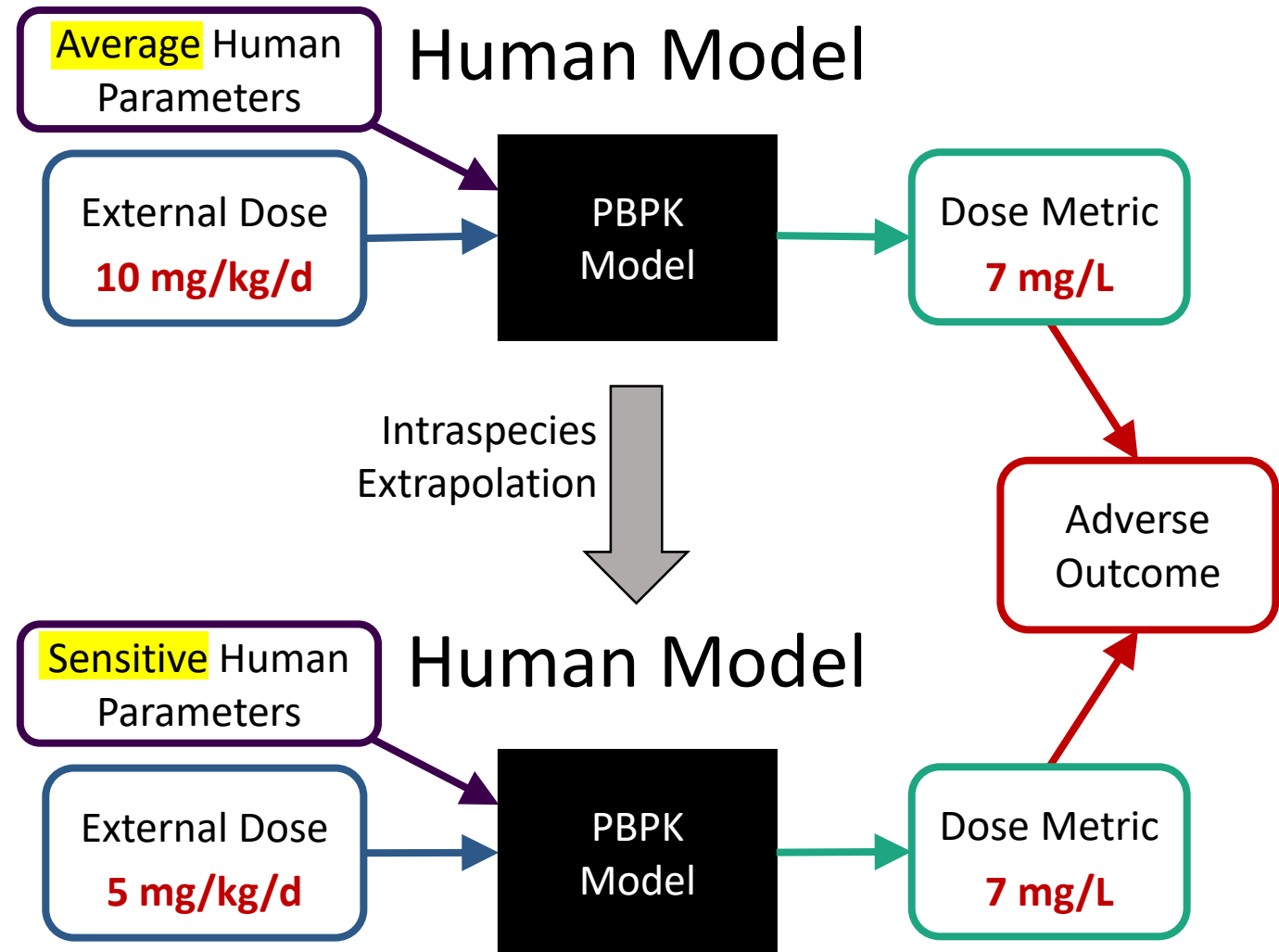
- Suppose we know the **external dose** that corresponds to an **adverse outcome** in average humans.
- We can run a simulation to calculate the relevant internal **dose metric**.
- Applying **intraspecies extrapolation**...
- ...we can then use reverse dosimetry to determine the **external dose** that leads to the same internal **dose metric** in sensitive humans.
- This **external dose** is therefore expected to lead to the same **adverse outcome** in **sensitive** humans.



# Replace $UF_{H(PK)}$ using PBPK Modeling

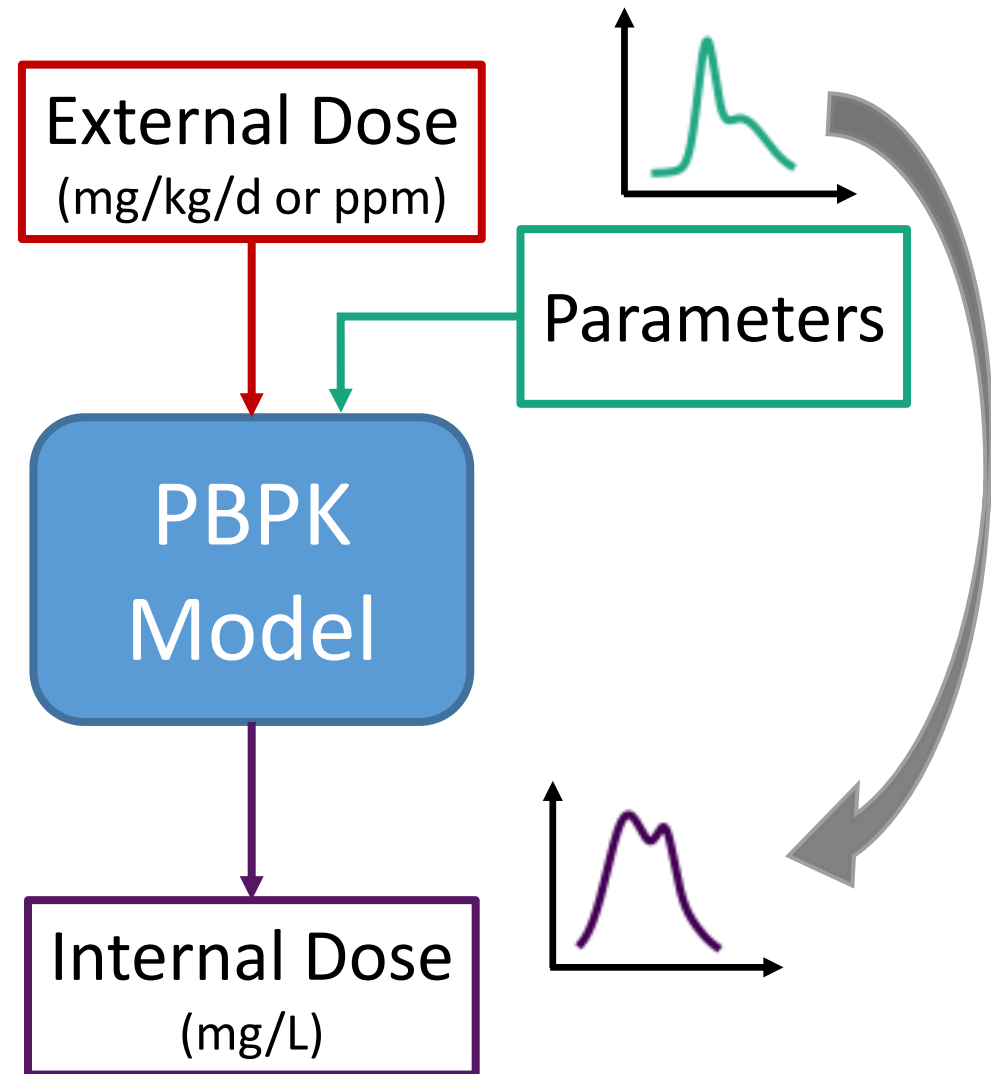
- Suppose the predicted **external dose** for **average** humans is 10 mg/kg/d and that for **sensitive** humans is 5 mg/kg/d.
- Then a chemical-specific, PBPK-based uncertainty factor for intraspecies PK differences can be calculated as

$$UF_{H(PK)} = \frac{10 \text{ mg/kg/d}}{5 \text{ mg/kg/d}} = 2.$$



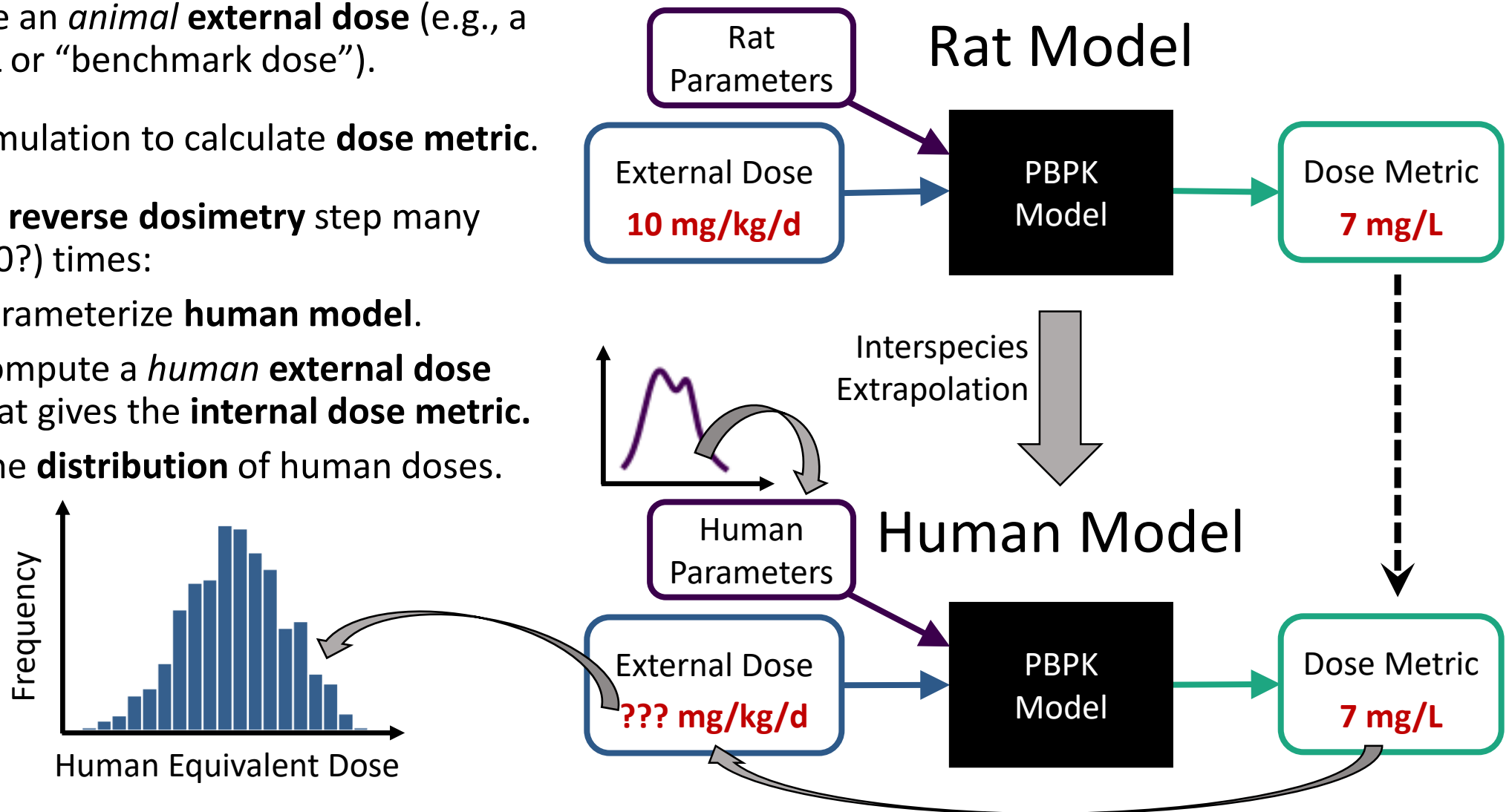
# PBPK Uncertainty and Variability

- **PBPK models** can be used to predict the relationship between **external dose** and **internal dose** of a chemical.
- Such models require various **parameters** in order to make predictions.
- Understanding and assessing the **uncertainty** and **variability** (U & V) in these **parameters** can help us to quantify the U & V in the **model predictions**.

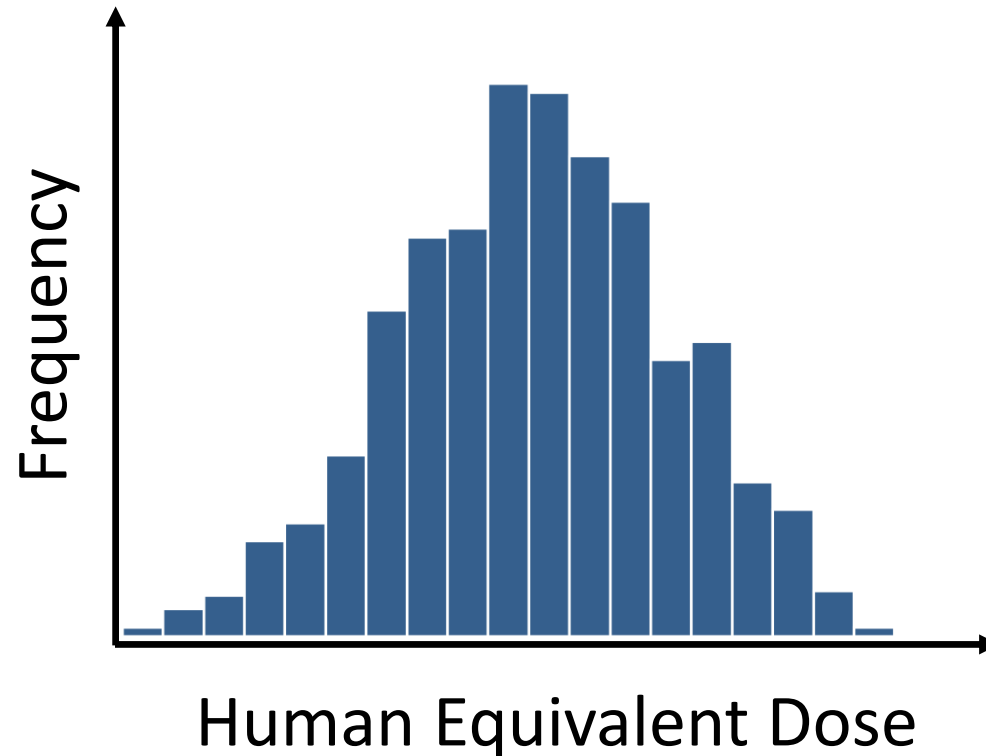


# Accounting for Intraspecies (Interindividual) Uncertainty and Variability

- Choose an *animal* **external dose** (e.g., a NOAEL or “benchmark dose”).
- Run simulation to calculate **dose metric**.
- Do the **reverse dosimetry** step many (10,000?) times:
  - Parameterize **human model**.
  - Compute a *human* **external dose** that gives the **internal dose metric**.
- Examine **distribution** of human doses.



# Accounting for Intraspecies (Interindividual) Uncertainty and Variability



- What AF (distribution) would allow conversion from a (given) POD to these HEDs?
- Given a chemical-specific PBPK model and distributional estimates of the parameters, how can we efficiently compute (and represent) this AF?
- Does the AF distribution change significantly if a different POD is used?
- Does the AF distribution typically conform to a standard distribution family (e.g., normal or log-normal)?

# New Paradigms in Risk Assessment

- **Benchmark Dose (BMD)** modeling methods now allow us **estimate** and **quantify uncertainty** in animal PODs.
- **PBPK** models allow us to **quantify uncertainty** and **variability** associated with differences in **toxicokinetics**:
  - Between species (lab animals and humans)
  - Between “sensitive” and “average” humans
- WHO IPCS guidance ([2017](#)) provides a **framework** for using all of this information together to compute a new type of “**probabilistic**” **reference dose** called the  $HD_M^I$ .
  - For the  $HD_M^I$ , one required input is the intraspecies PK AF.

# Practicum Project

- Generate methods, algorithms, and software for estimating the intraspecies PK AF.
- Chemical-specific PBPK model(s) will be provided (implemented in MCSim and R).
- Distributional parameter estimates will be provided.
  - Example:  $p \sim N(10, 1)$
  - Example:  $p \sim U(1, 4)$
  - Example:  $p \in S$ , where  $S$  is a sample from the distribution of values
- Products to be delivered:
  - Manuscript(s) or technical report(s) describing methods and providing examples.
  - Software that implements the algorithms (in R).

# Thank You!

## Questions?

Dustin Kapraun ([kapraun.dustin@epa.gov](mailto:kapraun.dustin@epa.gov))

Paul Schlosser ([schlosser.paul@epa.gov](mailto:schlosser.paul@epa.gov))