Categorical Default Approaches to Uncertainty Factor Development in Chemical Risk Assessment

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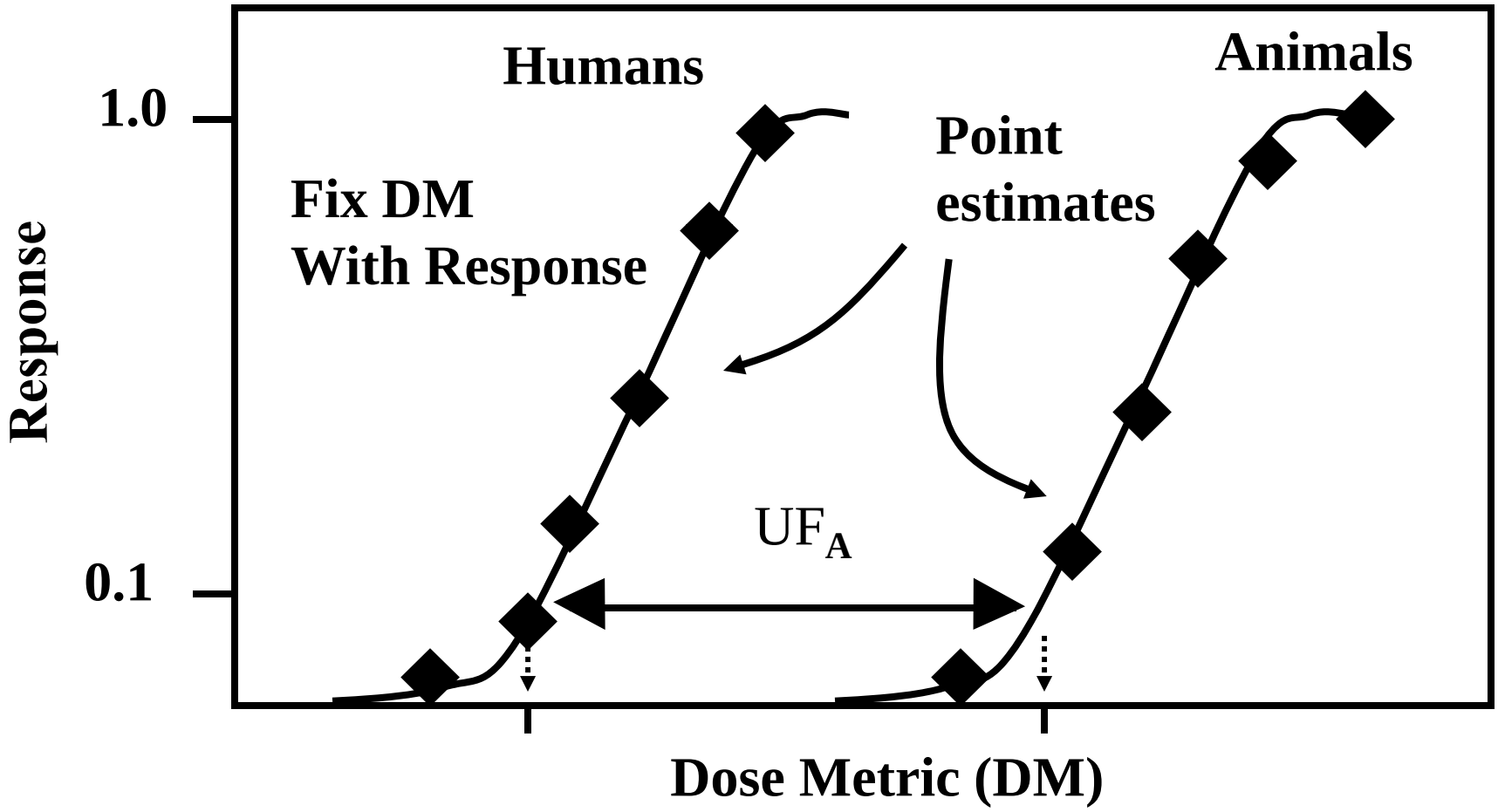
Success depends on…..

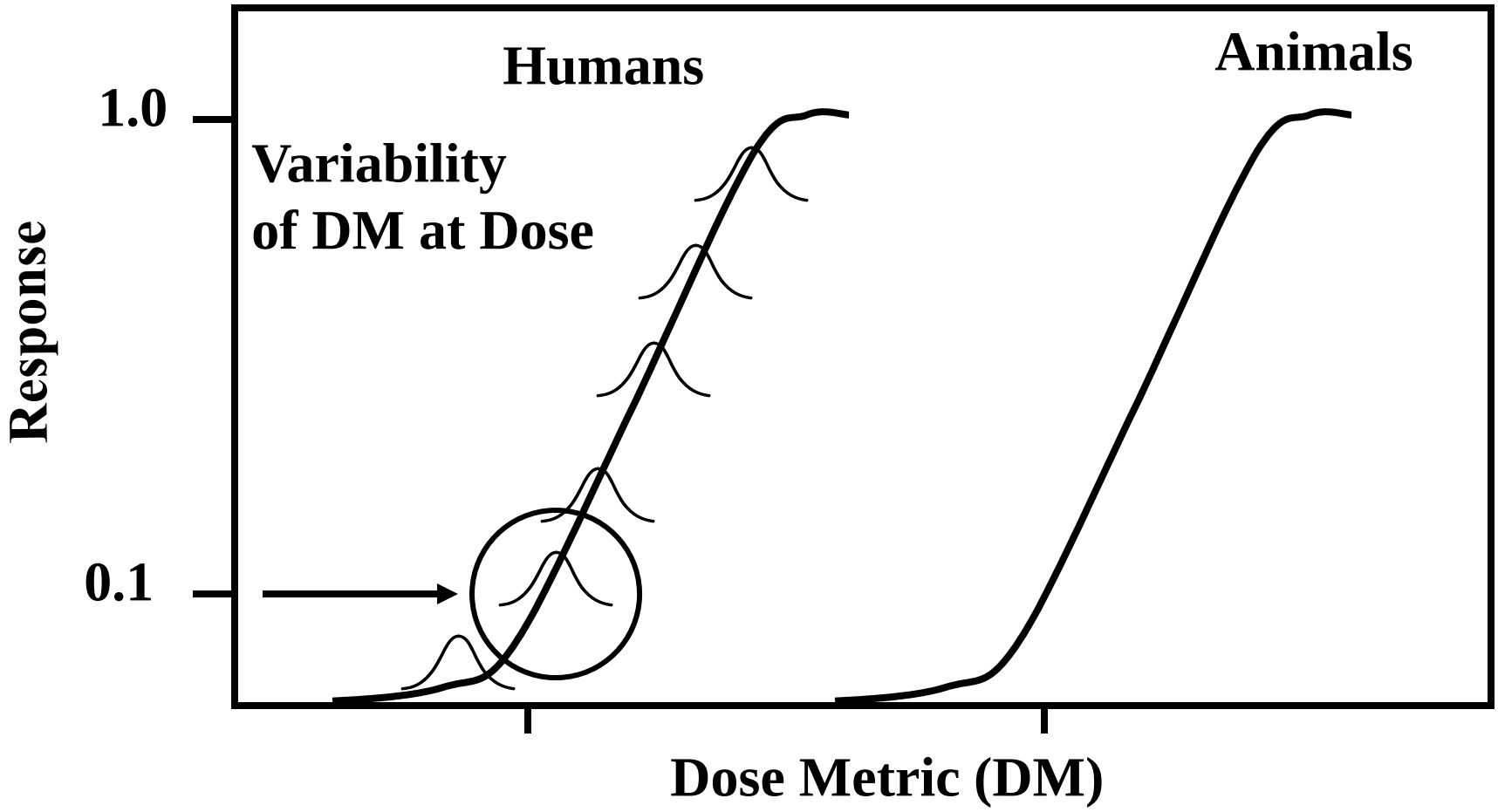
Understanding toxicity
Knowing target tissue
Assumptions/knowledge about dose metrics
Understanding biology
Having educated policy-makers

Dose metric – an expression of target tissue exposure. It can be in the form of concentration (AUC) or removal (clearance).

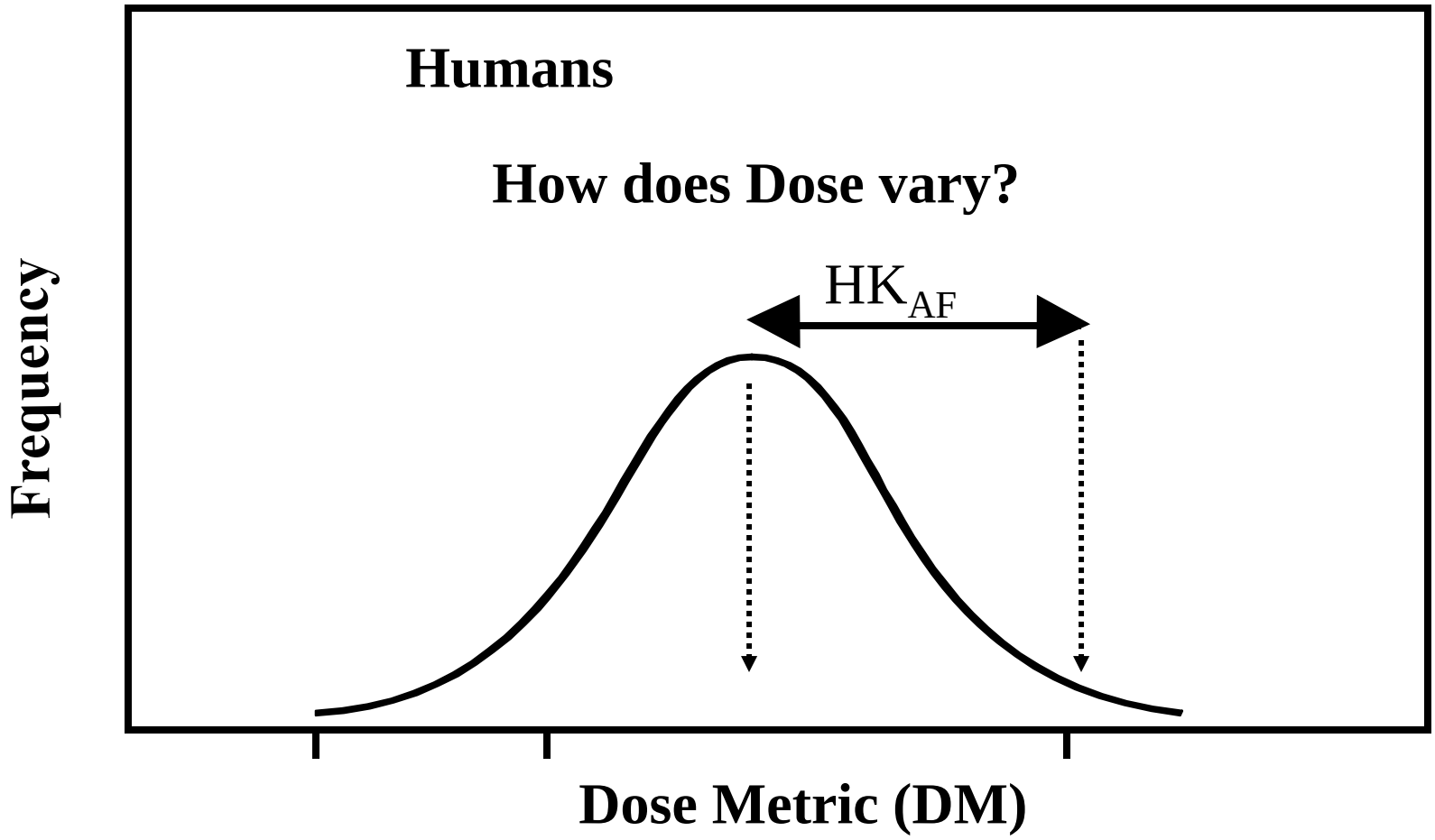
Inter (UF_A)- and Intra (UF_H)- Species Extrapolation



Inter (UF_A)- and Intra (UF_H)- Species Extrapolation



Intra (UF_H)- Species Extrapolation



Now What?

World Health Organization / International Programme for Chemical Safety (IPCS)

Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment (IPCS, 2005)

http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf

Toxicokinetics and Uncertainty Factors

Framework for Data Incorporation

Subdivision of UF values;
2 of 5 UFs addressed

AK_{AF} = Adjustment Factor, animal to human, Toxicokinetic

Uncertainty Factor (UF) used For default: UF_{AK}

Default, UF Values

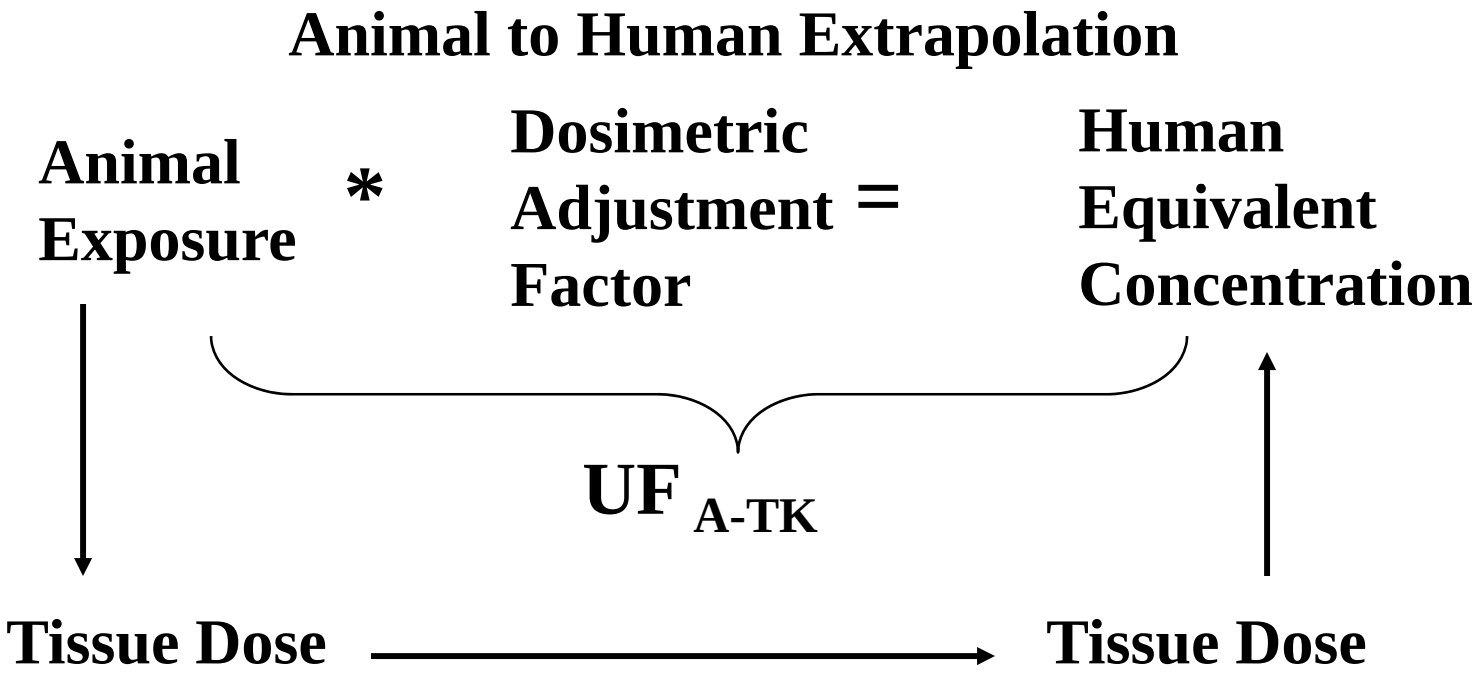
	UF_A	**UF_H**
PK	**4.0**	**3.16**
PD	**2.5**	**3.16**
	10	**10**

Categorical Default Uncertainty Factors

- **Worthless without a framework**
- **Inhalation**
  - **Portal of entry effects – Category 1 gases**
  - **Systemic effects – Category 3 gases**
- **Value based on by exposure (not type of response)**

<u>Category? Location of injury</u>

U.S. EPA: Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994)



TD component valued at one-half order of magnitude; 3 in practice

Human Equivalent Concentration

Inhalation RfC = HEC / UF

Employ species-specific anatomic and physiologic factors applied to duration-adjusted exposures

Duration adjust to week (#), document local or systemic (remote) location of effect, characterize and apply Species differences in factors.

Separately consider Category 1 (respiratory), reactive gases from Category 3 gases (systemic toxicants), those which exert toxicity in tissues remote to the respiratory tract.

 # 50 ppm * (6h/24h)*(5d/7d) = 8.9 ppm

Human Equivalent Concentration

Dosimetric Adjustment Factor - DAF

$HEC = NOAEL_{adj} * DAF$

Category 1 (reactive) gases: DAF based on ventilation rate and nasal passage surface area. Recommended DAF value is about 0.2. HECs are about 20% of the animal duration-adjusted concentration. RGDR approach used.

Default Chemical Category Specific

- **Category 1 gases:**
  - **Water soluble and/or rapidly reactive**
  - **Do not penetrate to blood**
  - **Cause effects in respiratory tract**
  - **DAF by Regional Gas Dose Rate (RGDR) approach, ventilation rate (V_E) and surface area (S_A) of the affected region (extrathorasic, ET; tracheobronchiolar, TB; pulmonary, PU)**
  - **$RGDR = (V_E / S_A)_{animal} / (V_E / S_A)_{human}$**

Default Values for V_E and S_A

	Human (70kg)	Rat (200g)
Ventilation Rates (VE)	**13.8 L/min** **20 m^3/day**	**0.14 L/min** **0.2 m^3/day**
S_A ET	**200 cm^2**	**15 cm^2**
S_A TB	**3,200 cm^2**	**22.5 cm^2**
S_A PU	**54 m^2**	**0.34 m^2**

Example: Category 1

Critical Effect: Degeneration of the olfactory epithelium (ET effect); used study-specific V_E and S_A values

Exposure: 6 hours/day, 5 days/week

$273\ mg/m^3 *[(6h/24h)*(5d/7d)] = 48.75\ mg/m^3$

$NOAEL_{adj} = 48.75\ mg/m^3$

$NOAEL_{hec} = NOAEL_{adj} \times RGDR_{ET}$

$NOAEL_{hec} = NOAEL_{adj} \times [V_E/S_A]_A/[V_E/S_A]_H$

$NOAEL_{hec} = 48.75 \times [0.23 / 11.6] / [20 / 177] = 8.7\ mg/m^3$

UF = 3 UF_A, 10 UF_H, 10 duration, 3 database (=1000)

RfC = $NOAEL_{hec}$/UF = 8.7 / 1000 = $0.009\ mg/m^3$

Hydrogen Sulfide

POD: Rat NOAEC; $NOAEC_{adj}$ = 3.48 mg/m^3
Site: Extrathoracic

Species	V_E (L/min)	S_A (cm^2)
Rat	0.19	15
Human	13.8	200

DAF = 0.184

$NOAEC_{hec}$ = 3.48 * 0.184 = 0.64 mg/m3
vs. (3.48/0.64 = 5.4)

http://www.epa.gov/iris/subst/0061.htm

Human Equivalent Concentration

Dosimetric Adjustment Factor - DAF

HEC = $NOAEL_{adj}$ * DAF

Category 3 gases are unreactive. DAF usually created by a ratio of the blood:air partition coefficients (animal:human). For many compounds, this ratio is >1; Agency policy is to "cap" a DAF determined in this manner to a maximal value of 1. May use PBPK Model.

The partition coefficient represents the ratio of concentrations of agent in blood and in air at equilibrium. These values are easily determined in the laboratory.

Default Chemical Category Specific

- **Category 3 gases:**
  - **Not reactive**
  - **Penetrate to blood and systemic tissues**
  - **Cause effects in remote tissues**
  - **DAF by blood:air partition coefficients**
  - **DAF = $(B:A\ PC)_{animal}$ / $(B:A\ PC)_{human}$**

Example: Category 3

Critical Effect: Systemic effects in liver

Employ Blood:Air Partition Coefficients

$NOAEL_{adj}$ = 48.75 mg/m^3

$NOAEL_{hec}$ = 48.75 mg/m^3 x [(B:A PC_A) / (B:A PC_H)]*

$NOAEL_{hec}$ = 48.75 mg/m^3 x [23 / 12.5]

$NOAEL_{hec}$ = 48.75 x [1] = 48.75 mg/m^3

UF = 3 UF_A, 10 UF_H, 10 duration, 3 database (=1000)

RfC = 48.75 mg/m^3 / 1000 = 0.05 mg/m^3

**Maximum value allowed is 1.0; US EPA, 1994*

Human Equivalent Dose

Analogous to HEC for Inhaled Substances

Oral Exposures

Timing of dose = day

Systemic, not portal effects

Allometric scaling applied

Human Equivalent Dose

No guidance, just recommendations
On DOSE SCALING*

$$\frac{\text{[DOSE (AMOUNT) * SCALING FACTOR]}}{\text{HUMAN BW}}$$

Oral exposures, employ Body Weight$^{0.75}$ scaling

(ratio of body weights raised to the 0.75 power; human:animal)

**** Risk Assessment Forum, U.S. EPA, 2002***

Human Equivalent Dose

CALCULATE THE DOSE (AMOUNT)

Rat Dose 5 mg/kg; Rat BW = 0.3 kg

Dose amount = 5 mg/kg * 0.3 kg = 1.5 mg

DETERMINE THE SCALING FACTOR

Animal / Human
70 kg / 0.3 kg = 233
$233^{0.75} = 60$

BODY WEIGHT RATIO
Human = 70 kg
Rat = 0.3 kg

RAISE TO 0.75 POWER

60 is the dose scaling factor

BW $^{0.75}$ Scaling in Estimating Delivered Oral Dose in Humans From Doses in Rats

Calculate the Dose (Amount)

Determine Scaling Factor

Divide by Human BW

Rat dose in mg/kg	Scaling	BW(H) / BW(R)	Scaling Factor	Scaled Dose
5 mg/kg * 0.3 kg = 1.5 mg	BW $^{0.75}$	70 kg / 0.3 kg = 233	233 $^{0.75}$ = 60	[(1.5 mg)* 60)] / 70 kg = 1.3 mg/kg

(1.5 mg * 60) / 70 kg = 1.3 mg/kg

Some Species-Specific Oral Dose Scaling Factors

Species	Body Weight (kg)	Scaling Factor	"Effective" UF
Mouse	0.03	335	7.0
Rat	0.25	68	4.1
Guinea pig	0.5	40	3.5
Rabbit	2.5	12.2	2.3
Human	70	1	

INTRASPECIES EXTRAPOLATION: Human Variability

UF_H

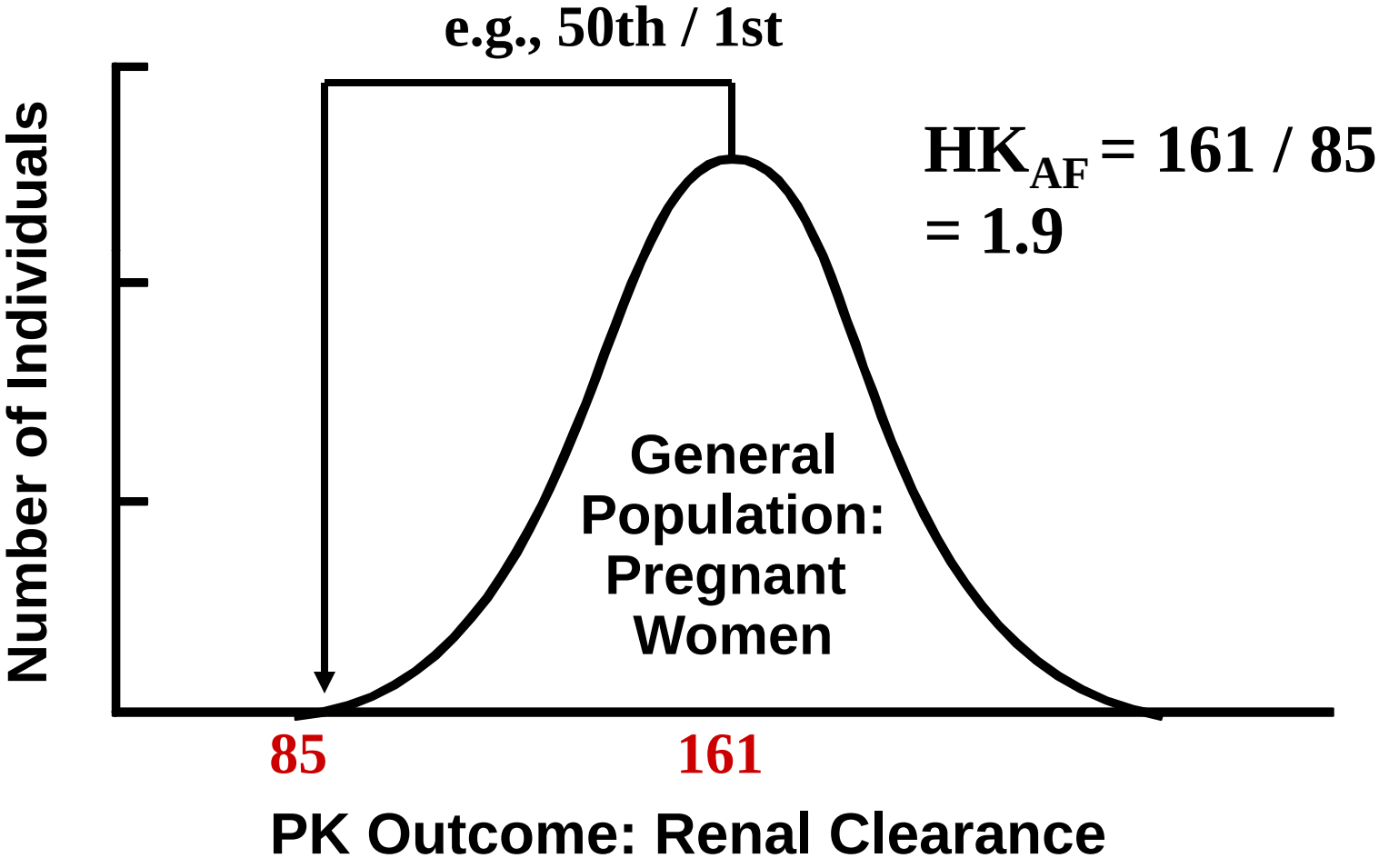
Human Interindividual Variability

Susceptible subpopulations

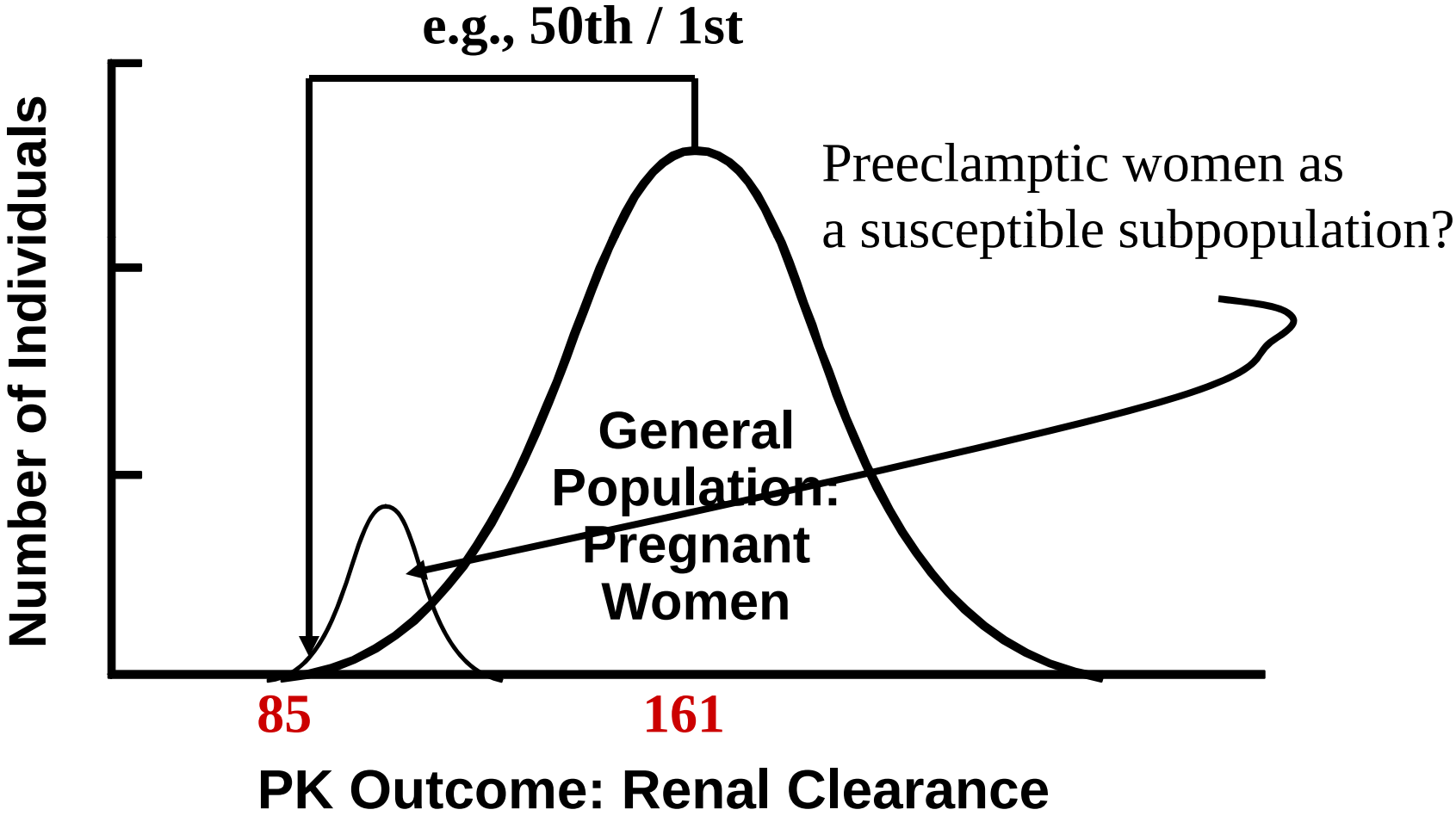
Genetic, Biochemical or Physiologic differences

Life Stages

Impact of Population Variability: Unimodal Distribution



Impact of Population Variability: Bimodal Distribution



Boron and Compounds

Human Variability per IPCS (2005)
PK model based on urinary clearance
AUC = Dose / Clearance

POD: Rat developmental toxicity
Parent compound cleared by renal filtration (GFR)
Category: GFR variability - among pregnant women
3 data sets of GFR values from 59 women

$$UF_{H\text{-}TK} = GFR_{mean} / (GFR_{mean} - 3*s.d.)$$

$UF_{H\text{-}TK}$ **set to a value of 2.0**

http://www.epa.gov/iris/toxreviews/0410-tr.pdf

Summary

Look first to Data

Understand Targets and Dose Metrics

Some Understanding of Dosimetric Differences

Toxicokinetic Equivalence Between Species

Data-Derived, Chemical-Specific, Categorical Default, Default Methods for UF values