Establishing OELs for Potent and Highly Potent Compounds

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World HPAPI Summit
May 30, 2013

Agenda

- Introduction
- Process of Occupational Exposure Limit (OEL) development
- Selection of safety and uncertainty factors
- Variability in interpretation of data and selection of endpoints
- Tackling inherent bias in risk assessment (RA)

What's the Big Deal?

- OELs and other RAs are not precise values
- Regulatory authorities may consider one value "correct", others "incorrect"
- Derivation should be evaluated as:
  - "consistent with current principles"
  - "not consistent with current principles"
- Applying a consistent and systematic evaluation process will provide confidence in the RA
- Transparency of derivations assures robustness

Establishing Health-Based OELs

$$\text{OEL } (mg/m^3) = \frac{\text{NOAEL } (mg/kg/day) \times \text{BW } (kg)}{UF_C \times MF \times \alpha \times V\ (m^3)}$$

where:

	OEL	=	Occupational Exposure Limit
	NOAEL	=	No-Observed-Adverse-Effect Level
	BW	=	Body Weight
	UF_C	=	Uncertainty Factor(s)
	MF	=	Modifying Factor
	α	=	Bioavailability adjustment
	V	=	Volume of air in 8 hour day

OEL Process

- Collect data
- Select critical endpoint
- Select point of departure (POD)
  - LOAEL / NOAEL
- Select pharmacokinetic factors
- Select safety / uncertainty factors
- Sensitive subpopulations
- Apply values to calculate OEL or other value
- Is this correct?
- How can this be wrong?

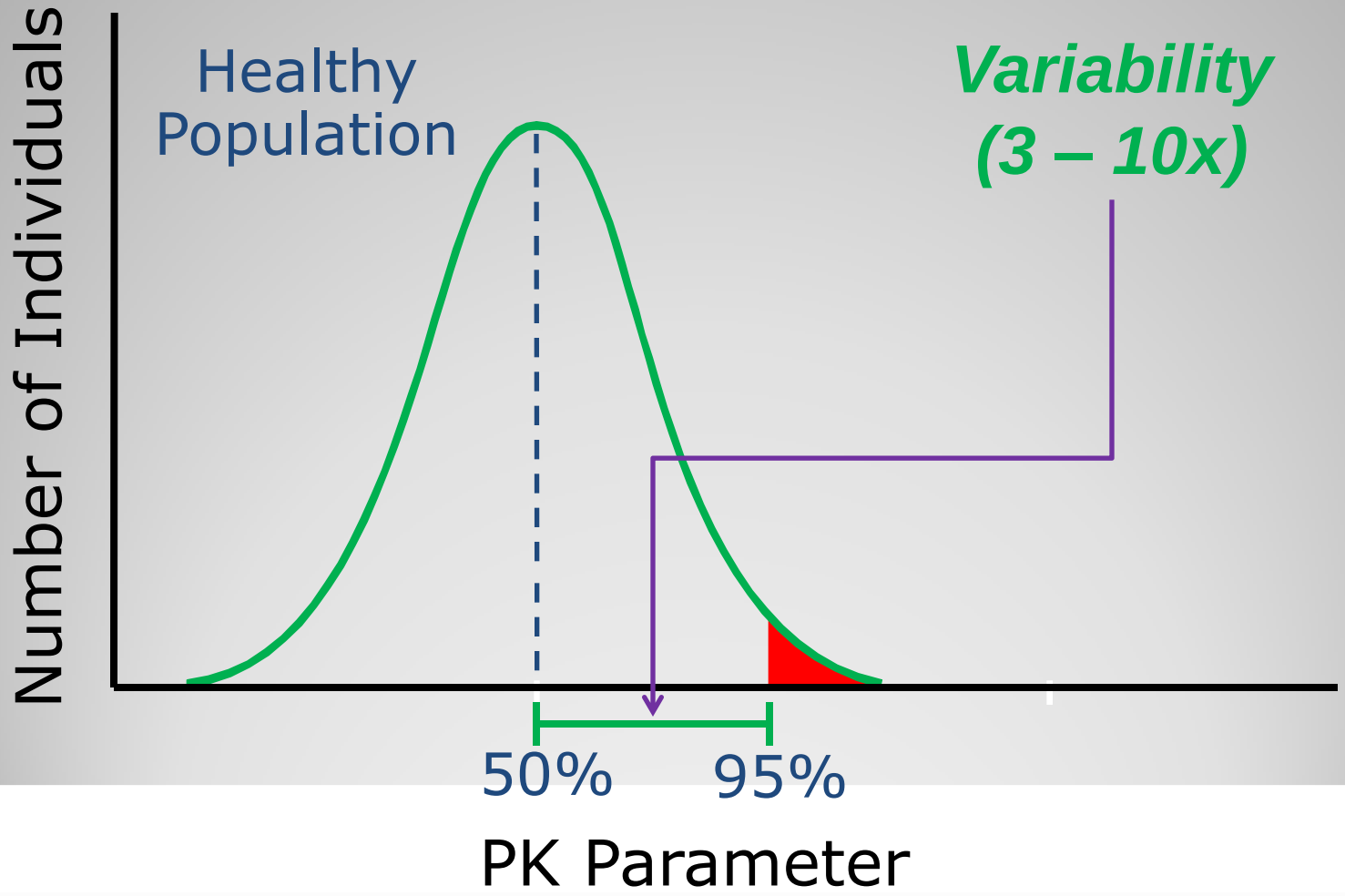
Identification of Critical Endpoint

- Pharmacology / Mode-of-action
- Acute toxicity / Dose-limiting toxicity
- Local tolerability / Sensitization
- Subchronic / Chronic toxicity
- Reproductive / Developmental toxicity
- Mutagenicity / Genotoxicity / Carcinogenicity
- Human safety / Efficacy

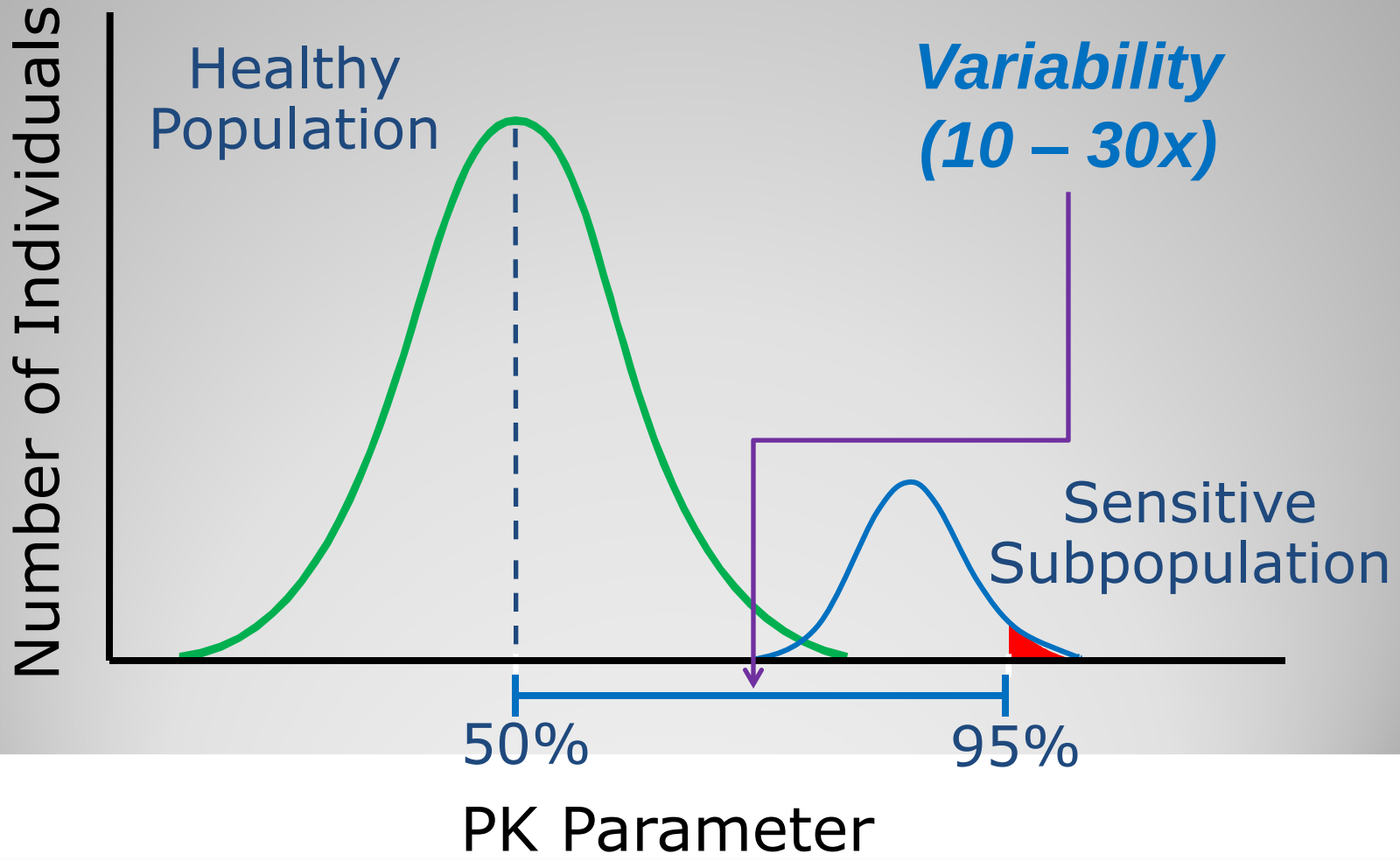
OELs and Critical Endpoint

- Preference for human data
- Chronic studies by the most relevant route
- Most sensitive animal species and organ system (target organ)
- NOAEL vs LOAEL
- Data quality

Unimodal Population



Bimodal Population



Interspecies (Animal to Human) Extrapolation

Allometric Scaling

- Uses species surface area/weight to equalize doses
- Surface area is a better factor than body weight – related to relative metabolism of the species
- Factors used for various species are as follows:
  - Dog = 2
  - Monkey = 2-3
  - Rabbit = 3-4
  - Rat = 4-6
  - Mouse = 7-12

LOEL to NOEL Extrapolation

- Original default = 10
- Compare data from Physicians Desk Reference

$$\frac{\text{Maximum Therapeutic Dose}}{\text{Minimum Therapeutic Dose}} \approx 3$$

Examples of Ranges for UFs

UF	Default	Range
UF_H	10	From 3 to 30, depending upon available data
UF_A	1 – 12	Data from human studies = 1, Mouse = 12
UF_S	3	Long-term = 1, Acute = 30-100
UF_L	3	NOAEL = 1, Frank effect = 10-30
UF_D	3	Extensive database = 1, Limited data 10
UF_C	**-**	**Usually minimum of 10 to max of 10,000**

Bioavailability Correction Factor

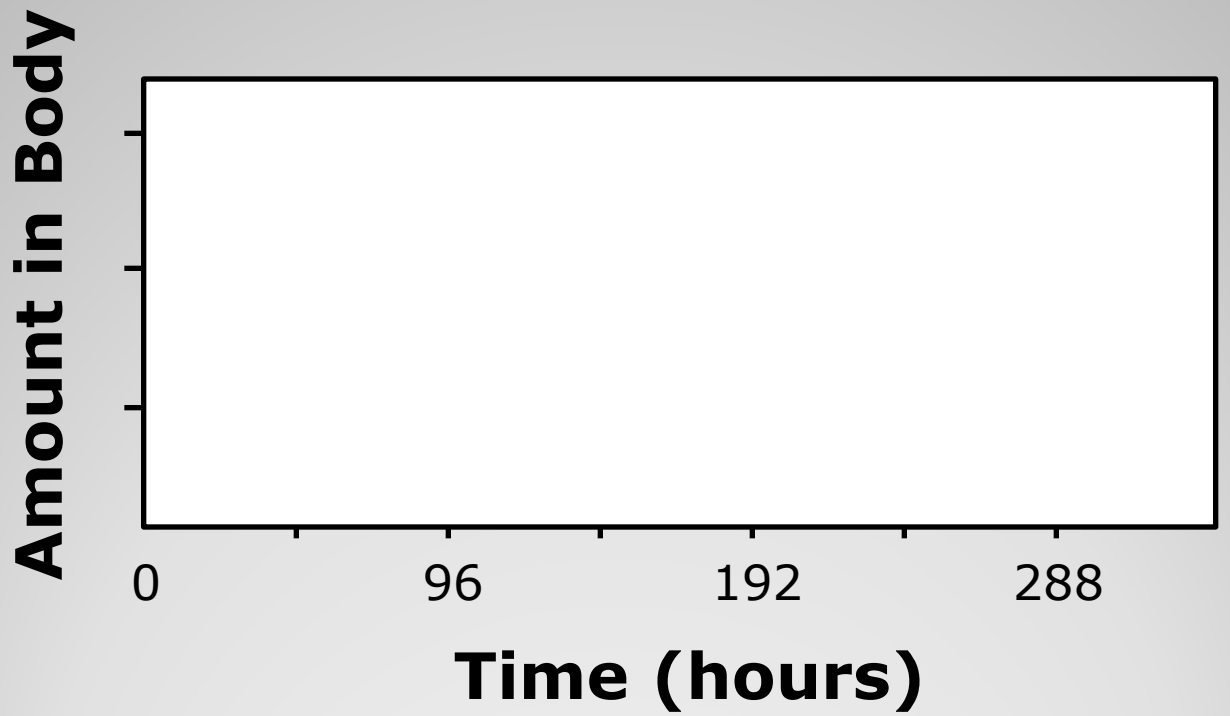
Based on oral data

- If oral low and inhalation high, lower OEL
- OEL set on effects from 100 mg oral dose
- Oral bioavailability = 5%
- Actual inhaled dose causing similar effects = 5 mg

➢ ***Can divide OEL by 20***

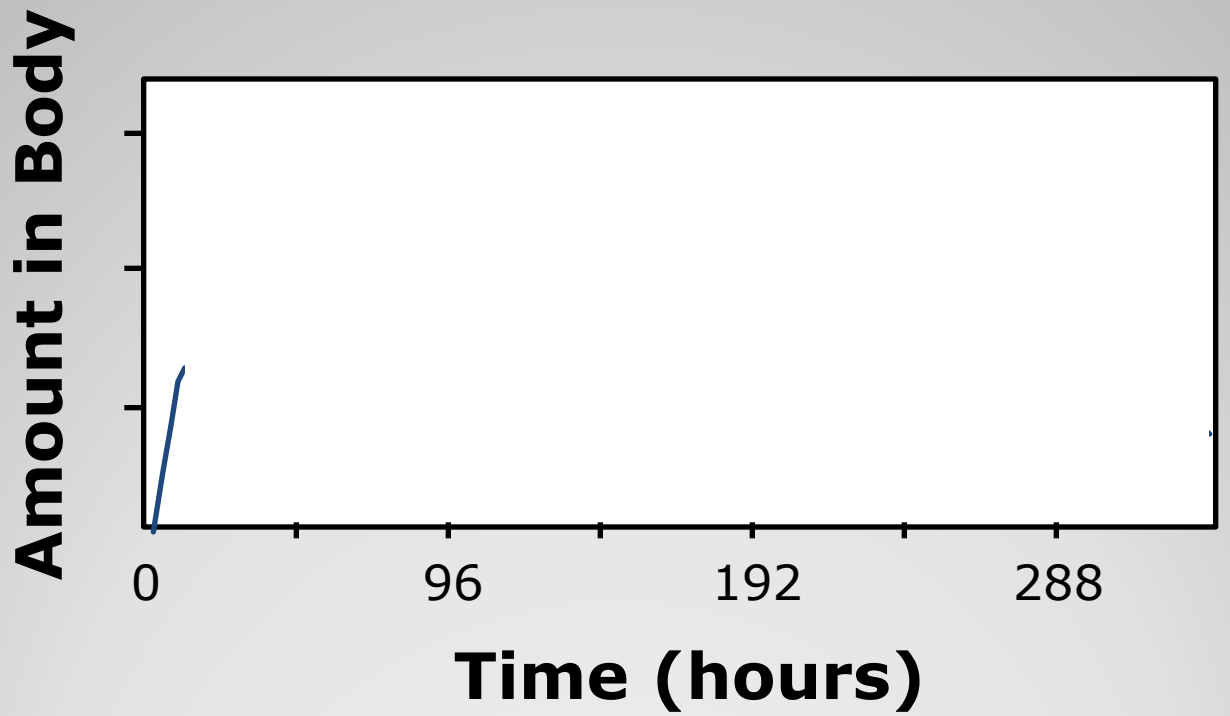
$$\alpha = \frac{A_{inh}}{A_{oral}} = \frac{1.0}{0.05} = 20$$

Bioaccumulation



From Sargent & Kirk (1988)

Bioaccumulation



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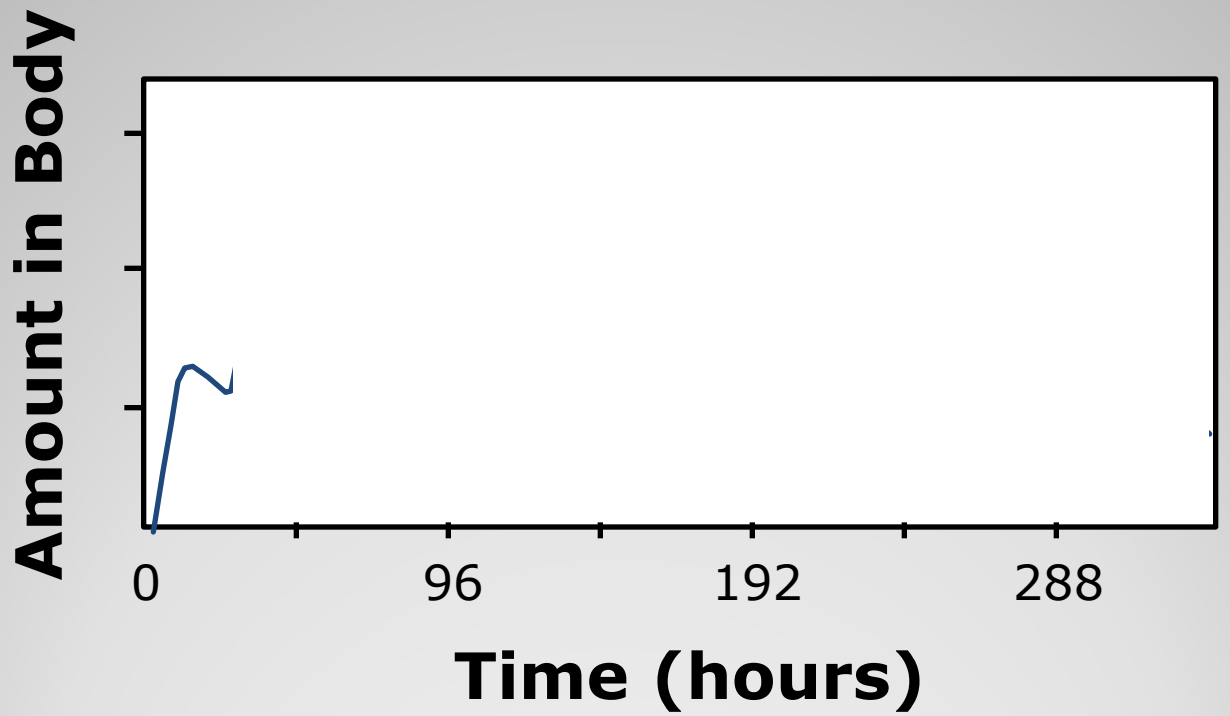
Bioaccumulation



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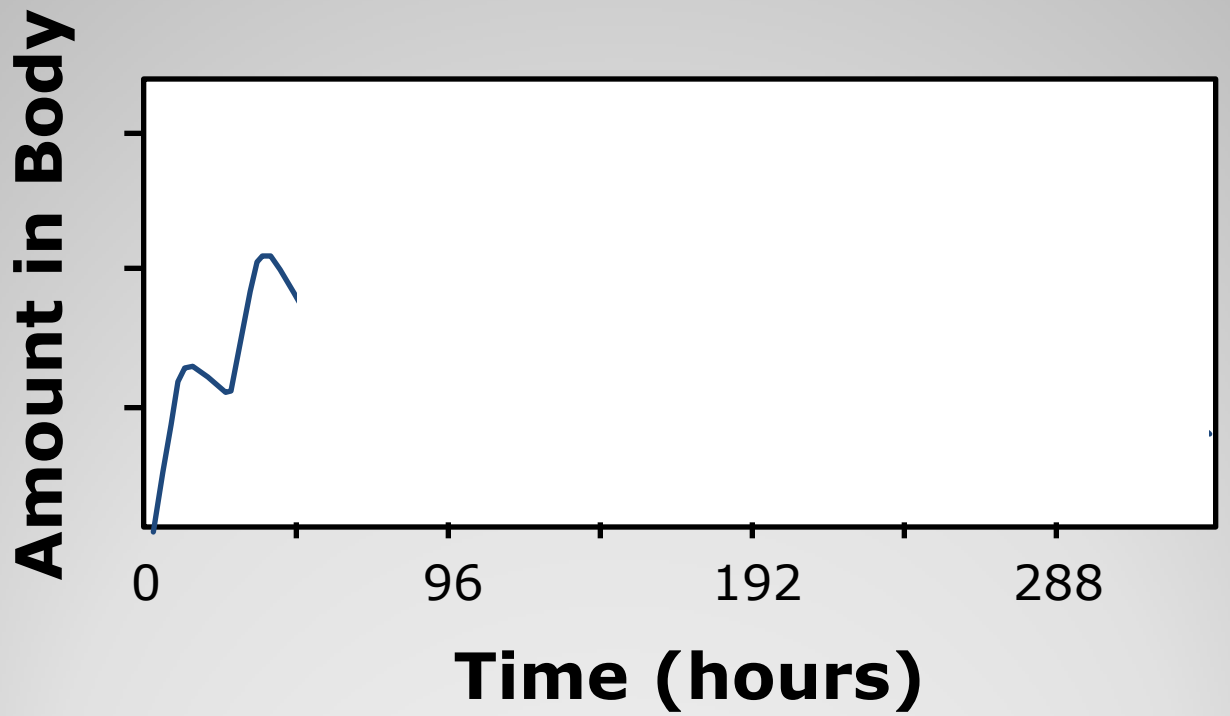
Bioaccumulation



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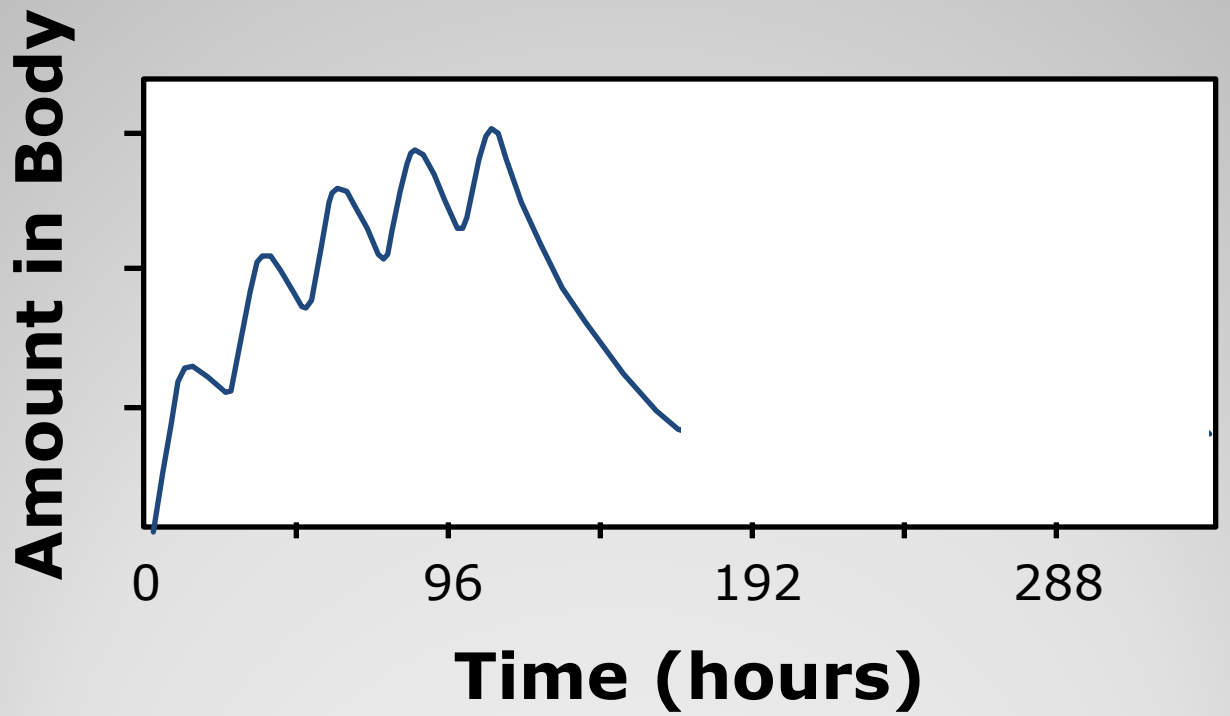

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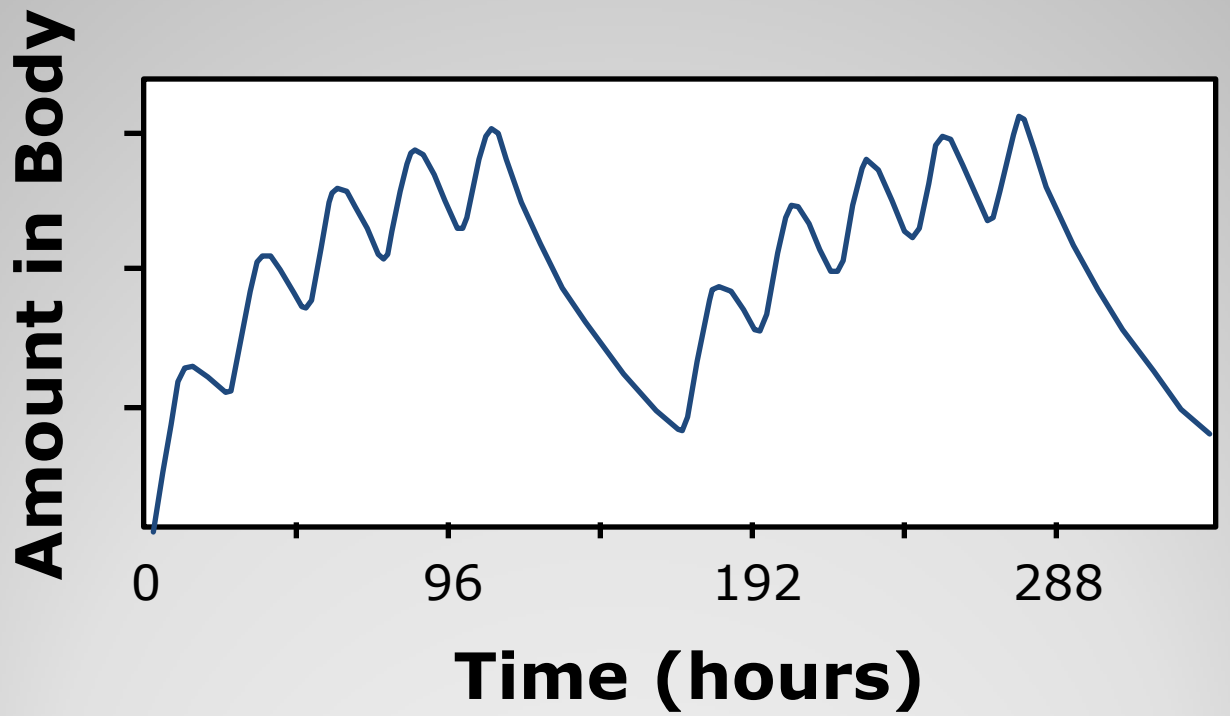


From Sargent & Kirk (1988)

Sensitive Subpopulations

- Healthy worker population
- Clinical trials conducted in "Special Populations"
  - Pediatric (5-17 yrs) and Elderly (>65)
  - Hepatic impairment, renal insufficiency, cardiovascular or respiratory disease
  - Genetic polymorphisms
- Further recommendations for pregnancy, labor and delivery, nursing mothers, concomitant drug use and diseases
- Dose adjustment recommendations provided in package insert can be used to modify LOAEL

Sources of Variability

- Endpoint and POD (NOAEL / LOAEL)
- Bioavailability and other toxicokinetics
- Sources of uncertainty
- Sensitive subpopulations
- Different RAs account for these variables in different ways
  - How do we standardize these factors?
  - Should we standardize?
  - How is professional judgment standardized?

Documentation

- Need for transparency
- Verification of robustness
- RA documentation may be requested by regulatory authorities
- No idea how authorities will handle different RA values submitted for same chemical

Documentation

- Introduction
- Data sources
- Pharmacological mechanism
- Therapeutic indication and dose
- Clinical effects
- PK / PD (including variability)
- Non-clinical data
  - Acute studies
  - Repeat-dose studies
  - Reproductive and developmental studies
  - Genetox and carcinogenicity studies

Documentation

- Derivation
  - Selection of endpoint and POD
  - PK adjustment (bioavailability & accumulation)
  - Selection of UFs
  - Modifying factors
  - Sensitive subpopulations
  - Calculation
  - ROUNDING!!!!
- Parallel derivations?
- Conclusion

Sample UF Table

Factor	Default	Value	Comment
UF_H	10	4.6	Default UF_{HD} of 3.16 x chemical-specific UF_{HK} of 1.47
UF_A	1-12	3	Studies performed in monkeys
UF_S	3	1	No study length factor required for developmental effects
UF_L	3	3	Default
UF_D	3	1	Database well developed and includes reproductive and developmental studies
UF_C	**-**	**41**	**4.6 x 3 x 1 x 3 x 1**

Rounding Convention

- One significant digit
- Second digit ok if:
  - First digit is less than 5, and
  - Value of second digit is 5
- For example:
  - 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90
  - 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9
  - etc.

Documentation

- References
- Author qualifications
- Reviewer qualifications
- CVs

Bias in Risk Assessment

SOT Code of Ethics

- "Conduct their work with objectivity…"

AIHA Code of Ethics

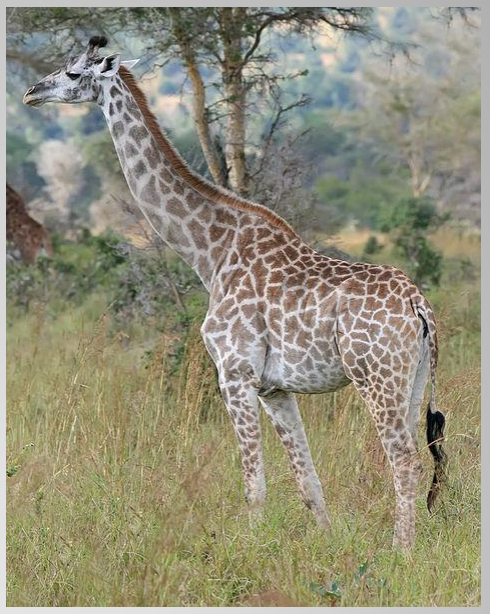
- "Deliver competent services… with objective and independent professional judgment…"

Professional judgment = bias

What Do These Animals Weigh?

3.5-9 kg
8-20 lbs

100-250 kg
220-550 lbs



1200 kg
2500 lbs

Which Are Most Similar?

- West Germany and East Germany (1960s)
- Sri Lanka and Nepal

Which Are Most *Different*?

- West Germany and East Germany (1960s)
- Sri Lanka and Nepal

Summary

- Quantitative RA is not an exact science
- The overall process involves applying safety and uncertainty factors to a NOAEL or LOAEL
- It is difficult to standardize professional judgment
- Provide transparent and robust monograph documenting the RA process
- Bias in RA is a good thing!