

***Uncertainty and variability in
PBPK models:
How do we put it all together for
risk assessment?***

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Outline

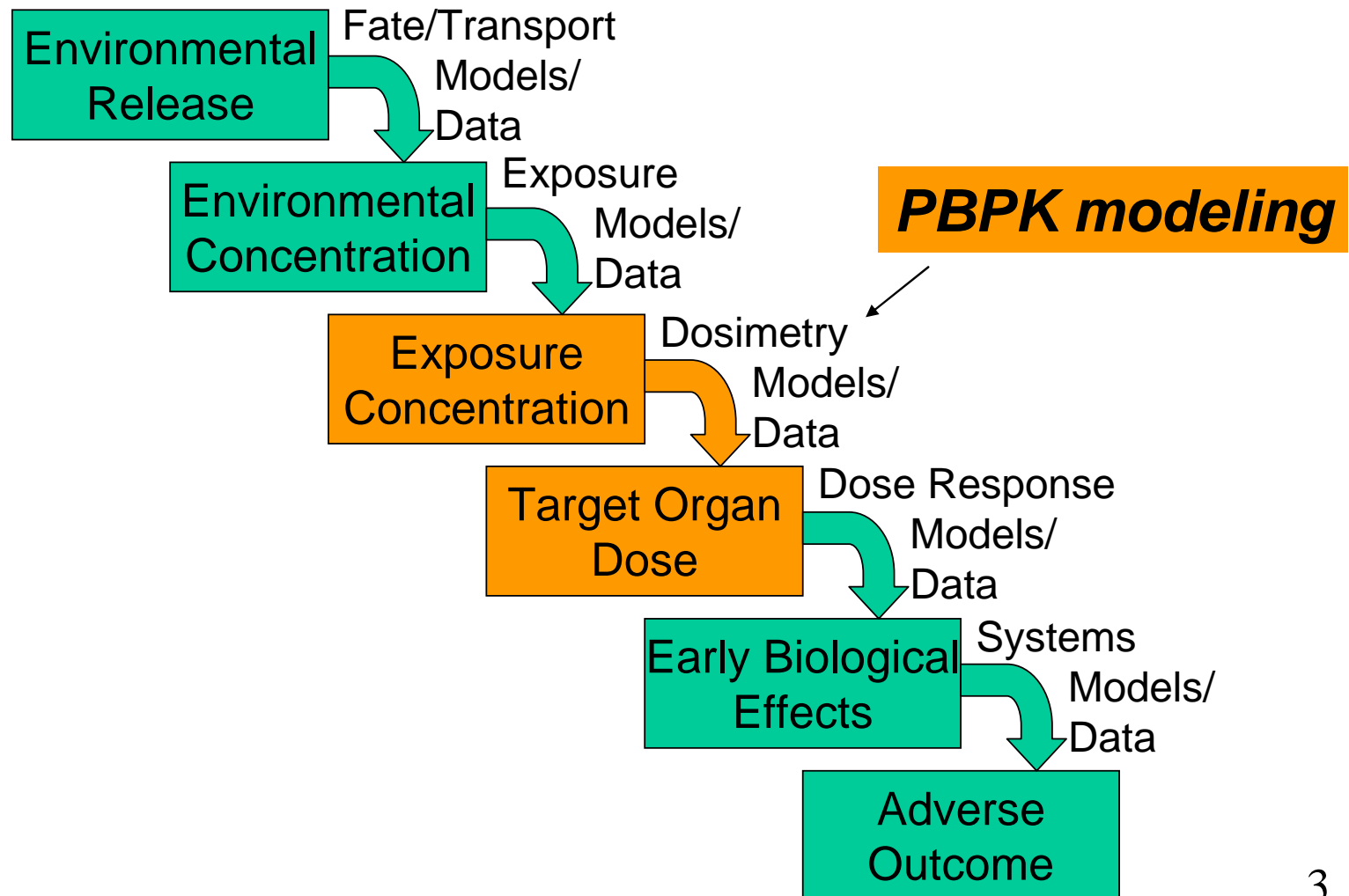
- PBPK models in the context of risk assessment, uncertainty and variability
- Common challenges to characterizing PBPK model uncertainty and variability
- Charge and scope of breakout groups



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Risk Assessment Source-to-Outcome Continuum



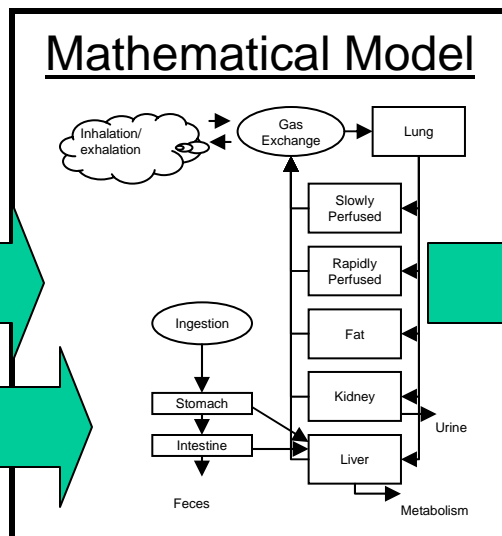
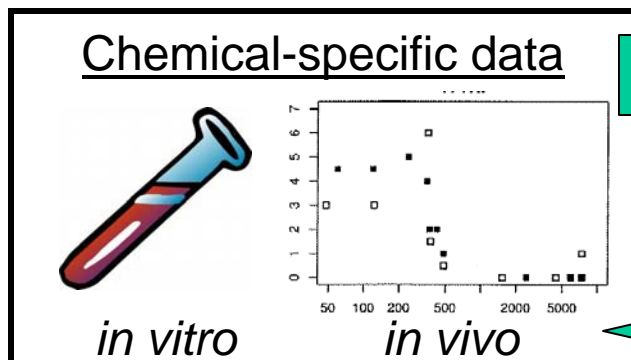
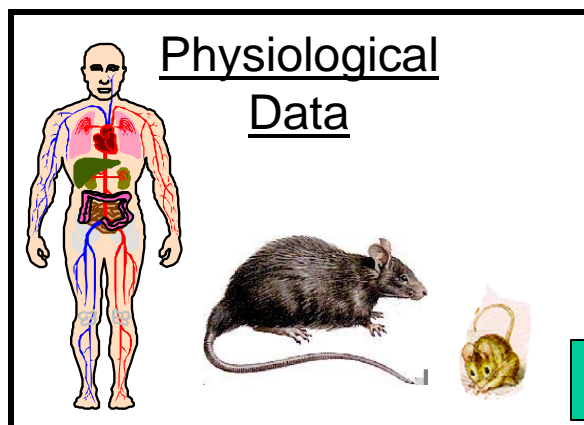


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Risk assessment need that could be addressed (in part) with PBPK modeling	Example of a “default” procedure
Route-to-route extrapolation (e.g., oral to inhalation exposure)	20 m ³ /day, 70 kg BW
High-to-low dose	Linear extrapolation
Duration adjustment	Concentration x Time
Interspecies extrapolation	BW ^{3/4} scaling
Inter-individual variability	10-fold uncertainty factor (parsed into a kinetic and dynamic factor)
Quantitative uncertainty analysis	—

However, **Uncertainty** and **Variability** are inherent in all components of **PBPK modeling**



- Predictions for Risk Assessment
- Inter-species extrapolation
 - Inter-individual variability
 - Route-to-route extrapolation
 - Dose-response analysis
 - etc.

Feedback to new hypotheses, improved experimental design



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Purposes of Uncertainty and Variability Analyses for Risk Assessment

Synthesize Scientific Data

- Characterize the range of risk values consistent with current knowledge and lack thereof
- Characterize what is known about the extent of human variability to risks, and what factors may lead to greater/ less susceptibility.
- Identify research/data needs that would have the greatest impact on reducing uncertainty

Aid Communication and Provide Context

- Determine the degree (or lack) of conservatism in an estimate
- Make clear and transparent to decision-makers and the public the ramifications of a risk assessment
- Allow evaluation of expert judgments, particularly if there are divergent perspectives

Adapted, in part, from NRC (1994)

Science and Judgment in Risk Assessment 6



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Common challenges to characterizing PBPK model uncertainty and variability

- Extrapolation to/among humans
 - Less data available as compared to laboratory animals
 - Overall population variability (vs. in a small number of healthy volunteers)
- Uncertainty in surrogate or “proxy” data
 - Rodent data as surrogate for humans (e.g., tissue-air partition coefficients; allometric scaling)
 - *In vitro* – *in vivo* extrapolation (e.g., microsomal metabolism)
- Availability/role of statistical models and methods
 - What level of rigor is necessary for different applications?
 - Sources of variability that are often ignored – among animals, intra-individual, inter-experimental?
- Model structure uncertainty



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Physiological data

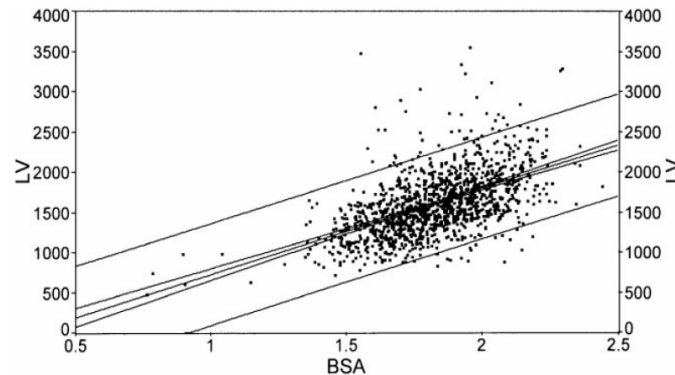
- Relatively good data on “central” estimates
 - Reviews (e.g., Brown et al. 1997)
 - “Reference” human individuals (ICRP 2003)
 - Includes adult males & females, embryos, infants and children
 - NHANES data
 - Anthropometric measurements (height, weight, bioimpedance)
 - Subject characteristics (sex, age)
 - NHANES III used by Price et al. (2003) to generate individual physiological parameters using body composition models
- Much data not statistically sample-based, but sufficient for providing plausible range for population means



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Limited data on human physiological variability



Liver weight in Caucasians (n=1332):

- $LW = 1613.6 \pm 389.9$ g

Correlated with body surface area (BSA)

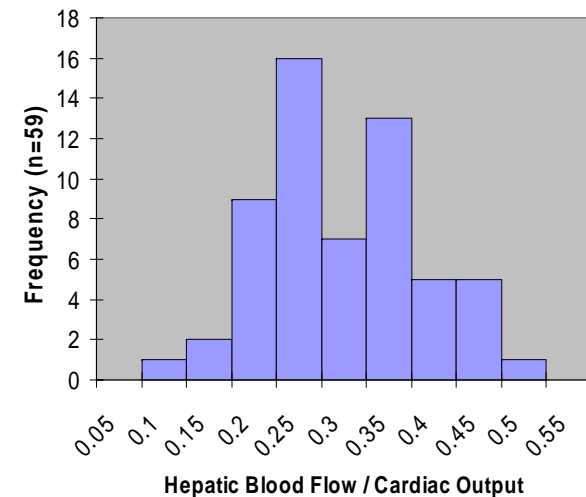
- $LV \sim 1072.8 * BSA - 345.7$ (SE = 328 mL)

Japanese liver volumes less by ~300 mL even after accounting for BSA differences

Source: Heinemann et al. (1999)

Standard Liver Volume in the Caucasian Population

Inter-individual Variability Data on Hepatic Blood Flow



Source: U.S. EPA (2006), Appendix C

Use of Physiologically Based Pharmacokinetic Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk



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Limited human in vivo toxicokinetic data as compared to rodents

- Historical studies
 - High (e.g., occupational) exposure levels, so need to extrapolate to low doses
 - Usually aggregated, rather than individual data
 - Volunteers are healthy, usually young Caucasian males
- More limited data collection
 - Data on parent chemical alone may only weakly constrain total metabolism
 - At most blood, urine, and exhaled air measurements (no tissue concentrations)



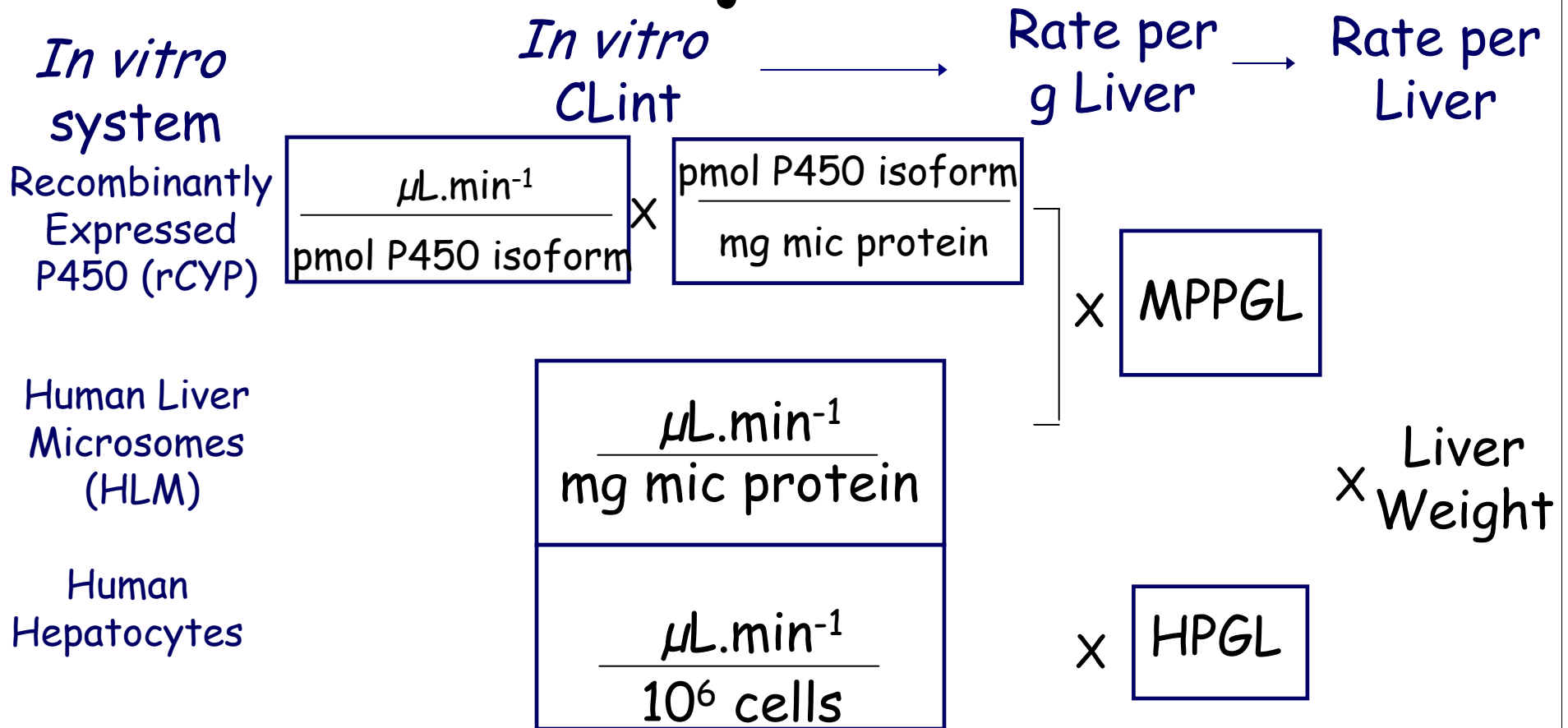
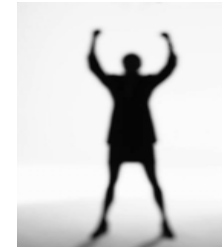
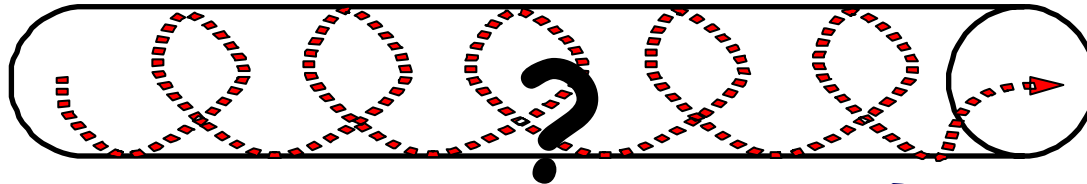
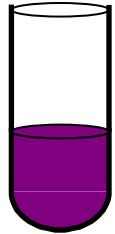
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Surrogate or Proxy Data

- Often do not have partition coefficient measurements in all species, tissues, chemicals of interest.
Alternatives:
 - Use rodent values for human tissue:air partition coefficients
 - Use “similar” tissue
 - Liver value for the kidney
 - Partition coefficients for lumped tissues (e.g., skin+muscle)
 - QSAR
- Extrapolation of metabolism
 - In vivo-in-vitro extrapolation (next page)
 - Most work done on P450 enzymes and microsomal preparations
 - Much less data on other preparations (e.g., freshly isolated hepatocytes) and enzyme systems
 - Allometric scaling (e.g., body weight^{3/4})
- What is the uncertainty and variability in these extrapolations?

E.g.: In vitro-in vivo scaling of metabolism



Source: presentation by Zoe Barter, University of Sheffield



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Statistical Models and Methods

A standard practice

- Deterministic PBPK model
- Fix physiological parameters, partition coefficients
- Fit metabolic parameters using in vivo data (e.g., gas uptake) by ordinary (absolute or relative) least squares
- Relatively easy to implement with generally available software once model structure has been specified and data collected
- Uncertainty and variability not easily characterized

An emerging practice

- Combine PBPK model with a statistical model for uncertainty and variability
 - E.g., Bayesian hierarchical population model
 - “Prior” distributions for all parameters
 - Likelihood function for data and model predictions
 - Markov chain Monte Carlo sampling to obtain “posterior” distributions
 - High level of effort, few available software tools
-
- What level of effort is needed for what applications?



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Uncertainty in PBPK Model Structure

- Some examples of PBPK model misfit motivating changes to model structure
- Can be addressed partially via sensitivity analysis
- But little statistically-based analysis of structural uncertainties
 - A few examples of using likelihood ratio test for nested models, but only when a few parameters are allowed to varied.
 - No examples based on Bayesian methods
 - Generally not addressed in risk assessment applications/predictions
- How to we simultaneously test structural hypotheses about the PBPK and statistical models?



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Why are we here?

Overall Charge Questions

- What are past/current practices, their strengths/limitations?
- What should be considered “best” practices?
- What could be done **now** to improve/expand use of “best” practices?
- What needs to be done medium-/long- term to further improve the characterization of uncertainty and variability in PBPK modeling?
- What needs to be included in reports of modeling activities, so that models are transparent for evaluation and use?



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Model Specification (Group 1)

Scope

- Deterministic model structure (mathematical representation of biological system and data)
 - Degree of lumping across and within tissues
 - Biological processes within/between compartments
 - Metabolic pathways
 - Evaluating alternative model structures
- Statistical model structure for parameter and data uncertainty and variability (overlap with Groups 2, 3)
 - Intra- and inter- subject/experiment/group variability
 - Structure of errors between data and model predictions
 - Representation of biological and statistical interdependencies, correlations, and autocorrelations



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Model Specification (Group 1)

Key Issues

- To what extent should model structure be tailored to database differences across species?
 - Amount of data (rodents >> humans)
 - Nature of data (in vivo vs. in vitro; direct vs. surrogate/ extrapolated).
 - Ensuring model and parameters are identifiable (role of statistical/sensitivity analyses?)
- Evaluating alternative models
 - What statistical methods are useful for comparing models?
 - How to weigh parsimony vs. completeness vs. desired use?
- How to integrate the statistical model for uncertainty and variability into model development?



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Model Calibration (Groups 2A/2B)

Scope

- Methodology for estimating parameters
 - Parameters to be estimated from *in vivo* kinetic data
 - Parameters to be fixed at literature/*in vitro* values
 - Estimating central tendencies, uncertainty, and variability
- Statistical structure for parameter and data uncertainty and variability (overlap with Groups 1 and 3)
 - Intra- and inter- subject/experiment/group variability
 - Structure of errors between data and model predictions
 - Representation of biological and statistical interdependencies, correlations, and autocorrelations
- Evaluation of consistency between model and data
 - Evidence for model's predictive power ("Validation")
 - Comparing alternative models



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Model Calibration (Groups 2A/2B)

Key Issues I

- To what extent should *in vivo* data be used for estimating parameters vs. “validating” the model?
 - Validation only
 - Split data into “calibration/validation” sets
 - Estimation only.
 - Other methods (e.g., cross-validation?)
- What depth/rigor of statistical model and parameter calibration is necessary?
 - When is it useful and practical to use a formal statistical population approach (e.g., Bayesian) to estimate all parameters from all datasets simultaneously?
 - When are less intensive approaches (e.g., fit-by-eye, fix some/fit others, sequential) sufficient?



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Model Calibration (Groups 2A/2B)

Key Issues II

- Implementation of the statistical model
 - When is it justifiable not to include all the data?
 - What sources of uncertainty/variability (Intra- and inter- subject/experiment/ group, measurement error, model error) to include (and how!)?
 - How to account for a variety of data collection issues?
 - Different experimental designs (longitudinal, serial sacrifice, closed chamber, number of data points)
 - Availability of individual vs. aggregated data
 - What statistical method(s) are the most appropriate/practical?
- How to evaluate model performance (deviance between predictions and data)?
 - Absolute (“is this good enough?”)
 - Relative (“is A better than B?”), while accounting for degree of model parsimony



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Model Prediction (Group 3)

Scope

- Methodology for characterizing uncertainty and variability in model predictions for risk assessment
 - Probabilistic vs. alternative methods.
 - Supplemental data *vis-à-vis* populations of interest
 - Uncertainty from alternative models (including “default” models)
- Statistical structure for parameter and prediction uncertainty and variability (overlap with Groups 1 and 2)
 - Intra- and inter- subject/experiment/group variability
 - Uncertainties carried over from calibration
 - Representation of biological and statistical interdependencies, correlations, and autocorrelations
- Feedback to data needs and experimental design



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Model Prediction (Group 3)

Key Issues

- What changes to the PBPK and statistical models and parameters are needed for risk assessment prediction?
 - Alternatives to probabilistic methods?
 - How to incorporate supplemental data on populations of interest?
 - What sources of uncertainty/variability should/should not be carried over from specification and calibration steps?
 - Structural changes based on differences between available data and risk assessment needs?
- How to characterize uncertainty from alternative PBPK and statistical models?
- How to provide feedback to data needs and experimental design?



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Closing thoughts for lunch

“The more you put into a model, the less you understand it.”
– Jeremiah P. Ostriker (Princeton U [my PhD astrophysics advisor])

“All models are wrong but some are useful.”
– George E.P. Box (U. Wisconsin)

« *Le doute n'est pas une condition agréable,
mais la certitude est absurde.* »*
– Letter from Voltaire to Frederick II of Prussia (April 6, 1767)

**Doubt [uncertainty] is uncomfortable, but certainty is absurd.*