

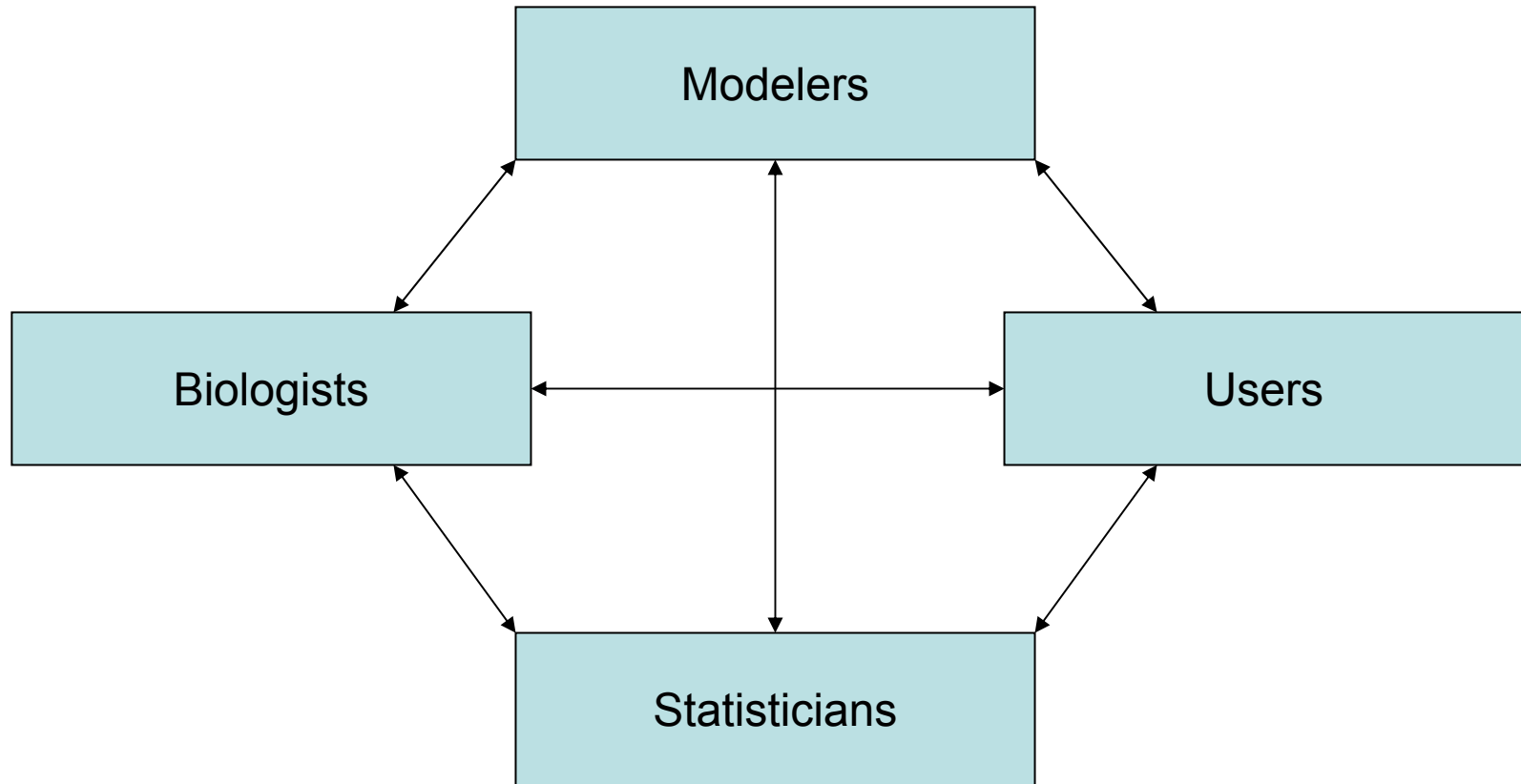
Break Out Group 1

Model Specification

How to integrate statistical model for uncertainty and variability into model development?

1. Define purpose of model
2. Create graphical representation
 - Based on hypothesis of PK
 - Dose metrics and risk assessment applications
3. Create deterministic model (mathematical)
4. Computer Implementation: Test model in variety of ways
 - Comparing to the data visually
 - Theoretical perturbations
 - Sensitivity analysis
 - Failures help inform model structure
5. Non-deterministic (statistical) modeling and implementation

The Tango

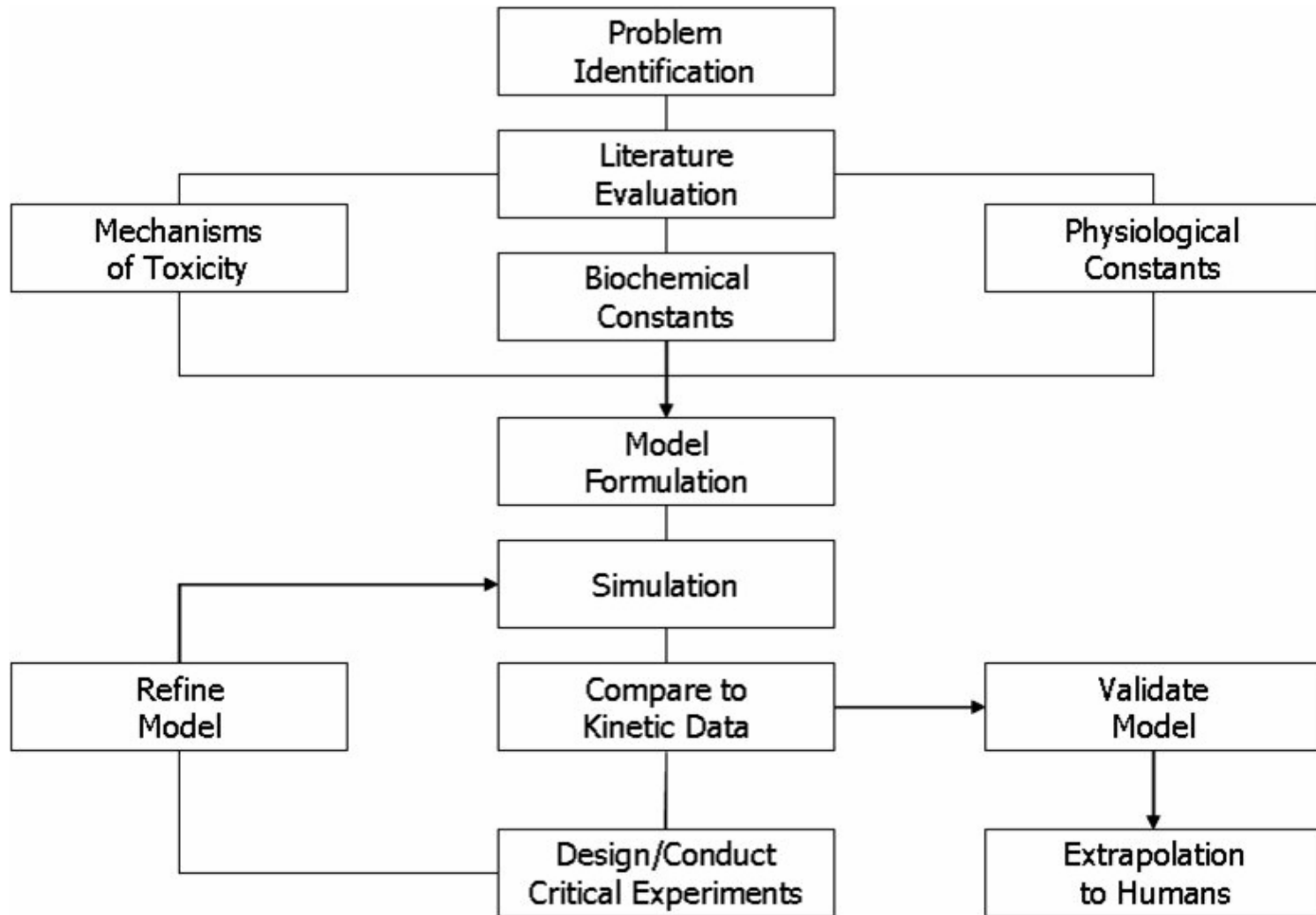


Biologists: Biologists, Toxicologists, Physiologists

Modelers: Modelers & Mathematicians

Users: Risk Assessors & Decision Makers

Model Specification Process



Flow diagram of iterative process from Specification White paper. Model formulation would need to include deterministic and non-deterministic models.

Inter-Disciplinary Modeling Team

Inter-disciplinary team involved throughout model specification, parameterization, and prediction

– Tiered approach

- Deterministic

- Eyeball fit

- Optimization (e.g., least squares, etc.)

- Non-deterministic

- Choice of theory and math

- » Probability

- » Possibility

- » Fuzzy

- Implementation and interpretation

Model Developers Input on Model Parameterization and Prediction

Have the biologists and modelers involved in:

- Defining likelihood
- Bayesian Implementation
 - Setting priors
 - Which parameters to update
 - Sensitivity driven
 - Data driven
 - Interpret posteriors

To what extent should model structure be tailored to database differences across species?

- Keep the same model structure for human based on that developed for animals
 - In the absence of biological evidence for a difference between human and animal physiology, metabolism, etc.
 - Understand unidentifiability issues and make case specific decisions (e.g., V_{Max} & $K_m \rightarrow k$)
- Animal variability \neq human variability

Interesting Ideas

- Chemical Space & PK Models: Do models in “unrepresented” regions lead to new structural ideas, provide perspective on model uncertainty, and help address “limited” data chemicals?
- Portfolios of models for simultaneous comparative analysis &/or model component libraries
- “Comparative” uncertainties (eg dose metrics, key toxicological pathway with limited data)
- Chemicals & physiology: Chemicals as probes of physiology with awareness that chemical exposures may also alter physiology

Recommendations

Learning tools for PBPK modeling and applications

- Compilation of papers
 - Model specification
 - Identifiability
 - Lumping
 - Model Comparisons
 - Local & global sensitivity analysis
 - Calibration, Prediction
- Case studies
 - Lessons learned
 - Theoretical analyses
- Training materials & courses – web-based

Recommendations

- Defining terms
- Website for repository of PBPK models
 - Code (with full documentation)
 - Data
 - Lessons learned
 - Models that failed
 - Models that succeeded

Lessons learned: models that failed & succeeded

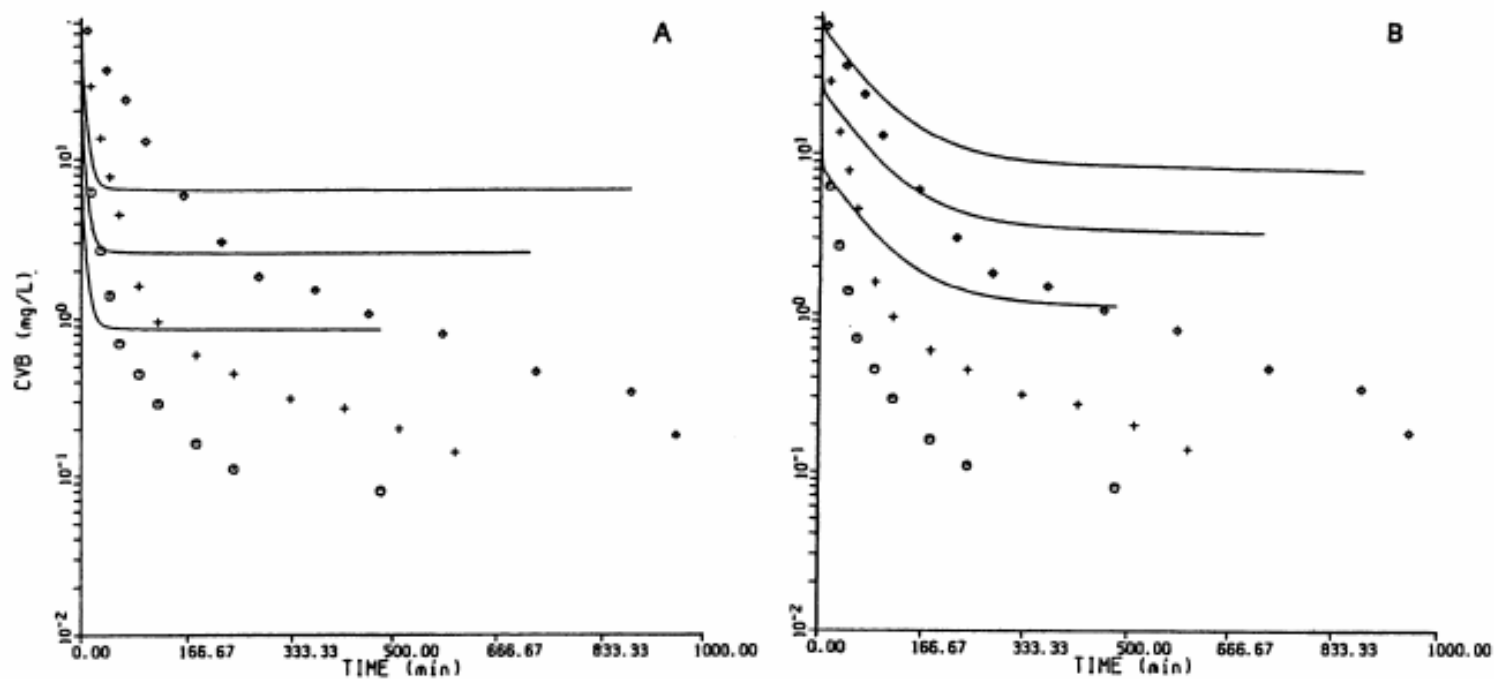
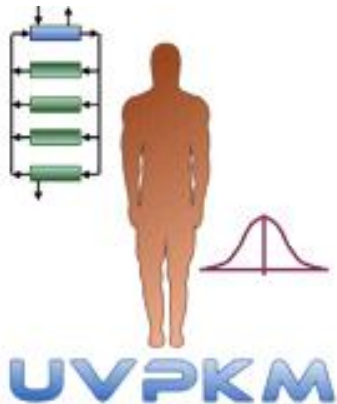


Fig. 2. Comparison of the experimental data (symbols) on the venous blood concentration of unchanged pyrene in rats with simulations (solid lines) of a PBPK model with that described uptake as a perfusion-limited process in all tissues (A) or as a diffusion-limited process in adipose tissues and slowly perfused tissues (B). The dose levels correspond to 2, 6 or 15 mg/kg (i.v.) of pyrene. Experimental data from Withey et al. (1991).

Figure of unsuccessful model fits. Publication then describes successful fit.

Recommendations

- USE DOSIMETRY
- USE PHARMACOKINETIC ANALYSES
- USE PBPK MODELS
- CONTINUE TO IMPROVE PRACTICE



**International Workshop on Uncertainty
and Variability in Physiologically Based
Pharmacokinetic (PBPK) Models**

October 31 - November 2, 2006 Research Triangle Park, NC