

Background

- Physiologically-based pharmacokinetic (PBPK) models are tools for estimating absorption, distribution, metabolism, and elimination (ADME) of chemicals in the body
 - Quantify internal (tissue/organ) dose vs exposure
 - Facilitate dose-response analysis/human extrapolation
 - Use chemical- and species-specific data (unlike default BW^{3/4} allometric scaling)
- Multiple alternative models or analyses in literature
 - “Being published is not enough”: EPA thoroughly evaluates models based on scientific and technical criteria prior to use in an assessment
 - IRIS uses a structures approach to evaluate quality and usability
- The evaluation process stresses: (1) clarity in the documentation of model purpose, structure, and biological characterization; (2) validation of mathematical descriptions, parameter values, and computer implementation; and (3) evaluation of each plausible dose metric.
- **NAS (2014) recommendations addressed**
 - **Develop and expand use of formal quantitative methods in data integration for dose-response assessment and derivation of toxicity values**
 - **Develop tools for assessing risk of bias in different types of studies**

Identification and Inventory of PBPK Models

- A thorough literature search is conducted to identify existing PBPK models
- A summary report is prepared of available models and their possible utility for use (**scoping**)
 - This work is conducted by the **Pharmacokinetics Workgroup (PKWG)***, in conjunction with information specialists
- Table 1 outlines typical summary information presented for each model at the scoping phase

Table 1. Example animal PBPK inventory table for model scoping

Author	Smith et al. (2003)				
Contact Email	xxxxx@email.com				
Contact Phone	xxx-xxx-xxxx				
Sponsor	N/A				
Model Summary					
Species	Rat				
Strain	F344				
Sex	Male and female				
Life-Stage	Adult				
Exposure Routes	Inhalation	Oral	I.V.	Skin	
Tissue Dosimetry	Blood	Liver	Kidney	Urine	Lung
Model Evaluation					
Language	ACSL 11.8				
Code Available	YES	Effort to Recreate Model	COMPLETE		
Code Received	YES	Effort to Migrate Code	SIGNIFICANT		
Structure Evaluated	YES				
Math Evaluated	YES				
Code Evaluated	YES. Issue (minor): Incorrect units listed in comments for liver metabolism (line 233). Issue (major): Mass balance error in stomach compartment				
Available PK Data	Urine (cumulative amount excreted) and blood (concentration) time course data for oral (gavage) and inhalation (6hr/day for 4 days) exposure. In vitro skin permeation.				

*The **Pharmacokinetics Workgroup (PKWG)** is convened by the National Center for Environment Assessment (NCEA) to support and promote consistent application of the best science in the field of mathematical modeling of pharmacokinetic processes and the data supporting it as applied in human health risk assessment. It is composed of scientists with specific expertise in the range of disciplines involved in the construction and development of pharmacokinetic models, evaluation of data supporting such models, statistical analysis of data and modeling results, and characterization of related uncertainty and variability.

Evaluation of PBPK Models

PBPK Model Scoping: Criteria A

- An evaluation of a model is required before accepting it for use in an assessment
 - Many models contain errors with varying degrees of impact on model predictions
- Initial judgments on the suitability of a model are separated into two categories: scientific and technical (Table 2)

Table 2. Evaluation criteria for PBPK models

Criteria	Example information
Scientific	Biological basis for the model is accurate. <ul style="list-style-type: none"> • Consistent with mechanisms that significantly impact dosimetry. • Predicts dose metrics expected to be relevant. • Applicable for relevant route(s) of exposure.
	Consideration of model fidelity to the biological system strengthens the scientific basis of the assessment relative to standard exposure-based extrapolation (default) approaches. <ul style="list-style-type: none"> • Can the model describe critical behavior, such as nonlinear kinetics in a relevant dose range, better than the default (i.e., BW^{3/4} scaling)? • Is the available metric a better predictor of risk than default? Specifically, model-based metrics may correlate better than the applied doses with animal/human dose-response data. Degree of certainty in model predictions vs. default is also a factor. For example, while target tissue metrics are generally considered better than blood concentration metrics, lack of data to validate tissue predictions when blood data are available may lead to a choice of the latter.
	Principle of parsimony <ul style="list-style-type: none"> • Model complexity or biological scale, including number and parameterization of (sub)compartments (e.g., tissue or subcellular levels) should be commensurate with data available to identify parameters.
	Model describes existing PK data reasonably well, both in “shape” (matches curvature, inflection points, peak concentration time, etc.) and quantitatively (e.g., within a factor of 2–3).
Initial technical	Model equations are consistent with biochemical understanding and biological plausibility.
	Well-documented model code is readily available to EPA and public.
	Set of published parameters clearly identified, including origin/derivation.
	Parameters do not vary unpredictably with dose (e.g., any dose dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling).
	Sensitivity and uncertainty analysis has been conducted for relevant exposure levels (local sensitivity analysis is sufficient, though global provides more information). <ul style="list-style-type: none"> • If a sensitivity analysis was not conducted, the PKWG would suggest this as additional work before using the model in the risk assessment. • A sound explanation should be provided when sensitivity of the dose metric to model parameters differs from what is reasonably expected based on experience.
BW^{3/4} = body-weight scaling to the 3/4 power; PK = pharmacokinetic; PKWG = Pharmacokinetic Working Group	

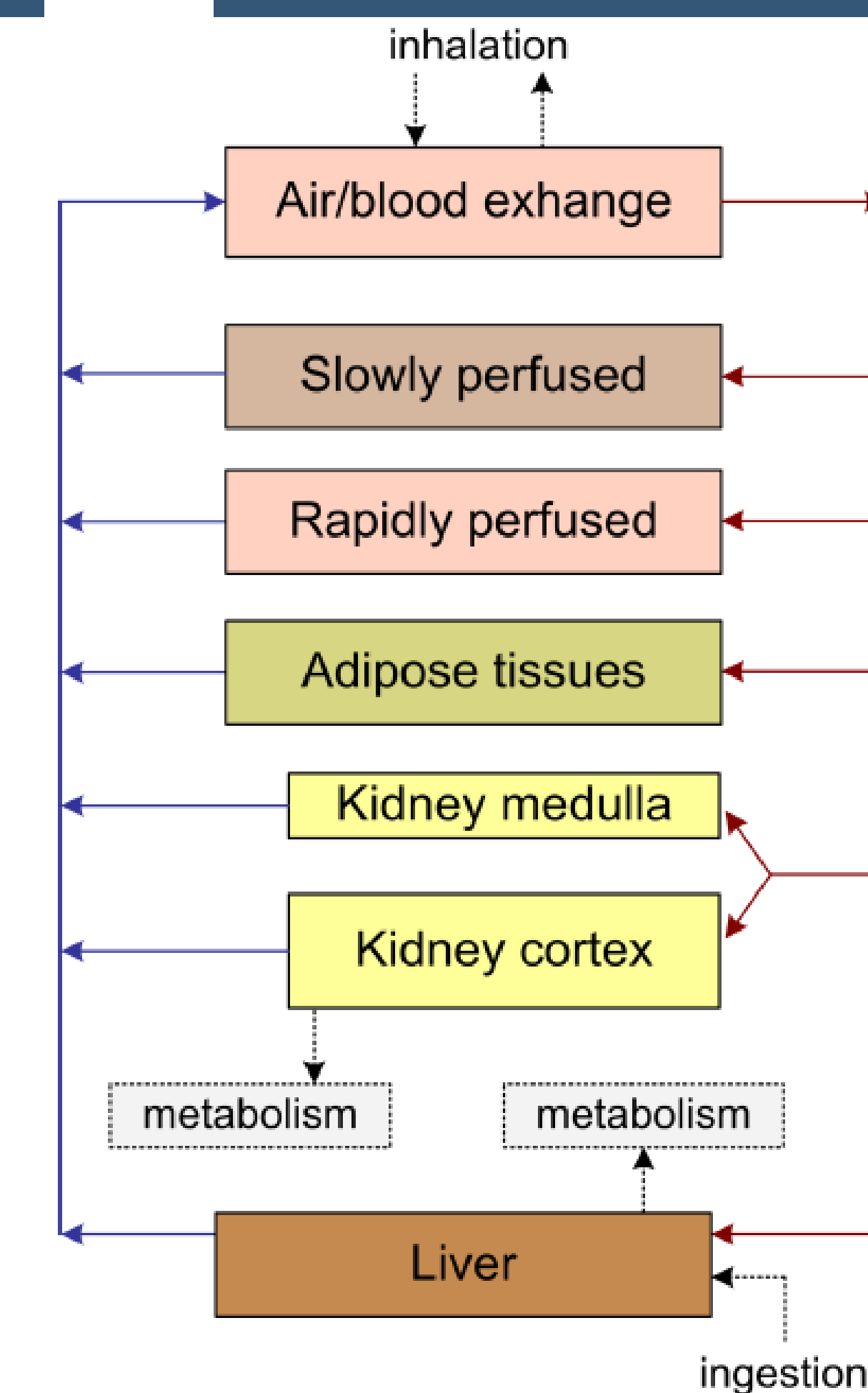
In-Depth Technical Evaluation: Criteria B

- Primarily address computational implementation and technical issues
- Only conducted on models that pass review for Criteria A
 - Criteria B evaluation is not possible without model code
- Model equations and parameters in computer codes match those in the manuscript or report
- Published figures/tables of model simulations are reproducible using the available code (within 10% of the publication).
- If errors in model code or parameters are found and corrected, the revised model must still be in agreement with data. Errors must be small enough to not invalidate the model, parameters, or assumptions.
 - Model predictions outside the range of the data are allowed to change by more than 10% of the original model or publication, since this would be considered a model correction.

Resource Considerations for PBPK Model Revision or Development: Criteria C

If existing models fail Criteria A or B, the potential value in implementing a PBPK in a risk assessment must be weighed against the time, effort, and possible expenses required to address model shortcomings.

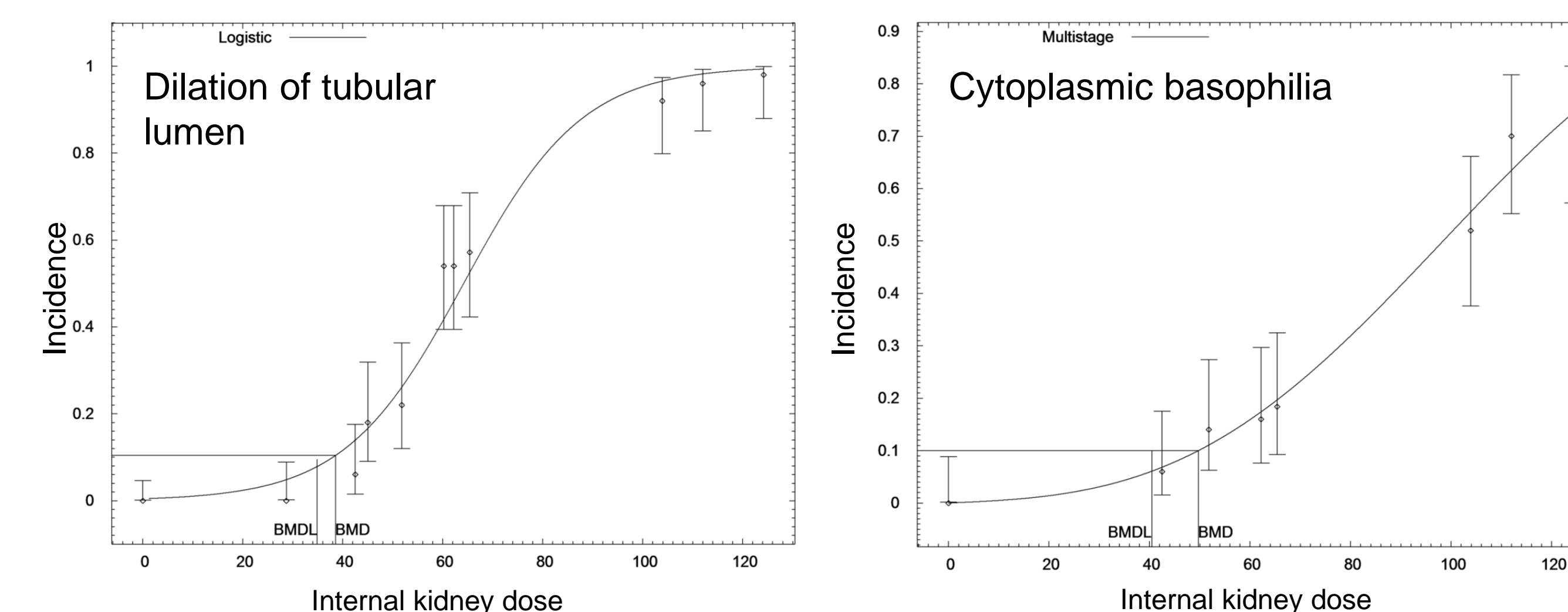
PBPK Evaluation Example: Chloroform



- Chloroform is a trihalomethane present in drinking water as a byproduct of disinfection
- Kidney and liver are target organs
 - Effects induced via production of reactive metabolites
- A PBPK model (left) was obtained during scoping and satisfied Criteria A
- Issues identified during in-depth technical evaluation:
 - Metabolic parameter derivation for the kidney cortex contained a units error, and the calculation was not performed consistently for humans and rodents
 - The volume ratio for kidney cortex and medulla was reversed in the code, and did not match the reported value or original reference

Upon evaluation under Criteria C, it was determined:

- Time and effort to correct the model was minimal
- Corrections led to little or no changes in model predictions of data
 - Estimates of the internal dose metric (kidney metabolism) changed significantly. Since there are no *in vivo* data available for this measure, this was considered a correction to the original model.
- Model was successfully revised by EPA, published as journal article (Sasso et al., 2013)



The revised PBPK model allows for improved quantitative dose-response modeling and data integration. Kidney endpoints can be evaluated across different routes of exposure and different species (Nagano et al., 2006, and Yamamoto et al., 2002). The figures above illustrate dose-responses for rats from multiple exposure routes (inhalation, oral, and combined inhalation+oral) on basis of PBPK-derived kidney dose.

Selected references

- McLanahan et al. (2012). Physiologically based pharmacokinetic model use in risk assessment—Why being published is not enough. *Tox. Sci.*, 126: 5-15.
- Nagano, et al. (2006). Enhancement of renal carcinogenicity by combined inhalation and oral exposures to chloroform in male rats. *J. Toxicol. Environ. Health Part A* 69, 1827–1842
- Sasso et al. (2013). Application of an updated physiologically based pharmacokinetic model for chloroform to evaluate CYP2E1-mediated renal toxicity in rats and mice. *Tox. Sci.*, 131: 360-374.
- Yamamoto, et al. (2002). Carcinogenicity and chronic toxicity in rats and mice exposed to chloroform by inhalation. *J. Occup. Health* 44, 283–293.