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Accelerating QA review of PBPK models: A template approach to model implementation

Amanda S. Bernstein, Bidya Prasad, Paul M. Schlosser, Dustin F. Kapraun

Office of Research and Development
Center for Public Health and Environmental Assessment

SRA Dose Response Specialty Group
September 13, 2022

Disclaimer

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Acknowledgement

This project was supported in part by an appointment to the Research Participation Program at the Center for Public Health and Environmental Assessment, U.S. Environmental Protection Agency, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and EPA.

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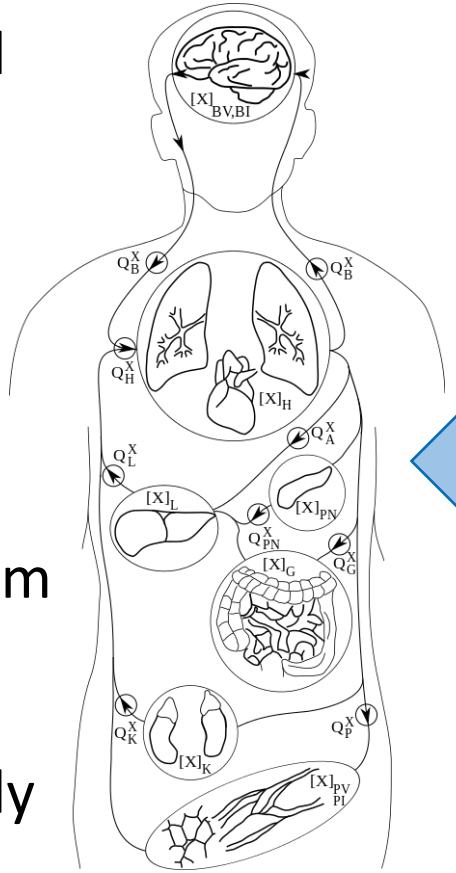
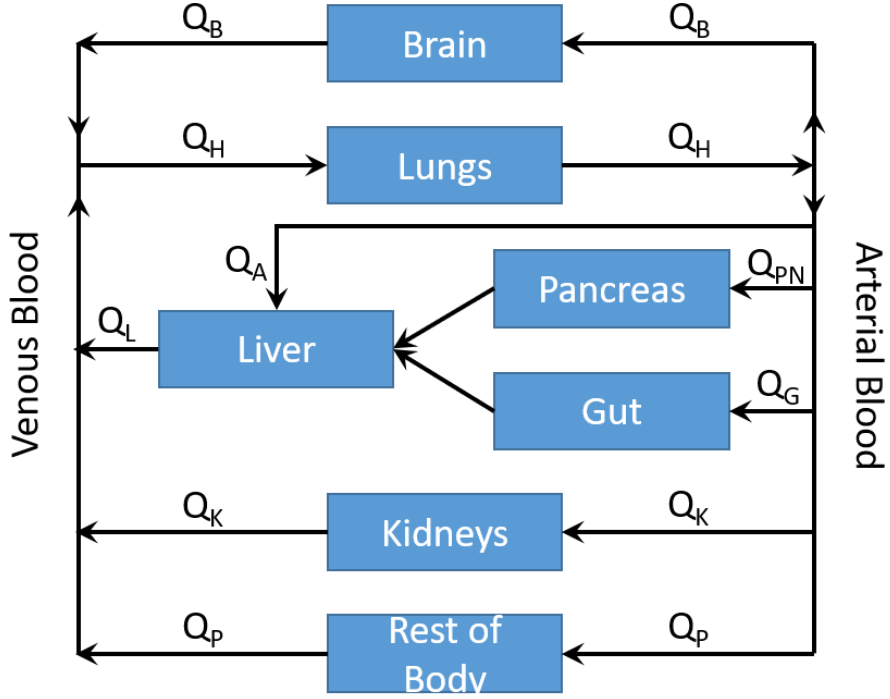
Overview

- What is a PBPK model?
- How are PBPK models used in risk assessment?
- What is the PBPK model template?
- What advantages does the model template provide over other PBPK modeling approaches?
- PBPK models for per- and polyfluoroalkyl substances (PFAS)
- PBPK models for volatile organic compounds (VOCs)
- Future improvements to the model template

Physiologically based pharmacokinetic (PBPK) models describe the disposition of a substance in various compartments of an organism's body

- Model parameters are based on anatomy, physiology, and biochemical properties.
- PBPK models can be used to perform various types of extrapolations.
  - Interspecies, intraspecies, or between exposure routes or scenarios
- Using PBPK models to perform extrapolations to determine equivalent doses **more precisely quantifies uncertainty** compared to only using default uncertainty factors.

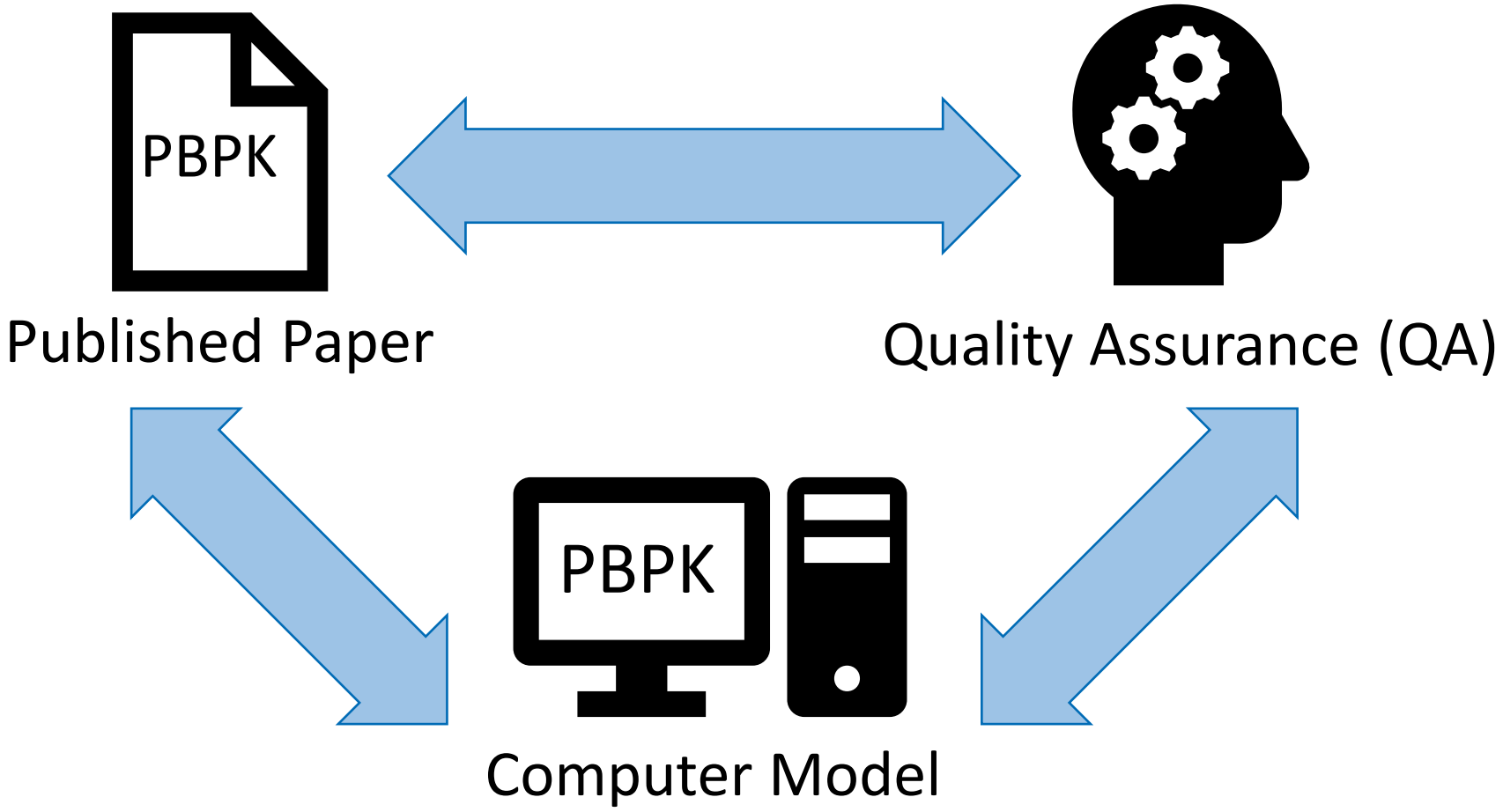




(Wikimedia Commons)

PBPK models are useful for risk assessment, but they must first be carefully reviewed.

- Risk assessors must ensure that the computer implementation of a model matches the published paper before use.



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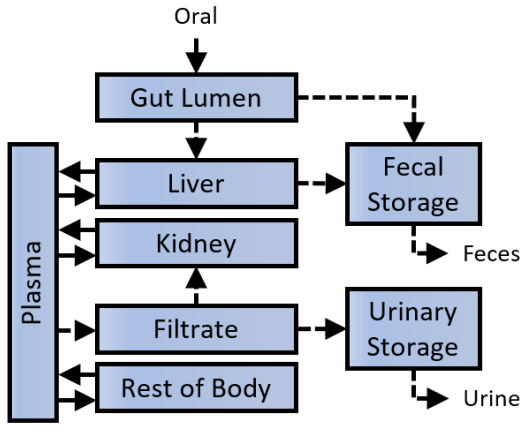
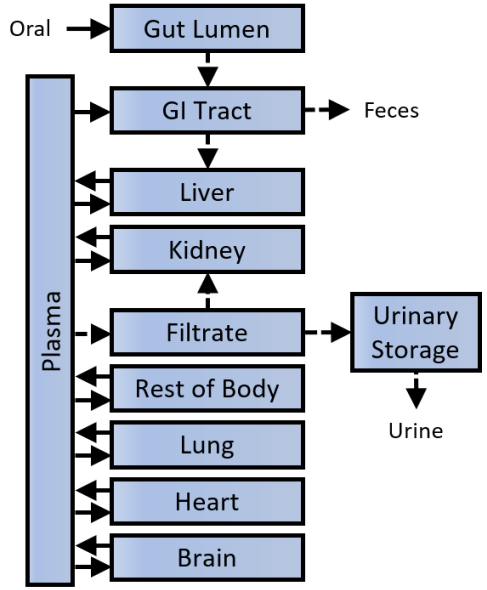
QA review considers many aspects of a model

- Evaluating the biological plausibility of the model
- Verifying the equations and logic used to implement the model
- Verifying that the written description of the model matches the computer implementation
- Verifying the data from the primary source
- Checking that data is consistent with the model implementation

To allow faster, more efficient implementation of PBPK models, we created a model template.



PFOA/PFOS



PFHxS

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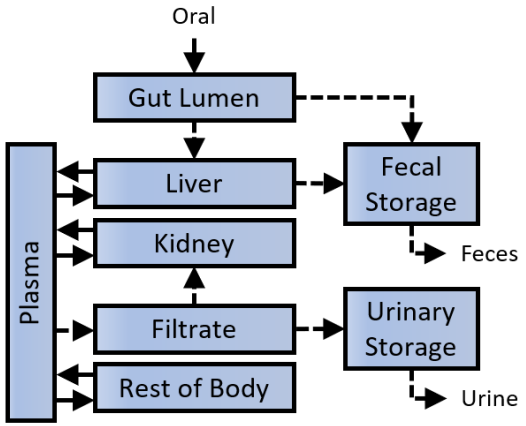

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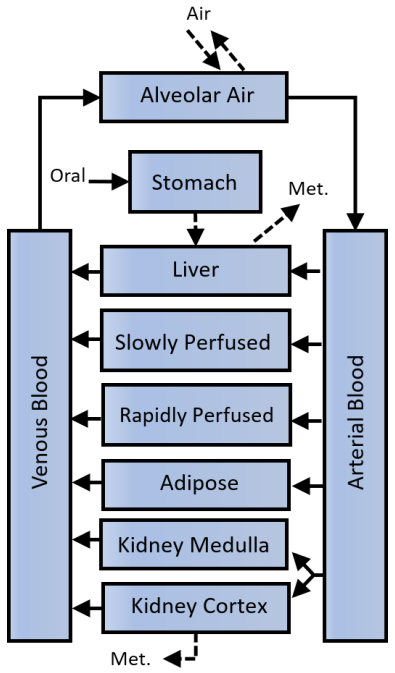
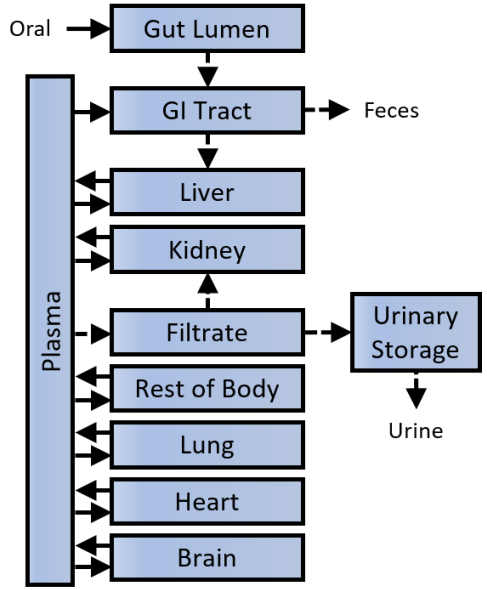
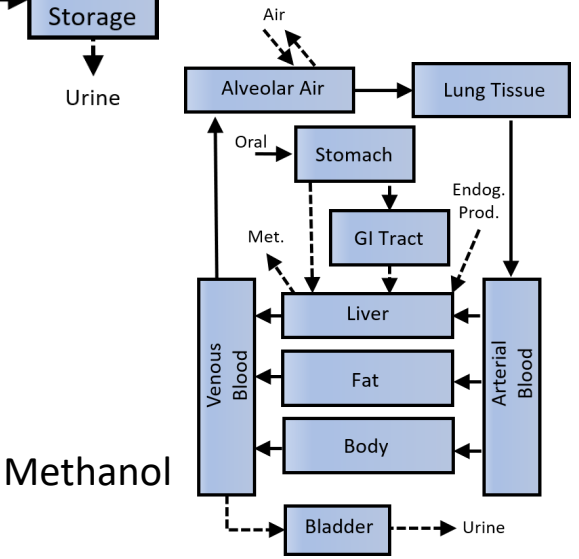


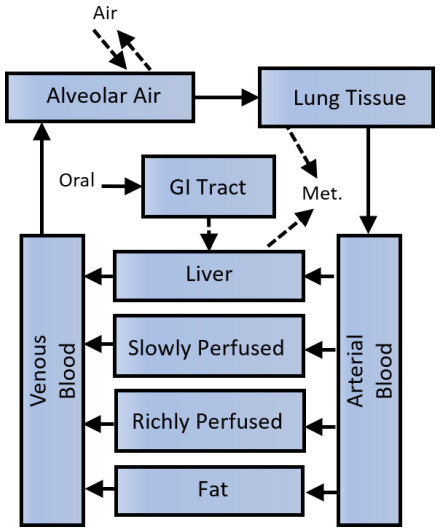
Chloroform



PFHxS



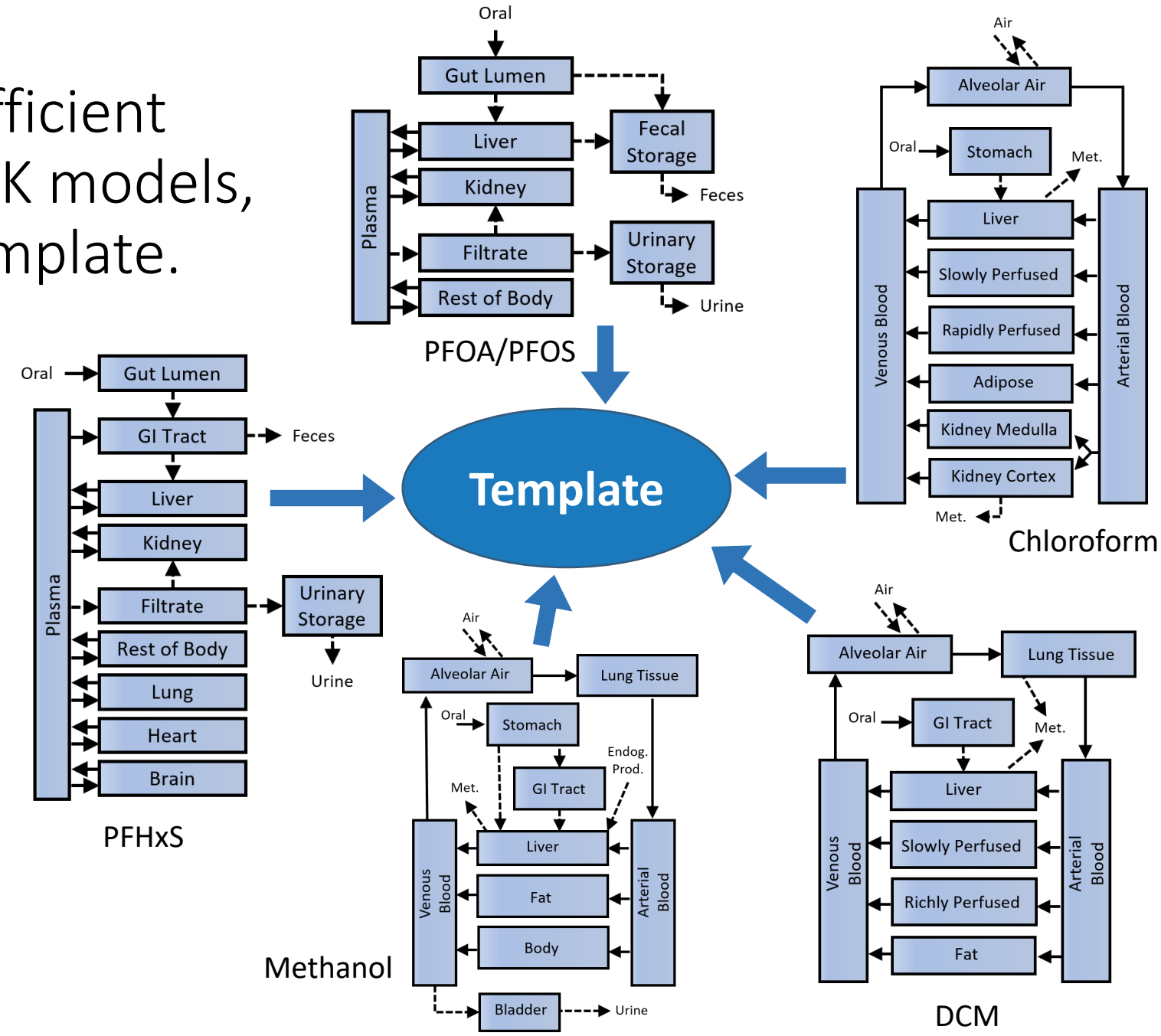
Methanol



DCM

To allow faster, more efficient implementation of PBPK models, we created a model template.

- The template is a tool to implement multiple chemical-specific models using one common model **superstructure**.
- It allows the user to implement models exactly without simplification or loss of detail.



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The PBPK model template improves modeling efforts

- Consistency – PBPK models are implemented using consistent models for specific features, e.g., metabolism, urinary excretion.
- Quality – Mathematical representation of included features is evaluated to ensure general biological plausibility and correct form.
- Efficiency – Modelers do not need to write code for the entire model. They can focus on feature selection and parameter identification.

The PBPK model template allows greater efficiency and speed in evaluating PBPK models

- Generic model equations in the template are reviewed using a rigorous QA process and don't require additional review for specific model implementations.
  - Umbrella quality assurance project plan (QAPP) for dosimetry and mechanism-based models, U.S. EPA (2020)

- For any specific implementation, the model and dosing scenario **input parameters** must be reviewed, and the reviewer must evaluate if the **chosen equations and logic** are appropriate to the model of interest.

The PBPK model template is not…

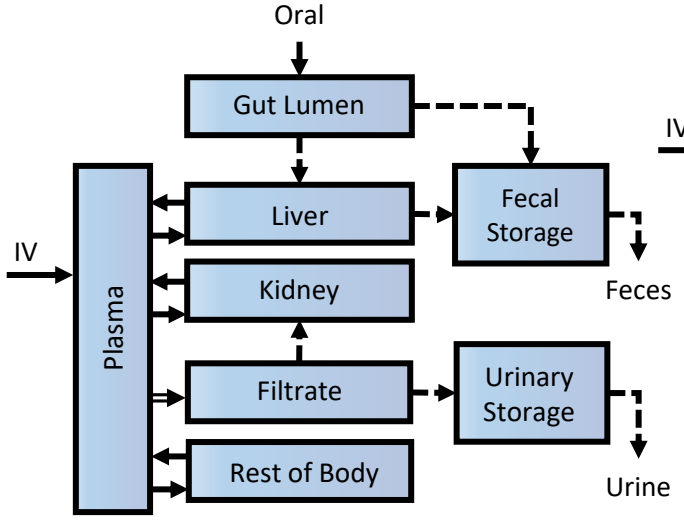
- × A generic model to be used for screening purposes that provides a simple, approximate PBPK model
  - Compare with httk (Pearce, et al. 2017) or ATSDR's PBPK tool-kit (Mumtaz et al. 2012)
- × A reporting template that provides all information needed to submit to a regulatory agency
  - Compare with the reporting template by Tan et al. (2020)

The PBPK model template is

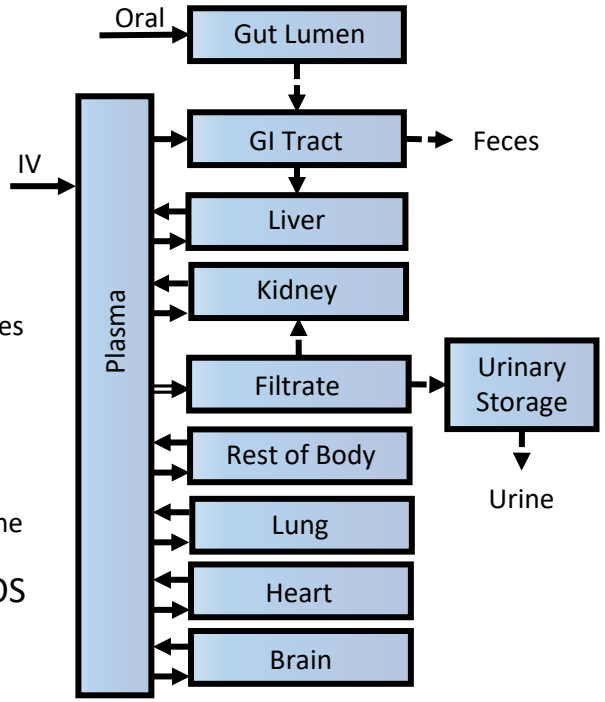
- ✓ A software tool to implement PBPK models exactly with no simplifications using parameter input spreadsheets with a uniform, easy to view structure

The first version of the PBPK model template could implement PFAS PBPK models.

- This work was presented by Bernstein et al. (2021).



Loccisano et al. (2012) model for PFOA/PFOS



Kim et al. (2018) model for PFHxS

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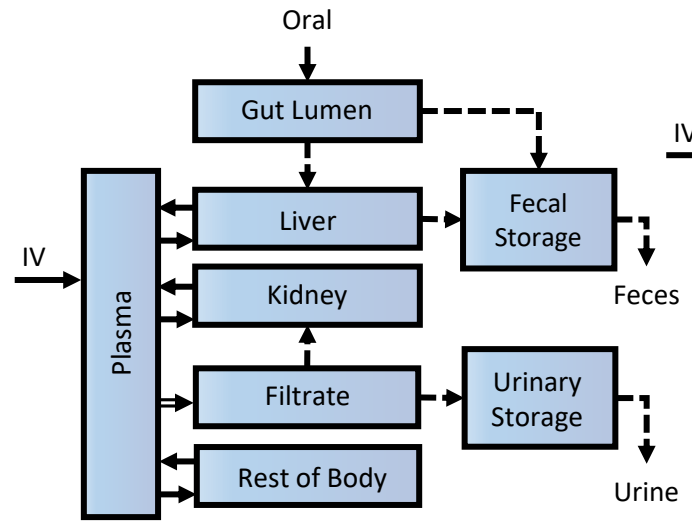

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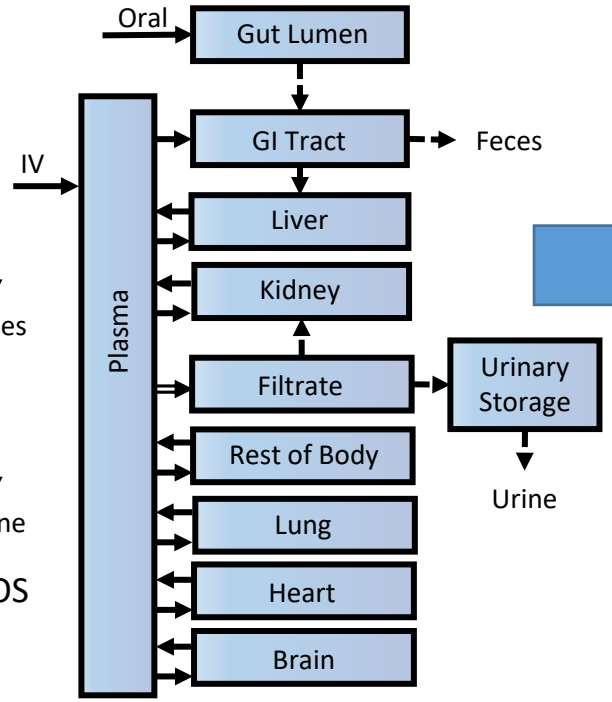

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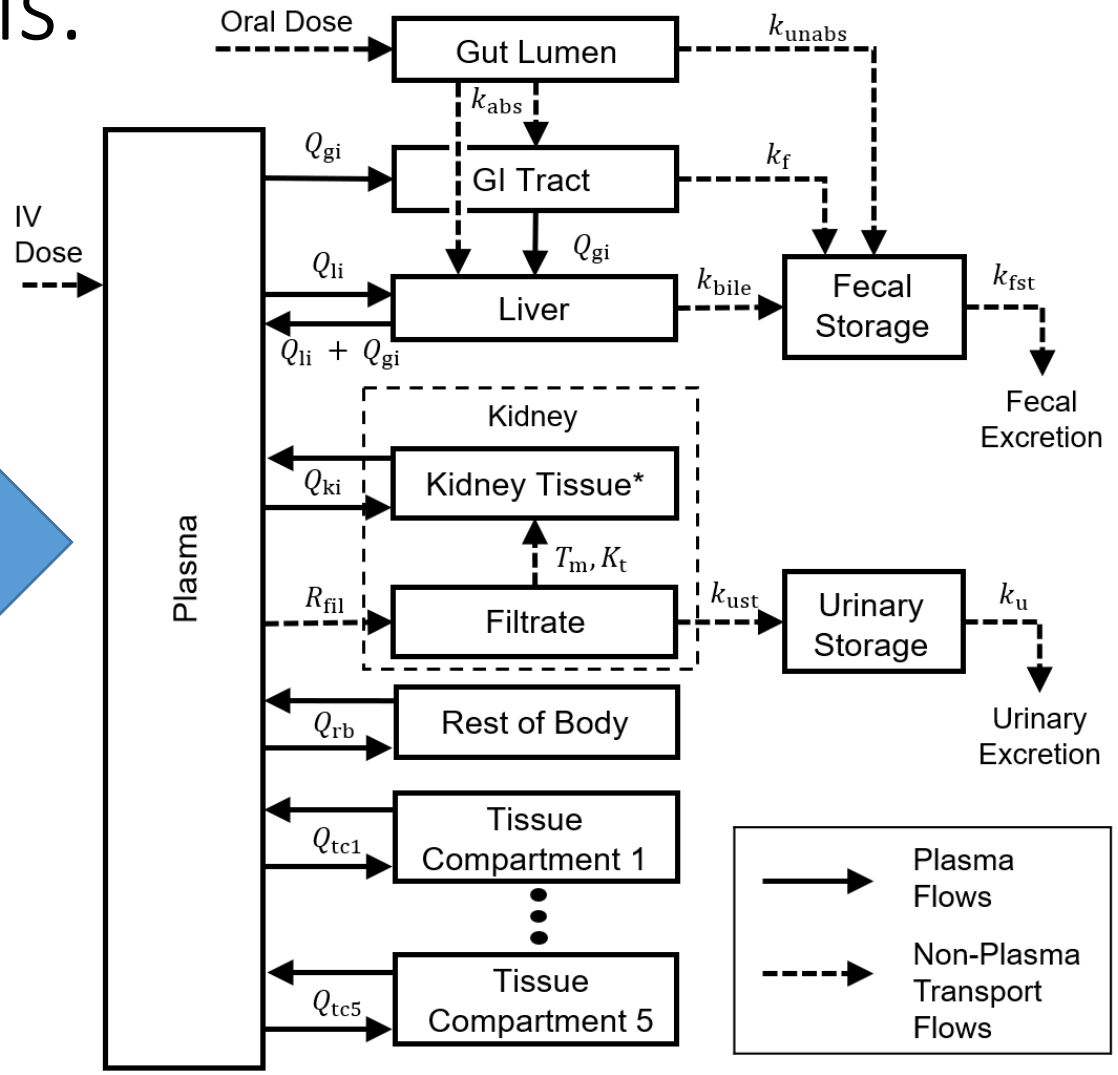
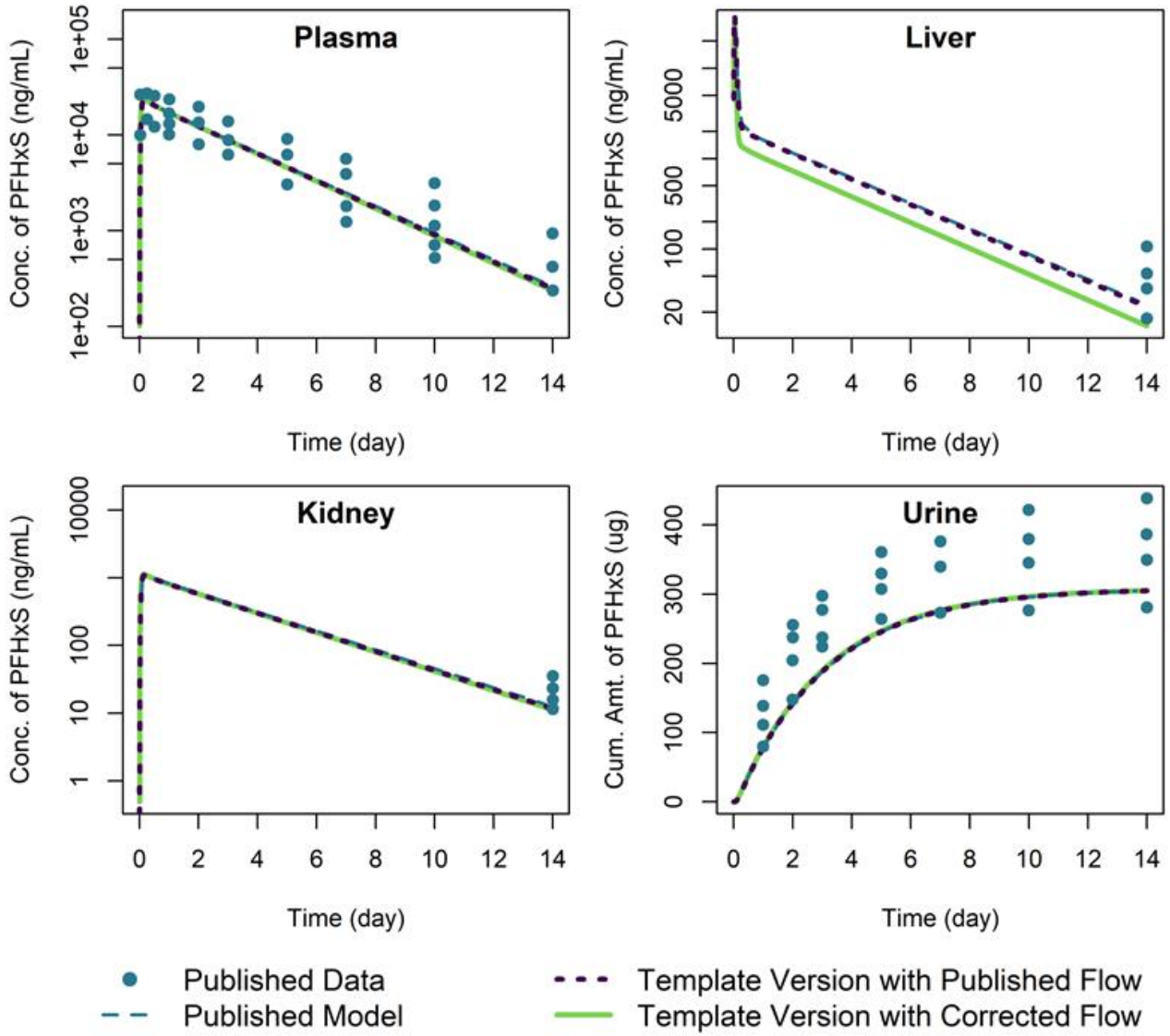


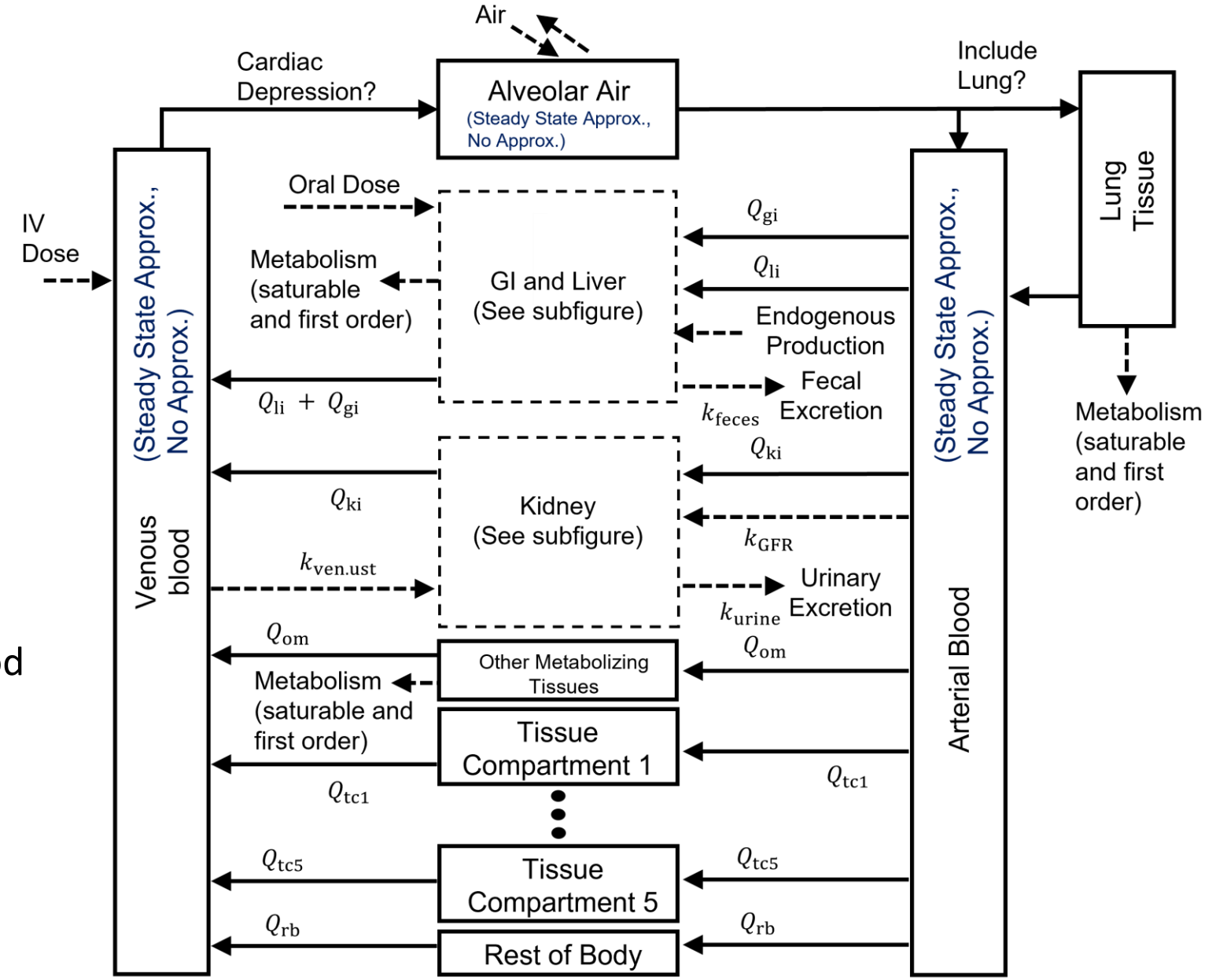
We reproduced simulation results from a published PBPK model for PFHxS.

- The figure shows observations and predictions of rats given an oral bolus dose of 4 mg/kg PFHxS.
- However, the model-predicted concentrations of PFHxS in the liver were lower than the published results, leading us to quickly realize that the published model contained an error.
- We also implemented and reproduced published results for an additional 4 PFAS using the template model.



We extended the template to accommodate more chemical-specific models.

- New features include:
  - Inhalation and gas exchange
  - Separate venous and arterial blood compartments
  - Metabolism pathways
  - Background rates of production
  - New options for urinary excretion models



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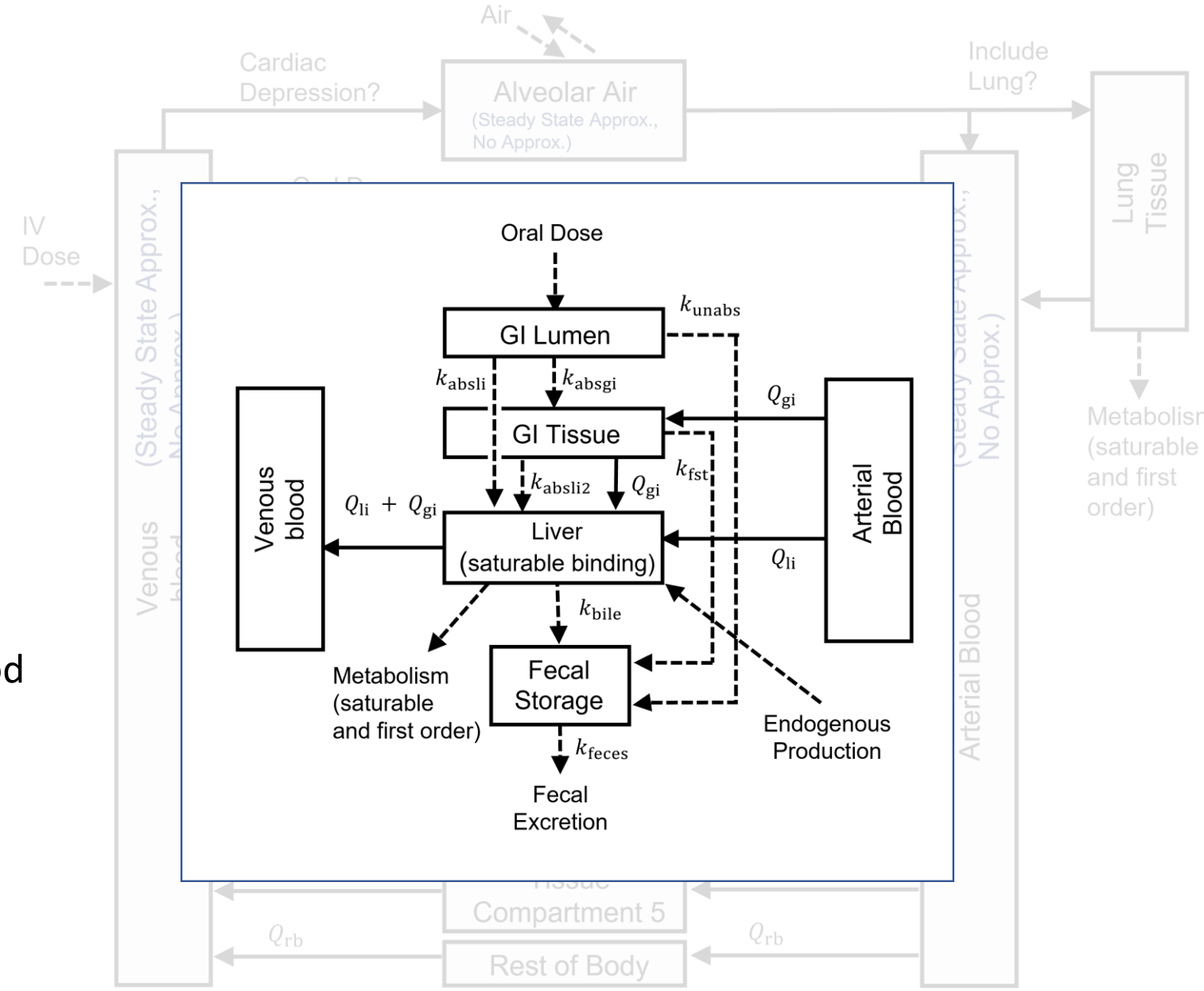

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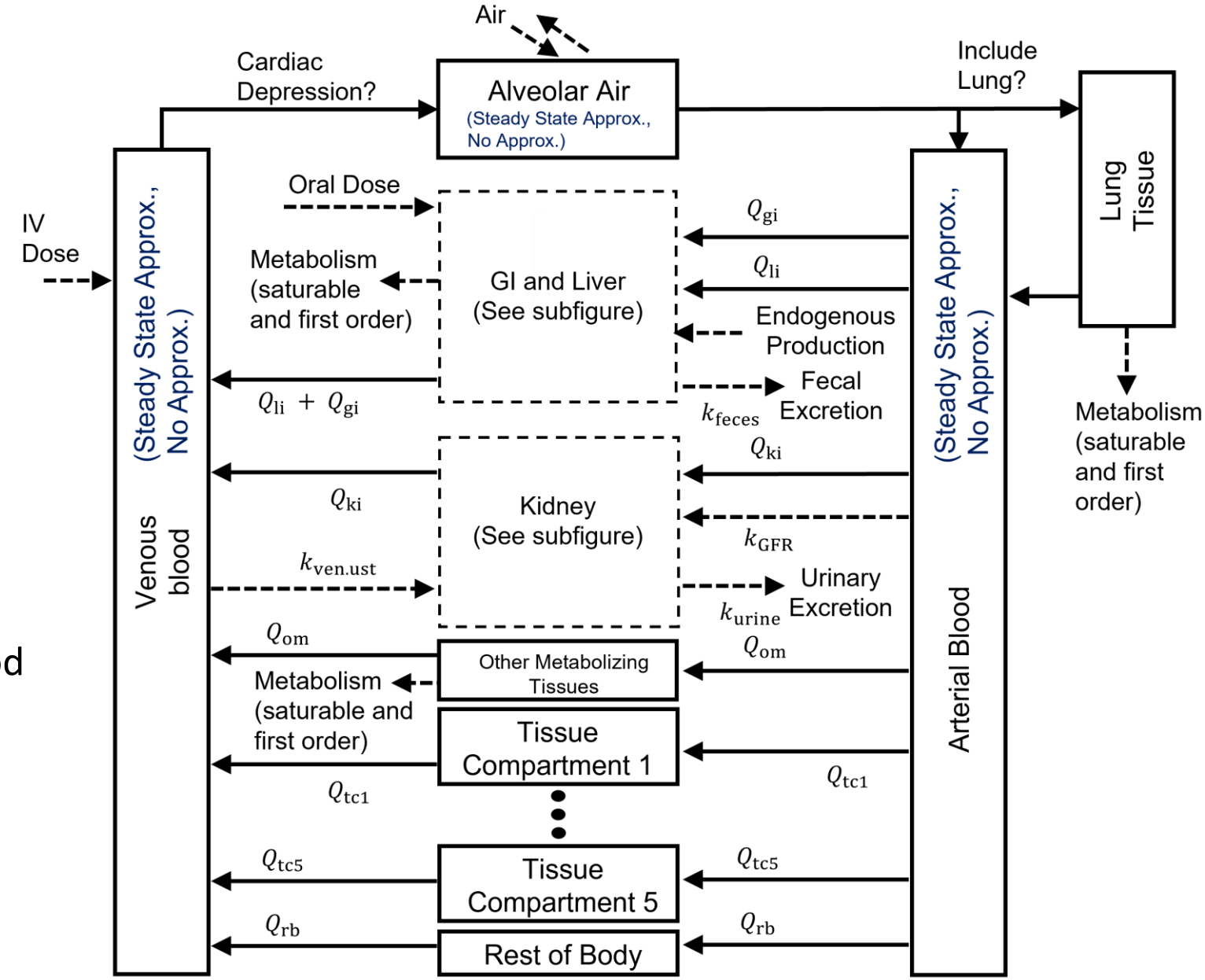

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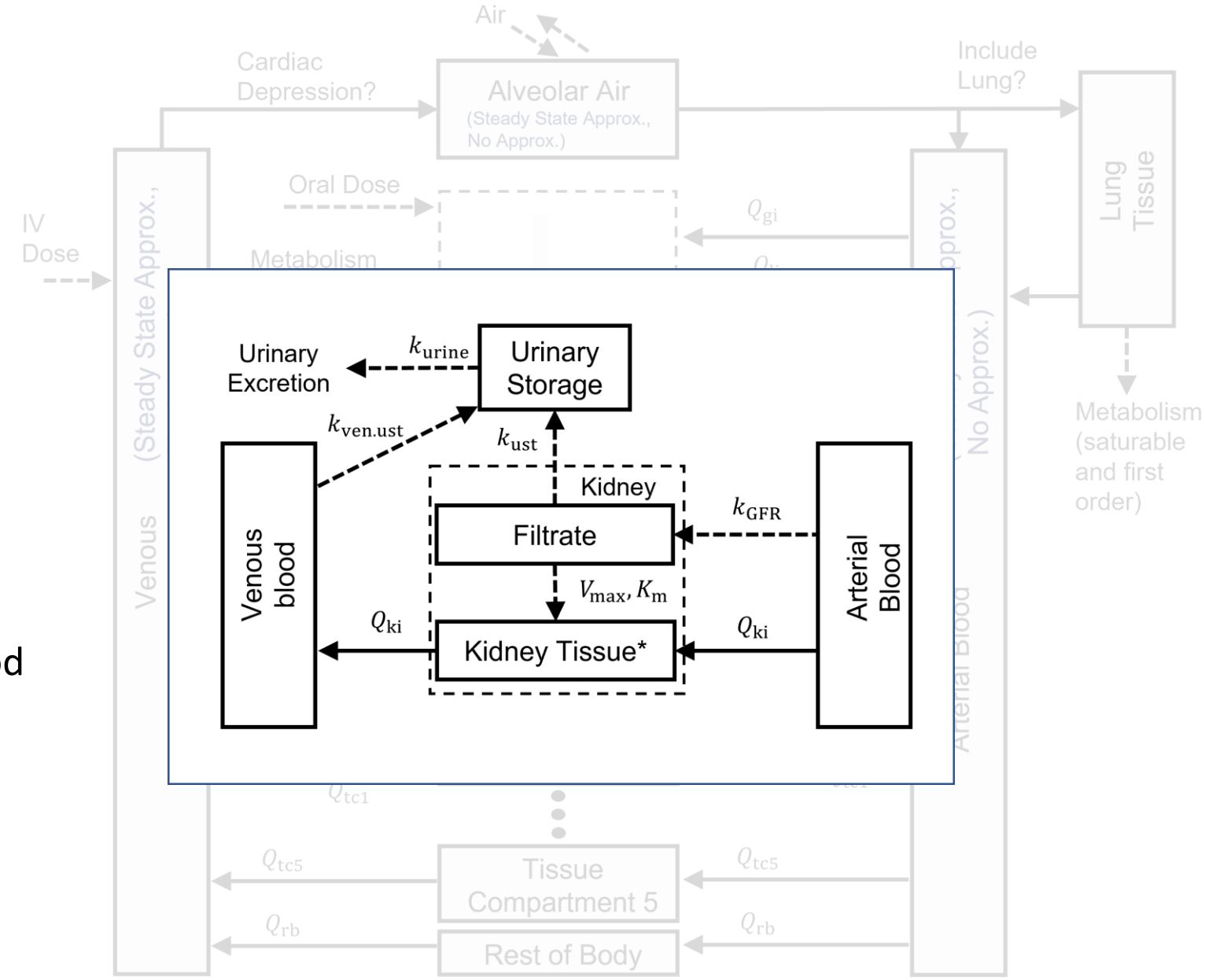

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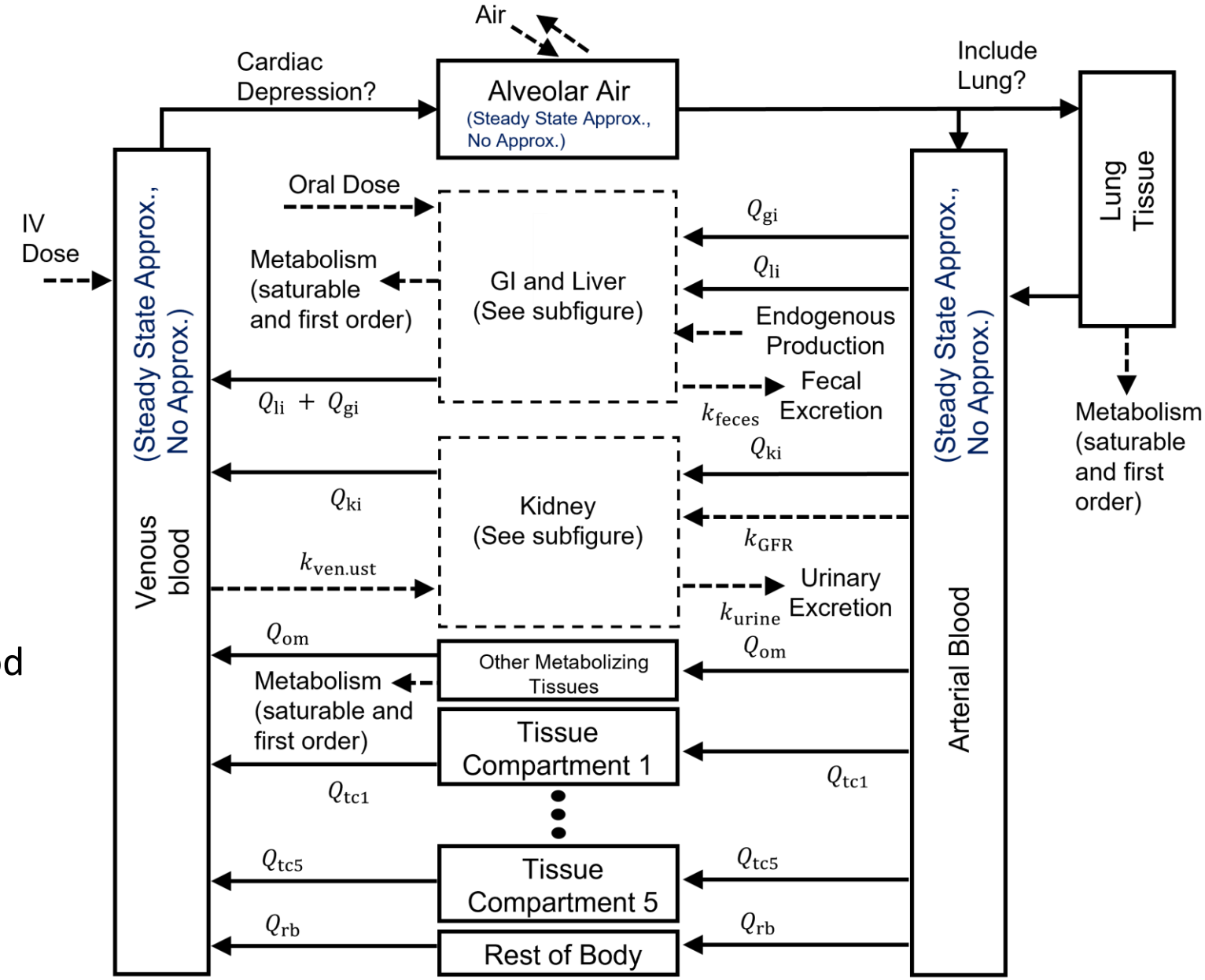
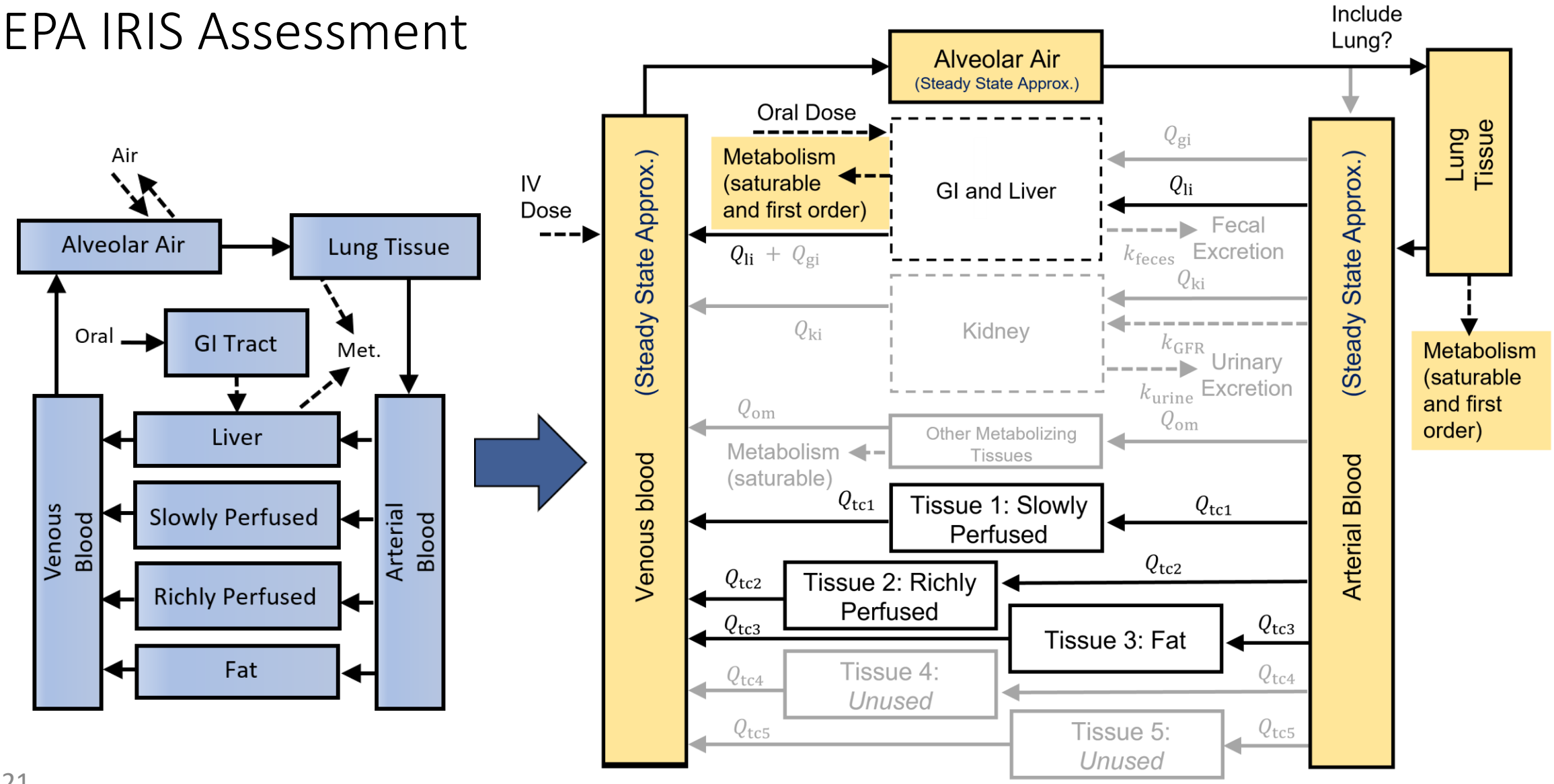
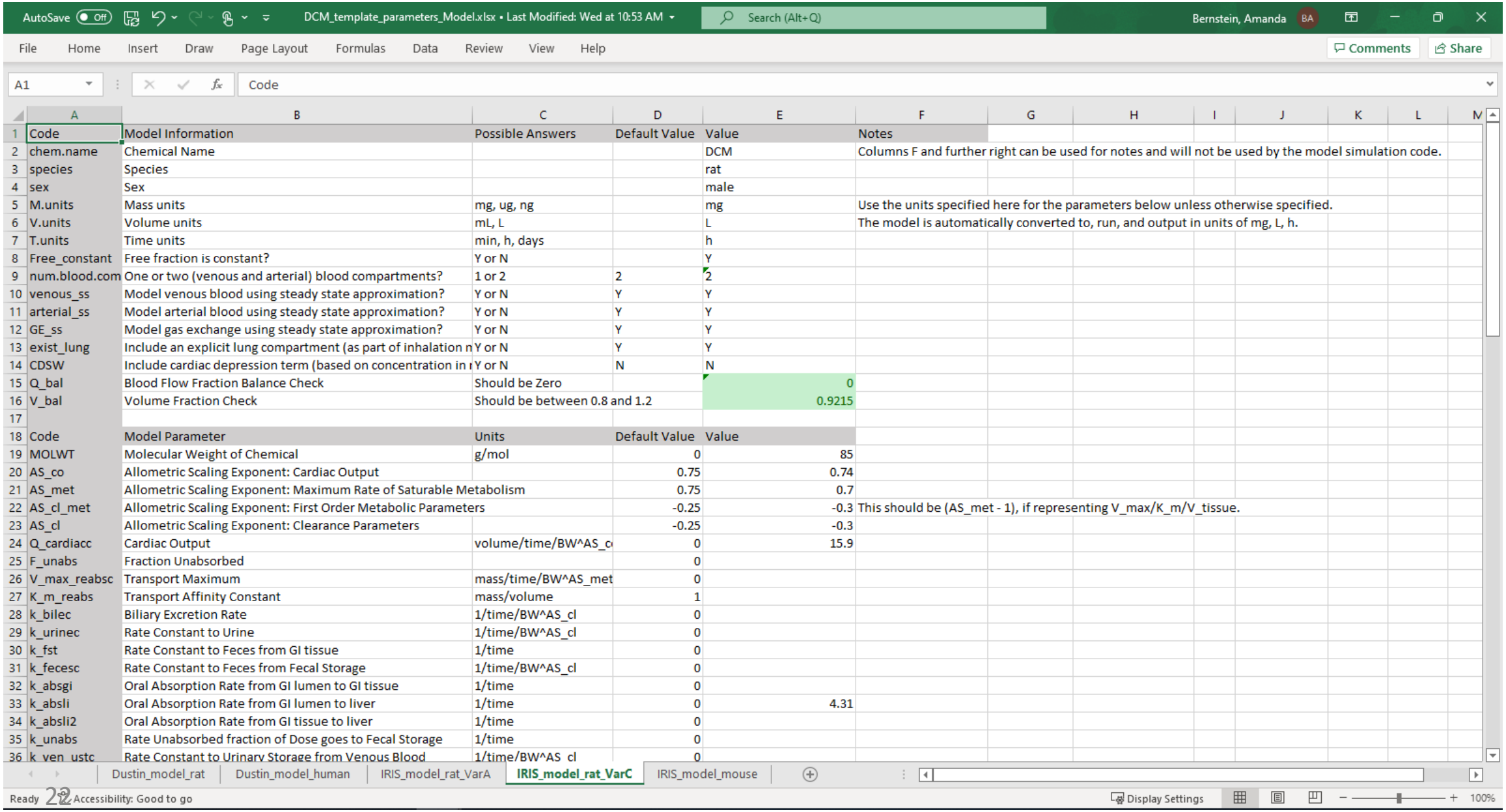


We implemented the PBPK model for DCM used in the EPA IRIS Assessment



We create an input spreadsheet for the model parameters

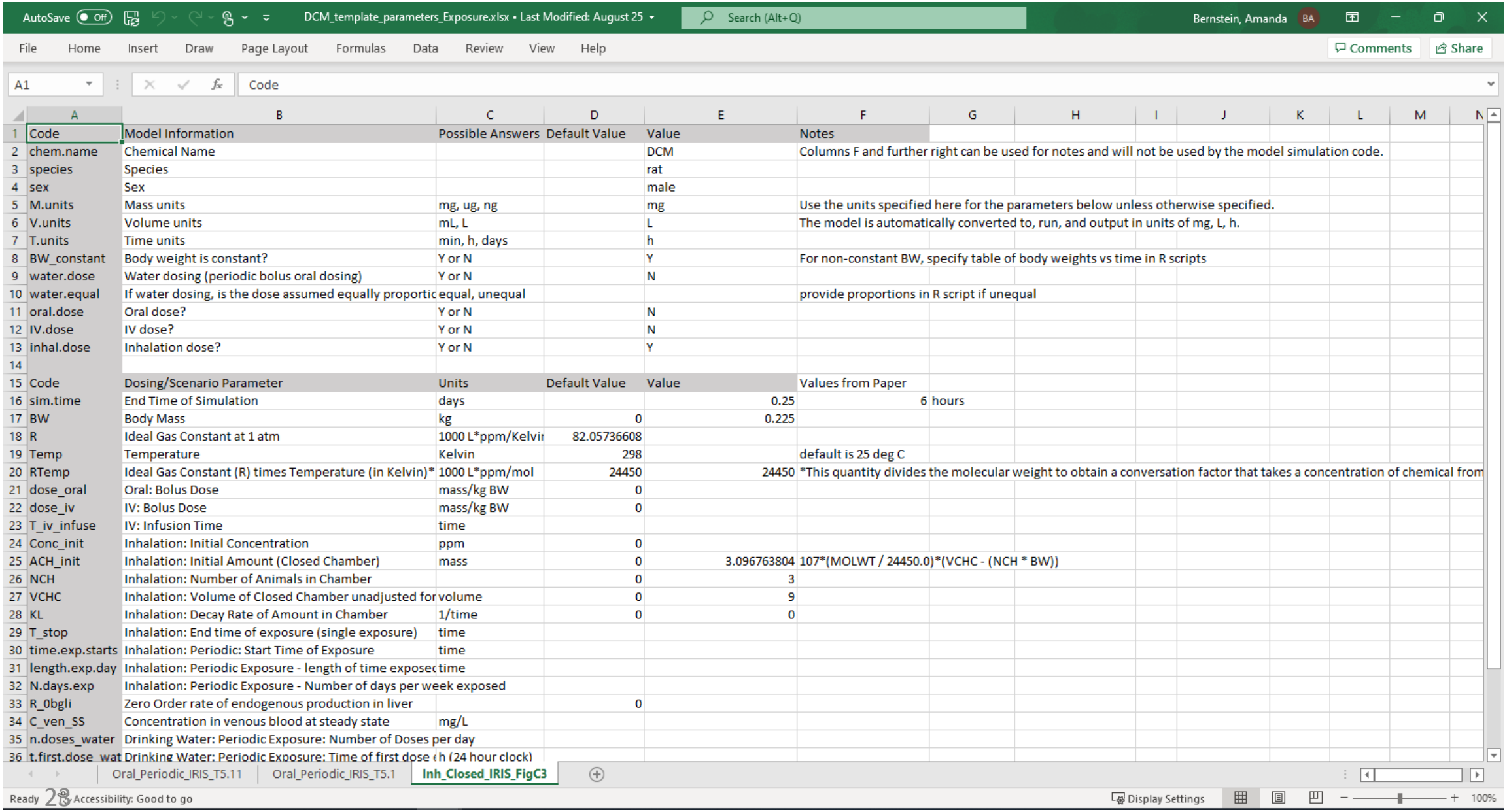


DCM_template_parameters_Model.xlsx • Last Modified: Wed at 10:53 AM

	A	B	C	D	E	F
1	Code	Model Information	Possible Answers	Default Value	Value	Notes
2	chem.name	Chemical Name			DCM	Columns F and further right can be used for notes and will not be used by the model simulation code.
3	species	Species			rat	
4	sex	Sex			male	
5	M.units	Mass units	mg, ug, ng		mg	Use the units specified here for the parameters below unless otherwise specified.
6	V.units	Volume units	mL, L		L	The model is automatically converted to, run, and output in units of mg, L, h.
7	T.units	Time units	min, h, days		h	
8	Free_constant	Free fraction is constant?	Y or N		Y	
9	num.blood.com	One or two (venous and arterial) blood compartments?	1 or 2	2	2	
10	venous_ss	Model venous blood using steady state approximation?	Y or N	Y	Y	
11	arterial_ss	Model arterial blood using steady state approximation?	Y or N	Y	Y	
12	GE_ss	Model gas exchange using steady state approximation?	Y or N	Y	Y	
13	exist_lung	Include an explicit lung compartment (as part of inhalation n	Y or N	Y	Y	
14	CDSW	Include cardiac depression term (based on concentration in r	Y or N	N	N	
15	Q_bal	Blood Flow Fraction Balance Check	Should be Zero		0	
16	V_bal	Volume Fraction Check	Should be between 0.8 and 1.2		0.9215	
17						
18	Code	Model Parameter	Units	Default Value	Value	
19	MOLWT	Molecular Weight of Chemical	g/mol	0	85	
20	AS_co	Allometric Scaling Exponent: Cardiac Output		0.75	0.74	
21	AS_met	Allometric Scaling Exponent: Maximum Rate of Saturable Metabolism		0.75	0.7	
22	AS_cl_met	Allometric Scaling Exponent: First Order Metabolic Parameters		-0.25	-0.3	This should be (AS_met - 1), if representing V_max/K_m/V_tissue.
23	AS_cl	Allometric Scaling Exponent: Clearance Parameters		-0.25	-0.3	
24	Q_cardiacc	Cardiac Output	volume/time/BW^AS_c	0	15.9	
25	F_unabs	Fraction Unabsorbed		0		
26	V_max_reabsc	Transport Maximum	mass/time/BW^AS_met	0		
27	K_m_reabs	Transport Affinity Constant	mass/volume	1		
28	k_bilec	Biliary Excretion Rate	1/time/BW^AS_cl	0		
29	k_urinec	Rate Constant to Urine	1/time/BW^AS_cl	0		
30	k_fst	Rate Constant to Feces from GI tissue	1/time	0		
31	k_fecesc	Rate Constant to Feces from Fecal Storage	1/time/BW^AS_cl	0		
32	k_absgi	Oral Absorption Rate from GI lumen to GI tissue	1/time	0		
33	k_absli	Oral Absorption Rate from GI lumen to liver	1/time	0	4.31	
34	k_absli2	Oral Absorption Rate from GI tissue to liver	1/time	0		
35	k_unabs	Rate Unabsorbed fraction of Dose goes to Fecal Storage	1/time	0		
36	k_ven_ustc	Rate Constant to Urinary Storage from Venous Blood	1/time/BW^AS_cl	0		

Dustin_model_rat | Dustin_model_human | IRIS_model_rat_VarA | IRIS_model_rat_VarC | IRIS_model_mouse

We create an input spreadsheet for the exposure specific parameters



DCM_template_parameters_Exposure.xlsx • Last Modified: August 25

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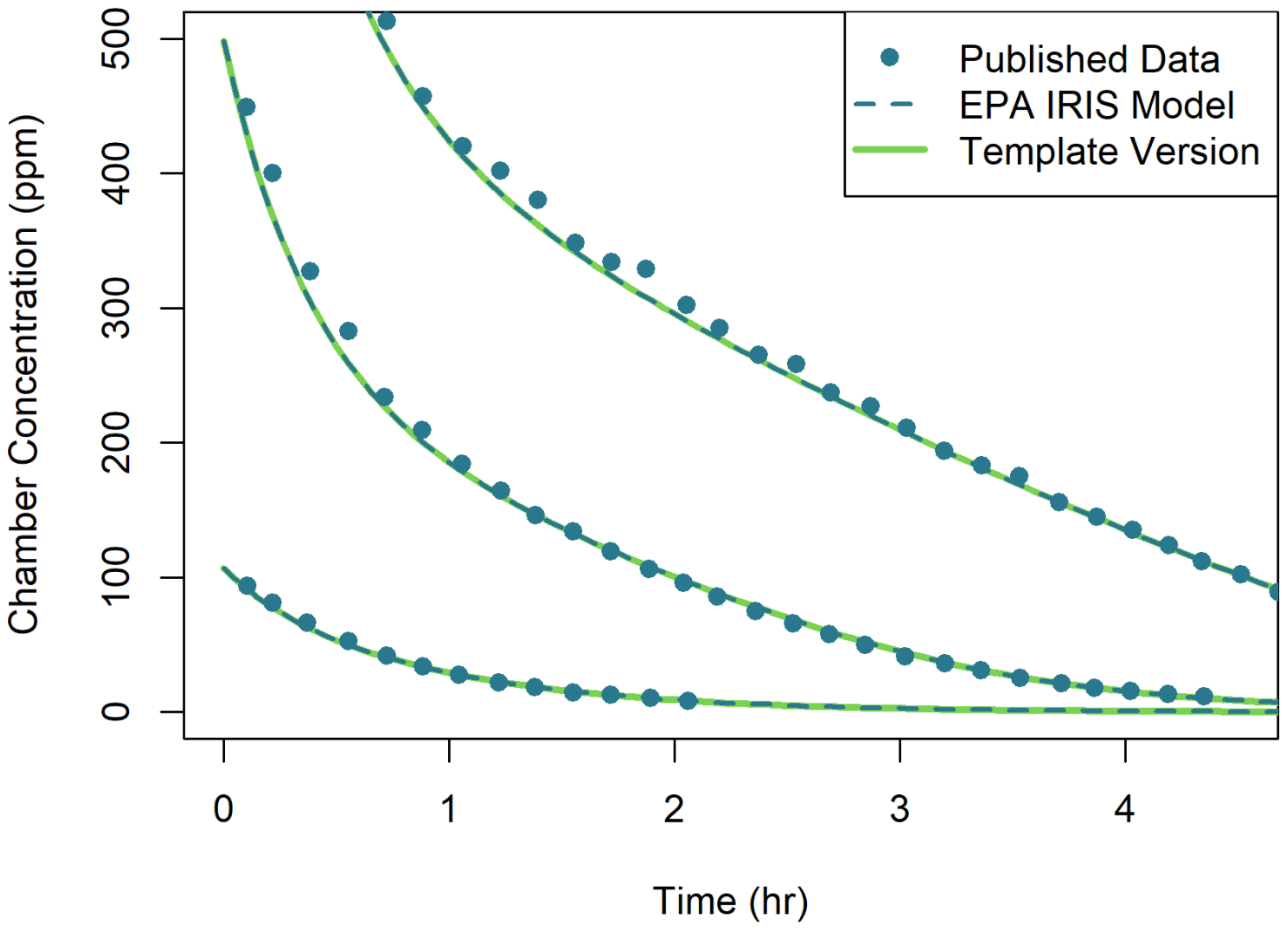
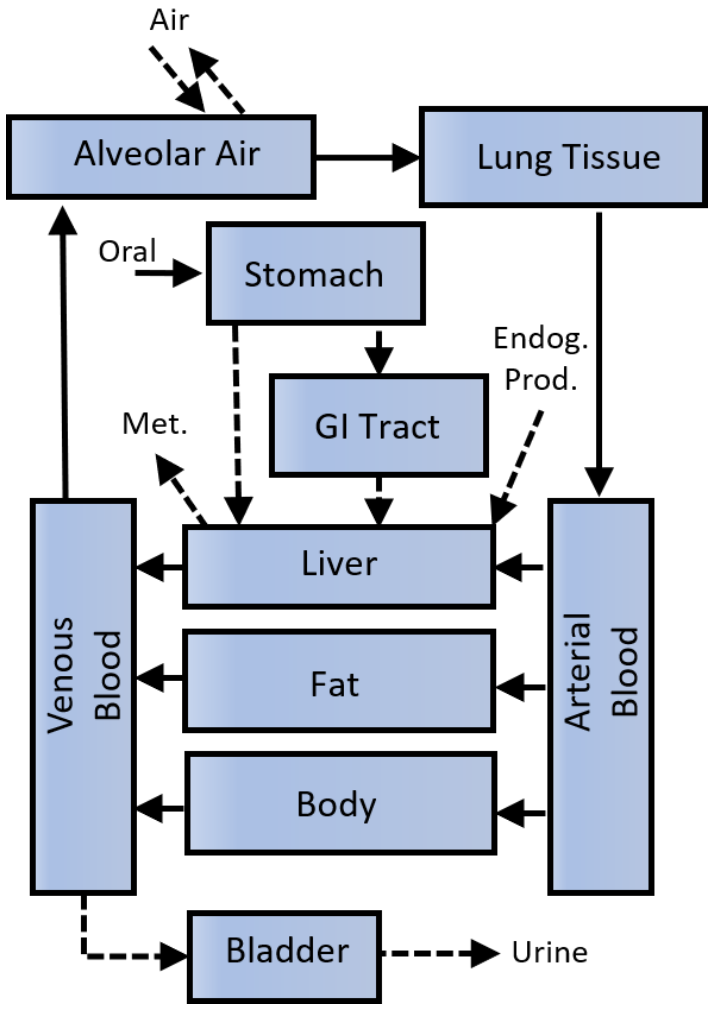
1	Code	Model Information	Possible Answers	Default Value	Value	Notes	
2	chem.name	Chemical Name			DCM	Columns F and further right can be used for notes and will not be used by the model simulation code.	
3	species	Species			rat		
4	sex	Sex			male		
5	M.units	Mass units	mg, ug, ng		mg	Use the units specified here for the parameters below unless otherwise specified.	
6	V.units	Volume units	mL, L		L	The model is automatically converted to, run, and output in units of mg, L, h.	
7	T.units	Time units	min, h, days		h		
8	BW_constant	Body weight is constant?	Y or N		Y	For non-constant BW, specify table of body weights vs time in R scripts	
9	water.dose	Water dosing (periodic bolus oral dosing)	Y or N		N		
10	water.equal	If water dosing, is the dose assumed equally proportic	equal, unequal			provide proportions in R script if unequal	
11	oral.dose	Oral dose?	Y or N		N		
12	IV.dose	IV dose?	Y or N		N		
13	inhal.dose	Inhalation dose?	Y or N		Y		
14							
15	Code	Dosing/Scenario Parameter	Units	Default Value	Value	Values from Paper	
16	sim.time	End Time of Simulation	days		0.25	6	hours
17	BW	Body Mass	kg	0	0.225		
18	R	Ideal Gas Constant at 1 atm	1000 L*ppm/Kelvi	82.05736608			
19	Temp	Temperature	Kelvin	298		default is 25 deg C	
20	RTemp	Ideal Gas Constant (R) times Temperature (in Kelvin)*	1000 L*ppm/mol	24450	24450	*This quantity divides the molecular weight to obtain a conversation factor that takes a concentration of chemical from	
21	dose_oral	Oral: Bolus Dose	mass/kg BW	0			
22	dose_iv	IV: Bolus Dose	mass/kg BW	0			
23	T_iv_infuse	IV: Infusion Time	time				
24	Conc_init	Inhalation: Initial Concentration	ppm	0			
25	ACH_init	Inhalation: Initial Amount (Closed Chamber)	mass	0	3.096763804	107*(MOLWT / 24450.0)*(VCHC - (NCH * BW))	
26	NCH	Inhalation: Number of Animals in Chamber		0	3		
27	VCHC	Inhalation: Volume of Closed Chamber unadjusted for	volume	0	9		
28	KL	Inhalation: Decay Rate of Amount in Chamber	1/time	0	0		
29	T_stop	Inhalation: End time of exposure (single exposure)	time				
30	time.exp.starts	Inhalation: Periodic: Start Time of Exposure	time				
31	length.exp.day	Inhalation: Periodic Exposure - length of time exposed	time				
32	N.days.exp	Inhalation: Periodic Exposure - Number of days per week exposed					
33	R_0bgli	Zero Order rate of endogenous production in liver		0			
34	C_ven_SS	Concentration in venous blood at steady state	mg/L				
35	n.doses_water	Drinking Water: Periodic Exposure: Number of Doses per day					
36	t.first.dose_wat	Drinking Water: Periodic Exposure: Time of first dose	h (24 hour clock)				

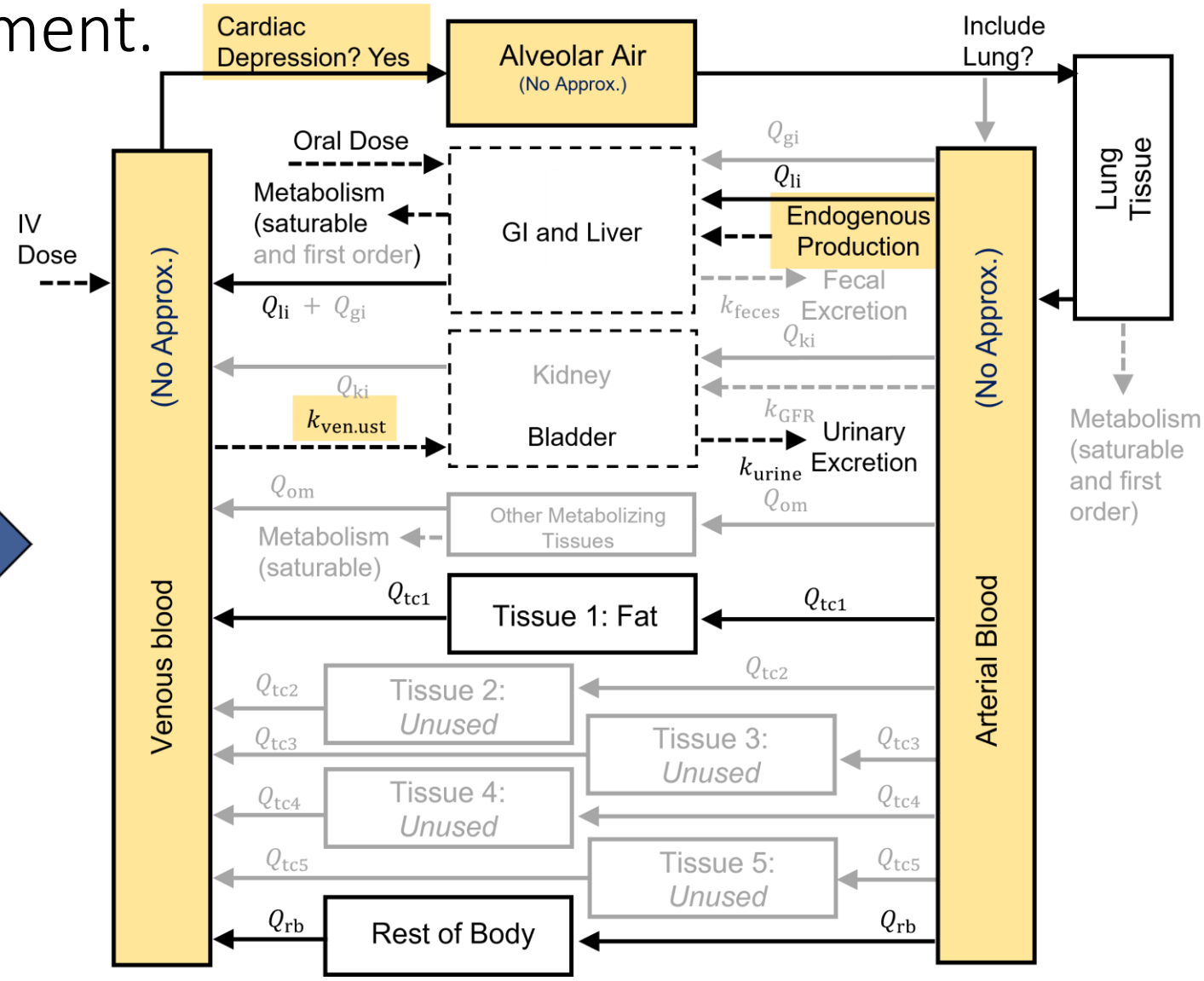
We reproduced published results for DCM from the EPA IRIS Assessment.

- The figure shows observations and predictions of respiratory uptake by 3 rats of 100 – 1000 ppm DCM in a closed chamber experiment.
- The simulation output from the template implementation matched the published output to within $5(10)^{-4}$ %.



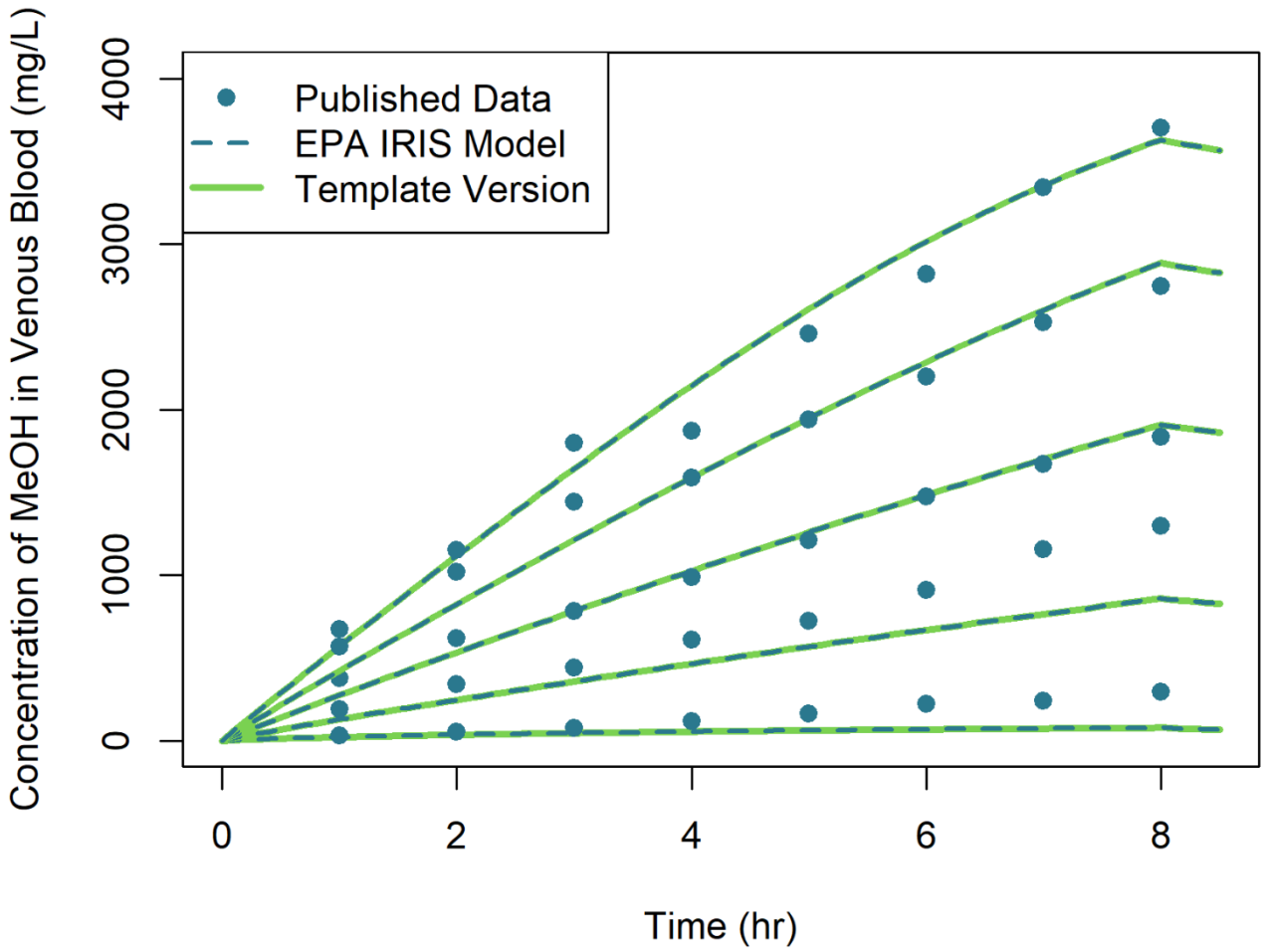
We added features to implement the PBPK model for methanol used in the EPA IRIS Assessment.



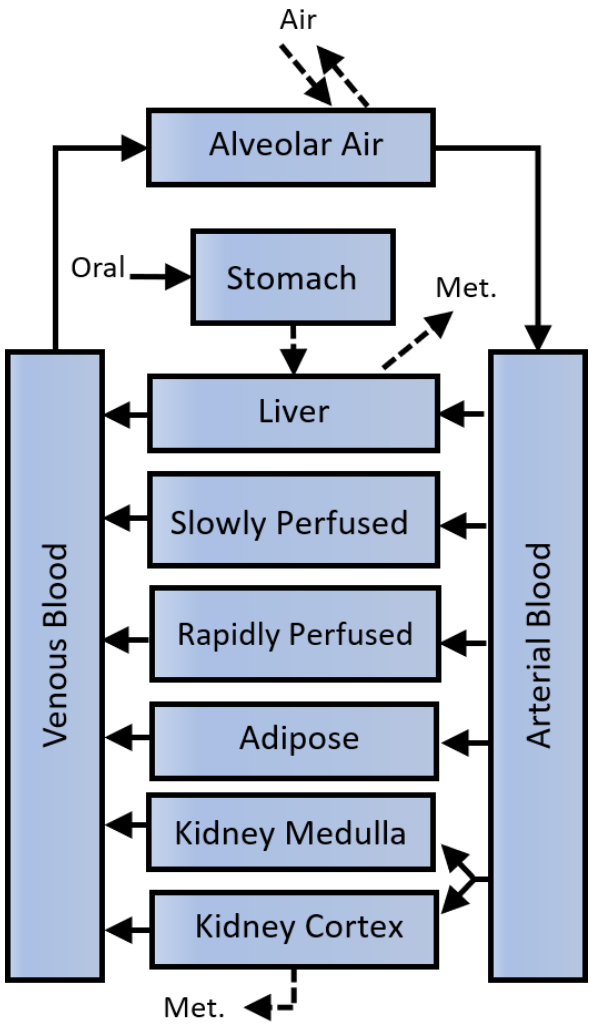


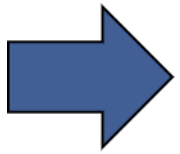
We reproduced published results for methanol from the EPA IRIS Assessment.

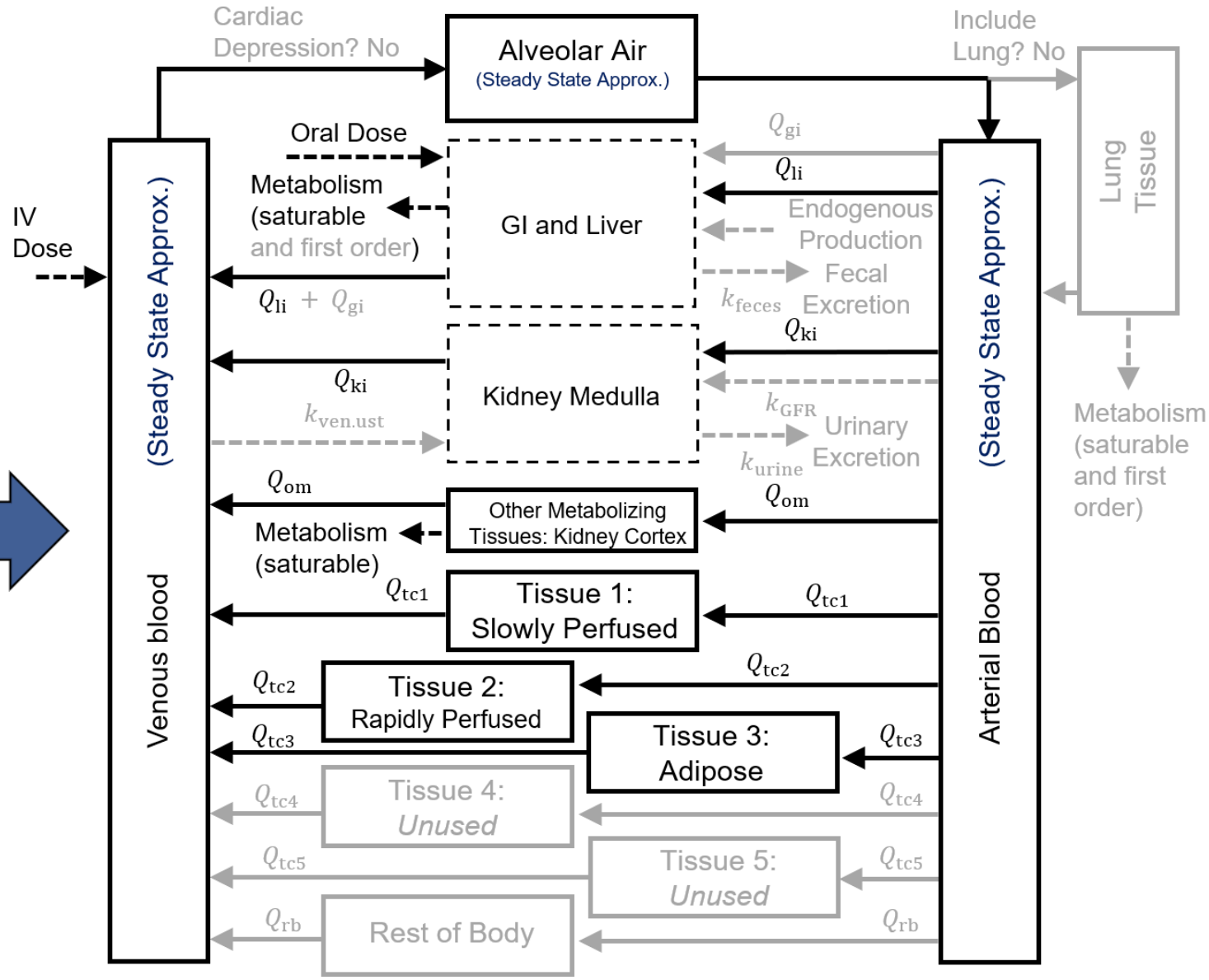
- The figure shows observations and predictions of methanol concentration in venous blood for 3 rats exposed to a constant concentration (100 ppm – 20,000 ppm) of methanol for 8 hours.
- The simulation output from the template implementation matched the published output to within $6(10)^{-4}$ %.



We used the template to quickly implement a published model for chloroform.







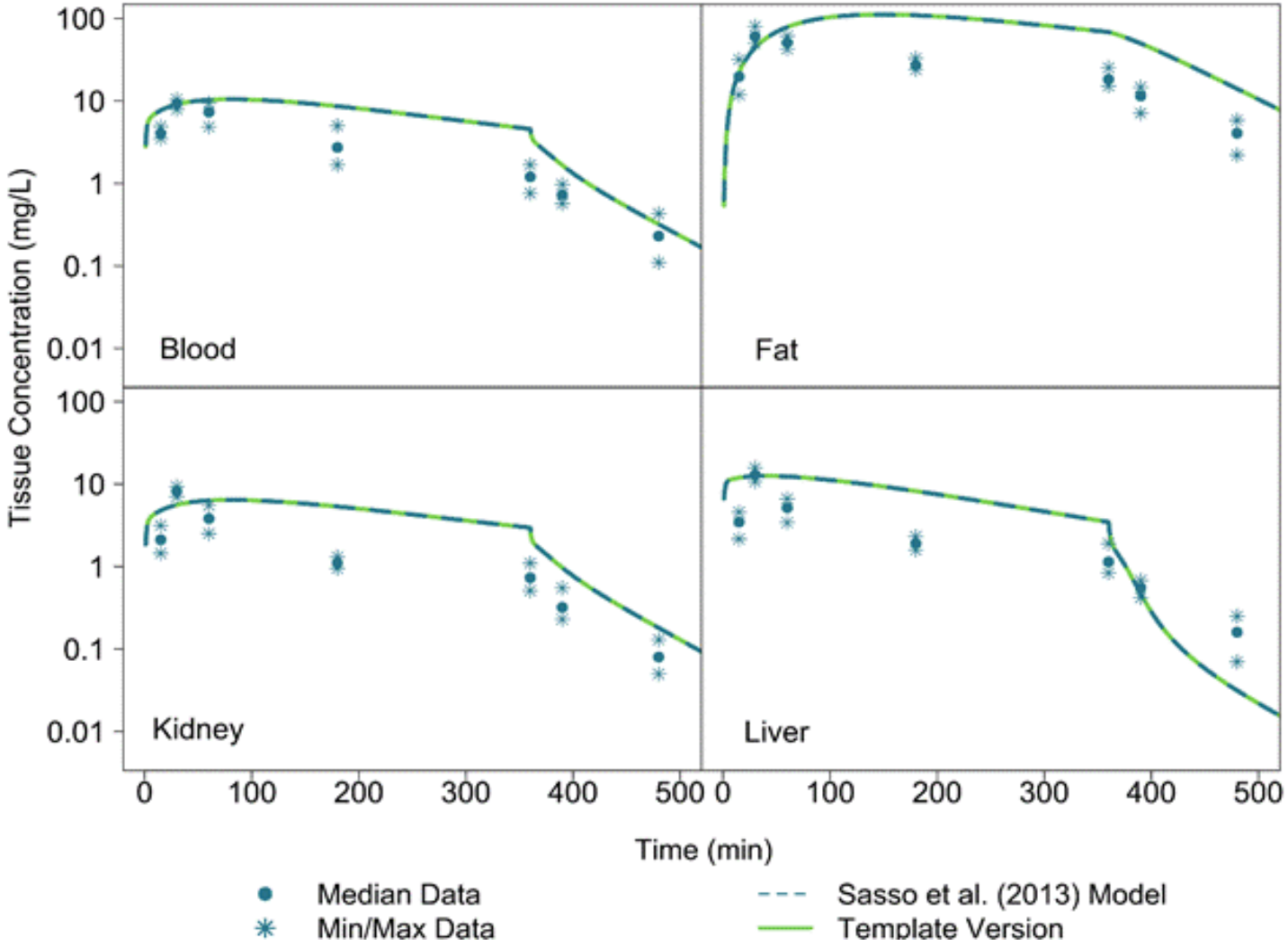
We reproduced simulation results from a published PBPK model for chloroform.

- The desired exposure was for 5 rats given an oral bolus dose of 55 mg/kg while also exposed to a constant concentration of 100 ppm of chloroform for 360 min.

	A	B	C	D	E	F
1	Code	Model Information	Possible Answers	Default Value	Value	Notes
2	chem.name	Chemical Name			chloroform	Columns F and f
3	species	Species			rat	
4	sex	Sex			male	
5	M.units	Mass units	mg, ug, ng		mg	Use the units sp
6	V.units	Volume units	mL, L		L	The model is aut
7	T.units	Time units	min, h, days		h	
8	water.dose	Water dosing (periodic bolus oral dosing)	Y or N		N	
9	water.equal	if water dosing: is the dose assumed equally proportio	equal, unequal			provide proporti
10	oral.dose	Oral dose?	Y or N		Y	
11	IV.dose	IV dose?	Y or N		N	
12	inhal.dose	Inhalation dose?	Y or N		Y	
13						
14	Code	Dosing/Scenario Parameter	Units	Default Value	Value	
15	sim.time	End Time of Simulation	days		0.347222222	
16	dose_oral	Oral: Bolus Dose	mass/kg BW	0	55	
17	dose_iv	IV: Bolus Dose	mass/kg BW	0		
18	T_iv_infuse	IV: Infusion Time	time			
19	Conc_init	Inhalation: Initial Concentration	ppm	0	100	
20	ACH_init	Inhalation: Initial Amount (Closed Chamber)	mass	0		
21	NCH	Inhalation: Number of Animals in Chamber		0	1	
22	VCHC	Inhalation: Volume of Closed Chamber unadjusted for	volume	0		
23	KL	Inhalation: Decay Rate of Amount in Chamber	1/time	0		
24	T_stop	Inhalation: End time of exposure (single exposure)	time		6	
25	time.exp.starts	Inhalation: Periodic: Start Time of Exposure	time			
26	length.exp.day	Inhalation: Periodic Exposure - length of time exposed	time			
27	N.days.exp	Inhalation: Periodic Exposure - Number of days per week exposed				
28	P_0hali	Zero-Order rate of endogenous production in liver		0		

We reproduced simulation results from a published PBPK model for chloroform.

- The figure shows observations and predictions of chloroform tissue concentrations for the rats.
- The simulation output from the template implementation matched the published output to within an absolute difference of 10^{-6}.



Next Steps

- We are adding functions to easily run Monte Carlo simulations and return summary statistical information.

- We are working to leverage other existing tools.
  - For example, httk-pop allows one to generate a random population of ‘in silico’ individuals based on NHANES data. We will provide functions to convert that population into the format needed by the template model.

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Next Steps

- Our goal is to be able to accommodate a wide range of chemicals and exposure scenarios.

- Features we plan to incorporate into the template model include:
  - Menstruation and lactation as excretion pathways
  - Dermal routes of exposure
  - Life stage modeling – pregnancy, growth
  - Tracking metabolites in addition to parent compounds

Summary

- The model template includes sufficient features to allow implementation of a wide range of PBPK models.
- We have added features in an iterative manner so that the template can continue to expand to accommodate additional chemical-specific PBPK models.
- Implementation of different models only requires changing parameter values in input files.
- Using the template can allow us to quickly identify errors in PBPK models.
- To perform QA review of template-implemented models, only the parameter files will require review.
- Model code for the first version of the model template focused on PFAS models can be found at the EPA's Environmental Dataset Gateway (https://doi.org/10.23719/1520081).

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Thank you to our team!

- Paul Schlosser
- Dustin Kapraun
- Bidya Prasad
- Viktor Morozov

Further Reading

- Bernstein AS, Kapraun DF, Schlosser PM. A Model Template Approach for Rapid Evaluation and Application of Physiologically Based Pharmacokinetic Models for Use in Human Health Risk Assessments: A Case Study on Per- and Polyfluoroalkyl Substances. Toxicol Sci. 2021 Aug 3;182(2):215-228. https://doi.org/10.1093/toxsci/kfab063.
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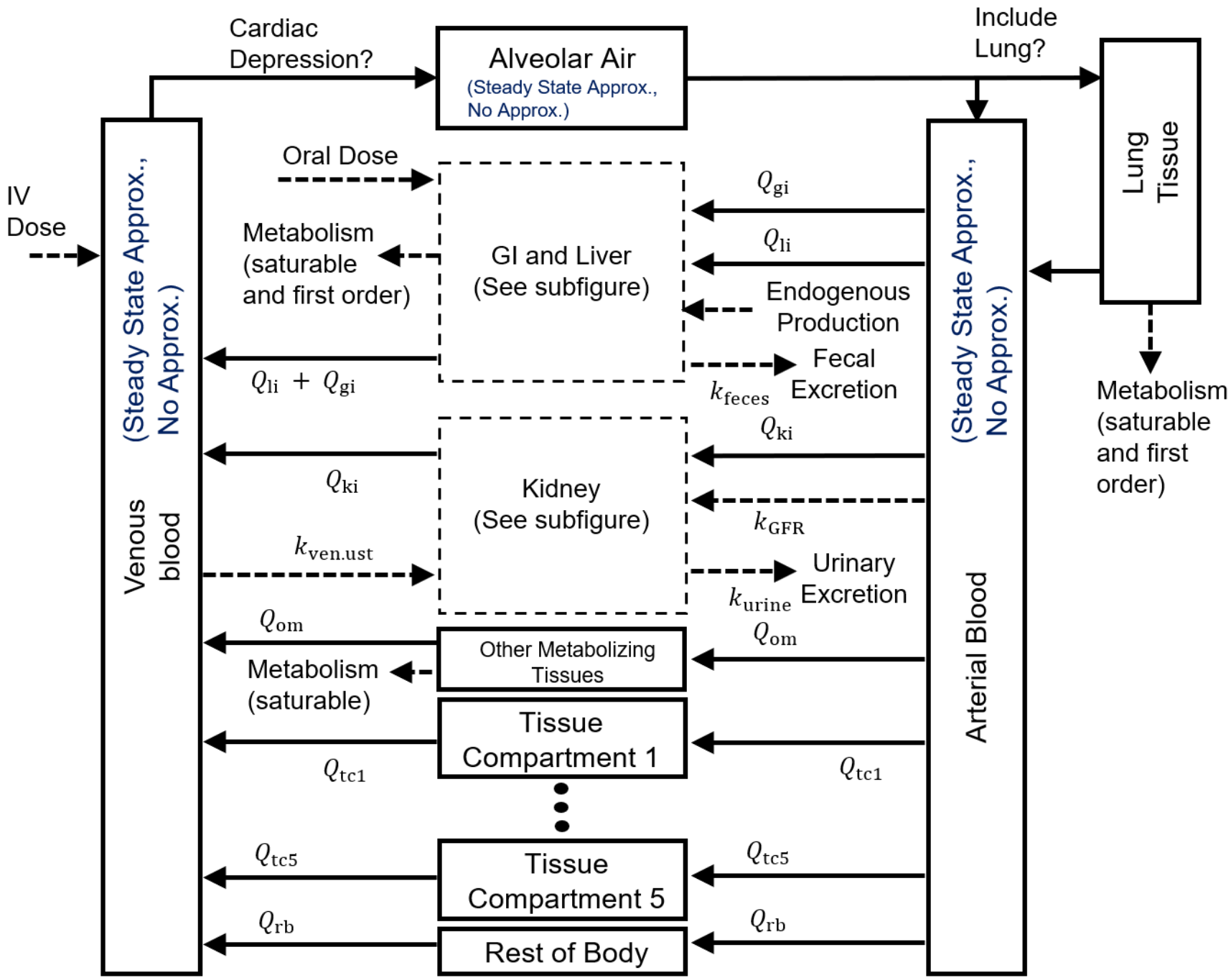
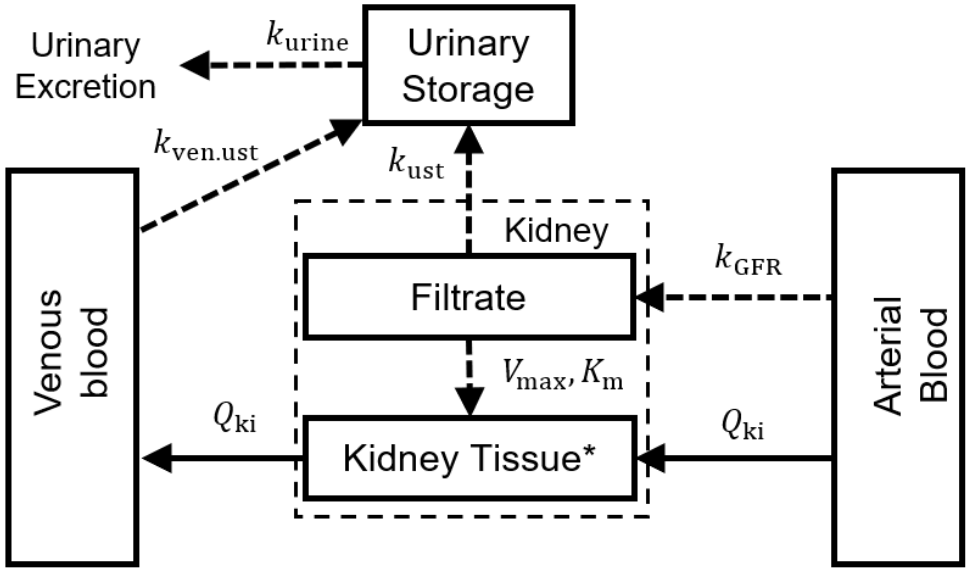
Support Slides

PBPK Model Template Structure

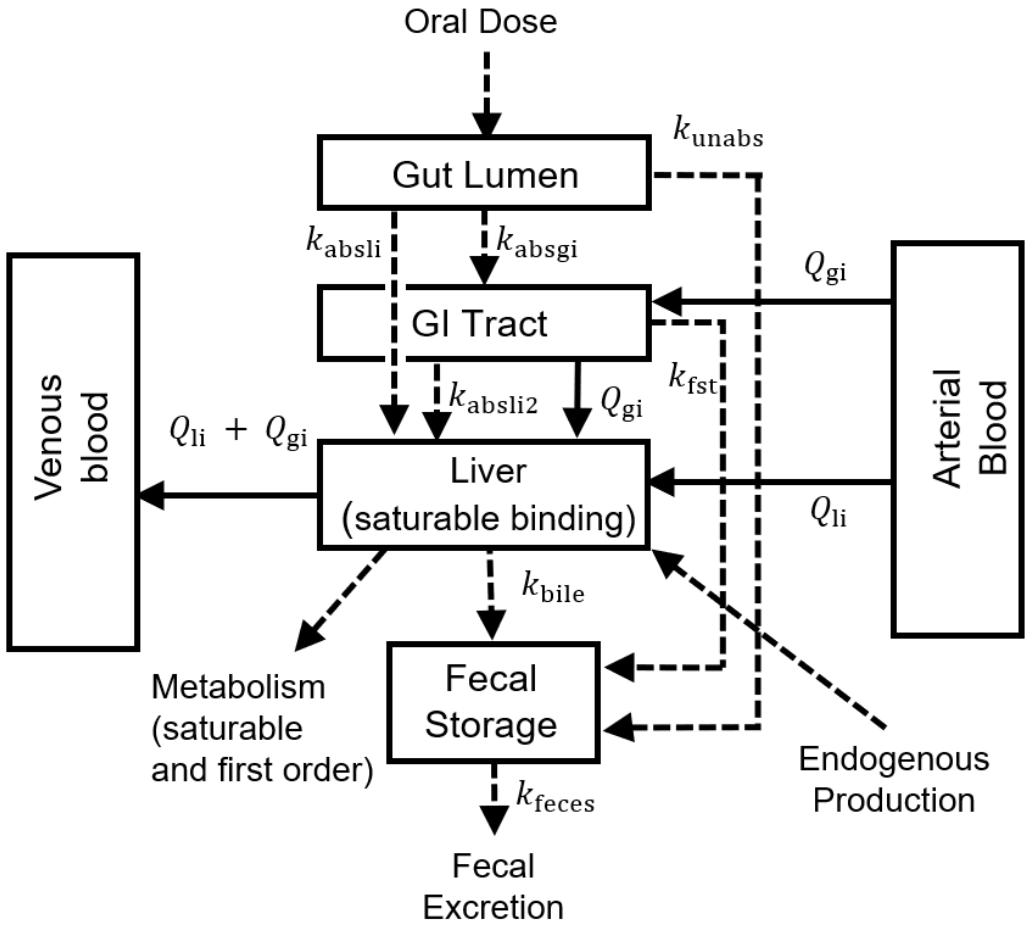


Model Template Subfigures

Kidney Subfigure

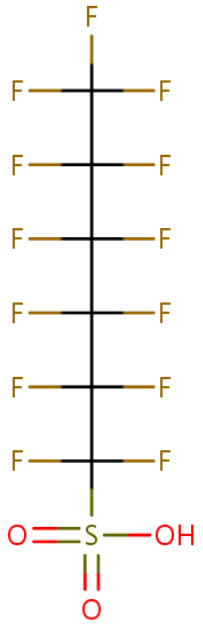


Liver and GI Subfigure

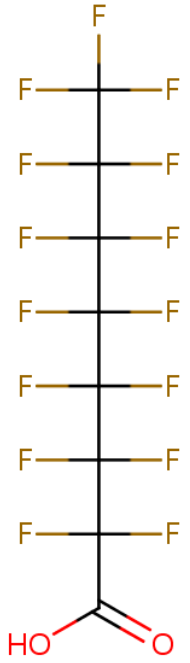


Chemical Structures

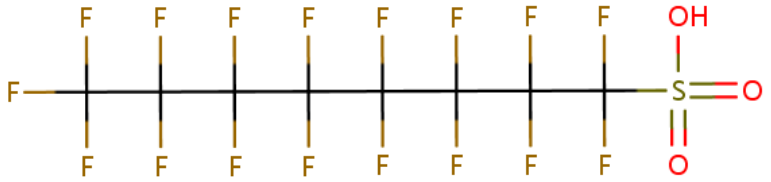
PFHxS



PFOA

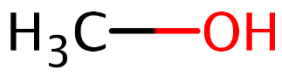


PFOS



DCM

Methanol



Chloroform