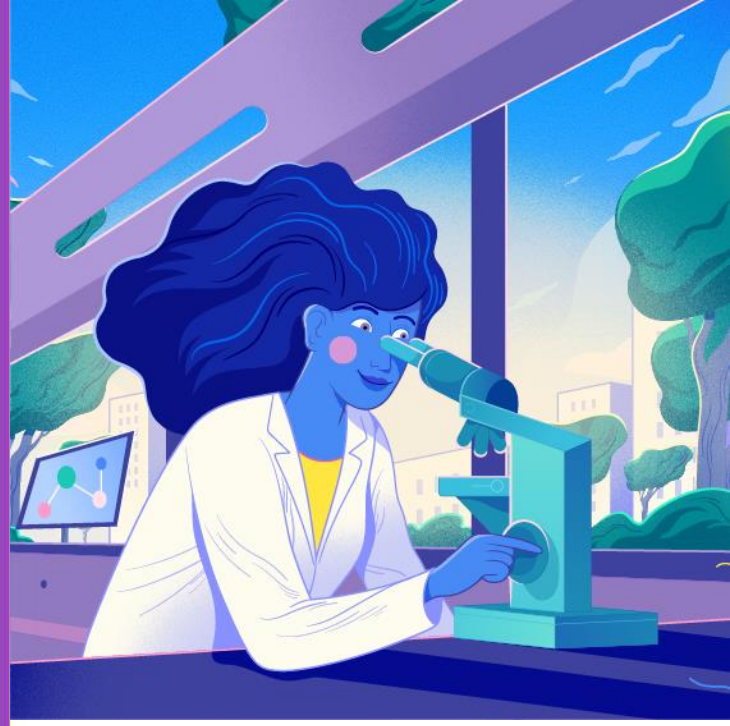
Application of physiologically based kinetic (PBK) modelling for systemic exposure estimation in the next generation risk assessment

Hequn Li, SEAC Science Leader



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What is PBK (physiologically based kinetic) modelling?

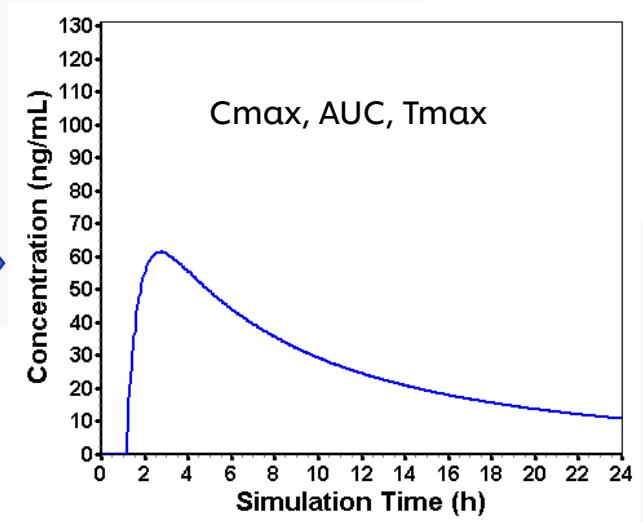
Input

ADME properties

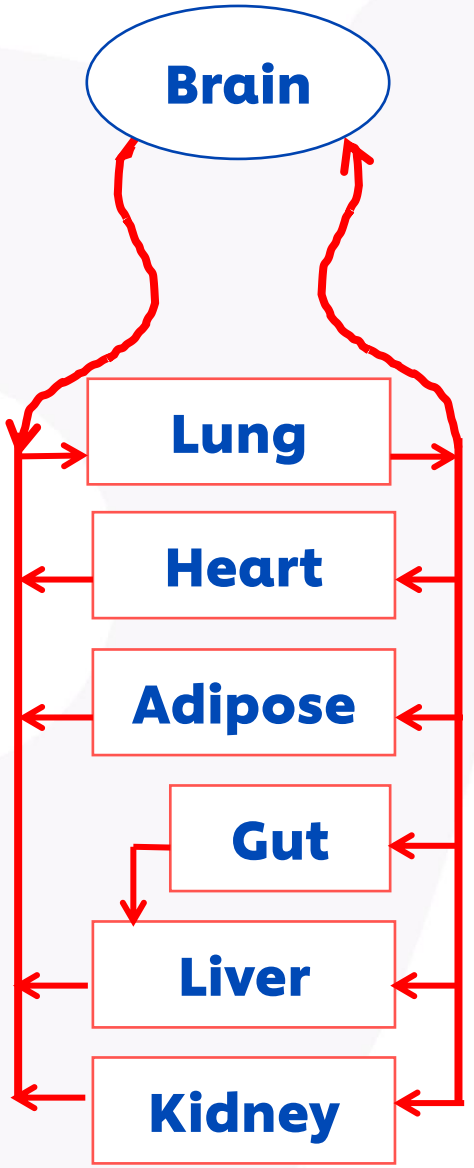
Absorption, Distribution, Metabolism, Excretion

- Physiological parameters (e.g. body weight, blood flow rates, tissue volume)
- Physico-chemical parameters (e.g. LogP, pKa)
- Kinetic parameters (e.g. dermal absorption, hepatic metabolism, renal excretion)
- Product use information (e.g. dose, frequency, site area, formulation)

Output



Population simulation
Uncertainty analysis



$$V_L \frac{dC_L}{dt} = Q_l\left(C_V - \frac{C_L}{P_L}\right)$$

$$V_B \frac{dC_B}{dt} = Q_B\left(C_V - \frac{C_B}{P_B}\right)$$

$$V_{SP} \frac{dC_{SP}}{dt} = Q_{SP}\left(C_V - \frac{C_{SP}}{P_{SP}}\right)$$

$$V_H \frac{dC_H}{dt} = Q_H\left(C_V - \frac{C_H}{P_H}\right)$$

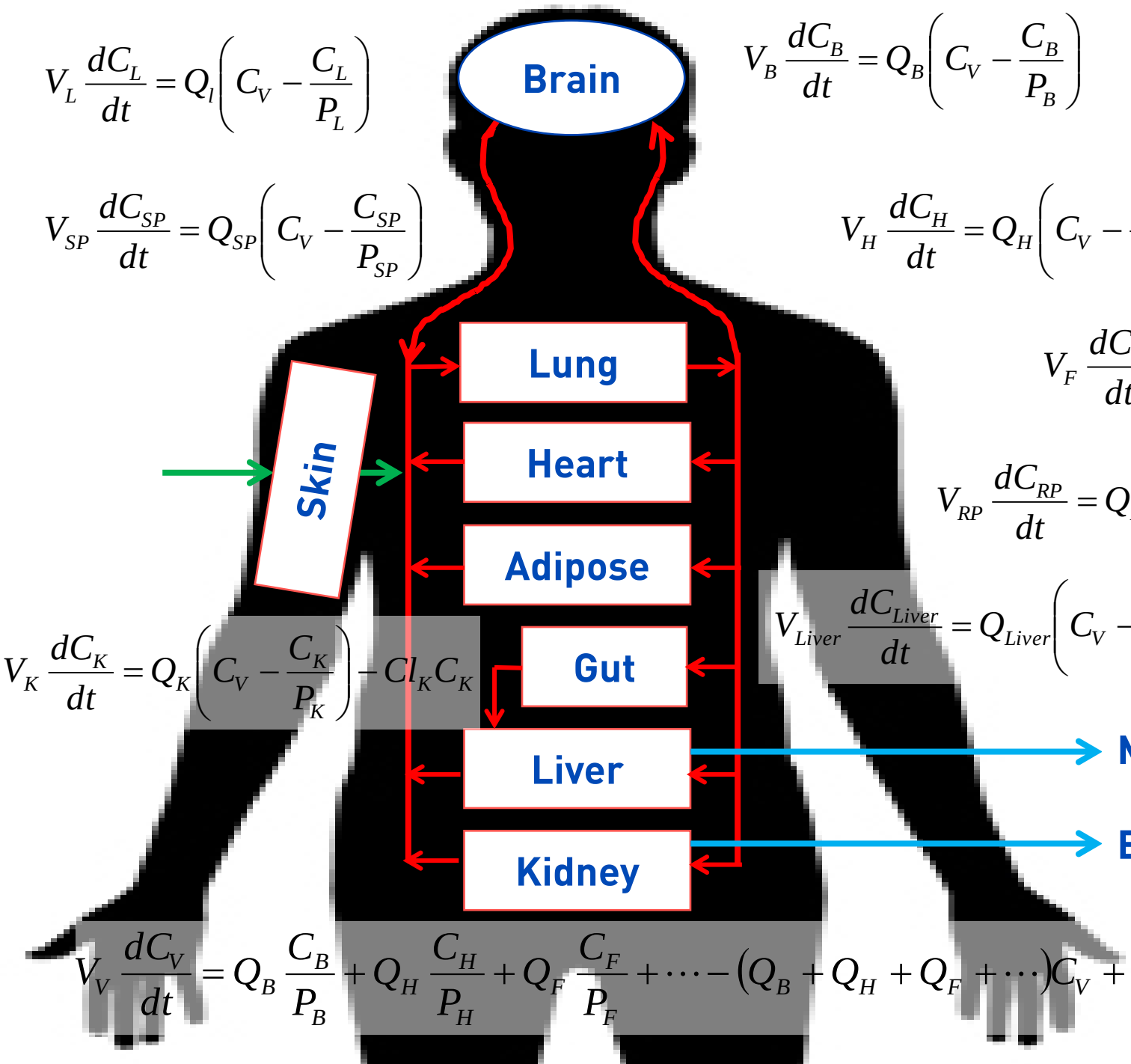
$$V_F \frac{dC_F}{dt} = Q_F\left(C_V - \frac{C_F}{P_F}\right)$$

$$V_{RP} \frac{dC_{RP}}{dt} = Q_{RP}\left(C_V - \frac{C_{RP}}{P_{RP}}\right)$$

$$V_{Liver} \frac{dC_{Liver}}{dt} = Q_{Liver}\left(C_V - \frac{C_{Liver}}{P_{Liver}}\right) - \frac{V_{\max} C_{Liver}}{K_m + C_{Liver}}$$

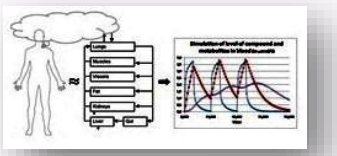
$$V_K \frac{dC_K}{dt} = Q_K\left(C_V - \frac{C_K}{P_K}\right) - Cl_K C_K$$

$$V_V \frac{dC_V}{dt} = Q_B \frac{C_B}{P_B} + Q_H \frac{C_H}{P_H} + Q_F \frac{C_F}{P_F} + \cdots - (Q_B + Q_H + Q_F + \cdots) C_V + dose(t)$$



How it works

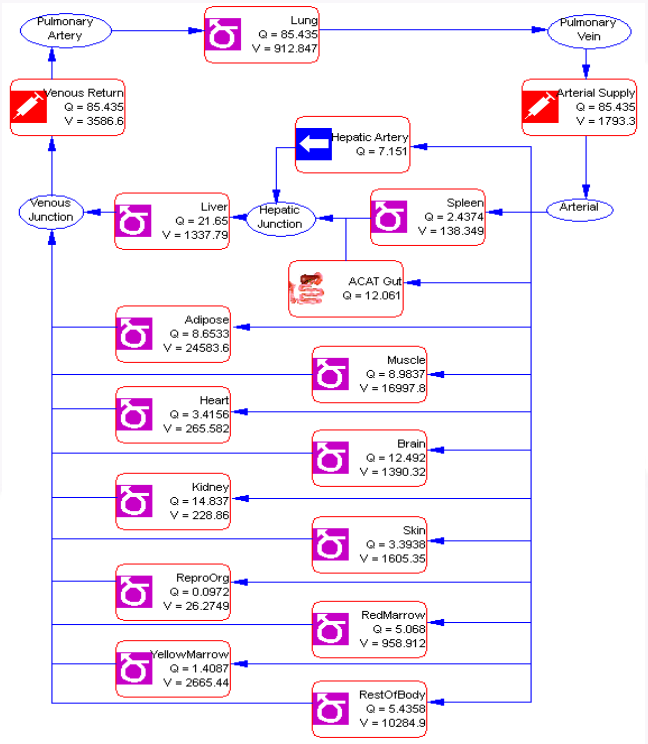
- Programming Languages
- Continuous Simulation Software
- Commercial Software
- Publicly Available Tools

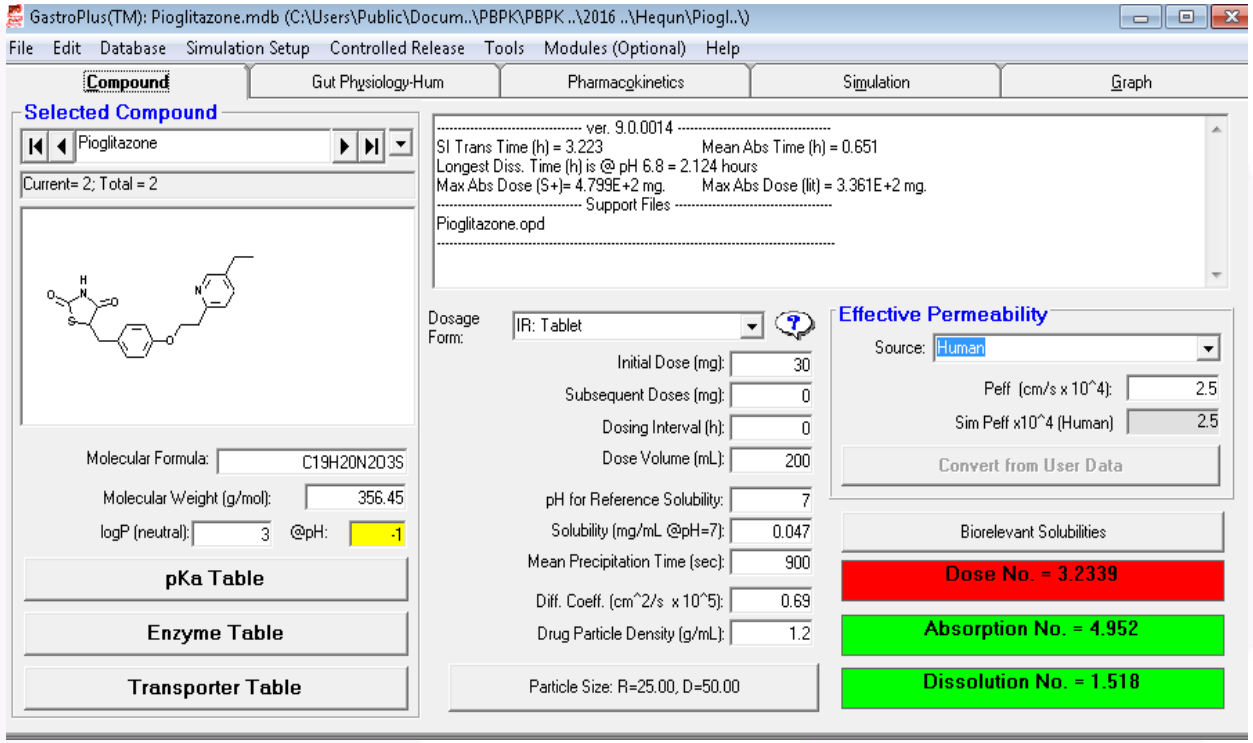


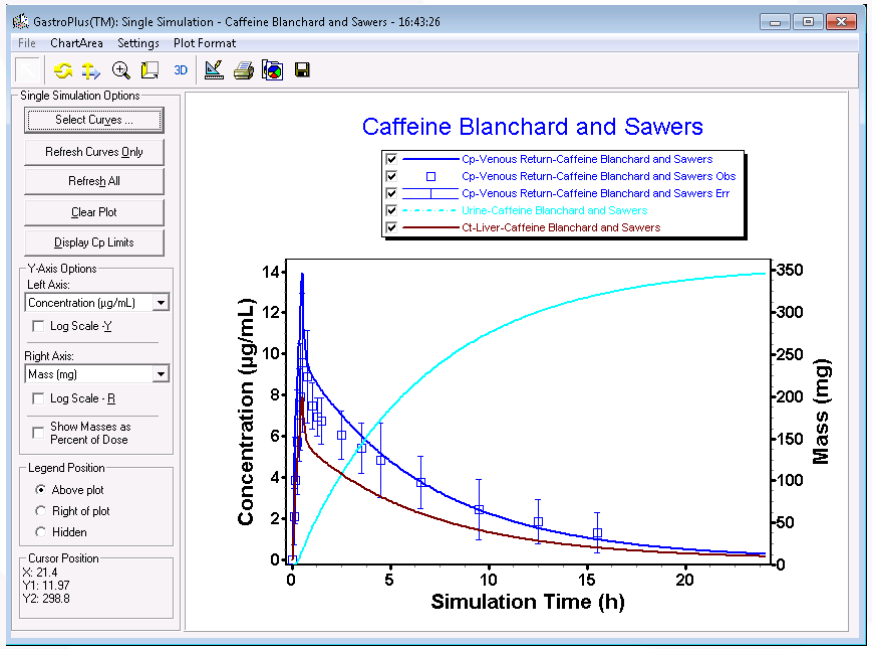
MEGen

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

PBK Tool: GastroPlus

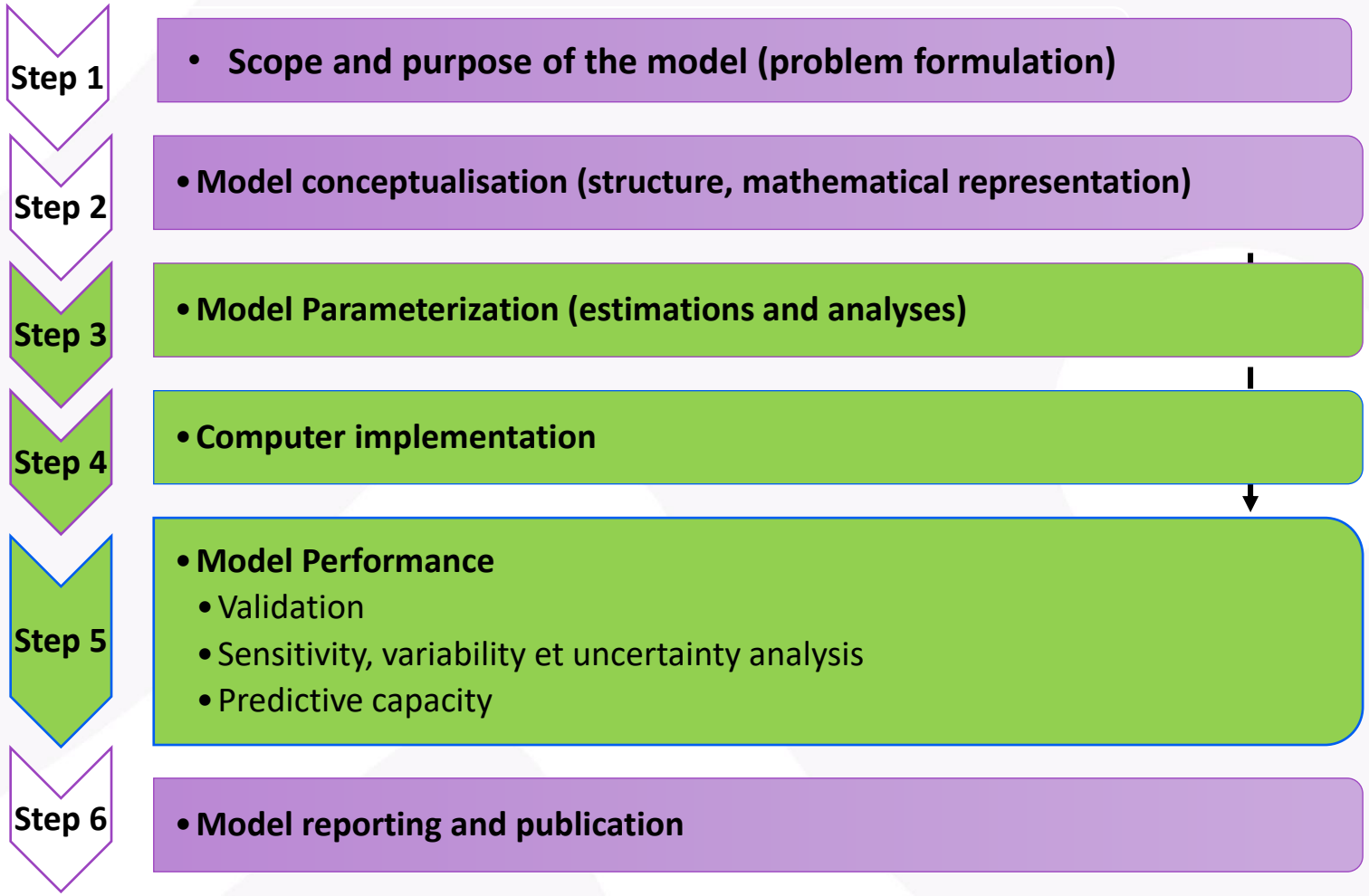






Other functions:
Sensitivity analysis
Uncertainty analysis

PBK Modelling Workflow: OECD 2021



OECD Guidance, 2021

Usefulness of PBK modelling in NGRA

NGRA:
human-relevant, **exposure-led**, hypothesis-driven and designed to prevent harm *(Dent et al,. 2018)*

- Estimating human exposure as early as possible in the safety assessment is crucial.

- When TTC is not sufficient to assure the safety, PBK modelling can be used to calculate internal metrics such as C_{max} or AUC of the test chemical, which may help to

  - Identify compartment(s) (plasma/organs) with highest exposure (e.g. BP4, phenoxyethanol)
  - Guide concentrations to be used for possible in vitro tests performed for the risk assessment
  - **Derive BER/MoE for decision making**

Dent, M., Teixeira, A.R., Amores Da Silva, P., Ansell, J., Boisleve, F., Masato, H., Hirose, A., Kasai, Y., Kern, P., Kreiling, R., Milstein, S., Montemayor, B., Oliveira, J., Richarz, A., Taalman, R., Vaillancourt, E., Verma, R., Posada, N.V.O.C., Weiss, C., Kojima, H., 2018. Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. Comput. Toxicol. 7, 20–26. https://doi.org/10.1016/j.comtox. 2018.06.001.

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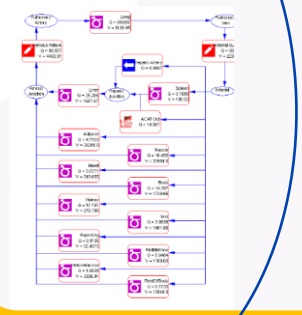
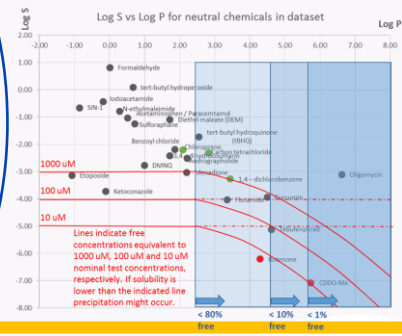
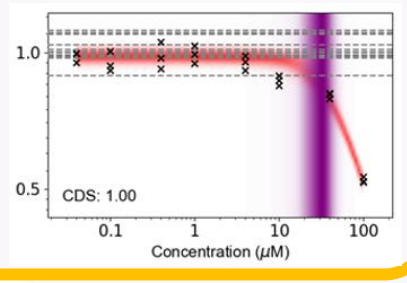
Toolbox and BER (MoE) Model Overview

PBK models

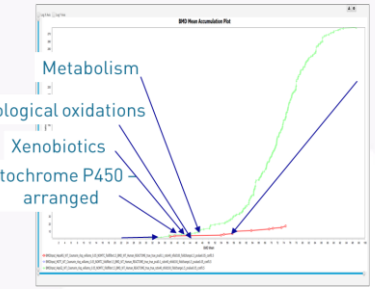


In vitro "True Dose" Dose Resp. models

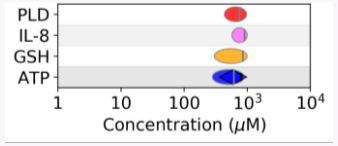




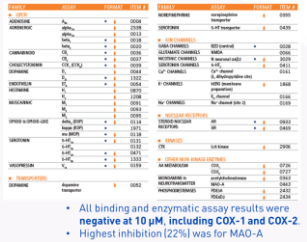
HTTr



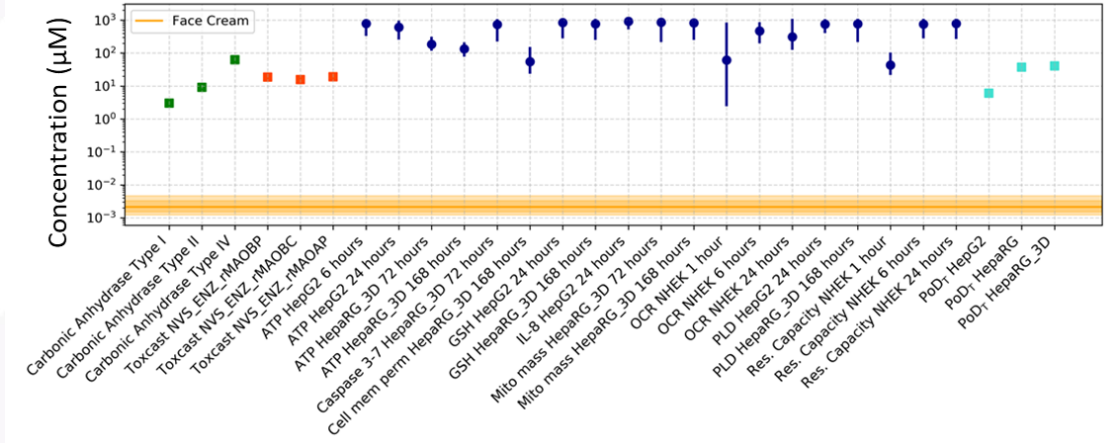
CSP



IPP



Bioactivity Exposure Ratio (BER)/ Margin of Exposure (MoE)



Inform safety decision

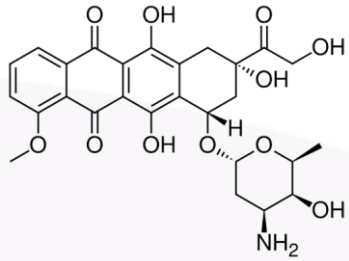
HTTr: High-throughput transcriptomics **CSP:** Cell Stress Panel **IPP:** In vitro pharmacological profiling

‘Traditional’ approach to constructing PBK models

Top-down PBK Modelling (empirical or data-driven modelling)

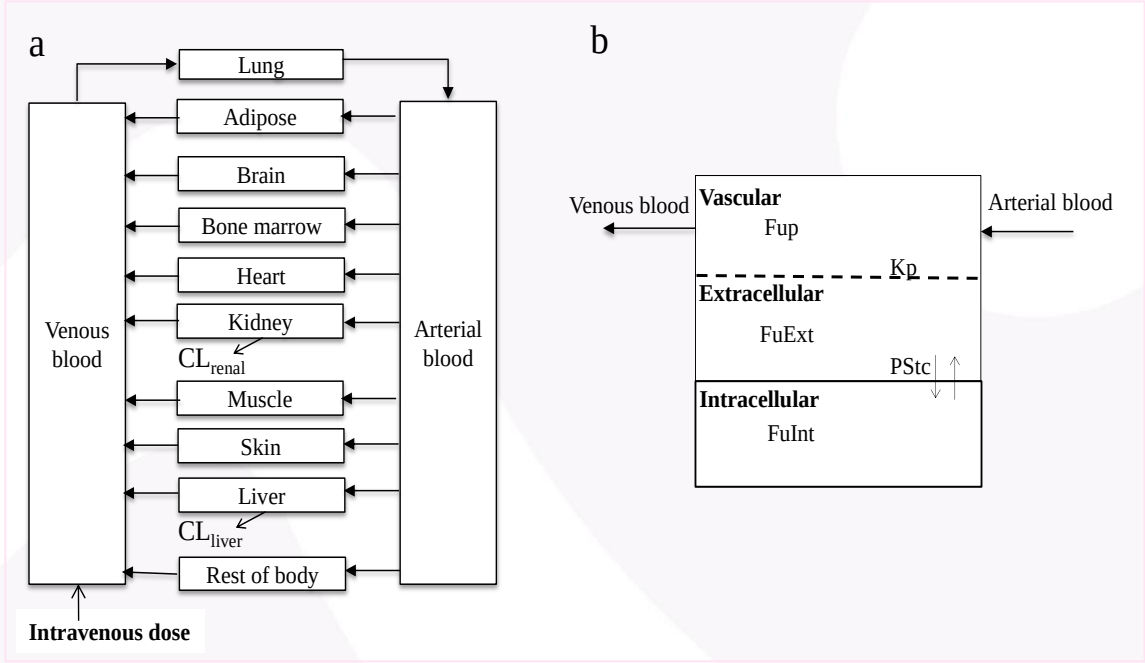
Doxorubicin case study–

- Chemotherapy medicine used to treat cancer
- PBK model developed to make estimation of systemic exposure (i.e. plasma and tissue C_{max} and AUC)
- Human PK data rich
- DOX binds to DNA



DOX

PBK structure

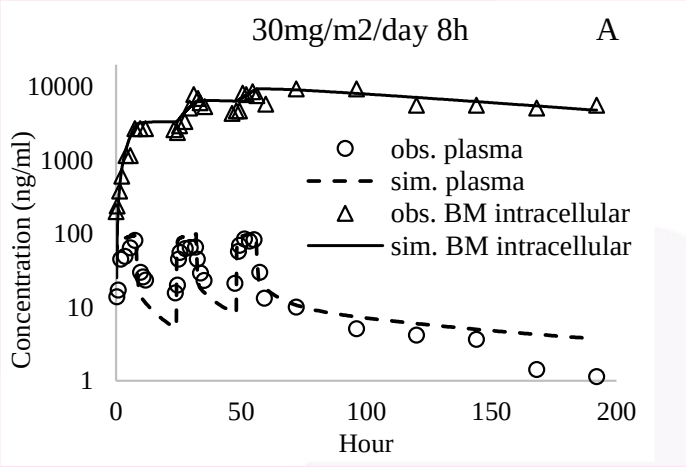


Li, H., et al., Next generation risk assessment (NGRA): Bridging in vitro points-of-departure to human safety assessment using physiologically-based kinetic (PBK) modelling – A case study of doxorubicin with dose metrics considerations, Toxicology in Vitro, Volume 74, 2021, 105171,

PBK model development for DOX: parameterisation

Parameters	Value	Source
Log P	1.27	(Hansch, Leo, & Hoekman, 1995)
Fup	25%	(Chassany, Urien, Claudepierre, Bastian, & Tillement, 1996) (Ryu et al., 2014)
p*Ka*	7.34(phenol); 8.46(amine); 9.46(est)	(SPARC, 2008)
CLtotal	0.894±0.308 L/h/kg	(Yoshida et al., 1994)
CLrenal	0.152±0.110 L/h/kg	(Yoshida et al., 1994)
Blood/plasma Conc Ratio	1.72±0.42	Value converted from the measured erythrocyte/plasma concentration ratio of 2.8±0.3 for DOX (Skorokhod et al., 2007)

Model development



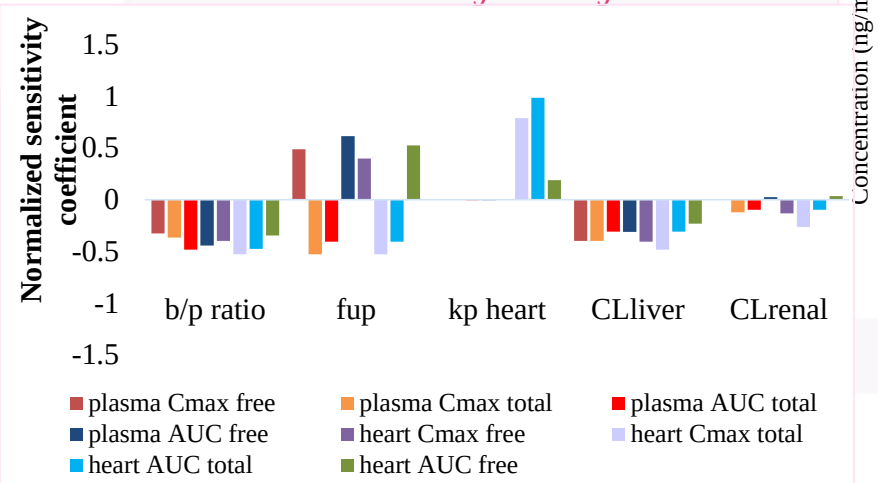
Speth et al., 1987a

Tissue	Kp	FuExt	FuInt	PStc (ml/s)
Lung	0.41	0.611	0.0005	10
Adipose	0.29	0.872	0.0005	10
Liver	0.31	0.795	0.0005	25
Heart	0.37	0.680	0.0005	10
Brain	0.29	0.874	0.0005	10
Bone Marrow	0.37	0.680	0.0005	10
Kidney	0.35	0.719	0.0005	10
Muscle	0.30	0.839	0.0005	10
Skin	0.46	0.546	0.0005	10
Rest of body	0.34	0.732	0.0005	10
Method	Poulin and Theil, 2000; Poulin and Theil, 2002		optimized	optimized

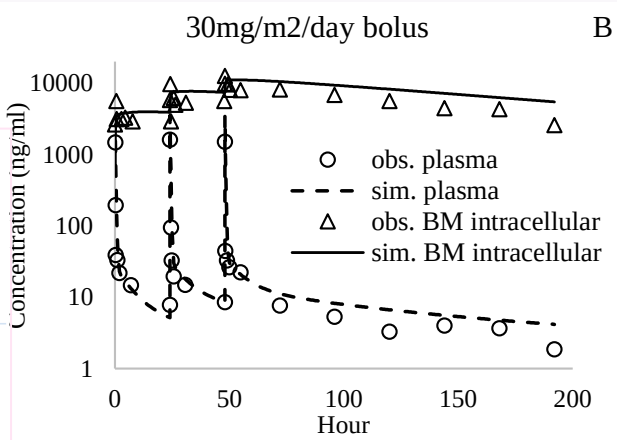
Kp, tissue/plasma partition coefficients; **FuExt,** unbound fraction in extracellular space; **FuInt**, unbound fraction in intracellular space; **PStc,** permeability*tissue cellular surface area product.

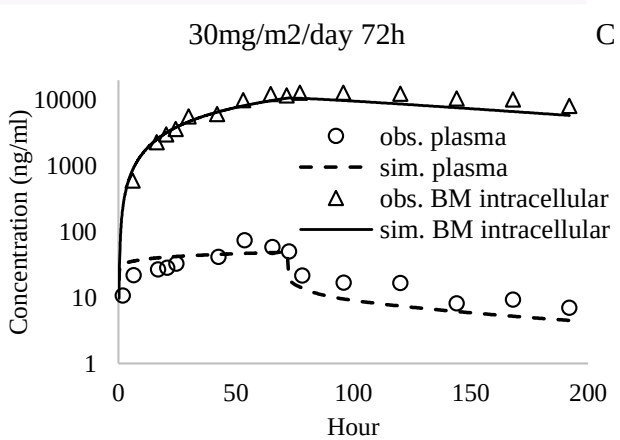
PBK model validation against human PK data

Local sensitivity analysis

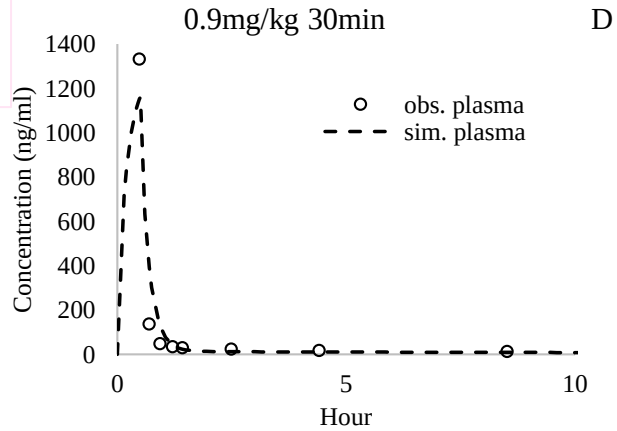


Model validation

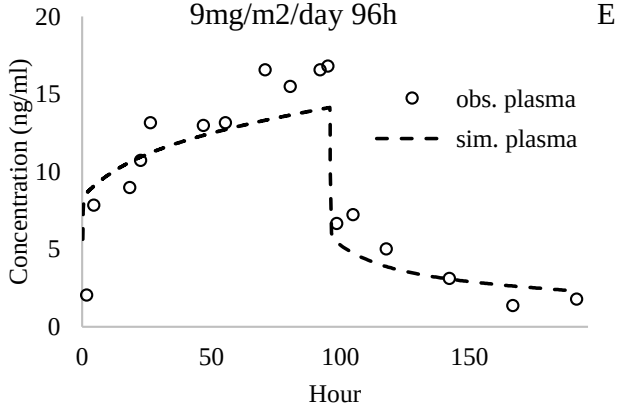




Speth et al., 1987a



Yoshida et al., 1994



Speth et al., 1987b

However, the primary challenge in utilizing PBK modeling in the cosmetic field is…..

Very few clinical PK studies are available on cosmetic ingredients to help validate/calibrate PBK models, and performing such studies is expensive and time consuming.

Therefore, the modelling strategy for cosmetic ingredients, when human data is lacking, is…

- parameterizing models partially or entirely **based on data from in vitro and in silico studies** in a **bottom-up** manner.

- using **relevant** and **robust** approaches for parameter determination to support the **reliability of input parameters** and provide a **sound biological basis** for the model structure.

- **addressing uncertainty**

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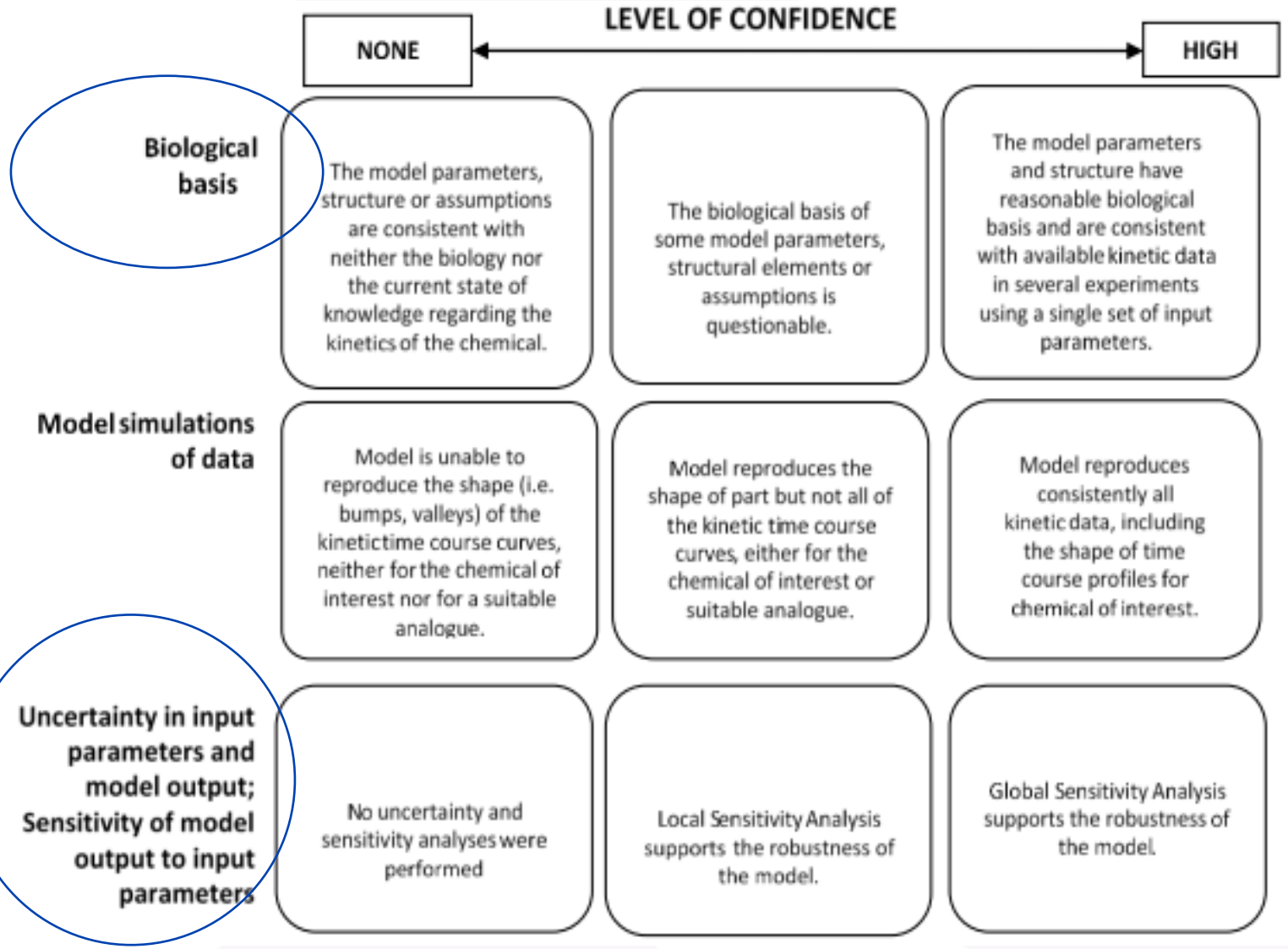
Key Questions –



PBK

How confident are we in the PBK models used for risk assessment?

- Where are we most/least confident?
- How wrong do we think we are?
- How can we address the spaces where we are least confident?

An illustrative scale of confidence levels for a PBK model (OECD Guidance, 2021)

Exposure estimation: from applied dose to internal exposure based on NAMs

Level 0:

Characterise exposure scenario (who, where, how often, and how much)

Product & chemical information

Level 1:

Predictions from in silico only

parameterisation & sensitivity

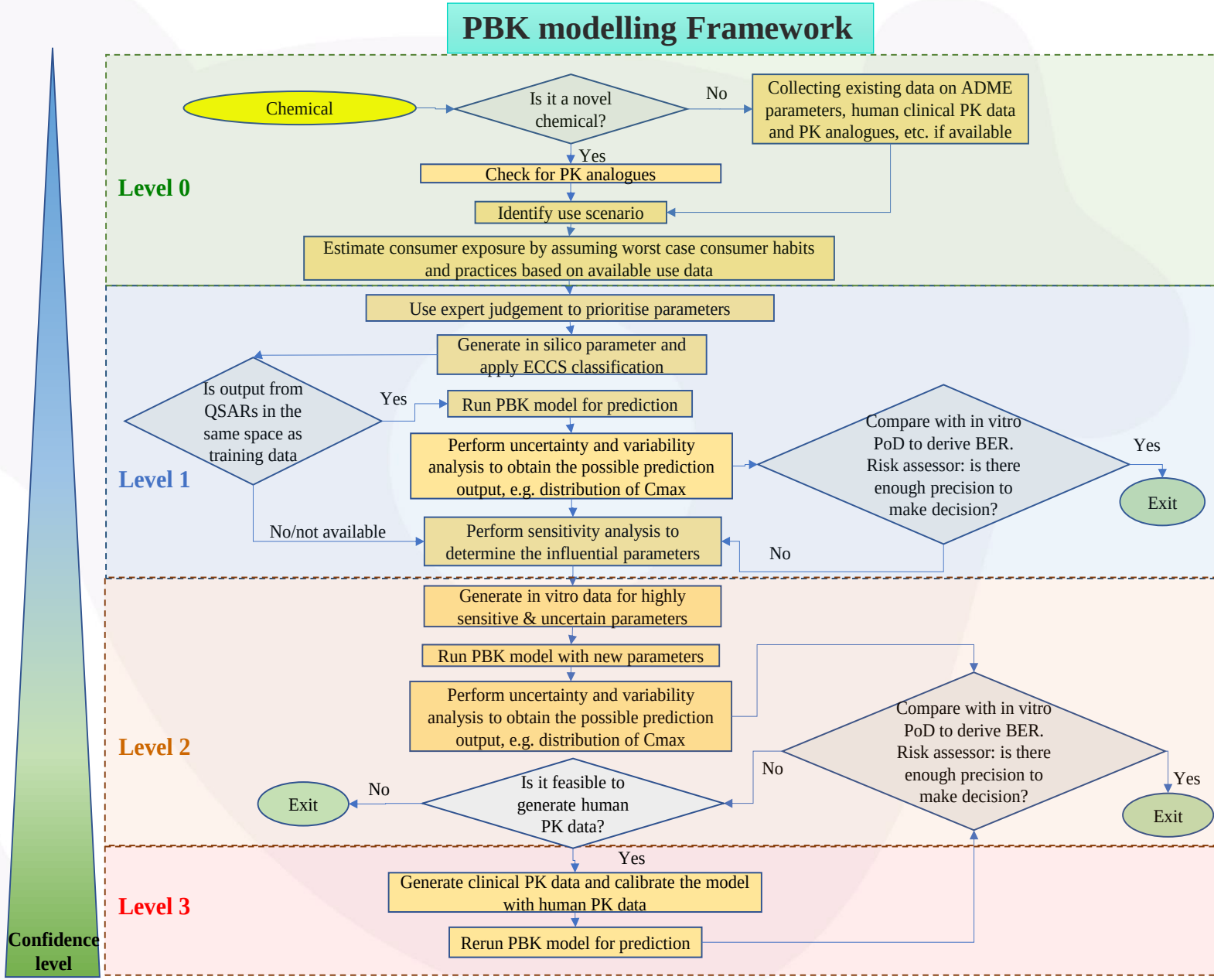
Level 2:

PBK modelling based on in vitro parameterisation

Level 3:

Generating human PK data for validation or/and calibration

- The progression between levels is closely related to the risk assessment process
- Use tools that are as complex as necessary to make the decision
- move to more complex tools if more data is needed



Li, H., et al., PBK modelling of topical application and characterisation of the uncertainty of Cmax estimate: A case study approach. Toxicology and Applied Pharmacology, 2022: p. 115992.

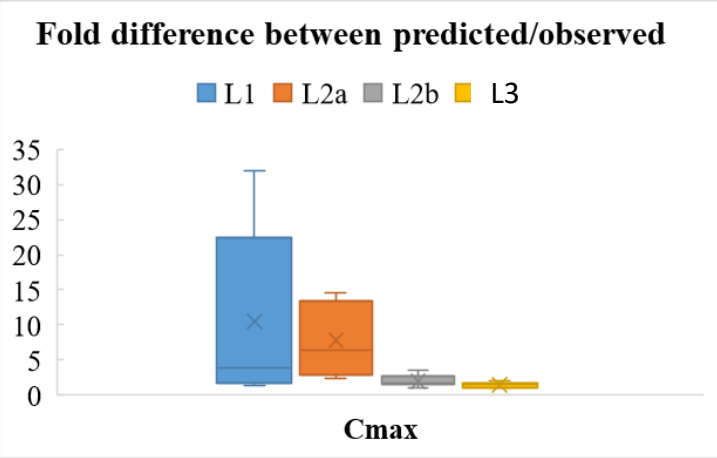
Phys-chem & ADME parameters required for building PBK model and the source to obtain/search the parameter values

Main parameters	Level 1-In silico predictions	Level 2-In vitro measurements		
	Source	Source (from literature or in-house experiments)		
Log P	ADMET predictor, EPA dashboard	Shake flask method	HPLC method	Website: PubChem, Drugbank, Chemspider
pKa	ADMET predictor, EPA dashboard			
Water solubility	ADMET predictor, EPA dashboard	Thermodynamic solubility assays		
Unbound fraction in plasma (f_{up})/protein binding	ADMET predictor	Rapid Equilibrium Dialysis assay (RED)	Ultrafiltration method	
Blood: plasma ratio	ADMET predictor	Blood partitioning method		
Hepatic intrinsic clearance (L/h)	ADMET predictor with total Human Liver Microsome	Human hepatocyte incubation/stability assay (ul/min/million cells)	Hepatopac for slow clearance chemicals (ul/min/million cells)	Human microsomal (or S9) incubation/stability assay) (µl/min/mg protein)
Renal excretion	Set to 0 or GFR*Fup, based on ECCS classification			
Tissue: plasma partition coefficient	Estimated using different algorithms in Gastroplus (mainly the Lukacova and Berezovsky equations)			
Intestinal absorption (for oral exposure)	ADMET predictor	Caco-2 assays		
Vehicle/Water partition coefficient	CosmoTherm (not applicable for complex formulations)	Fitted against skin pen data	PDMS system for formulation effect	
Stratum corneum/water partition coefficient	GastroPlus equations	Fitted against absorption vs time in receptor fluid and/or skin layers using ex vivo human skin	Direct measurements in different skin layers using ex vivo human skin	Extrapolating skin pen to infusion rate
Stratum corneum diffusivity (cm2/s)				
Epidermis/water partition coefficient				
Epidermis diffusivity (cm2/s)				
Dermis/water partition coefficient				
Dermis diffusivity (cm2/s)				

Case study: PBK simulation of topical clinicals for five chemicals

caffeine

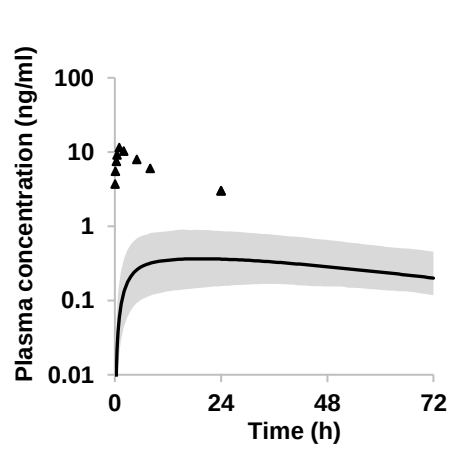
Level	Skin Absorption	DME parameters	
1	In silico	In silico	
2a	In silico	In vitro	
2b	In vitro	In vitro	
3	In vitro	In vitro	Calibrated against human IV/Oral PK data



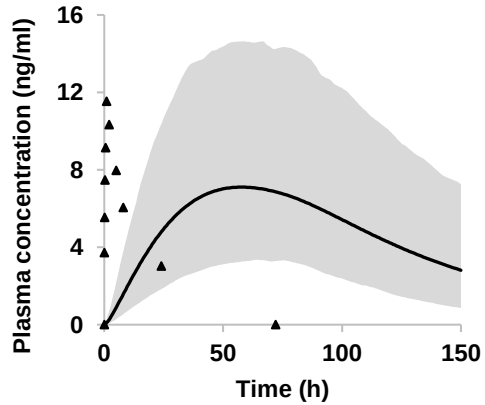
Confidence on Cmax prediction increased

from using solely in silico data
to in vitro data from our best approaches

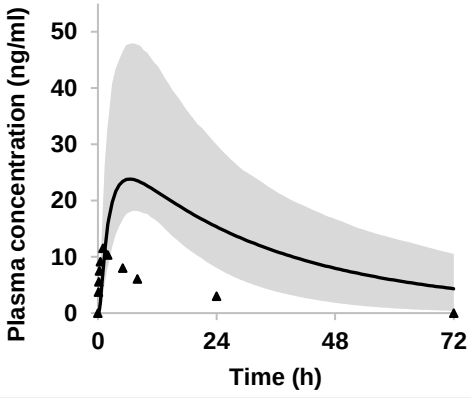
Level 1



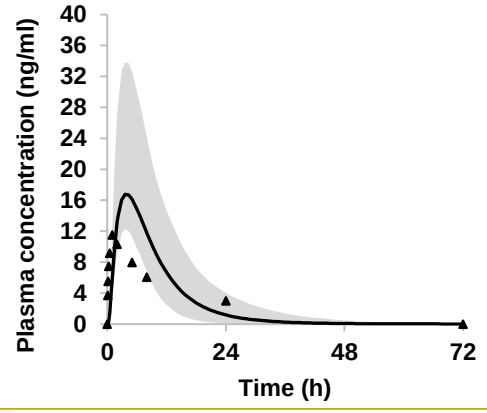
Level 2a



Level 2b



Level 3

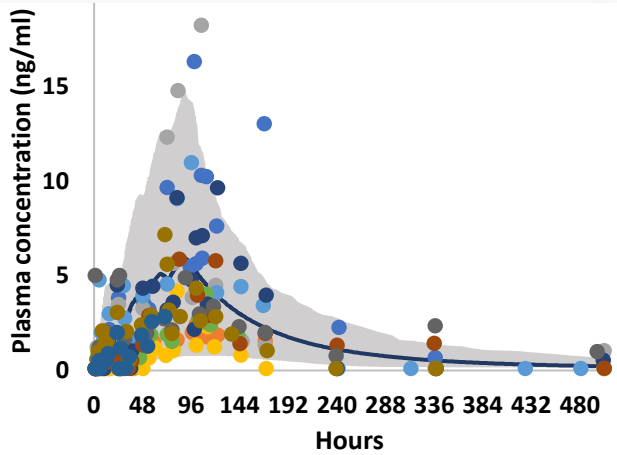


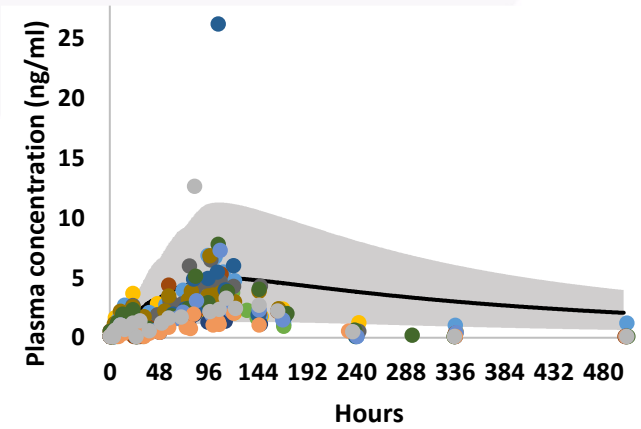
Paper in preparation

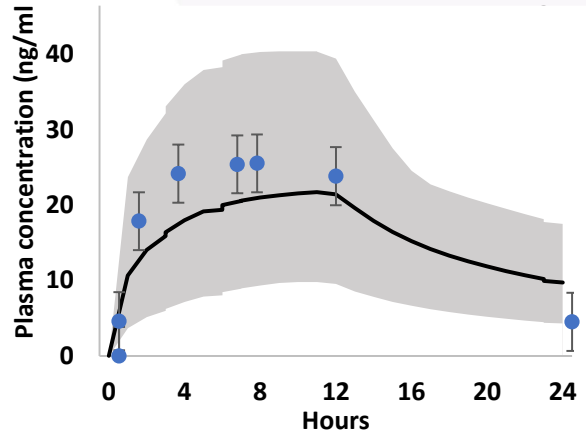
Li, H., et al., PBK modelling of topical application and characterisation of the uncertainty of Cmax estimate: A case study approach. Toxicology and Applied Pharmacology, 2022: p. 115992.

More case study: Level 2 PBK model constructed based on quality in vitro data

comparison between observed (dots, different color represents different subject data and PBK simulated (solid curve, mean) plasma concentration time profiles ***<u>for three UV filters</u>***







Li, H., et al., ADME characterisation and PBK model development of 3 highly protein-bound UV filters via topical application: essential considerations and lessons learn, in preparation

Strategies in addressing uncertainty in PBK estimation

Deterministic PBK modelling

Point estimate values for input parameters

Model

Individual modelled (30 year-old 60 kg female, European)

Probabilistic population PBK modelling

Parameter Uncertainty ('informed' distribution for the most sensitive parameters)

Model

Population Variability

Probabilistic population PBK+ CMED modelling

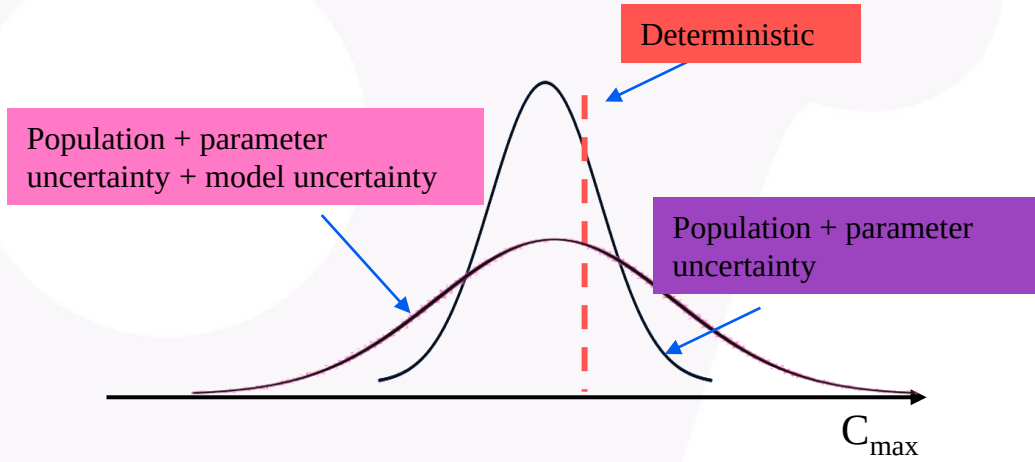
Parameter Uncertainty

Model Uncertainty

Model

Population Variability

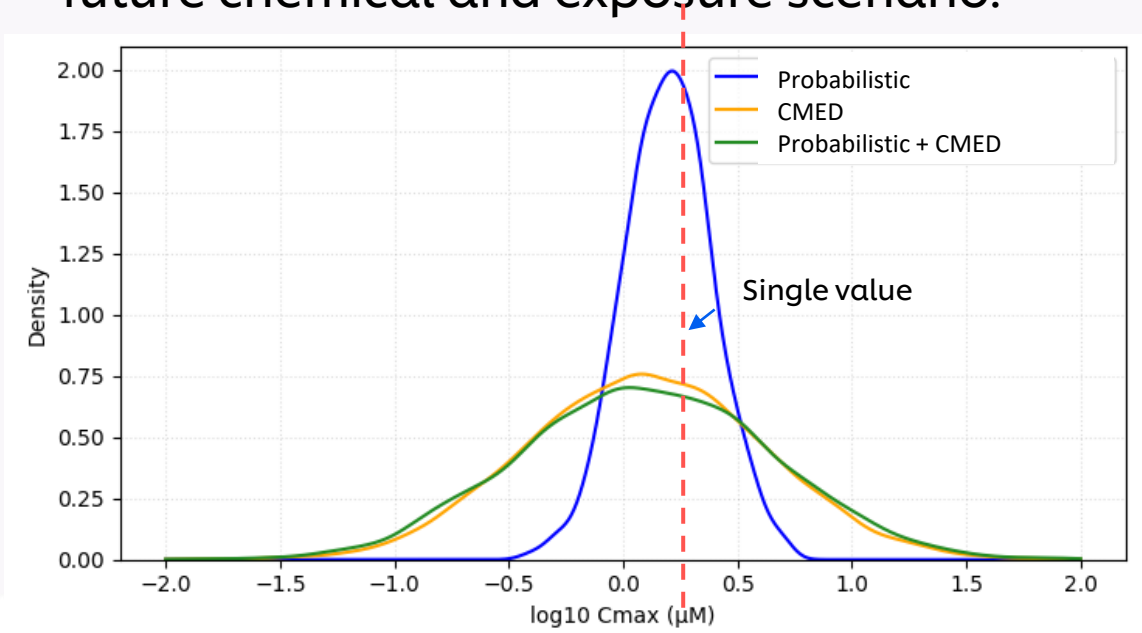
Predicted C_{max} based on different approaches characterising uncertainty



Probabilistic PBK modelling + CMED model to account for population, parameter and model uncertainty

To account unknown-unknows e.g. model uncertainty

- C_{max} Error Distribution (CMED): A complementary approach to characterise PBK prediction uncertainty as published in *Li et al. 2022* and *Middleton et al.* 2022.
- This model can be used to estimate the distribution of the possible prediction errors for future chemical and exposure scenario.



Plasma C_{max} estimations (µM)

PBK model for female adult 60 kg individual	**Distribution of C_{max} (probabilistic simulation+CMED)**	
point estimate	**Median**	**95th percentile**
2.1	1.3 (0.11, 15)	9.8

Example of BP4

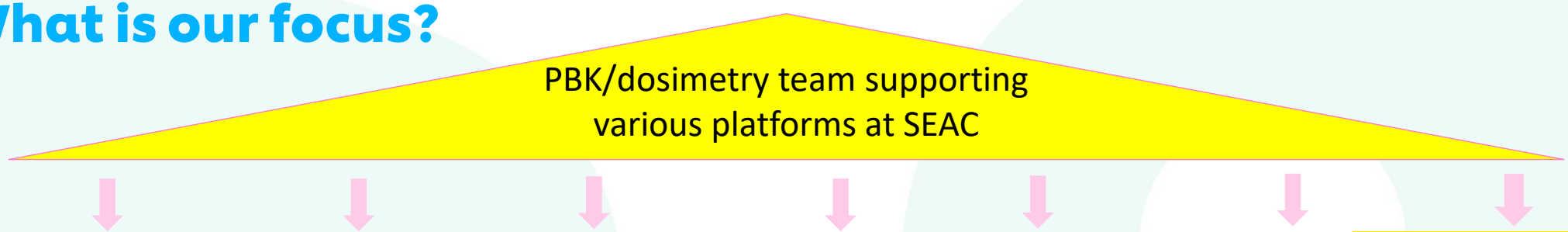
Li H, Reynolds J, Sorrell I, Sheffield D, Pendlington R, Cubberley R, Nicol B. PBK modelling of topical application and characterisation of the uncertainty of Cmax estimate: A case study approach. Toxicol Appl Pharmacol. 2022 May 1;442:115992. doi: 10.1016/j.taap.2022.115992. Epub 2022 Mar 25. PMID: 35346730.

Middleton, A.M., et al., Are Non-animal Systemic Safety Assessments Protective? A Toolbox and Workflow. Toxicological Sciences, 2022. 189(1): p. 124-147.

PBK modeling and dosimetry team

Get to know our team!

What is our focus?



Systemic safety platform
- Improving L2 PBK confidence (highly bound to plasma proteins chemicals)
- Formulation effect on dermal absorption
- Quantifying uncertainty

LRSS case studies
- Active transporter investigation

DART platform
- Placental transfer capability build

ECHA
- ADME data generation and PBK modelling strategy on mixture
- Occupational exposure modelling

Environment safety
- One compartmental modelling on exposure estimation in fish

Digital platform
- In silico ADME prediction workflow and evaluation

Gaps to address
- Evaluation of different PBK software for regulatory acceptance
- Best practice in skin pen modelling
- Liver models comparison

Capability build

Business risk assessment/Dossier submission (e.g. SCCS, ECHA)

Application

Upskilling and training the team

ICCS/ CosEU | **RiskHunt3r** | **WUR/WFSR** | **EPAA** | **MSCA** | Syngenta | NICEATM | EPA | CFSA

External activities

Unilever