ONTOX HT-PBK: High-throughput PBK modelling for the *in silico* prediction of chemical levels in humans

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... because the dose makes the poison!

Background

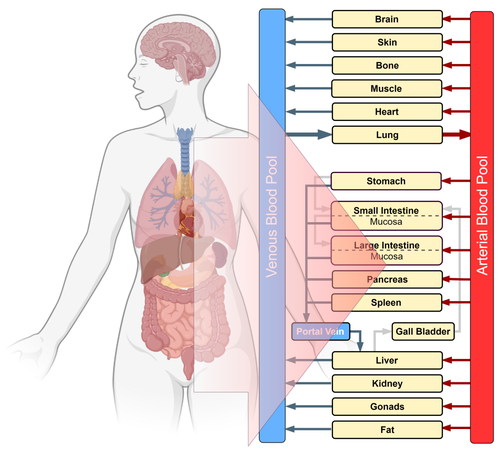

Figure 1: The generic structure of a whole-body PBK model.

Physiologically-based kinetic (PBK) modelling is a computational method that allows the prediction of toxicokinetics, i.e. the *in vivo* distribution of chemicals in the body.

Traditionally, models are build by progressively integrating **data from animal and human studies**.

The Problem

Next Generation Risk Assessment (NGRA) requires the prediction of toxicokinetics

a) **without animal or human data**
b) in **high-throughput**

to be able to assess the risk of thousands of chemicals without the need for animal testing.

The Solution

A **Next Generation/High-throughput PBK modelling** strategy that solely relieson data from *in silico* and *in vitro* sources to build reliable and accurate PBK models.

Our Strategy

1. **Predicting** relevant chemical properties (clearance, fu etc.) with various *in silico* tools

2. **Simulating** daily oral exposure using predicted properties for PBK modelling

3. **Categorising** compounds based on their total amount in the body

Validation

Our approach is based on a study previously performed within the ONTOX project using data of

200+ chemicals

2000+ concentration-time profiles (i.v. and oral)

Paper submitted: *"Systematic Evaluation of High-throughput PBK Modelling Strategies for the Prediction of Intravenous and Oral Pharmacokinetics in Humans"* - Geci et al. (2024)

Property predictions

OPERA · Bayer · ADMETlab 2.0 · Chemaxon · pkCSM - pharmacokinetics · ProtoPRED

Lipophilicity
Fraction unbound
Clearance
Solubility
CACO2
... and more

Software

PK-Sim® · R Programming

PBK Simulation Examples

PBK models integrate all information about:

- Lipophilicity
- Solubility
- Intestinal permeability
- Fraction unbound
- Clearance

etc.

to predict compound concentrations in the body.

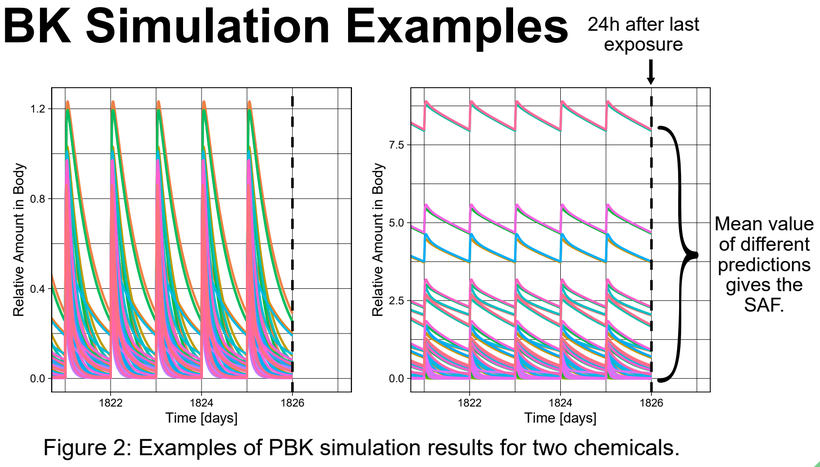

Figure 2: Examples of PBK simulation results for two chemicals.

Systemic Availability Factor (SAF)

$$\text{Systemic Availability Factor (SAF)} = \frac{\text{Amount in the body (24h after last exposure)}}{\text{Average Daily Dose}}$$

SAF > 200% = High Systemic Availability
10% < SAF < 200% = Medium Systemic Availability
SAF ⩽ 10% = Low Systemic Availability

Example

Amount in the body: 0.6 µg / Average Daily Dose: 1 µg = SAF is 60%

Categorisation Results

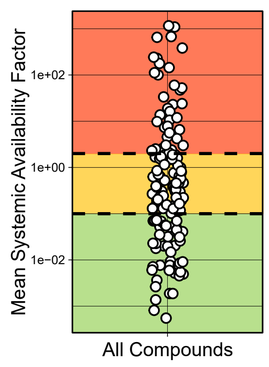

Figure 3: Distribution of calculated Systemic Availability Factors of all Designathon compounds.

High Systemic Availability: 38 compounds

Medium Systemic Availability: 56 compounds

Low Systemic Availability: 44 compounds

Examples

Vitamin D2, PFOA, Bifenthrin, Hexabromocyclododecane...

Valproic Acid, Ketoconazole, D-Sorbitol...

Cyanamide, Benzoate, Asparagine...

Not applicable: 12 compounds due to high molecular weight, or being organometallics outside the applicability domain of the utilised in silico tools.

Outlook

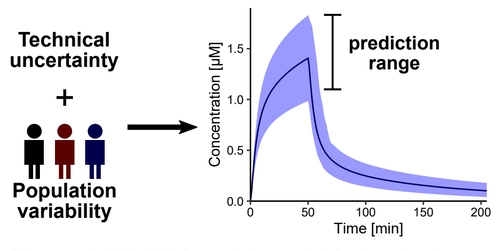

Figure 4: HT-PBK models could further be integrated with demographic data to also capture population variability in model simulations.

Open Questions

1. Conceptual relevance:
Is the total amount in the body the most relevant readout? Are peak concentrations more relevant?

2. Validation of categorisation:
What kind of data could be used to confirm that categorisation results are "correct"?

OPEN SYSTEMS PHARMACOLOGY · esqLABS WE EMPOWER HEALTH CARE · UNIKLINIK RWTH AACHEN · ONTOX

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