Application of a high throughput physiology based pharmacokinetic/toxicokinetic (httk) dermal route using human in vivo caffeine exposure data

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Introduction

- Exposure to caffeine may occur through beverages, food supplements, and cosmetic products (hair and makeup products)
- Caffeine is a well-studied chemical with known pharmacokinetics parameters in humans (Otberg et al 2008)
- Toxicokinetic data for caffeine is also available in rodents and available for extrapolation
- Due to the amount of available data, caffeine can be a case example for PBPK modeling including dermal absorption.
- In vitro technology exists for quantification of caffeine dermal absorption
- PBPK modeling in combination with in vitro data have become an important application for risk assessment
- Httk (high throughput toxicokinetics) is an open source generic PBPK model available for evaluation of chemicals
- A dermal route has been added to httk
- Caffeine is being used as a case study for dermal evaluation with httk

Potts-Guy Equation

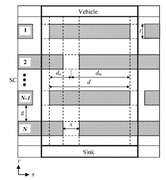
The Potts-Guy equation uses Quantitative structural-activity relations (QSAR) to predict dermal penetration, Kp in cm/h. Molecular descriptors used are MW and logP.

QSAR -> MW and logP → Kp, cm/h

$$\text{LogKp (cm/h)} = -2.7 + 0.71\text{logP} - 0.0061\text{MW}$$

Surrey 2D Model

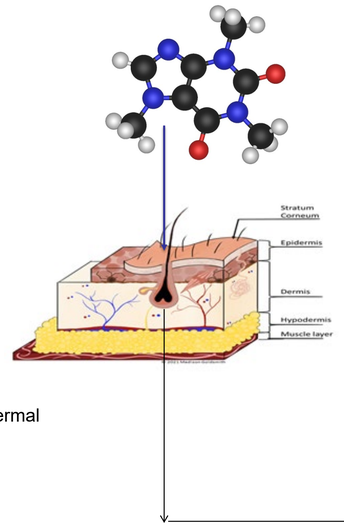
The Surrey 2D model combines QSAR with a mechanistic diffusion model to determine Kp

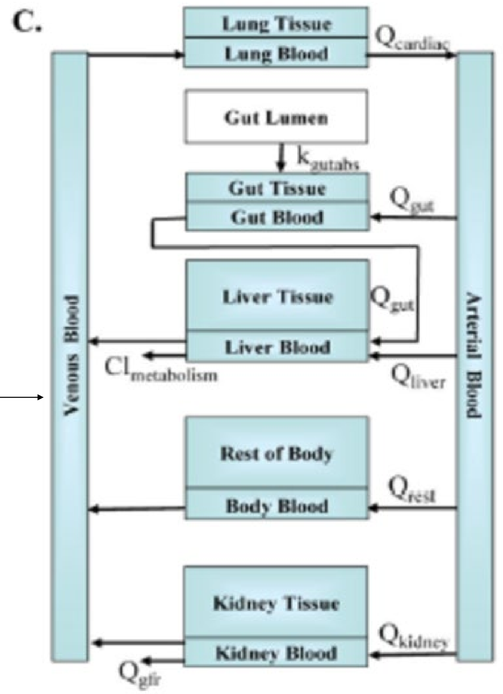
QSAR -> MW and logP →  → Kp, cm/h

Diffusion model of SC layers

$$\text{logKp (cm/h)} = -2.55 + 0.65*\text{logP} - 0.0085*\text{MW}$$

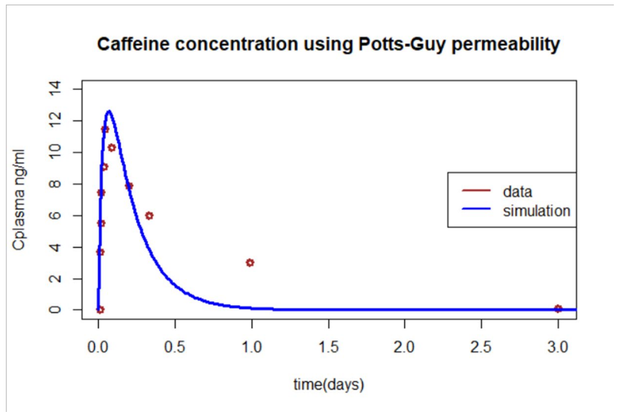
High throughput toxicokinetics (httk)

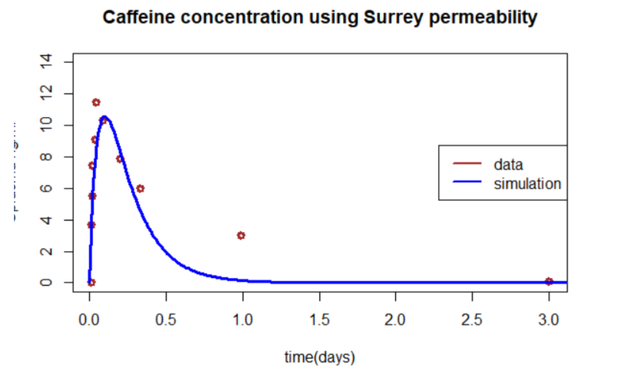




Generic PBPK (httk) with dermal route added

Potts-Guy and Surrey model comparison





Summary

- Caffeine was used to evaluate dermal predictions obtained with httk
- httk was successfully adapted to include a dermal route to predict dermal absorption
- Both permeability estimates (Potts-Guy and Surrey) achieved similar plasma concentration prediction
- The largest uncertainty in physiological estimates needed were:
  - Metabolic clearance ranging from 0.1 to 1 L/hr/kg(Li et al., 2022)
  - Fraction unbound ranging from 0.65-0.8(Li et al., 2022)

Otberg, N., et al., 2008. The role of hair follicles in the percutaneous absorption of caffeine. Br. J. Clin. Pharmacol. 65 (4), 488–492.

Li, H., Reynolds, J., Sorrell, I., Sheffield, D., Pendlington, R., Cubberley, R., & Nicol, B. (2022). PBK modelling of topical application and characterisation of the uncertainty of Cmax estimate: A case study approach. *Toxicology and Applied Pharmacology*, *442*, 115992.