Establishing scientific confidence in PBK models for QIVIVE in the absence of in vivo kinetic data

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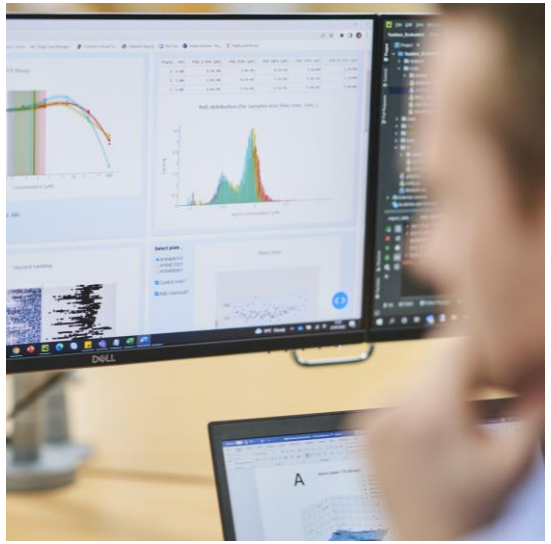

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PBK modelling in next generation risk assessment (NGRA)

- PBK modelling critical in NGRA to predict **internal concentrations** for quantitative in vitro to in vivo extrapolations (QIVIVE)
- At present (human) in vivo is still needed to validate the model, which are often not available
- Exploring means to establish scientific confidence in PBK **model prediction without in vivo data** is needed

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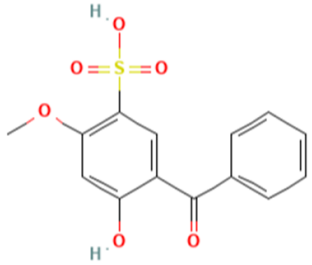
Case study on Benzophenone-4 (BP-4)

- **BP-4 is an UV-filter ingredient used in sunscreen cosmetics** to prevent sunburns or photodegradation by inhibiting the infiltration of UV light.
- In 2019, the European Commission defined a list of 28 cosmetic ingredients with potential endocrine activity, including BP-4.
- Case study work with Cosmetic Europe Long Range Science Strategy (LRSS) on developing new approaches for safety assessment without using animals
- **PBK model development of BP-4 based on NAMs** to make estimates of systemic exposure levels in NGRA



Chemical name: Benzophenone-4 (Sulisobenzone)

CAS: 4065-45-6

EINECS: 223-772-2

SMILES: COC1=C(C=C(C(=C1)O)C(=O)C2=CC=CC=C2)S(=O)(=O)O)

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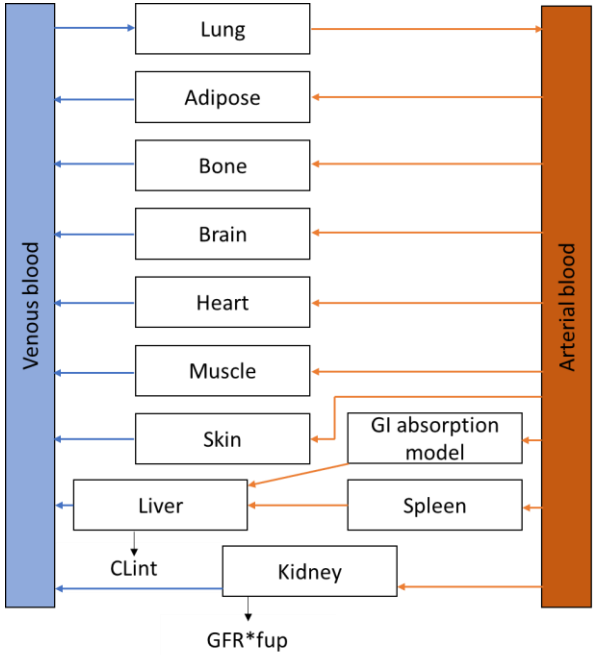
PBK model development based on in vitro and in silico input data

Core model input:

- Absorption (dermal in case of BP-4)
- Partition coefficients, fraction unbound, blood:plasma ratio
- Liver metabolism
- Passive renal excretion (glomerular filtration rate * fraction unbound)

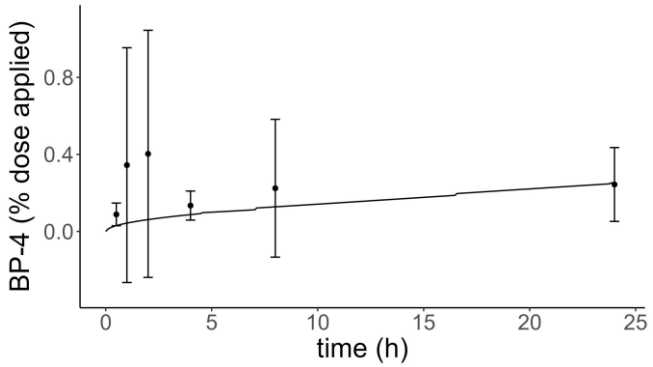


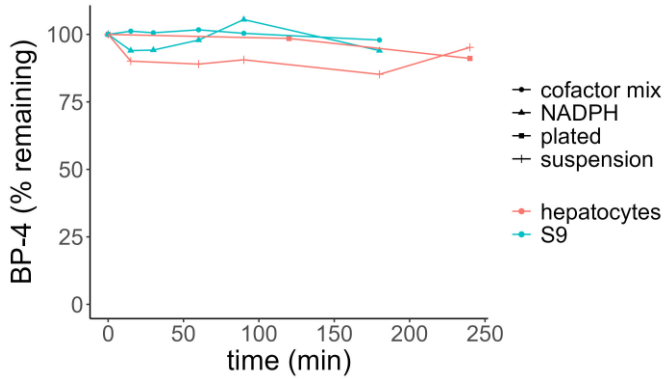
Advanced input (when needed):

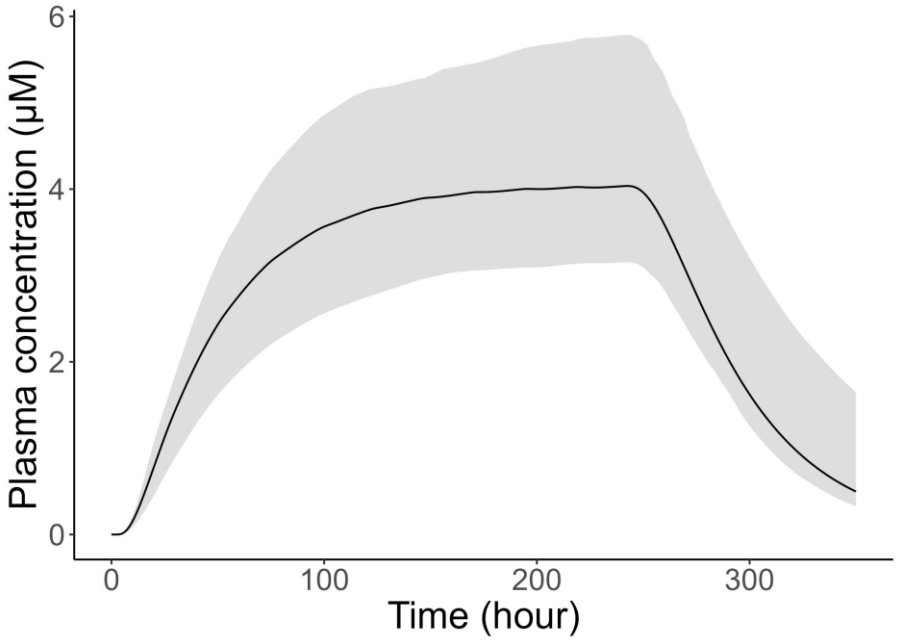
e.g. transporter kinetics , extrahepatic metabolism, enterohepatic circulation (depending on the results of the Core model)

Core PBK model results BP-4

- Limited dermal absorption (±0.4% within 24h, based on an in vitro skin penetration study)
- No metabolic clearance (S9, hepatocytes)
- In silico partition coefficients, in vitro Fup (0.0157) and BP (0.6)
- Predicted plasma concentration 4 µM (3.2-5.8 µM) after 10 days of using 18g (5%) product per day (2 applications, 1 shower/rinse off/day)
- Limited cell permeability and lack of metabolic clearance suggest a role of transporters in BP-4 kinetics

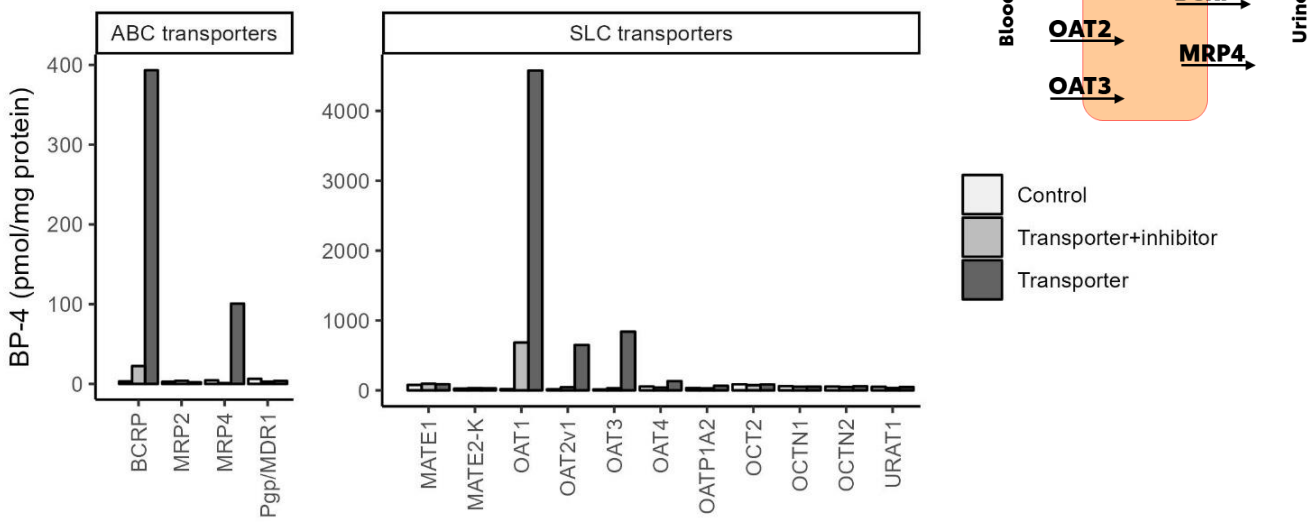


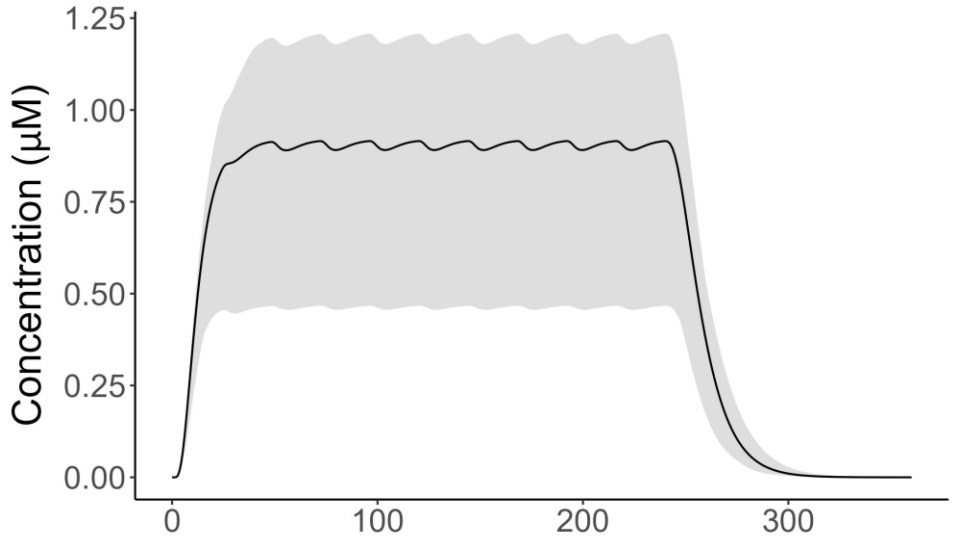




Advanced data collection BP-4

- BP-4 is a substrate of OAT1, OAT2, OAT3, BCRP, and MRP4.
- In vitro kinetic constants scaled in the PBK model to liver and kidney based on the relative expression.
- Net efflux is predicted
  - BP-4 moves from blood to cells via OAT1/2
  - BP-4 moves from cells to urine or bile via BCRP and MRP4.
- Predicted plasma concentration 0.9 µM (0.4-1.24 µM)
  - 10 days of using 18 mL product per day (2 applications, 1 shower/rinse off/day)
  - Sensitivity analysis: dermal absorption, OAT1 kinetics are the key input parameters





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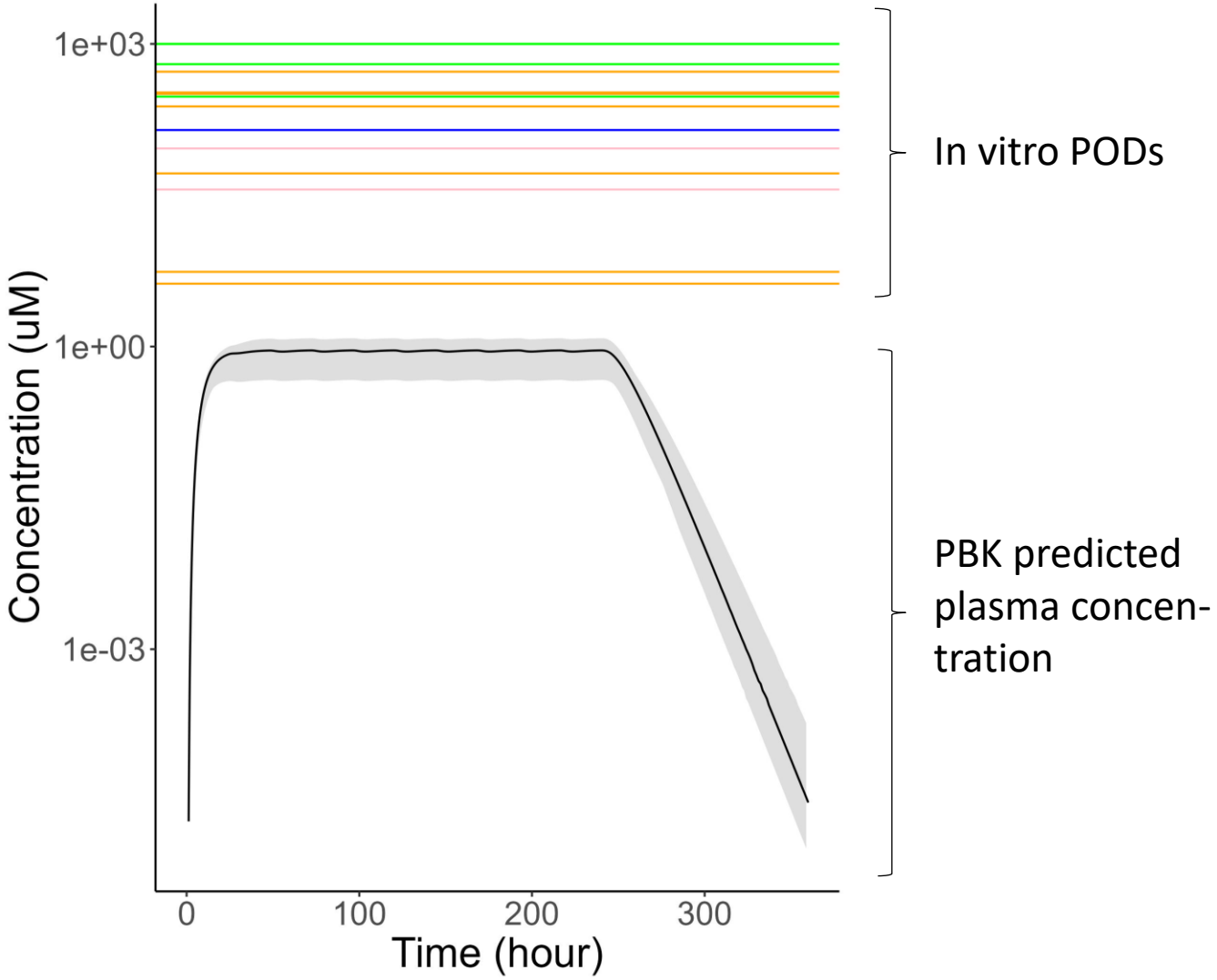
Use of the PBK model results in a NGRA

Conclusion: BP-4, used as a UV filter in body lotion at a concentration of 5%, does not exhibit significant biological activities at consumer-relevant exposures



Establishing scientific confidence in PBK models without support of human in vivo data

- Use chemical characteristics to identify key kinetic processes. (e.g., BP-4's lack of metabolic clearance and low tissue permeability suggest transporter involvement).
- Making use of good quality of in vitro and in silico input data.
- Sensitivity analysis, uncertainty analysis, population variability

Next steps:

- Apply various PBK software (commercial software versus R script).
- Learn from compounds with known human in vivo data.
  - ➢ e.g. define the general level of uncertainty that can be expected in the model predictions, and to develop decision trees for PBK model development.

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