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Best practices in physiologically based kinetic (PBK) modelling for next generation risk assessment (NGRA)

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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 data is still needed to validate a model, which are often not available
- Best practices are needed to establish scientific confidence in PBK **model predictions without in vivo data**

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Best practices in PBK modelling for NGRA

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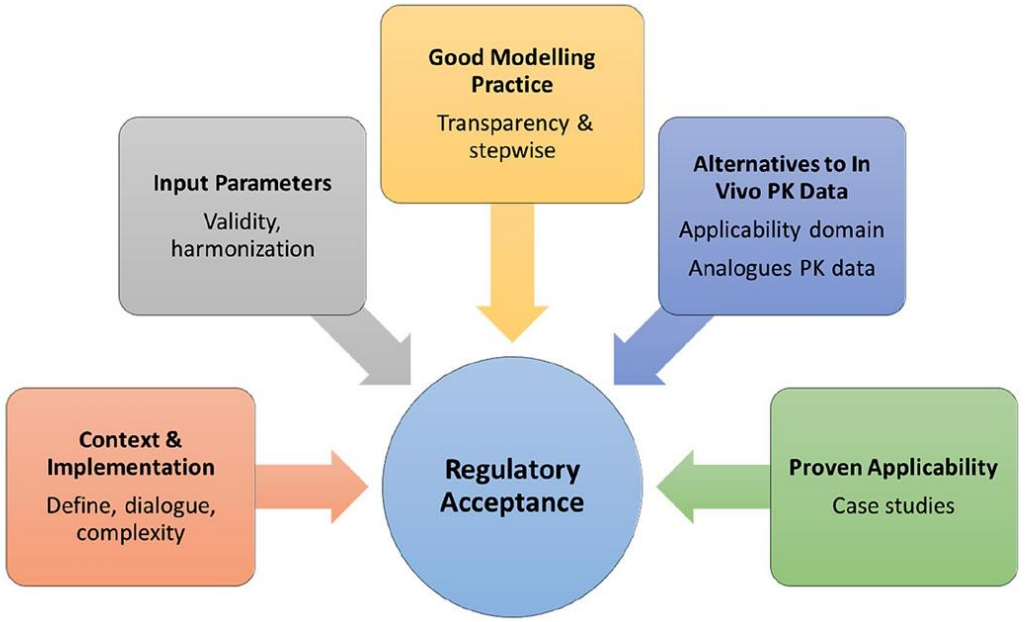
- Communication (context of use and transparency in the modelling approach)
- Validity and harmonisation of input parameters
- Alternatives to evaluation against in vivo data (building confidence without reliance on in vivo data)
- Demonstrated applicability based on case studies



ECETOC expert workshop, recommended steps to improve regulatory adoption of PBK models (Najjar et al (2022) *Arch Tox*, Volume 96)

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Communication: OECD guidance 331

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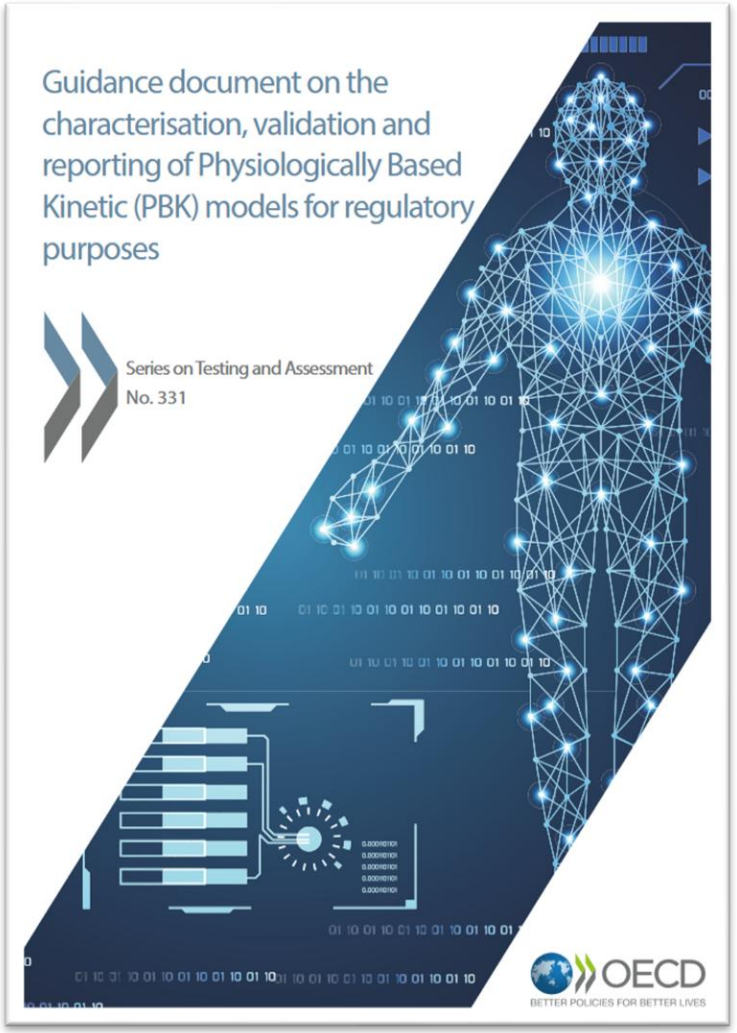
- Guidance on PBK model development (including in vitro and in silico inputs)
- **Transparent reporting** (including a template covering context of use, modelling strategy, data sources, model code, sensitivity analysis, and model evaluation)
- Checklist to support regulatory evaluation
- Case studies demonstrating practical applications



OECD 331 (2021), currently being revised

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In vitro and in silico methods to parameterize PBK models

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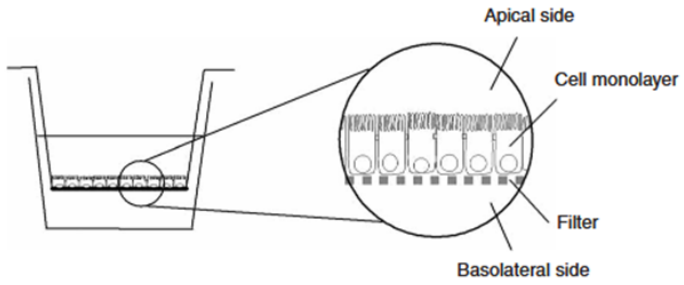
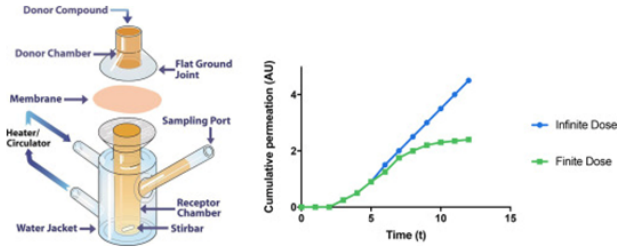
Caco-2 model for intestinal absorption



e.g. Hubatsch et al (2007), *Nature Protocols 2, 2111-2119*

Skin absorption (Franz cell)



e.g. Lane (2024), *European Journal of Pharmaceutical Sciences 201, 106873*

Metabolic clearance (hepatocytes, S9 or microsomes)

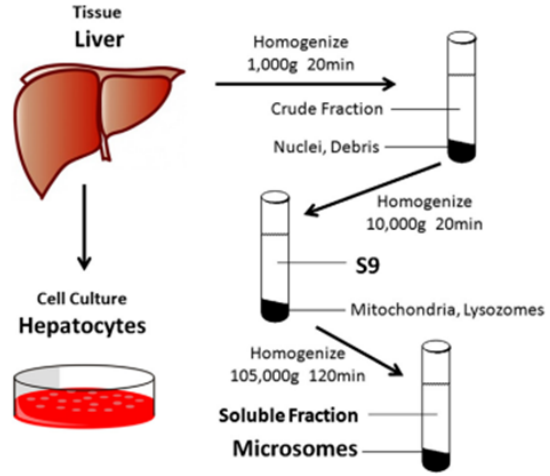
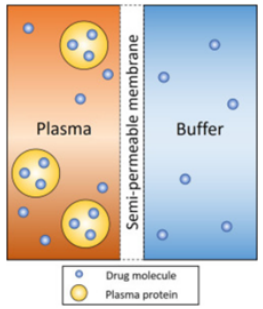


FIGURE 3.6 Preparation of microsomal, S9, and soluble fractions commonly used in drug metabolism studies.

e.g. Vrbanac and Slauter (2016), *ADME in Drug Discovery. Book: A Comprehensive Guide to Toxicology in Nonclinical Drug Development, pp. 39-67*

Plasma protein binding



e.g. Hann et al. (2022), Chapter Three - The importance of plasma protein and tissue binding in a drug discovery program to successfully deliver a preclinical candidate. *Book: Progress in Medicinal Chemistry, pp. 163 - 214*

Partition coefficients (in silico based on logP and pKa)

$$Kpu = \left[\begin{array}{l} f_{EW} + \left(\frac{1+X}{1+Y} \cdot f_{IW} \right) \\ \quad + \left(\frac{(P \cdot f_{NL} + ((0.3P + 0.7) \cdot f_{NP}))}{1+Y} \right) \\ \quad + \left(\frac{Ka \cdot [AP^-]_T \cdot X}{1+Y} \right) \end{array} \right]$$

e.g. Rodgers and Rowland (2006), *Journal of Pharmaceutical Sciences 95, 1238-1257*

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Best practices for in vitro measurements

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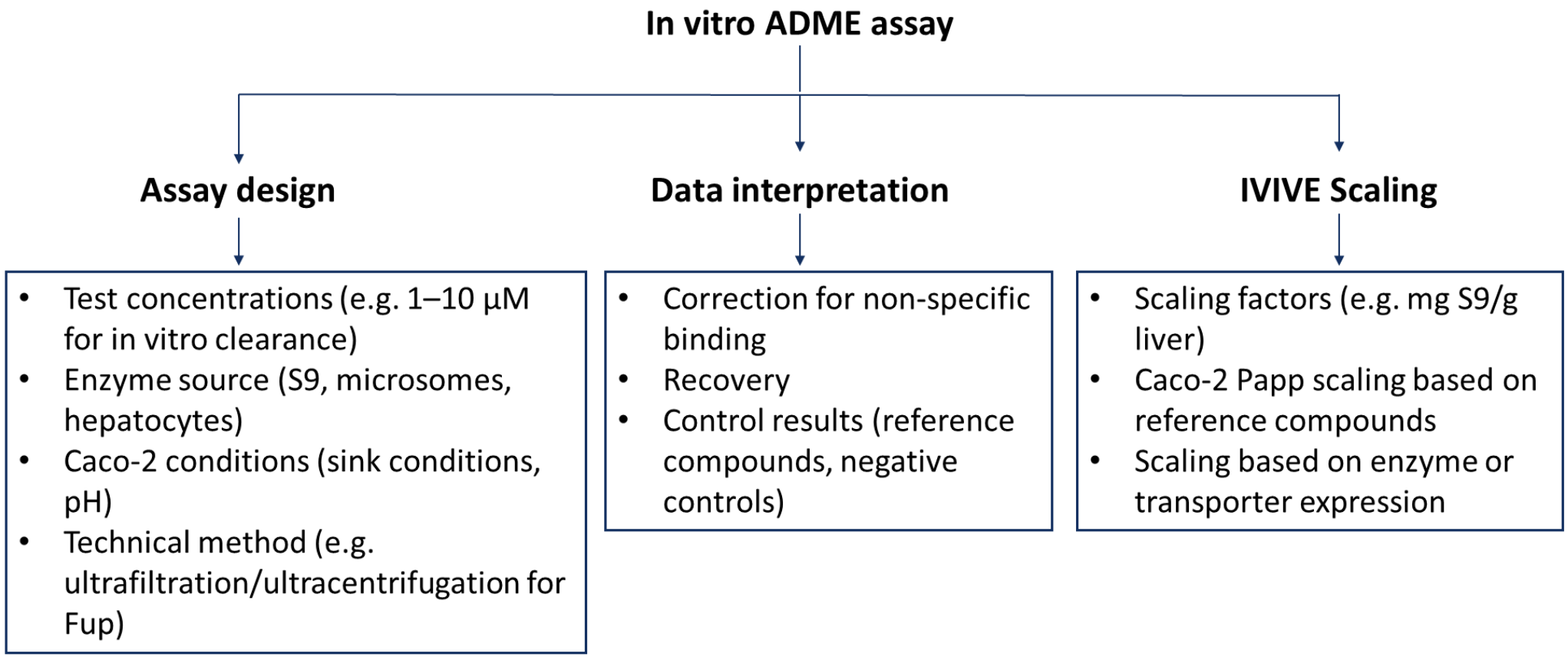

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OECD Test Guidelines needed; currently only available for in vitro skin absorption assay (OECD 428)

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

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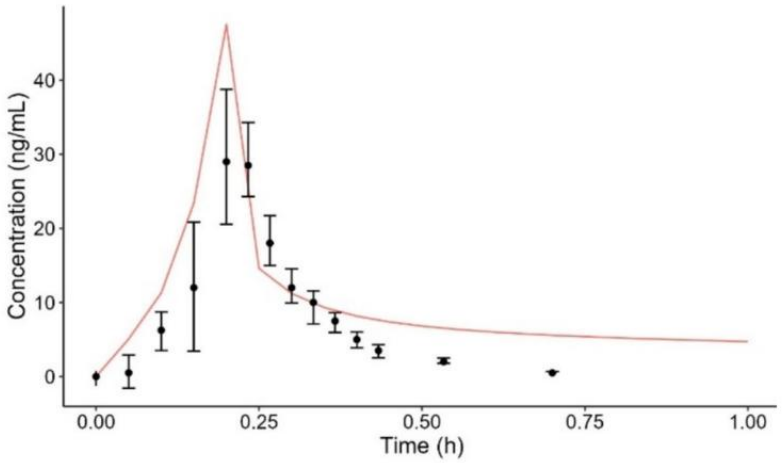
Evaluation against in vivo/clinical observed data



Predicted (red line) and observed plasma concentration hegenamine in humans (IV dose) (Pinckaers et al (2025) *Arch Tox*, Volume 99)

Alternatives to in vivo PK-data

- General predictive performance of bottom-up PBK models.
- Compare results across modelling platforms (e.g. PBK software vs differential-equation scripts.
- Incorporate read-across from structurally or mechanistically similar chemicals.

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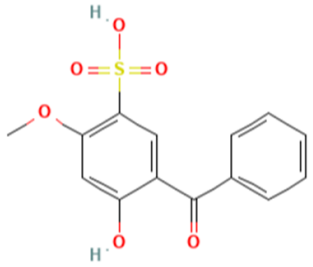
Example case study: benzophenone-4

- **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)

Microsoft PowerPoint Stock Image

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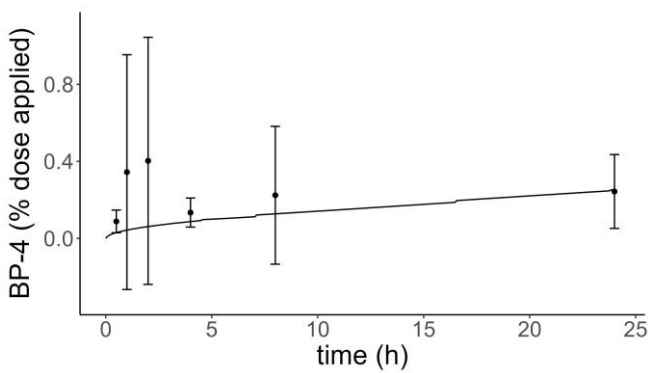
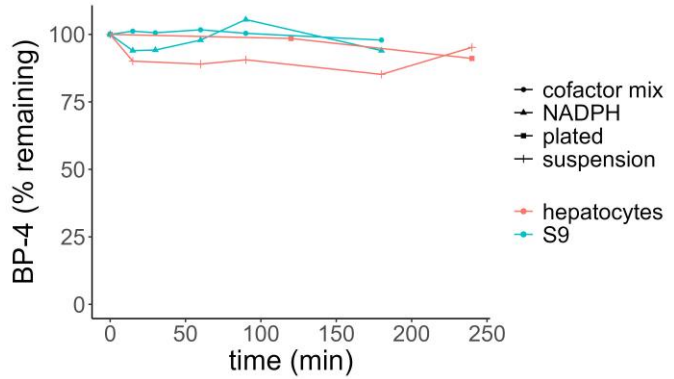
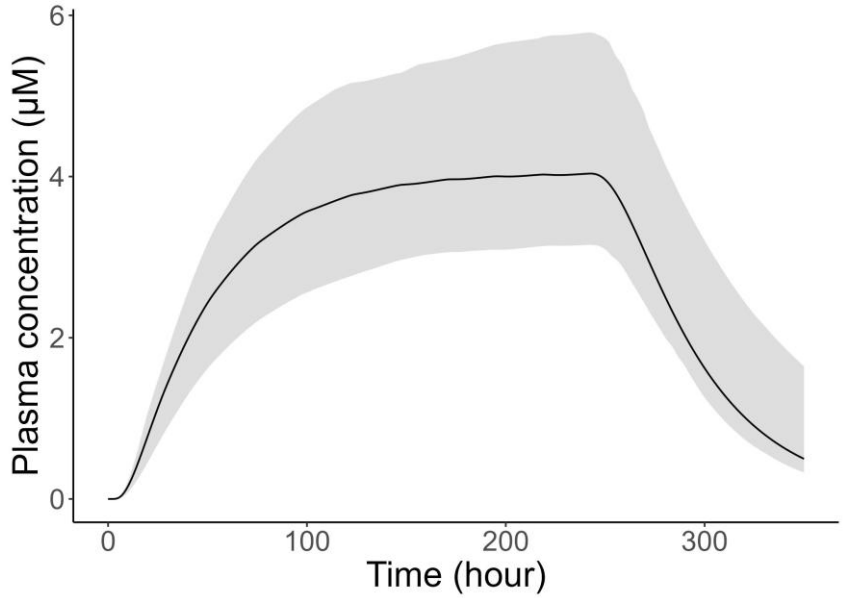
Core PBK model results BP-4

- 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 18 g (5%) product per day (2 applications, 1 shower/rinse off/day)
- Lack of metabolic clearance suggests a role of transporters in BP-4 kinetics







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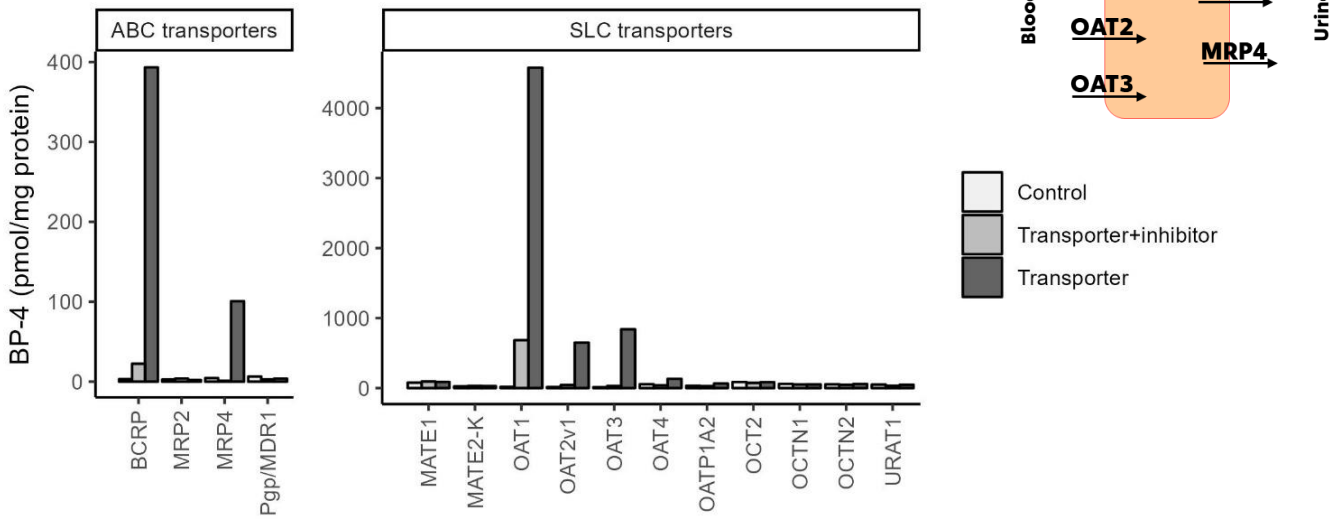
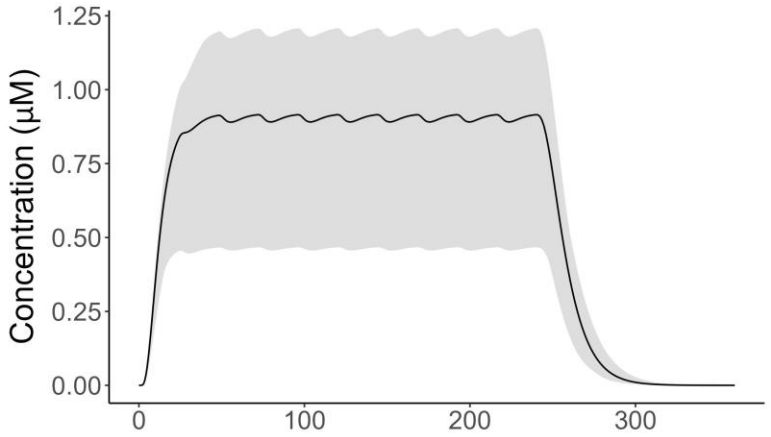
Punt *et al.* (2026), *Altex*, Volume 43, Issue 1

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 g 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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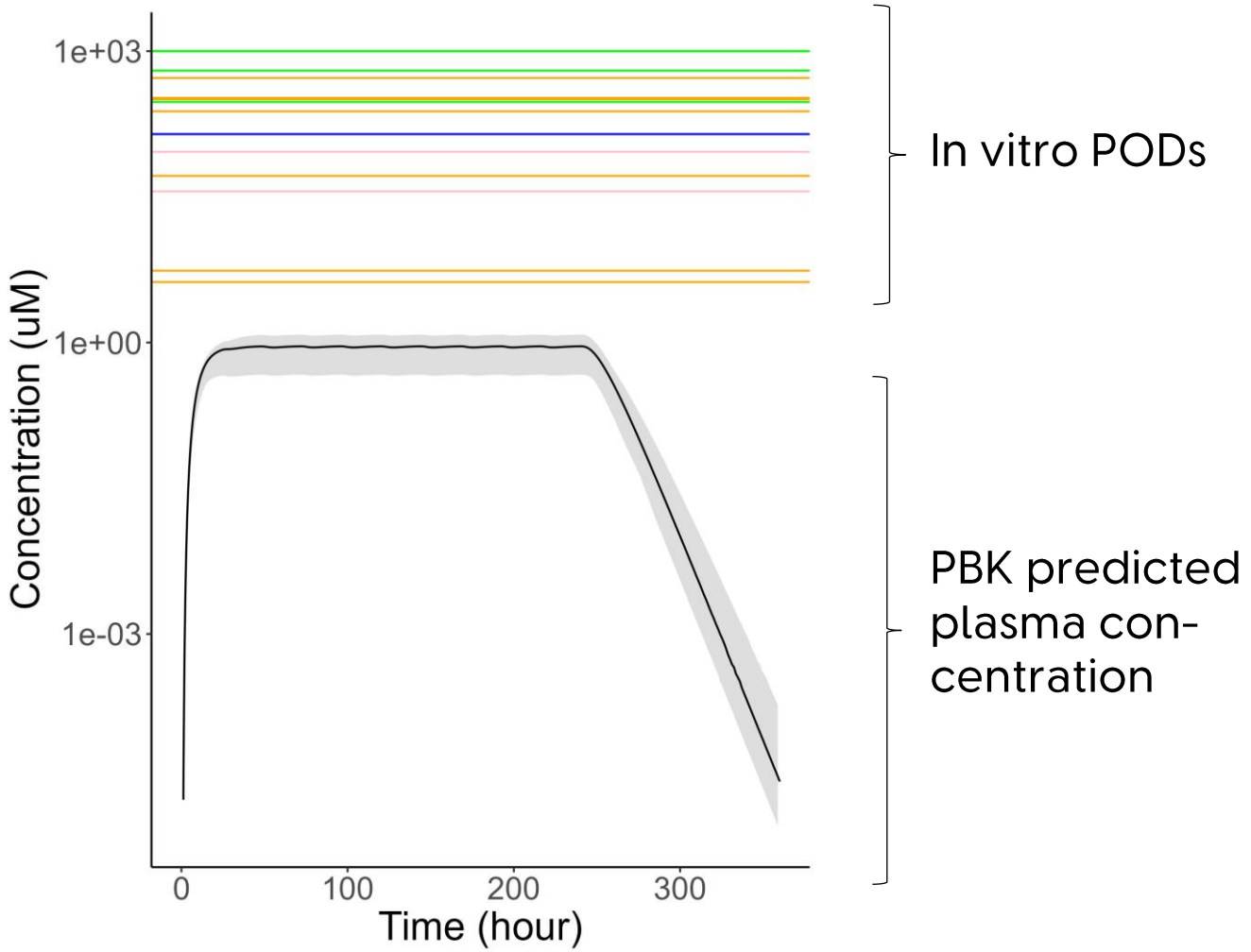
Punt *et al.* (2026), *Altex*, Volume 43, Issue 1

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



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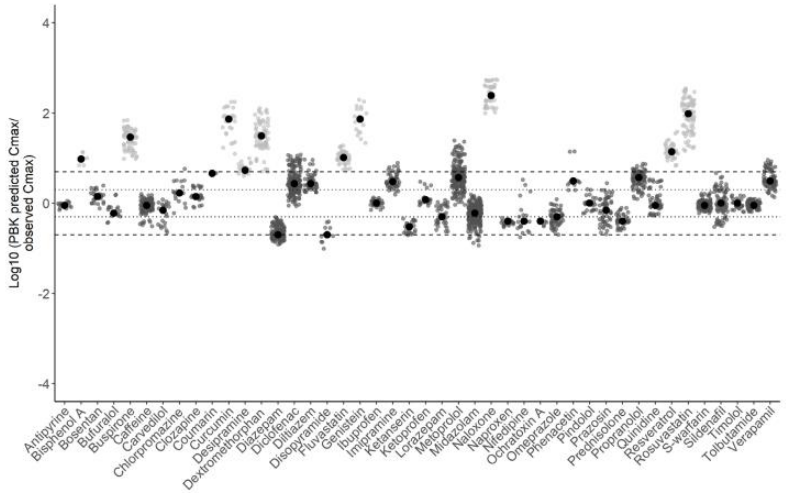
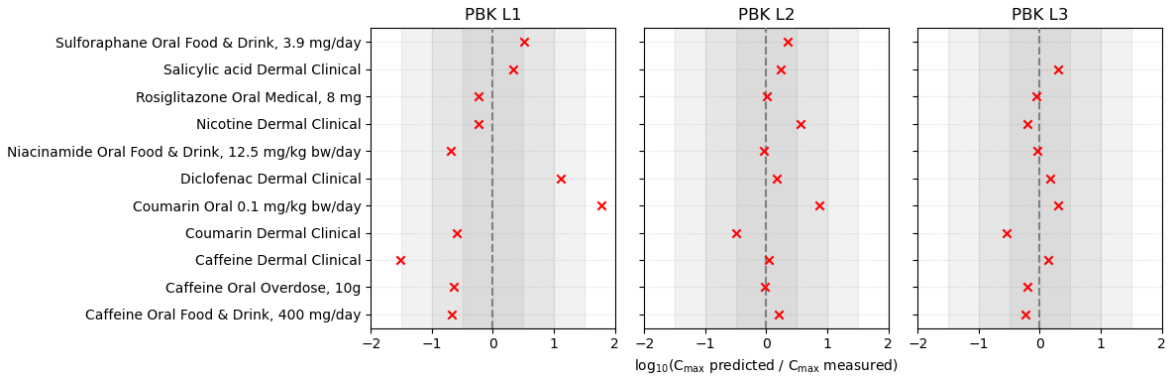
Baltazar *et al.* (2025), *Altex*, Volume 42, Issue 3

General predictive performance of bottom-up PBK models

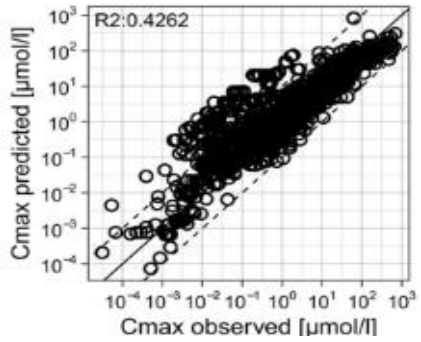
- Bottom-up PBK models predicted Cmax values within a 5- to 11-fold range of available human data
- In general, human kinetic studies themselves also show variability across studies (e.g. Punt et al., 2022)



Punt *et al.* (2022), *Altex*, Volume 39, Issue 2



Middleton *et al.* (2022), *Tox Sci*, Volume 189, Issue 1



Geci *et al.* (2022), *Arch Tox*, Volume 99.

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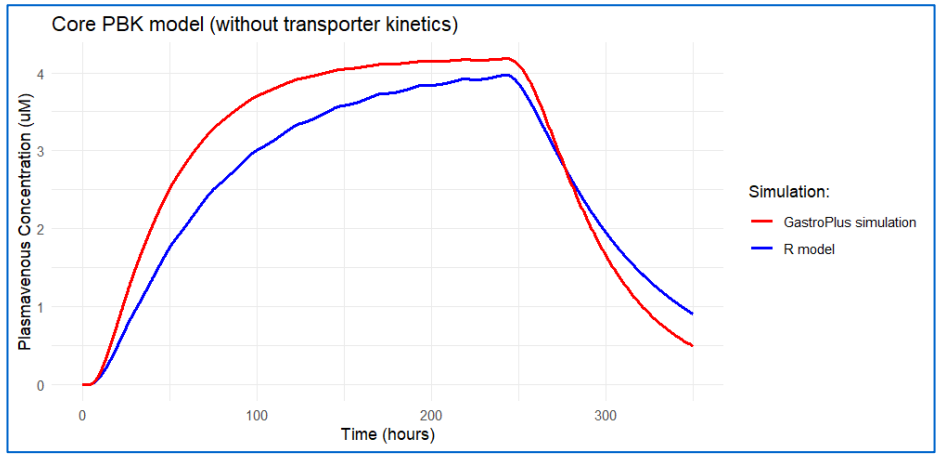
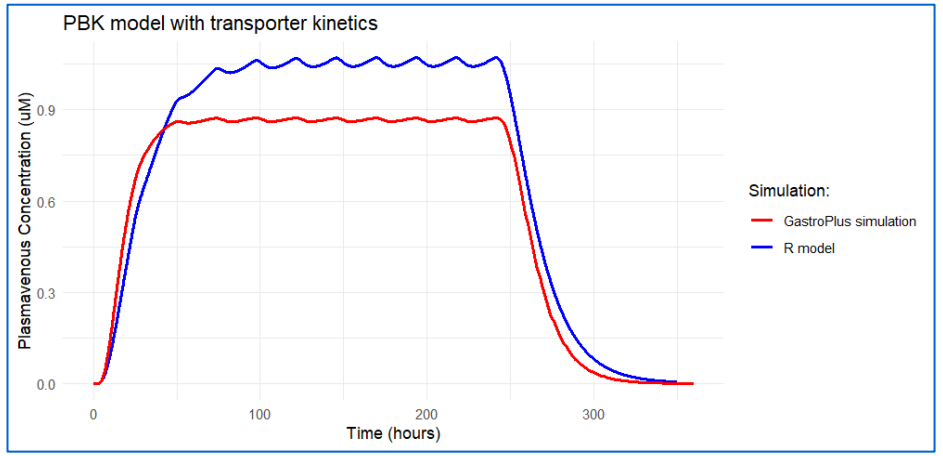
Comparison of results across modelling platforms

- PBK model comparison: **GastroPlus vs R** (differential-equation script)
- Both the core model (no transporters) and the model that includes transporters were evaluated
- **Similar model results** were obtained across platforms





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Unpublished data, do not cite.

Incorporate read-across from structurally or mechanistically similar chemicals

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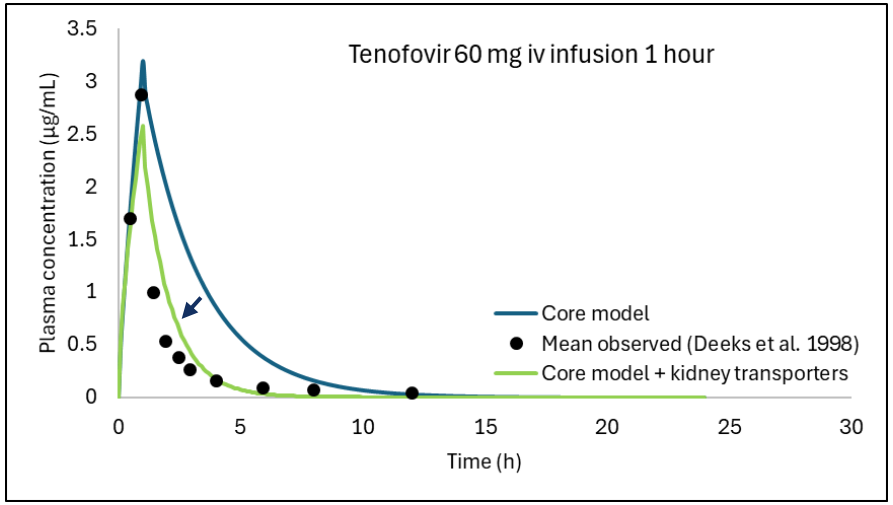
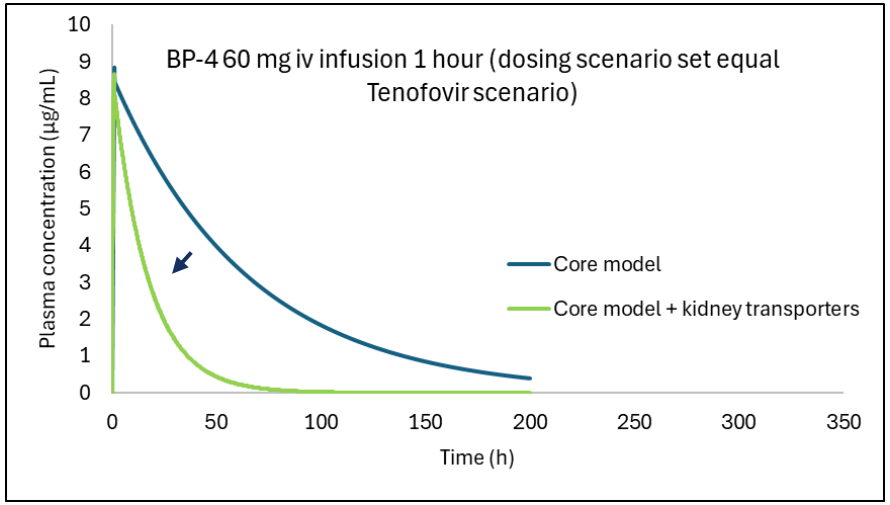
- No structural analogue available for BP-4 with existing human *in vivo* kinetic data
- Compare results with **mechanistically similar chemicals**
- Antiviral agent **Tenofovir** is not chemically related to BP4 but is subject to active renal excretion by OAT1 and MRP4 (like BP-4).
- Comparison allows to compare impact of transporter kinetics on plasma concentrations





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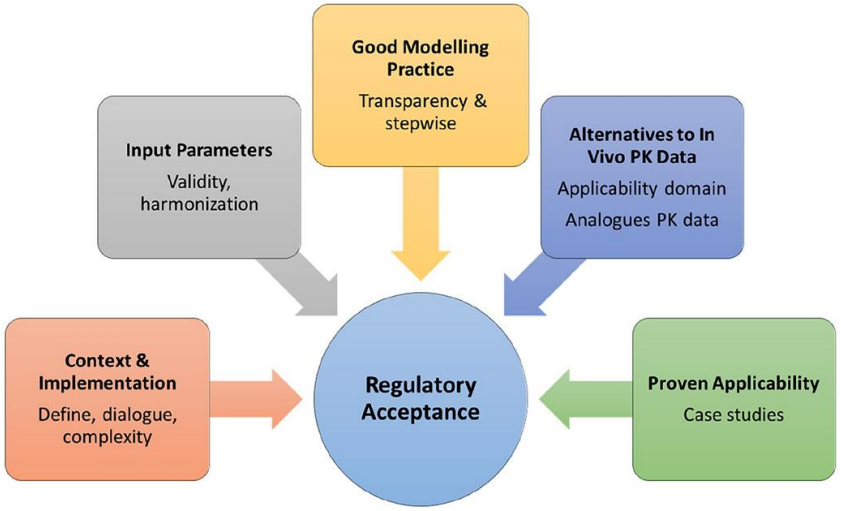
Unpublished data, do not cite.

Conclusions

- PBK modelling has a crucial role in NGRA to translate human exposure scenarios to internal doses that can be compared with *in vitro* bioactivity data
- Best practice is about **communication** (context of use and transparency in modelling approach), **validity of input parameters**, **alternatives to in vivo data** for validation, and **proven applicability** with case studies
- Confidence can be built in conservative model output without human in vivo data.



Najjar et al (2022) *Arch Tox*, Volume 96

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