Grouping Concepts in toxicokinetics : Assess the bioavailability of PM compounds using PBK modelling

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WP6

Contents

- Compound selection
- PBK Modelling and Proof of Concept
- Read Across Approach (RAX)
- Risk Assessment based on internal concentrations

Persistent – Mobile Compounds

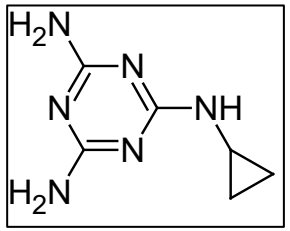
- Selection Strategy

For the persistent and mobile [9] substances, three classes of compounds were selected, namely:

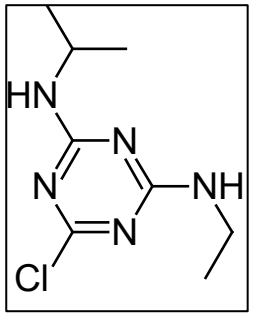
Triazines Triazoles Per- and polyfluoroalkyl substances (PFAS)

- Persistent an Mobile compounds
- Per class - data rich compounds - in vivo animal studies with repeated oral exposure and ADME

Triazines – **9** compounds selected

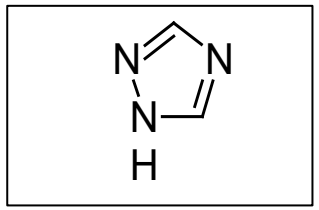


Cyromazine

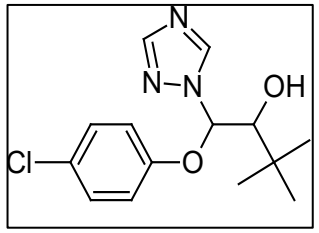


Atrazine

Triazoles – **16** compounds selected

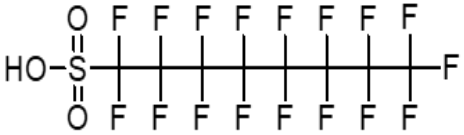


1,2,4 - triazole

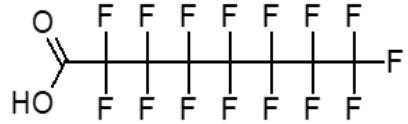


Triadimenol

PFAS – **11** compounds selected



PFOS

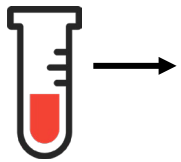


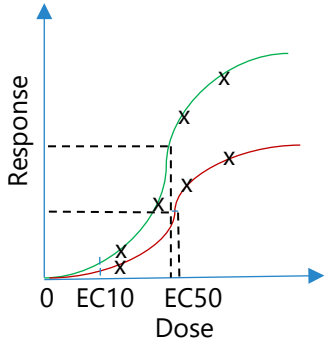
PFOA

Application of PBK models in QIVIVE process

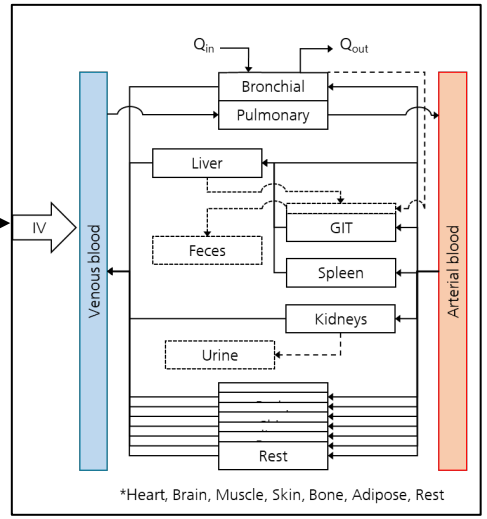
IVIVE based PBPK Modelling for PM compounds

In vitro biokinetic

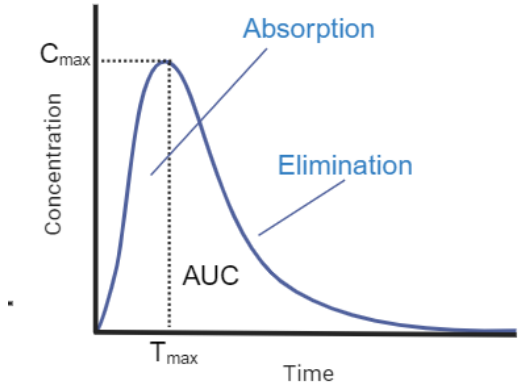




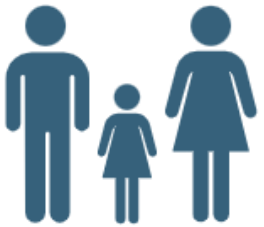
PBK Model



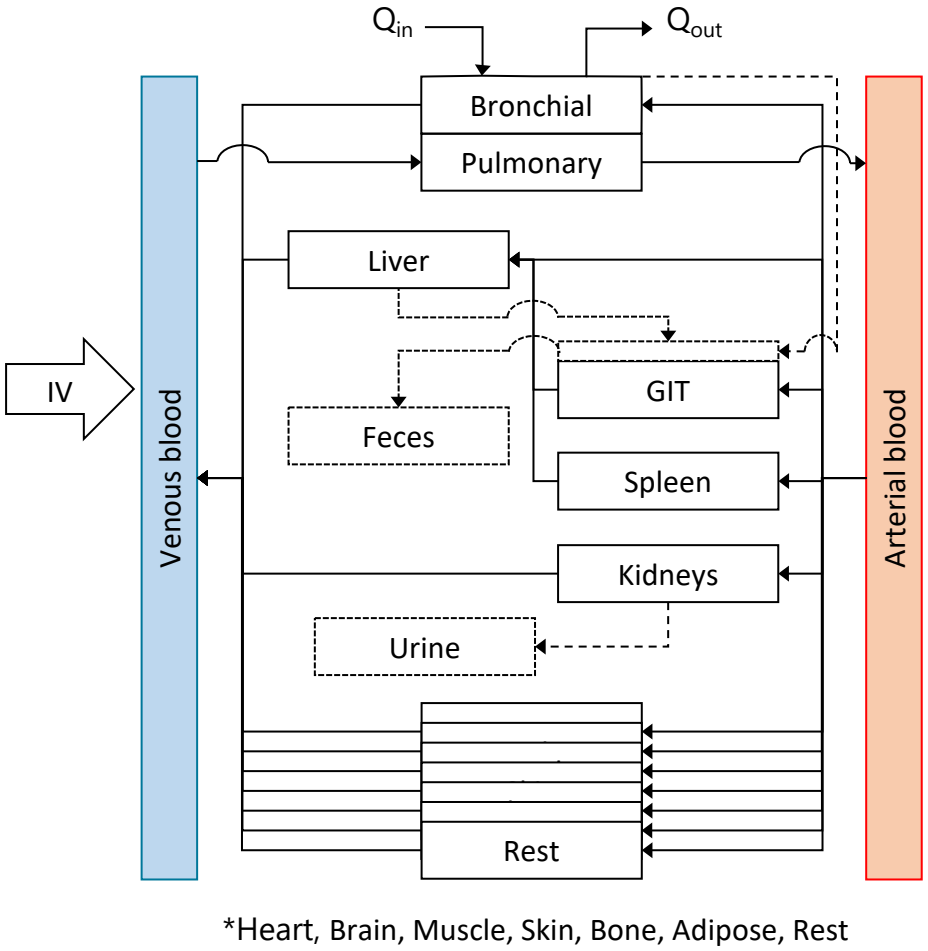
Plasma concentration curve



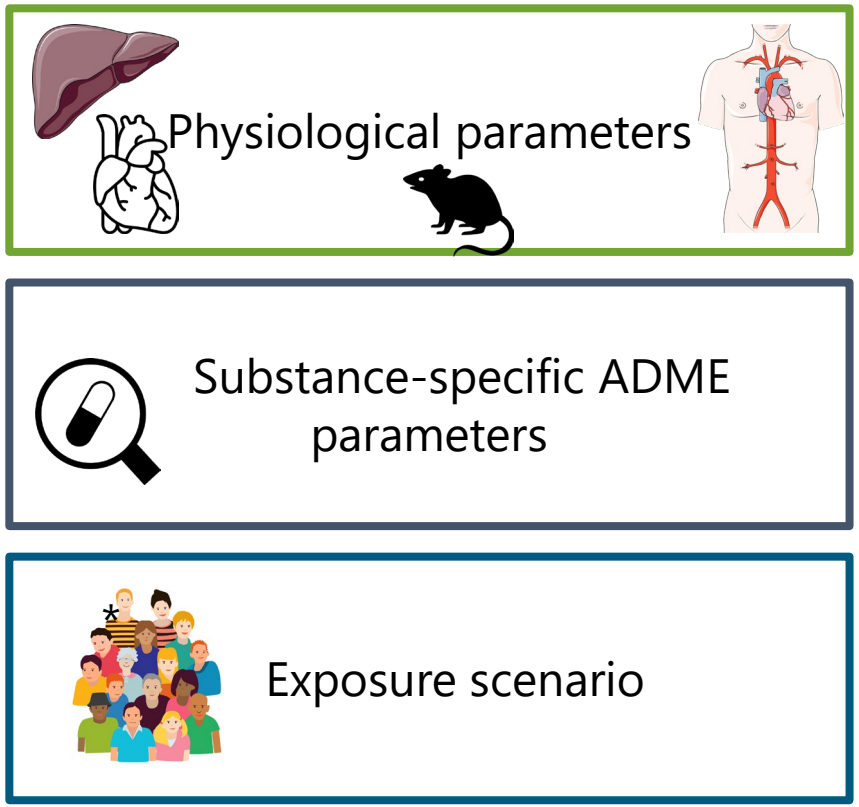
External concentration



Build Physiologically Based Kinetic (PBK) models



*Heart, Brain, Muscle, Skin, Bone, Adipose, Rest



✔

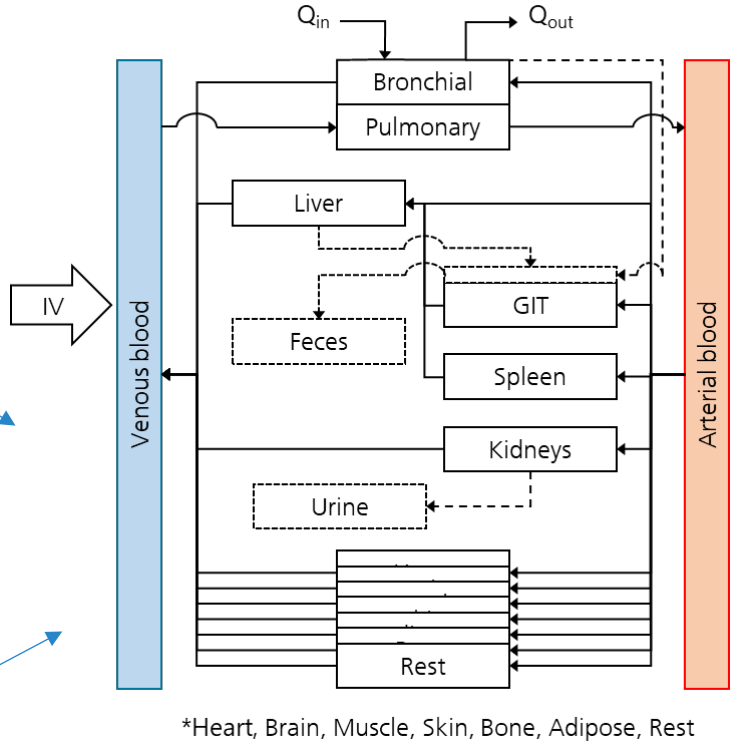
Generic PBK model - compound specific data from New Approach Methods (NAMs)

Proof that the PBK model provides reliable predictions

*FreeVector.com

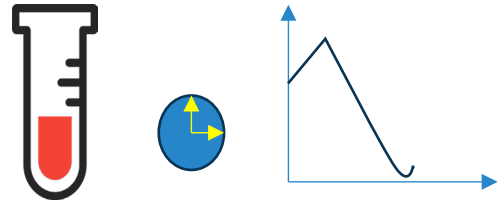
Build generic PBK Model and Assess performance

Blood : plasma ratio

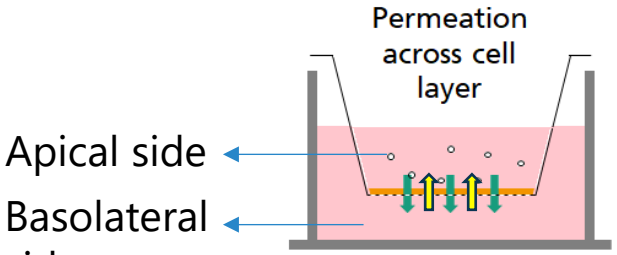


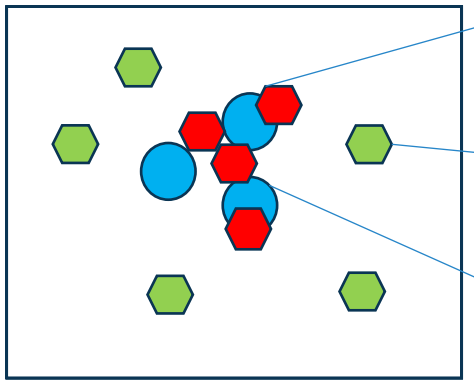
*Heart, Brain, Muscle, Skin, Bone, Adipose, Rest

Measuring intrinsic hepatic clearance in PHH in µg/min/10^6 cells



Time dependent CLint





Fraction unbound

CaCo2 Assay → Measuring premeability across the intestinal cells in cm/s

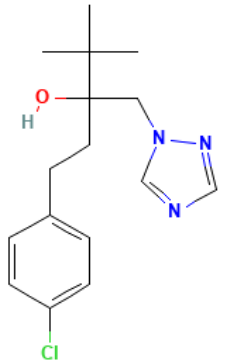
Output of rat PBK model is compared to the rat in vivo oral data

Sensitivity and Uncertainity analysis

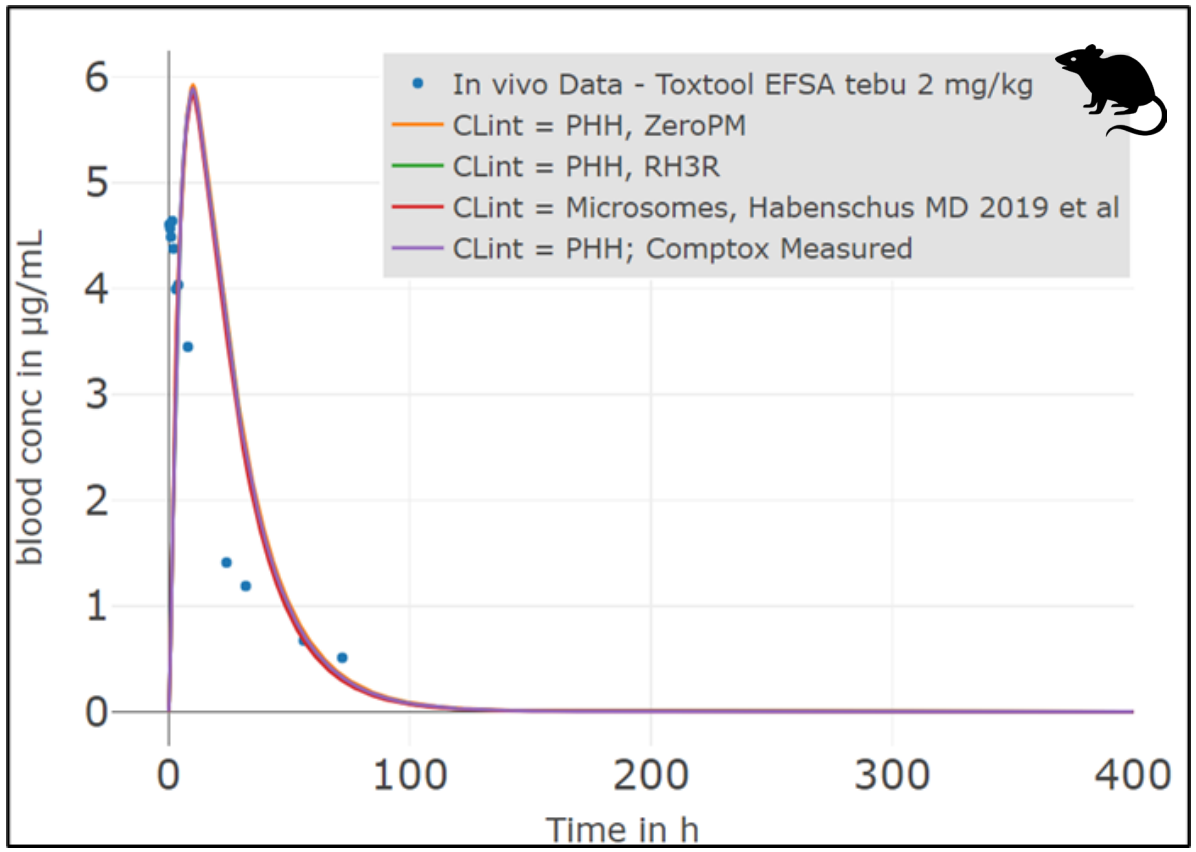
Proof of concept

- Rat Model

Tebuconazole

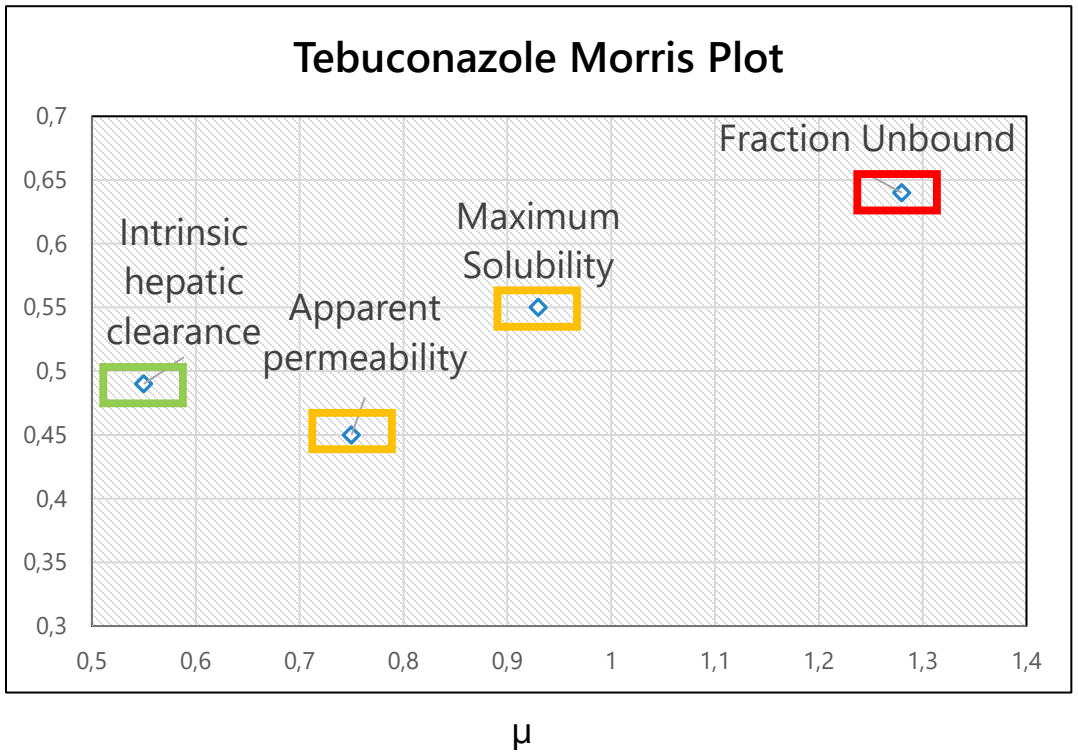


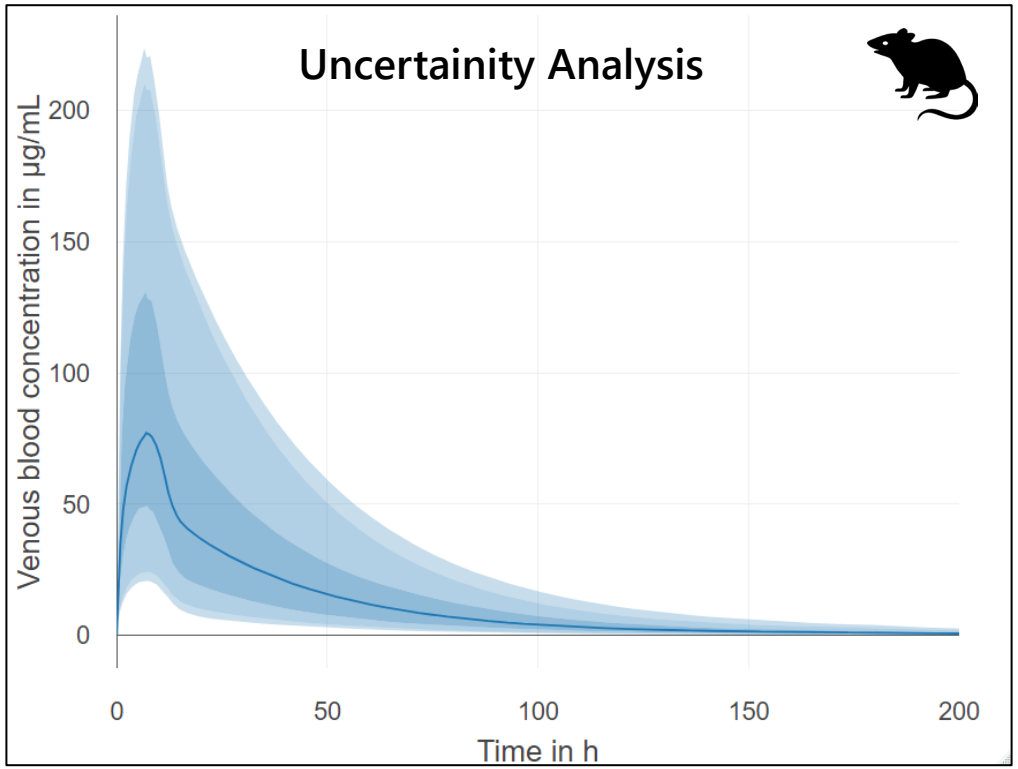
Data type	Clint PHH = 3.62 [µl/min/million cells]	In Vivo Data	In vitro / In vivo
C_max [µg/ml]	5.91	4.63	1.27
T_max [h]	7.11	1.53	4.64
AUC [µg/mL * h]	154.5	112.36	1.37



Sensitivity Analysis

- Tebuconazole – Rat PBK Model



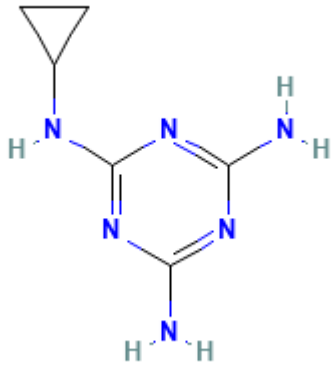


Order of the highest sensitive parameters

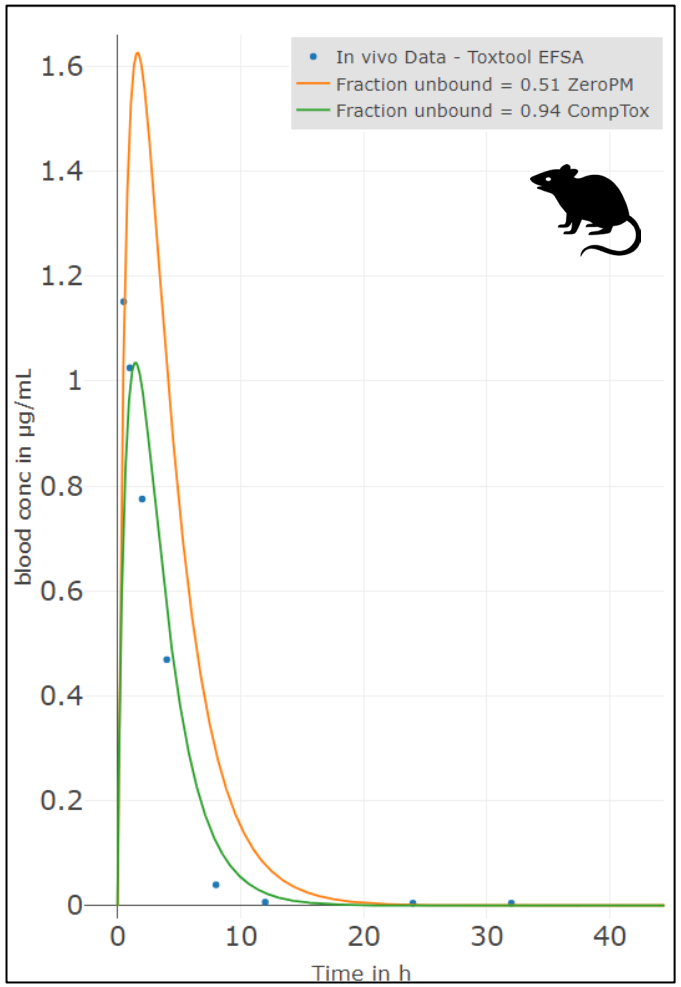
- Fraction Unbound > Solubility > Apparent permeability > Intrinsic hepatic clearance

Also true for Triazines?

Rat Model



Cyromazine



Input concentration to rat: 3 mg/kg

Data type	C_max µg/ml	T_max h	AUC µg/mL * h
Fu (ZeroPM)	1.61	1.53	8.49
Fu (CompTox)	1.12	1.39	4.72
In vivo data[4]	1.151	3.06	4.41
In vitro / In vivo ratio (ZeroPM)	1.19	1.46	1.92
In vitro / In vivo ratio (CompTox)	0.76	0.45	0.85

- **AUC, C_max, T_max is within the factor of 2 for both of the cases, thus validating the model**

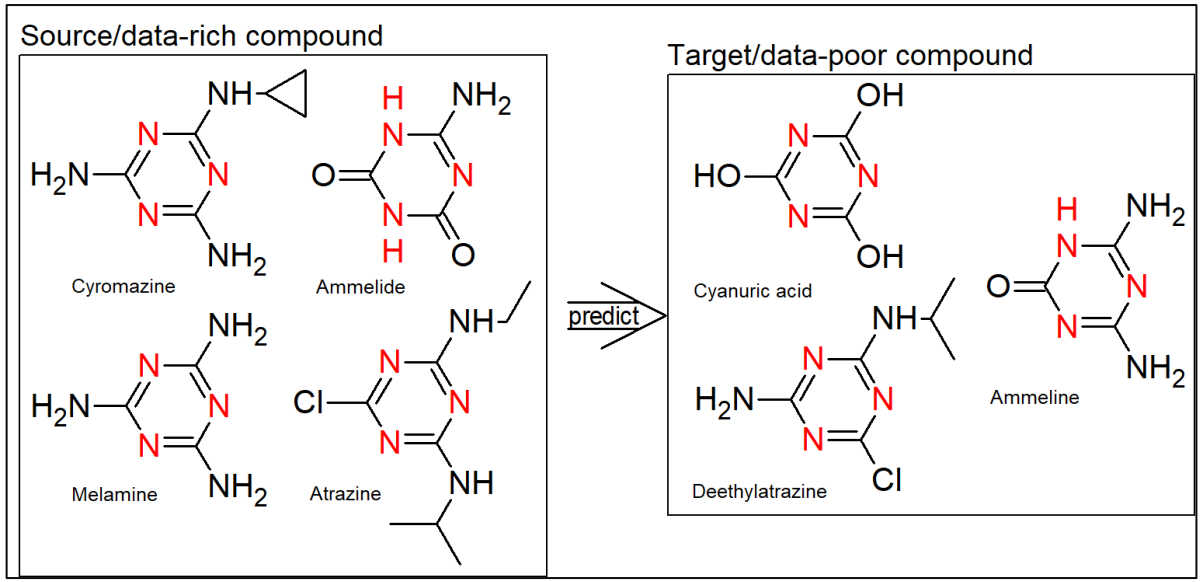
Summary – Simple NAM parameterized PBK model works fairly well

- Proof is provided for rat data
- Simple PBK model is good enough to model the bioavailable concentration
- Use same assuptions to model human
- Application of the same model to the compounds in triazine and triazole class

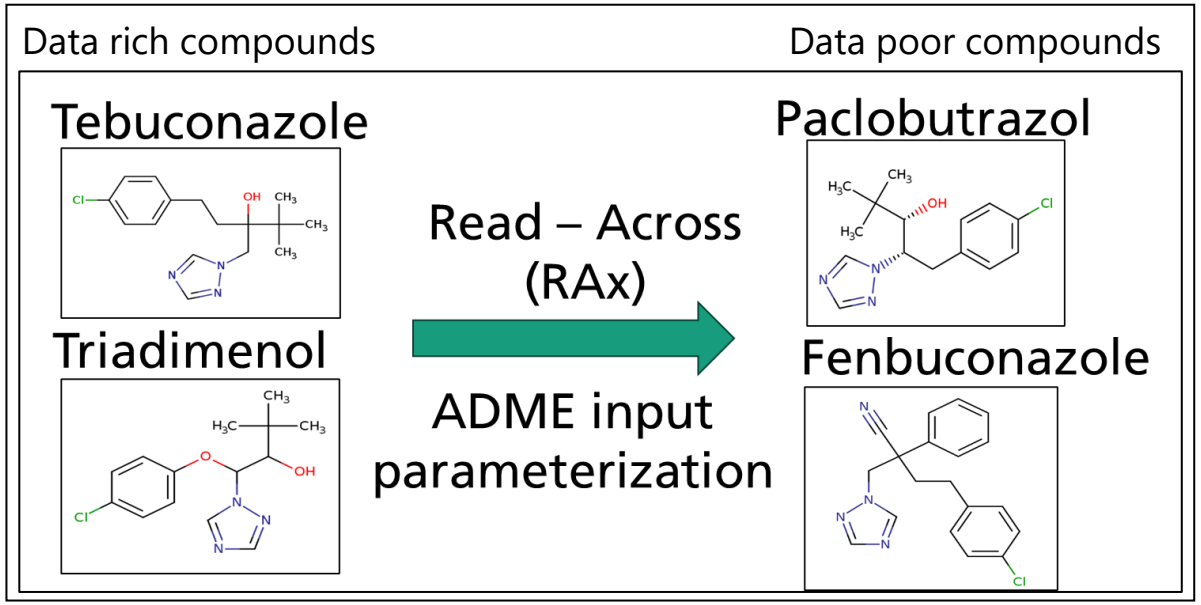
Read across approach – Rax Triazines & Triazoles

Fraunhofer ITEM

Triazines



Triazoles

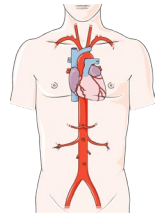


RAx approach to parameterize the similar class of compounds to paramerize PBK Model

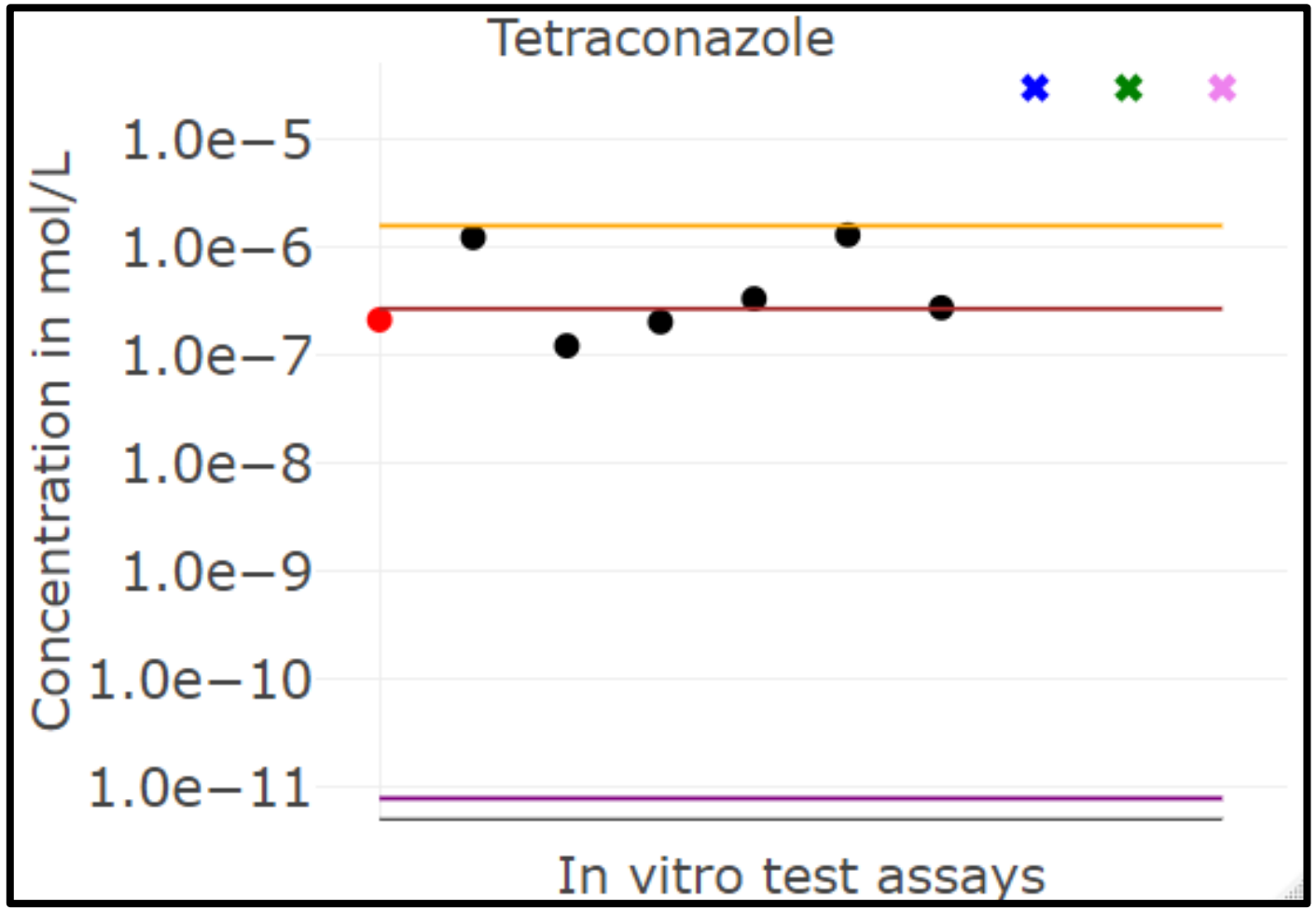
- **Estimate ADME properties** like intrinsic hepatic clearance value from „data rich“ to „data poor“.
- All the data rich compounds show low intrinsic clearance > Prediction is low clearance for all RAX compounds.

Tetraconazole – Comparison

Free unbound plasma concentration



Fraunhofer ITEM



max water solubility

LOAEL

Surface water

Ground water

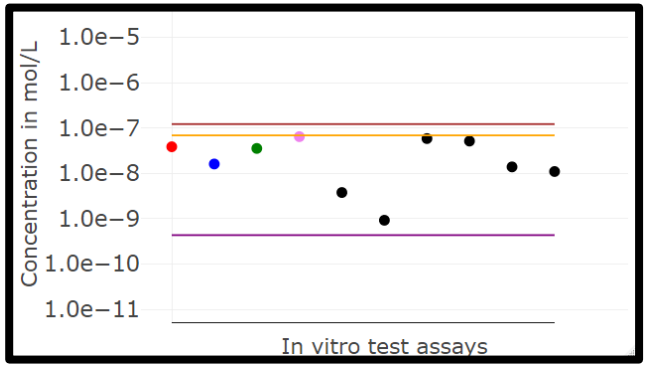
Legend

- Androgen receptor Antagonism – EC_{20} free medium
- Estrogen receptor Antagonism – EC_{20} free medium
- Thyroid receptor Antagonism – EC_{20} free medium
- TTR Binding Assay– EC_{20} free medium
- H295R Steroidogenesis – $EC_{1.5}$ free medium
- Estrogen Receptor Inactivity
- Thyroid Receptor Inactivity
- TTR Binding Assay Inactivity

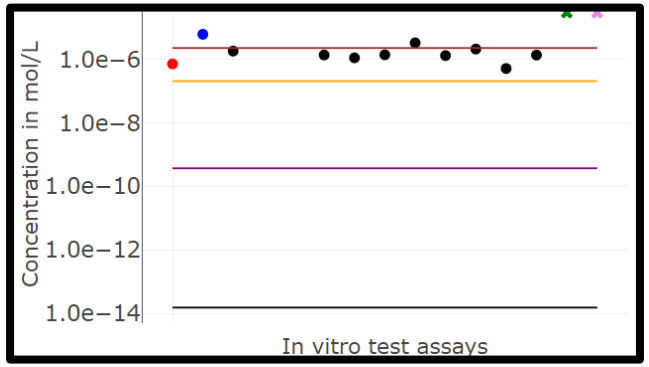
Triazoles Comparison

Fraunhofer ITEM

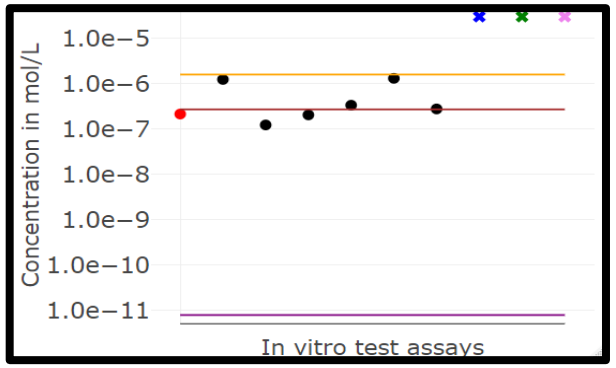
Difenoconazole



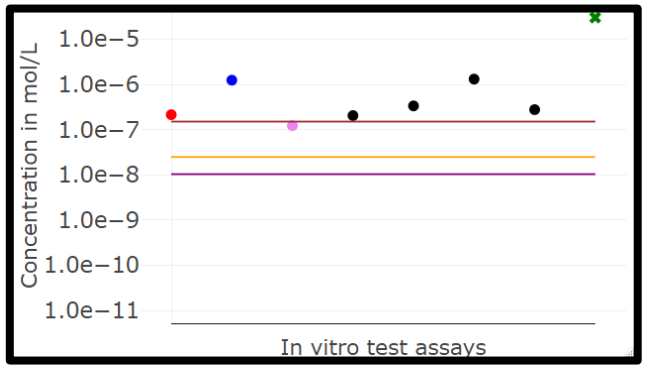
Tebuconazole



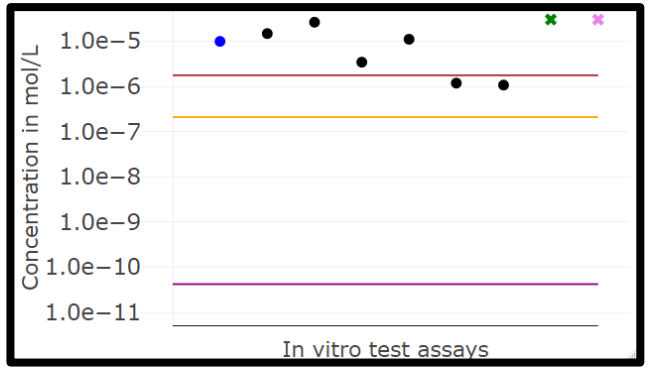
Tetraconazole



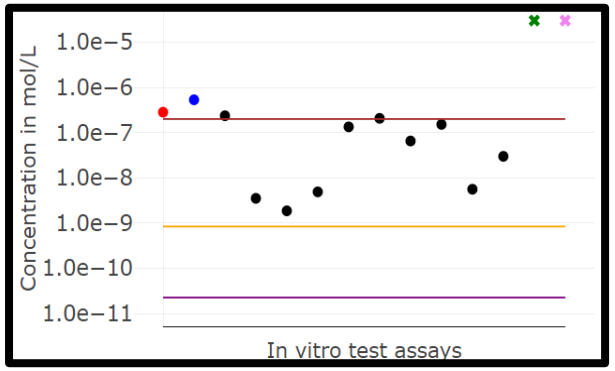
Bitertanol



Paclobutrazol



Fenbuconazole

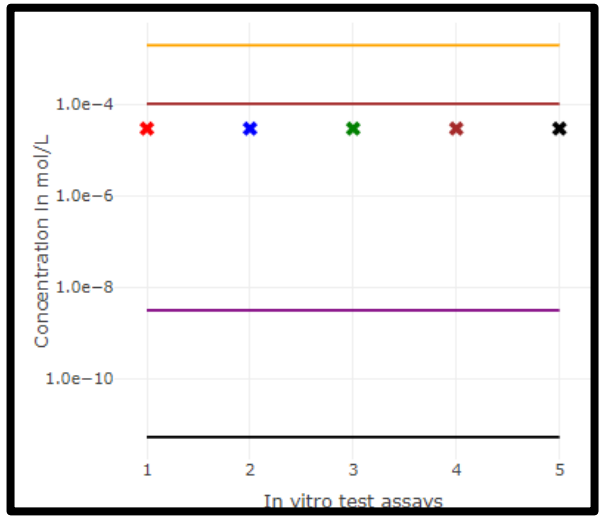


Legend

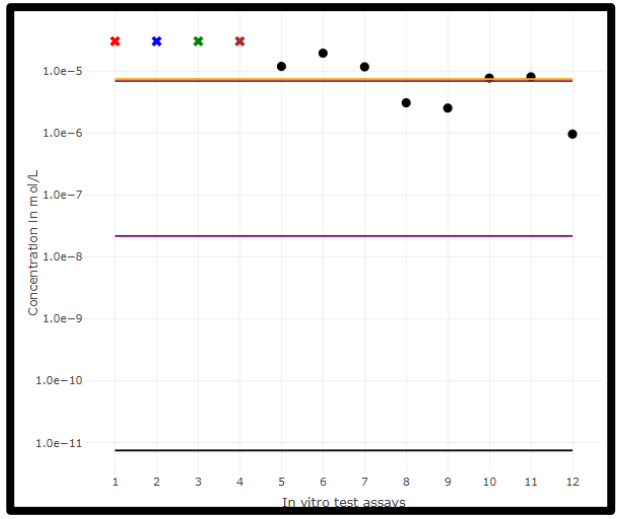
- Androgen receptor Antagonism – EC_{20} free medium
- Estrogen receptor Antagonism – EC_{20} free medium
- Thyroid receptor Antagonism – EC_{20} free medium
- TTR Binding Assay– EC_{20} free medium
- H295R Steroidogenesis – $EC_{1.5}$ free medium
- Maximum Water Solubility
- LOAEL Concentration
- Surface water concentration
- Ground water concentration
- Estrogen Receptor Inactivity
- Thyroid Receptor Inactivity
- TTR Binding Assay Inactivity

Triazines Comparison

Cyromazine



Atrazine



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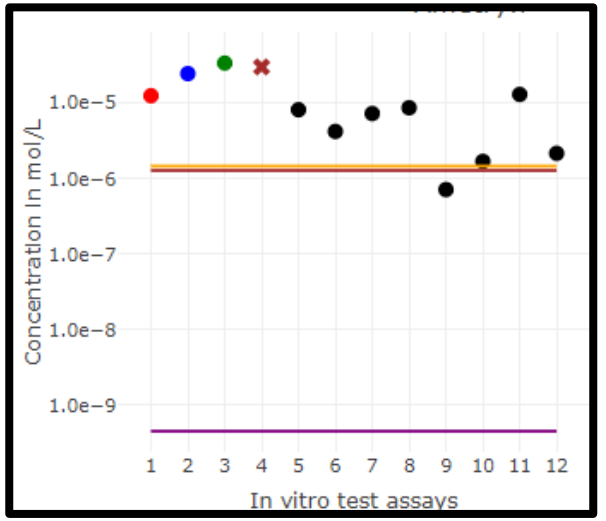

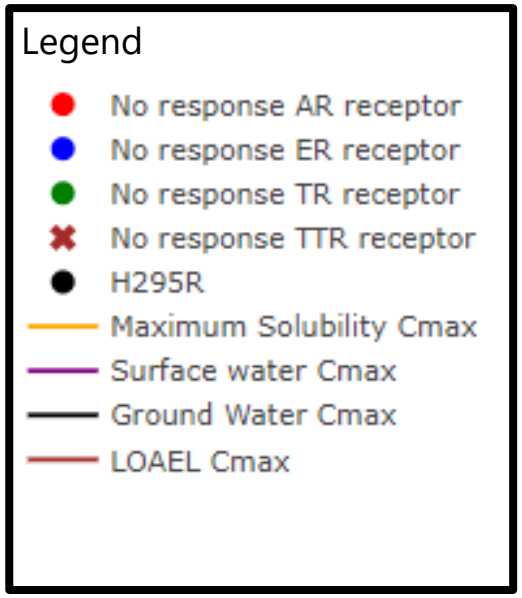

Conclusion

- **In vitro data are protective** - Using QIVIVE the corrected free medium (EC20) concentrations from the NAM test battery are in the same range or lower compared to the values derived from the in vivo LOAEL values.

- **Large Margin of Exposure** - The surface water and ground water derived unbound human plasma concentrations are about 100 – 1000 times smaller than those values derived from the in vitro/in vivo studies.

Next steps → Modelling and extrapolation for PFAS compounds

Reference

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11 NORMAN Database System (norman-network.com) → Norman database system for ground and surface water concentrations

Acknowledgement

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Jenny Irwan[1], Max Spänig[1], Anke Londenberg[1], Maxim Carlier[2], Timo Hamers[2], Nicole Zümbulte[3], Todd Gouin[4], Patrik Lundquist[5], Pawel Barenczewski[5], Tanja Hansen[1], Sylvia E. Escher[1]

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