The Final EUTOXRISK Symposium 3

PBPK methods used and established in the project (WP4)

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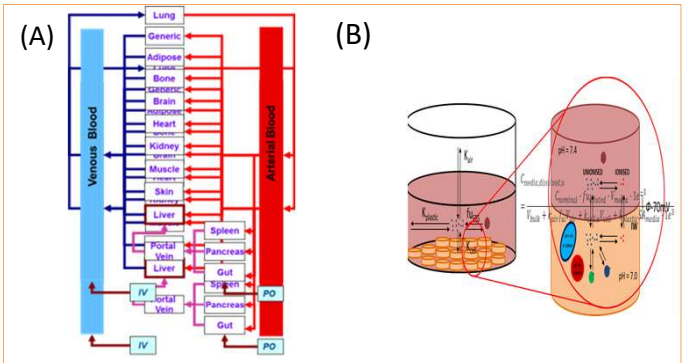
Background Information

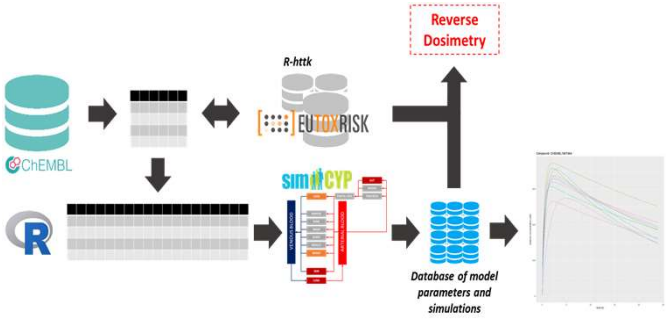
- To predict/understand toxicological responses it is essential to know the concentration and duration of exposure to a chemical at the site of the toxic event.
- In the EU-ToxRisk project mathematical models were used to describe the concentration of chemicals in the human body and in *in vitro* systems.
- Physiologically based pharmacokinetic (PBPK) models incorporating population variability were constructed for the case study compounds. PBPK models were parameterised using *in vitro-in vivo* extrapolation approaches.
- As part of the project a novel *in vitro* cell model (VIVD) was developed and used to predict the intracellular concentrations of case study compounds (Fisher at al., Toxicol. In Vitro, 58, 42-50, 2019).
- After consideration of uncertainties in the model predictions, the data generated using the PBPK and cellular models was used in the risk assessment activities undertaken as part of the EU-ToxRisk project.



Schematic representation of (A) a PBPK model and (B) a model of an *in vitro* cell system

The technology

- PBPK models for different populations (e.g., adults and children) were constructed in the Simcyp Simulator.
- During the course of the project specific models were developed to describe (A) the liver as a multi-compartment model, (B) the lung as a multi-compartment model that could be used to model inhalation of chemicals, and (C) a feto-placental model. All models were implemented into the Simcyp PBPK platform.
- The VIVD cell model was implemented in the Simcyp *in vitro* data analysis toolkit (SIVA).
- A high-throughput workflow was assembled to allow automated reverse dosimetry of chemicals and linked to the CHEMBL database.



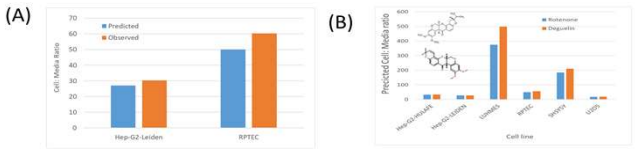
Schematic representation of a PBPK workflow

Application examples

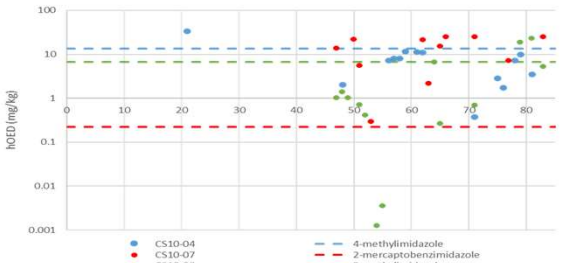
- PBPK models were developed for more than 100 different chemicals to support the different case studies (CSs).
- PBPK and *in vitro* cellular models were used to define relevant nominal concentrations to be tested in *in vitro* assays.
- Points of departure were defined using reverse dosimetry approaches.
- These approaches were applied in CS1, 2, 4, 5, 6, 10, 11, 14, 16.

Some example applications are shown in the panel opposite

- The upper panel shows the predicted and observed *in vitro* cell concentrations for rotenone that were completed to support CS4.
- The lower panel shows the predicted human oral equivalent dose (hOED; mg/kg) based on reverse dosimetry from individual NAM based points of departure (data points) vs the predicitions of hOED based on allometric scaling of LOELs determined in historical animal studies.



(A) Measured (mean of all data) and predicted cell: media ratios of rotenone in HEP G2 and RPTEC cells. (B) Predicted cell:media ratios of rotenone and deguelin in five different cell lines.



Predicted human oral equivalent doses (hOED mg/kg) for 3 compounds based on reverse dosimetry from individual NAM based points of departure (y axis) . The different NAM systems are shown on the x axis by sequential number. The dashed lines are the hOED (mg/kg) based on allometric scaling of LOELs from animal.

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www.eu-toxrisk.eu/