NOTOX

Predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures

In silico solutions for predictive toxicity - multi-scale modeling and *in vitro in vivo* extrapolation

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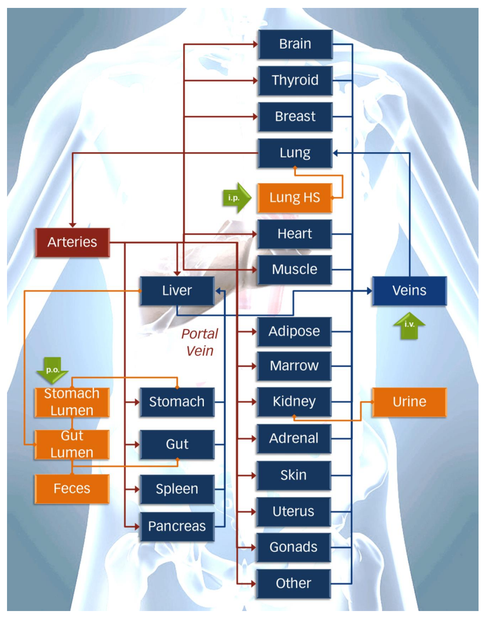
Project aims

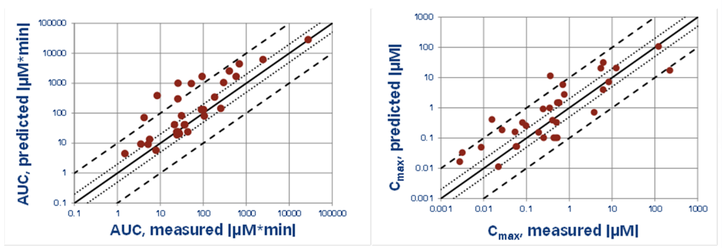
The aim of our project is to establish model-driven approaches capable of predicting toxic events and assessing individual or stratified risks in a fast and reliable way .

Models and algorithms are validated using experimental data for test compounds



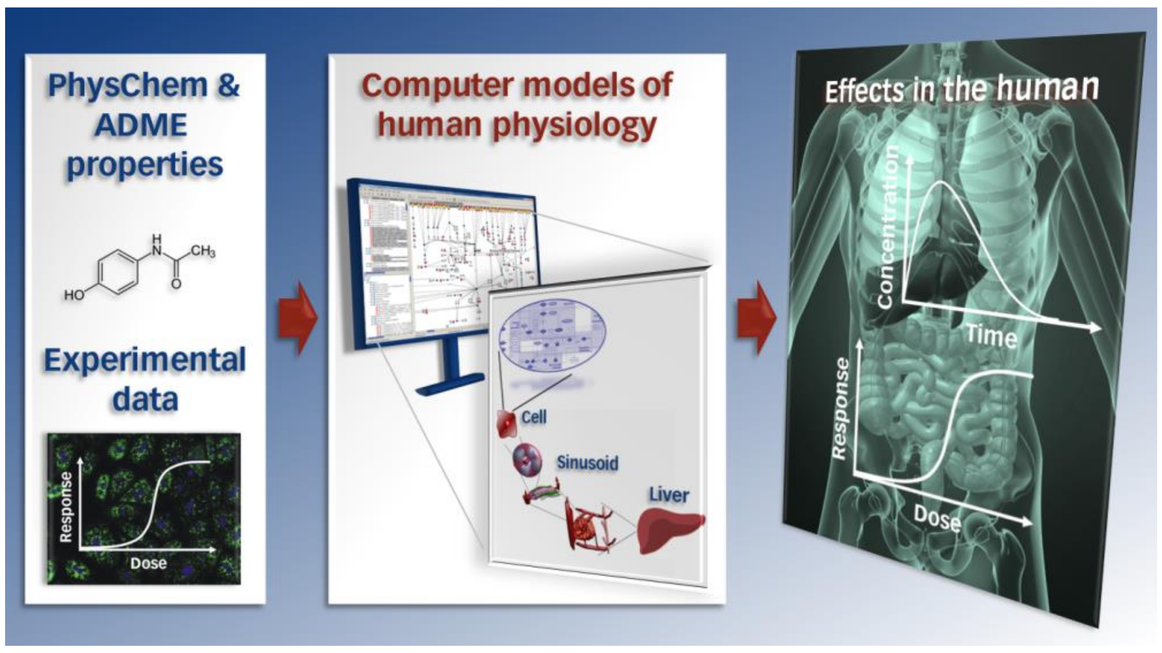
Generic physiologically based pharmacokinetic model for **predicting drug concentrations in the whole body**.

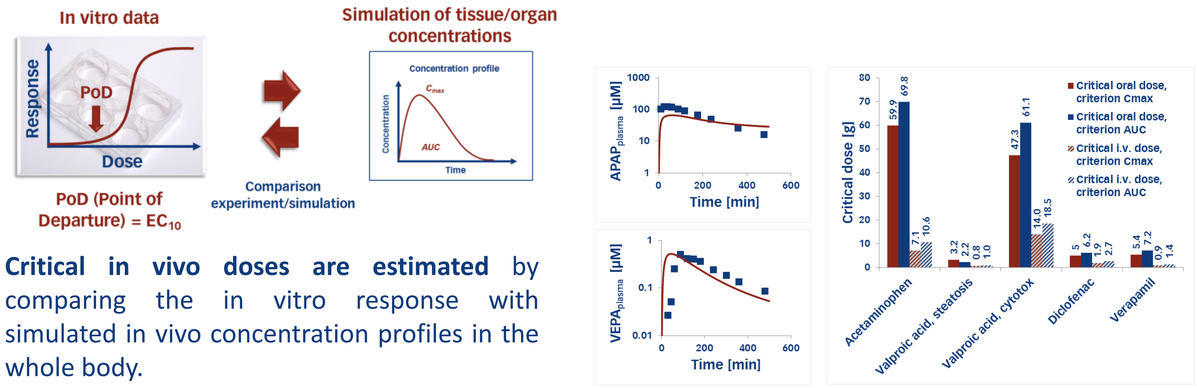
Exemplary **validation of pharmacokinetics predictions**. The PBPK model was validated using in vivo pharmacokinetic data for more than 40 compounds and in total more than 50 experiments following intravenous or oral administration of the compound.



Predicted AUC (left panel) and C_{max} (right panel) vs. AUC and C_{max} calculated from in vivo plasma concentration profiles.

Applying computer models, critical in vivo doses are predicted from experiments

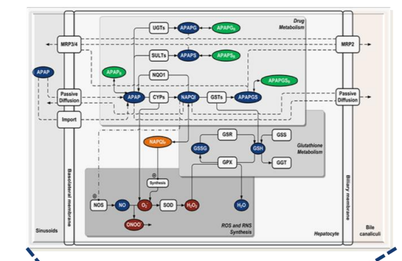


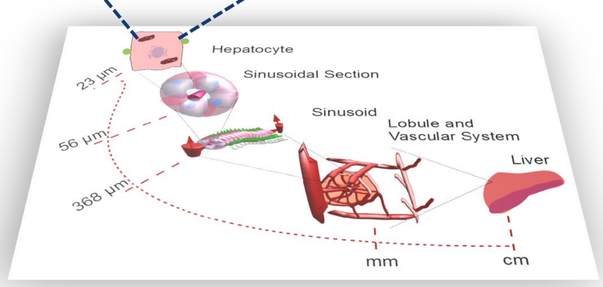


Critical in vivo doses are estimated by comparing the in vitro response with simulated in vivo concentration profiles in the whole body.

Comparison of predicted concentration profiles (left, lines) for acetaminophen (APAP) and verapamil (VEPA) with in vivo data (left, squares). **Predicted critical maximal** single **doses** following oral or intravenous (i.v.) application using C_{max} or AUC as toxicity criterion (right). For valproic acid, different dose response curves for lipid accumulation (steatosis) and NADH depletion (cytotox) were used.

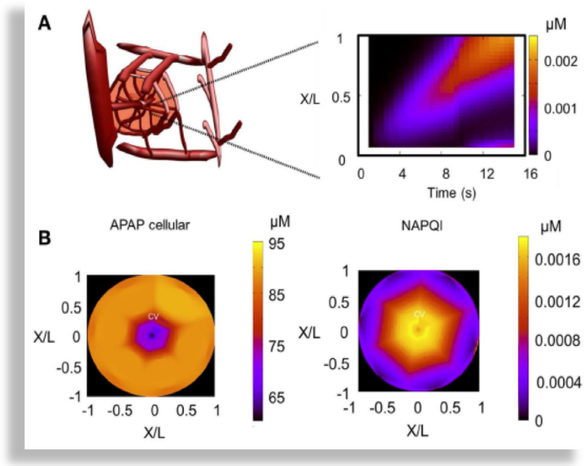
Multi-scale modeling – case study acetaminophen toxicity



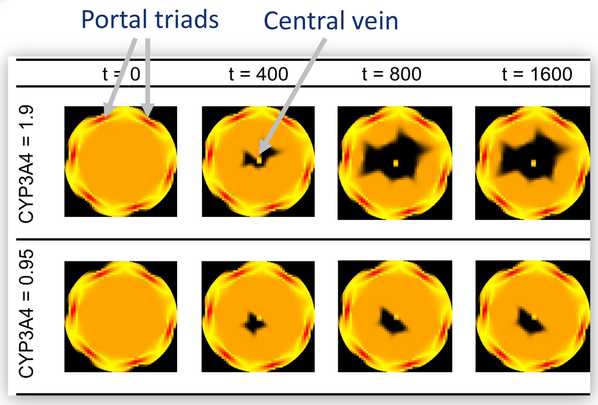


Hepatocyte model and structure of the liver model.

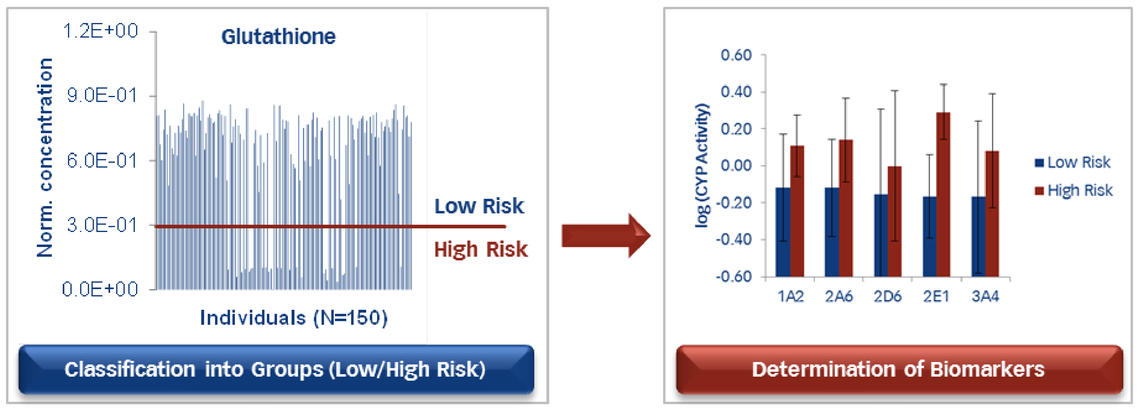
Integration of cellular models into organ and whole body models
The metabolic network model for the hepatocytes for metabolism and toxicity of acetaminophen (APAP), was set-up based on literature data.
Individual cells ordered along a sinusoid are integrated into a model of the lobule.
Different CYP activities in different lobule zones are represented in the model.
Hepatic lobules are interconnected to form a liver model.
The liver model is then integrated into a whole body model where the other organs are represented as compartments.



Structured organ models allow the prediction of concentration profiles for parent compound, metabolites and toxic compounds such as, e.g., NAPQI and ROS in different parts of the organ.



Prediction of the viability of hepatocytes in vivo. High acetaminophen load results in high concentrations of reactive species and eventually liver failure (black, dead cells in lobule; time in min).



Model simulations for different individuals allow for (i) classification into high risk/low risk groups and (ii) determination of significant differences between groups.

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