Introduction and Aims

The physiological functions of an organism coexist across several temporal and spatial orders of magnitude. Therefore, the toxic effects of a substance should be examined in all those scales. Understanding and integrating the information and dynamical behaviour in all these spatio-temporal scales is essential for developing a more coherent approach in toxicology. Multi-scale modelling has been developed as a computational approach to deal with this scale diversity and several techniques have been developed and applied with success to other fields. The main objective of this work is to study the feasibility of the application of these methodologies in toxicology to overcome the problems associated with the gaps between scales. This will allow to explore the continuum toxic effects and to establish an interface between different levels in terms of data and results transferability. We have developed a first case study with acetaminophen, in single and multiple dose situations (data from DETECTIVE), and with two species of interest, rats and humans. We have developed cell toxicokinetic/toxicodynamic (TK/TD) models, TK/TD organ models and organism PBPK models. The coupling between the models allows performing in vitro in vivo extrapolation (IVIVE) producing estimated effects close to actual values. Furthermore, the differences relative to kinetics (metabolism in particular) explained a large part of interspecies differences. Additionally, with an \textit{in silico} model of liver we couple the internal metabolism of the hepatocytes (NOTOX) with a simple 3D model of the liver and predict toxic effects distributed in space and time inside the organ.

Results: Acetaminophen case study

\textbf{Rat and Human PBTK models:}

Kinetics could explain a large part of the differences between species (comparable liver AUC and \(C_{\text{max}}\) for liver for 350 mg/kg for humans and 1000 mg/kg for rats, which correspond to first lethal effect concentrations).

\textbf{3T3, HEPG2 and HEPARG Cell-based assay models:}

Experimental and simulated viability data, population dynamics and dissolved and internal concentration profiles as a function of the \textit{in vitro} dose.

\textbf{In Vivo In Vitro Forcing (IVIVF):}

Conclusions

A proof of concept on how to link \textit{in vivo} and \textit{in vitro} approaches through a modelling framework taking into account biokinetics aspects has been illustrated for the acetaminophen case study. More research is needed using other compounds and species for assessing the validity of the approach. This approach can be easily extended from single dose to repeated dose conditions.

The coupling of the 3D liver model in the PBTK model and that of a Systems Biology approach in the cell-based model will help in covering the missing relevant spatio-temporal scales.

Methods

The method consists of coupling a cell-based assay model with a PBTK (physiologically based toxicokinetic) model, both developed using experimental data (literature data or \textit{in silico} predictions) at their level, \textit{i.e.} \textit{in vitro} concentrations-response for the cell-based assay model, species concentrations versus time for the PBTK model, and then using corrected target organ concentrations profiles from the species of interest to force the \textit{in vitro} validated cell-based assay to analyse the viability under these conditions. This method should be called \textit{in vivo to in vitro} forcing (IVIVF). 3D liver in the PBTK model and a System Biology approach in the cell-based model will help in covering the missing relevant spatio-temporal scales.

References


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