Automated Tool for Route to Route and In Vitro to In Vivo Extrapolation

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Introduction

Automation is universal in today’s society, from operating equipment such as machinery, processes in factories, to self-parking systems. These examples illustrate how efficient automated processes that are based on mathematical algorithms can be. Mathematical models, such as Physiologically-Based Kinetic and Dynamic (PBK/D) models [1], and the Virtual Cell Assay (VCA) [1, 2], can be applied in the form of automated tools to support the chemical risk assessment process. Future human safety assessments will rely increasingly on the combined and integrated use of computational models to perform, for instance, route to route (RtoR) or in vitro to in vivo extrapolation (IVIVE).

Conclusions

- We developed a new tool to predict in an automated way AUC, Cmax, cell viability and mitochondrial membrane potential (mmp) of caffeine as an integrated model implemented into the KNIME workbench, and extended to calculate MOIE, which could be used as thresholds in the risk assessment process.
- This resulted in a user-friendly graphical workflow for the processing and analysis of data to perform route to route, in vitro to in vivo extrapolation, and forward as well as backward automated extrapolation.
- These workflows can be extended to other chemicals.
- The workflows developed are available via the KNIME web portal, by registering to the COSMOS space (see methodology).

Results

- The results presents an automated integrated use of modelling approaches for the selected cosmetic chemical caffeine.
- [Workflow 1] VCA and PBK/D were applied to simulate the following dynamic parameters after oral or dermal exposure: cell viability and mitochondrial membrane potential for caffeine (Figure 1) and do forward (from ‘Input Dose to Predicted Viability’) or reverse (from ‘Input Viability to Predicted Dose’) dosimetry (Table 1).
- [Workflow 2] A human and rat PBK model for caffeine and metabolites for dermal and oral exposure was built into KNIME for simulation of time response profile curves; AUC and Cmax, were simulated based on exposure scenario reported in Table 2 (Figure 2 & 3).
- The AUC and Cmax results from the automated model were used to derive human Margin of Internal Exposure (MOIE) [3] for both oral and dermal routes (Table 3).
- COSMOS Space: We report graphical view of the newly developed automated tool for IVIVE or RtoR extrapolation of the KNIME webportal (Figures 4 to 7).

References


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www.cosmostox.eu

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