Research activities on kinetic modelling and quantitative in vitro-in vivo extrapolation for next generation risk assessment in the H2020 ONTOX project

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INTRODUCTION

The ONTOX is an EU-funded consortium launched in May 2021, which aims to provide a functional and sustainable solution for advancing human risk assessment of chemicals without the use of animal testing. ONTOX will deliver a generic strategy to create innovative new approach methodologies (NAMs) in order to predict systemic repeated dose toxicity effects that, upon combination with tailored exposure assessment, will enable human risk assessment. The aim is to develop ontologies for chemical-induced liver steatosis and cirrhosis, acute liver injury and crystallopathy, as well as neurodevelopmental toxicity and neurodegeneration. One of the pillars of such an ontology is a thorough understanding of the toxicokinetics of case study chemicals. Toxicokinetics and chemical exposures are addressed in work package four (WP4) of the project.

METHODOLOGY

Research in WP4 focuses on developing two types of in silico models: i. generic physiologically based kinetics (PBK) models for simulating in vivo distribution kinetics and characterising the ADME properties to predict tissue exposure for the selected chemicals and their systemic repeated dose toxicity effects, ii. in vitro distribution kinetics models for estimating cell-associated in vitro effect concentrations to accurately define and rank chemical potencies and in vitro assay sensitivity.

RESULTS

Preliminary predictions results from these in silico models, to predict the free in vitro concentration response curve; in addition the qIVIVE approach to characterise in vivo human dose response from in vitro toxicity data will be presented based on the endpoint selected in the ONTOX consortia.

DISCUSSION

These models are necessary to establish quantitative adverse outcome pathways (qAOP), the framework used to integrate the plethora of NAM data generated in the ONTOX project, as well as perform quantitative in vitro-in vivo extrapolations (QIVIVE). Gap analysis and data mining will be performed to evaluate and extend the definition of the chemical and biological applicability domains of these in silico approaches. Uncertainty, sensitivity analyses and model validation will be discussed in order to gain confidence in the application of such models by risk assessors and decision makers.