Use of the Open-Source Software Open Systems Pharmacology Suite (PK-Sim® and MoBi®) in Next Generation Risk Assessment (NGRA)

Main author: Stephan Schaller (esqlabs GmbH)

Co-authors: Alicia Paini, Susana Proenca Nynke Kramer

INTRODUCTION

Chemical risk assessment and toxicological sciences seek to reduce, and eventually replace, the use of animals for the prediction of toxicity in humans by relying on new approach methodologies. In this context, physiologically based kinetic (PBK) modelling has emerged as a tool and used in several sectors (pharma, veterinary, medicine, cosmetics, agrochemicals, and pesticides) where they play a pivotal role in next-generation risk assessment (NGRA).

METHODOLOGY

PBK models are a mathematical representation of the body, describing the adsorption, distribution, biotransformation (metabolism), and elimination of xenobiotics. PBK models are built using in vitro and in-silico kinetic data. They have the potential to play significant role in reducing animal testing, by providing a methodology capable of incorporating in vitro human data to facilitate the development of in vitro to in vivo extrapolation (IVIVE) of hazard information. As new approach methodologies (NAMs) such as IVIVE are being more and more refined, the role of PBK modelling is key when it comes to interpretation and extrapolation of the data from in vitro to in vivo.

RESULTS

The open-source software Open Systems Pharmacology Suite (OSPS, with tools PK-Sim and MoBi, www.open.systems-pharmacology.org) is specifically tailored towards user-friendly, robust, and workflow-supported (GUI-based) modelling and simulation. It combines the ease and efficiency of the GUI-based professional PBK tool PK-Sim with the customisability of the GUI-based mechanistic modelling tool MoBi (similar to Sim-Biology). PK-Sim provides physiology databases of multiple animal species and human populations (including maternal-foetal and preterm neonates).

MoBi allows mechanistic modelling in all its detail and full user-based customisation of PBK models through mechanistic modelling workflows, allowing extensions of compartmental

structures to any level of detail and the addition of complex kinetic/dynamic mechanisms for an integrated quantitative in-vitro in-vivo (QIVIVE) extrapolation framework.

DISCUSSION

With this presentation, we discuss the use of the open-source software Open Systems Pharmacology Suite (PK-Sim® and MoBi®) platform in IVIVE and in support of regulatory decision-making under the toxicology and risk-assessment paradigm. The strengths, gaps, uncertainties, and limitations of the platform will be discussed as well as how the validity and credibility of predictions are achieved. All this is in an effort to establish a higher degree of confidence in the application of such models in a regulatory context.