Exploiting Knowledge From Existing Physiologically-Based Kinetic Models To Improve Model Development

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Physiologically-based kinetic (PBK) models combine information on exposure scenarios, physico-chemical information for a chemical of interest, anatomical and physiological parameters, to simulate the concentration-time profile of a chemical, in plasma or in individual tissues. The models can provide unparalleled detail of the time-course of a xenobiotic in the body, so helping to determine the true likelihood of an effect being elicited by a particular chemical. PBK models are applied across a range of disciplines, such as development and safety assessment of drugs, cosmetics and chemicals for agricultural or household use. However, their construction, validation and application present several challenges. These include: (i) the limited number of PBK models available, compared to the vast number of chemicals in use, (ii) extensive data requirements for model building, that may necessitate searching of disparate resources (iii) insufficient high-quality data for model validation (iv) lack of consistency in model evaluation and reporting and (v) a paucity of expertise in developing and using models.

Recently, collaborative research efforts have aimed to address these shortcomings. For example, the publication of a PBK Modelling Dataset (PMD; a collation of over 7,500 published models for more than 1,100 chemicals) [1], with an associated KNIME workflow, enables appropriate PBK models to be identified from within the PMD [2]. Leveraging data from these models can assist the development of models for new chemicals, where data are lacking. Ongoing research is expanding the PMD with more recently published models. Additionally, this information is being used to construct an overview of how model quality is typically assessed, so identifying best practice in model development and evaluation.

Researchers associated with the Health and Environmental Sciences Institute (HESI) have been investigating these models, specifically, in relation to how oral absorption and brain distribution are characterised. The aim of this work is to determine common assumptions and sources of uncertainty within the models, that will enable recommendations to be made for using PBK models in risk assessment in a more consistent manner. To address the paucity of expertise in PBK modelling and to provide a single resource for the PBK modelling community, a "Webhub" has been proposed, serving as a repository for training resources, tools, datasets, guidance and other PBK-relevant resources. This presentation will provide an overview of these initiatives, outlining key progress to date, and future plans for advancing PBK model development and application.

1. Thompson, CV et al, Altern Lab Anim, **2021**, 49(5), 197-208.
2. Thompson, CV et al Comp Tox, **2024**, 29:100292

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