## Upgrading the Population Life-course Exposure to Health Effects Model

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The LRI-funded PLETHEM modeling framework was developed as a tool to overcome the technical challenges involved in performing PBPK modeling. The suite of tools now contains PBPK modeling for various exposure routes, commonly used PBPK modeling workflows, QSAR models, and the ability to communicate with multiple external tools for data import. In 2022 we worked to identify and mitigate critical issues in PLETHEM. Our efforts in 2023 will focus on upgrading PLETHEM to improve user experience, as well as on conducting outreach to key stakeholders.

The goal of this upgrade will be to update the modeling framework and optimize performance and user experiences. Major upgrades will improve user experience to match the needs for chemical assessment, including route-to-route and species extrapolation. The new release of the PBPK modeling tool will be streamlined with a simplified interface and generate comprehensive results in a template as suggested by the OECD working group on PBK modeling. The addition of a library of various PBPK models from the literature will also be included in the final stage of work. Past user experiences with the legacy work will also be addressed during the final development.

**Education and Outreach**

<u>Video Tutorials based on Workflow Documents.</u> In recognition that our stakeholders consume information from different media modes, we will extend the documentation we produced for the key workflows of Scito-Sim to include video tutorials that walk through these processes step-by-step. We will break the creation of the tutorials into two parts. First, we will develop a pilot video that we will test with stakeholders. Feedback from this process will inform the development of the remaining videos.

<u>Development of Modular Online Training.</u> ScitoVation will develop a short training course that will be targeted to potentially influential users in the government and in industry. For 2023, we will create a total of 4 hours of material that will be broken into lectures that will cover the basics of PBPK modeling, its use in risk assessment, and how PLETHEM can be used to meet the needs of the chemical safety community. This online training module will be freely accessible.

<u>Engagement with Expert Working Groups</u>. In 2023, we will continue our involvement with the HESI working group focused on using PBPK modeling to explore Kinetically Derived Maximum Dose. This group is exploring the impact of non-linear pharmacokinetics on in-life study outcomes. The goal is to establish study design criteria that minimize the occurrence of confounding off-target toxicity from saturation of ADME processes. PLETHEM is an attractive tool for the working group's case studies because it is open source and can be customized to suit the needs of an evolving project. Currently, we are collaborating with the working group to determine the impact of intraspecies variability on the identification of dose non-linearity. We plan to submit this work for publication in early 2023.

As the final development of the PBPK modeling tool progresses, ScitoVation will recruit external experts to gain feedback and improve the user experience in the process. At the same time, we will look for collaborative opportunities to champion the new PBPK modeling tool while keeping LRI abreast of developments with relevant projects.

**Implications:** The technologies developed here form a comprehensive and user- friendly platform that can be used by the ACC, their member chemical companies, and other stakeholders. With PLETHEM, they will be able to reality-check exposure estimates, improve quantitative risk assessments, interpret human biomarker data, evaluate early life sensitivity, and identify false associations in epidemiological studies.

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