

Population Life-course Exposure to Health Effects Model (PLETHEM) – Continued Platform Development

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Over the past five years, ScitoVation has been working in close collaboration with scientists from the U.S. Environmental Protection Agency's (EPA) Office of Research and Development to create a flexible, open-source modeling platform called PLETHEM (Population Life-course Exposure to Health Effects Model). This free, publicly available modeling platform will enable users to produce more accurate quantitative risk assessments by reducing uncertainties in the source-to-outcome continuum. This goal is being achieved by combining high-throughput exposure prediction programs and rapid physiologically based pharmacokinetic modeling (PBPK) into a single framework. The development of PLETHEM has drawn on the advanced modeling technologies pioneered by ScitoVation scientists under the continuing support of the ACC LRI. PLETHEM provides a previously unavailable capability for rapidly predicting chemical dosimetry to support risk assessments ranging from high-throughput screening to TSCA risk evaluations, as evidenced by the fact that the EPA Office of Pesticides has already adopted PLETHEM as a user-friendly, open-source platform for their evaluations of PBPK models submitted in support of pesticide risk evaluations.

In 2020 PLETHEM development will conclude. Efforts will focus on incorporation of community efforts pertaining to reporting PBPK modeling inputs, runs, and results. In 2020, the following activities will be conducted to educate users on various workflows within PLETHEM and their utilities:

1. ScitoVation will create written step by step user guides for each of the various workflows in PLETHEM that will answer the following questions:
 - a. How PLETHEM can be used with biomonitoring data and in conjunction with product use to determine margin of exposure (using exposure estimation tools, PBPK modeling and reverse dosimetry).
 - b. How PLETHEM can be used to develop Biomonitoring Equivalents (using exposure estimation tools, PBPK modeling, and forward dosimetry).
 - c. How PLETHEM can be used to convert an existing external dose POD to an internal dose POD, and then extrapolated to calculate the equivalent external doses that correspond to other routes of exposure (exposure estimation, PBPK modeling and route to route extrapolation)
 - d. How PLETHEM can be used to convert data from in vitro studies to equivalent human external exposures to obtain margin of exposure screening values using PODs (e.g., AC10, AC50, BMD) from in-vitro studies, IVIVE workflows in PLETHEM, exposure estimation tools, HTIVIVE and PBPK models to calculate margins of exposure.
 - e. How PLETHEM can be used to calculate a kinetically-derived maximum tolerated dose for dose setting for in vivo lab animal toxicity studies.
 - f. How PBPK models within PLETHEM can be used for ecotoxicology applications.
 - g. ScitoVation will also create additional written step by step user guides that will walk users through all the different configurations in which PLETHEM models can be simulated.
2. ScitoVation will incorporate reporting tools within PLETHEM that abide by the upcoming HESI PBPK model reporting guidelines. ScitoVation will also create a series of written step by step user guides for teaching users how to generate models, results and reports within PLETHEM that adhere to those guidelines.
3. ScitoVation will develop a QSAR model for predicting intrinsic clearance for a chemical from its structure. This tool will be added into PLETHEM. This will supplement the existing QSAR models in PLETHEM that predict tissue partitioning and chemical properties.

4. ScitoVation will submit updated versions of the package into CRAN making it easier for users to download and install PLETHEM on their local machines.

Implications: The technologies developed here serve as the basis for a more 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. Eventually, PLETHEM will incorporate more *in vitro* and *in silico* tools that can assist in providing a quantitative estimate for margins of safety surrounding chemical use.

Collaborations: None.

Key words: exposure, HT-IVIVE, PBPK, TTC, pharmacokinetics, biological modeling, PLETHEM

Current project start and end dates: January 2020 – December 2020

Peer-reviewed publication(s):

Pendse S. N., Efremenko A. Y., Hack C. E., Moreau M., Mallick. P., Dzierlenga M., Nicolas C. E., Yoon M., Clewell H. J., McMullen P. D. (2019). Population life-course exposure to health effects model (PLETHEM): An R package for PBPK modelling, *Computational Toxicology* 13 (2020): 100115

Yoon, M. and Clewell III, H. J. (2016). Addressing early life sensitivity using physiologically based pharmacokinetic modeling and *in vitro* to *in vivo* extrapolation. *Toxicology Research* 32:15-20.

Presentation(s):

Pendse S.N. (2019). Using *in vitro* assays, MoAViz, and PLETHEM to determine an *in vivo* point of departure Oral presentation at NURA: Integrated Approaches to Testing and Assessment, Houston, TX, Dec 11-12, 2019

Pendse S.N. (2019). Using HT-IVIVE and PBPK modeling in PLETHEM to establish a margin of exposure for risk assessment. Oral presentation at NURA: Evaluating toxicological information using modern science. Gaithersburg MD, May 21-22, 2019.

Pendse S. N., Efremenko A. Y., Nicolas C. I., Clewell H. J., McMullen P. D. (2019). Extending the PLETHEM platform for PBPK modeling: batch mode processing, dermal route of exposure, and integration with mode-of-action tools. Poster presented at the Society of Toxicology 58th Annual Meeting, Baltimore, MD, March 10-14, 2019.

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Pendse, S. (2018). Unification of exposure and pharmacokinetic tools under the PLETHEM framework. ACC SST Webinar Series. September 2018.

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Pendse, S., Diallo, I., Nicolas, C., Efremenko, A.Y., Hack E, Housand, C., McMullen, P., Yoon, M., Clewell, H.J. (2018). Incorporation of public exposure models into the PLETHEM pharmacokinetic framework. EuroTox 2018, Brussels, Belgium, September 2-5, 2018.

Pendse, S., Diallo, I., Nicolas, C., Efremenko, A. Y., Housand, C., McMullen, P.D., Yoon, M., Clewell, H.J. (2018). Unification of exposure and pharmacokinetic tools under the PLETHEM framework. Poster Presentation. OpenTox, USA 2018.

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Pendse, S. N., Diallo, I., Nicolas, C., Efremenko, A. Y., Housand, C., McMullen, P., Yoon, M., Clewell, H. (2018) Unification of exposure and pharmacokinetic tools under the PLETHEM framework. ICCA-LRI Workshop, Ottawa, Canada, June 21-22, 2018.

Pendse, S. N., (2018) PLETHEM training. ICCA-LRI Workshop, Ottawa, Canada, June 20-21, 2018.

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Pendse S.N., Efremenko, A., McMullen, P., Yoon, M., Clewell, H. (2017). PLETHEM: an interactive open-source platform for bridging the source-to-outcome continuum, Poster Presented at Annual Society of Toxicology 56th Annual Meeting, Baltimore, Maryland, 2017.

Other publication(s): None to date.

Abstract revision date: April 2020