Development of additional workflows for risk assessment and prioritization for the PLETHEM R Package

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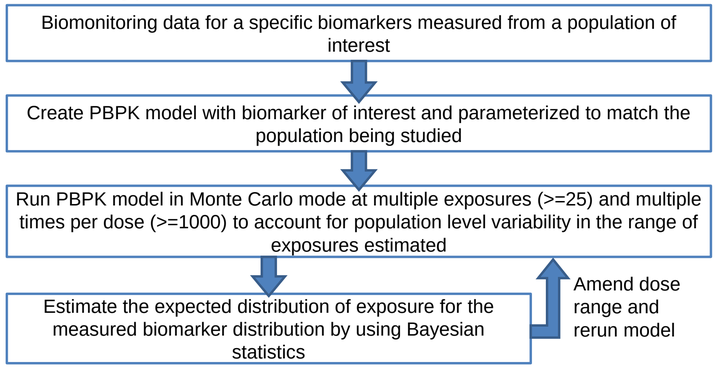
Abstract

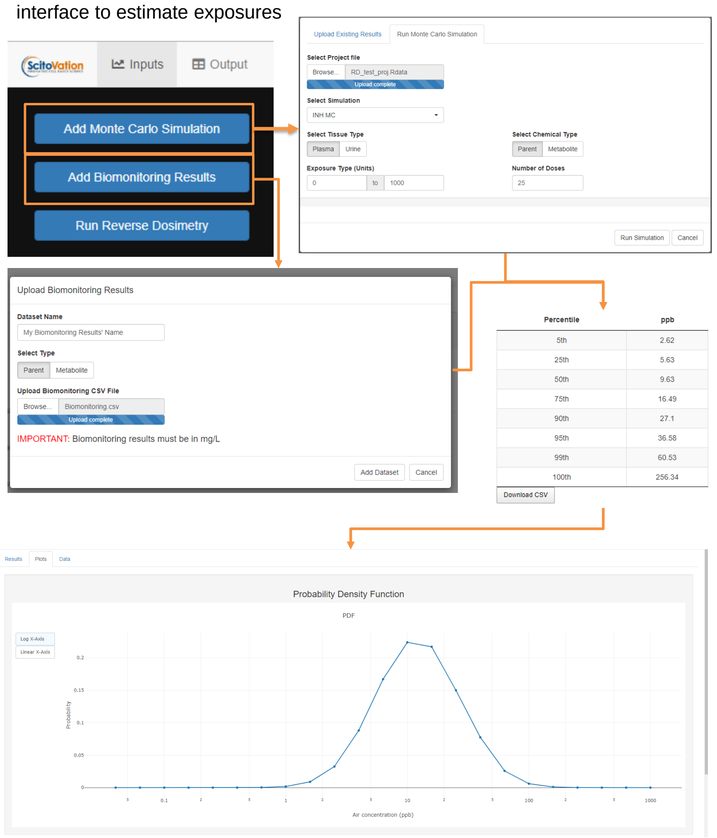
Over the past three years we have been developing the population life-course exposure to health effects model (PLETHEM) – the open source R package that is designed to provide tools that can be used to bridge the source-to-outcome continuum. Pharmacokinetic modeling is becoming increasingly important in chemical safety decision making, with applications in prioritizing risk assessment by establishing margins of exposure for chemicals and extrapolating hazard across different ages, population cohorts, or occupational classes. As a part of our effort to provide the community with an easy-to-use yet capable modeling tool, we have continued to develop the PLETHEM package. We have created workflows for automated reverse dosimetry and route to route extrapolation, modeling for ecotoxicology applications, and kinetically derived maximum tolerated dose estimation. The automated reverse dosimetry module implements the Discretized Bayesian Approach as described by Tan et al. (2007) along with an easy-to-use interface to run the workflow. Simulation results from existing PBPK models or from models parameterized within PLETHEM can be imported for dose reconstruction. We have also added the ability to perform automated route-to-route extrapolations within PLETHEM. The user can parameterize the model for a given route of exposure using the existing forward dosimetry interface within PLETHEM and use this parameterized model to estimate exposure along a different route using this workflow. Next, as a part of this update, we have added a fish PBPK model described by Krishnan et al. (2009), physiological datasets for this model and an easy to use modeling interface to help stakeholders address ecotoxicology concerns. Lastly, we are incorporating into PLETHEM additional features to make kinetically derived maximum tolerated dose (KMD) modeling more accessible. KMD makes use of kinetic modeling to identify dose ranges that avoid saturating ADME processes, which would convolute the interpretation of the study. McFadden et al. (2012) described a statistical method to determine KMD values for toxicokinetic studies. We are adding to PLETHEM an interface that allows users to import their own toxicokinetic datasets or simulated PBPK models from PLETHEM to estimate a KMD. PLETHEM is freely available via the Comprehensive R Archive Network (CRAN). We are also hosting some of these workflows as standalone apps online to provide users with easy access to them.

Reverse Dosimetry

PBPK models can be used to estimate external exposure that can lead to observed biomarker distribution in a population of interest. Reverse dosimetry workflows are used to perform this extrapolation using either Exposure Conversion Factor Approach (ECF), Discretized Bayesian Approach (DBA), or Markov-chain Monte Carlo Approach. Of these we have implemented DBA within PLETHEM. The approach was first described by Tan et al (2007) . DBA uses the following process to estimate external exposure that may lead to the observed biomonitoring profile.

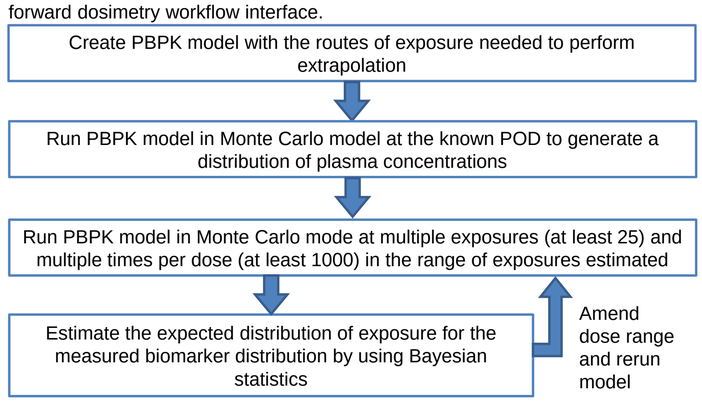


Each of the steps above can be completed in PLETHEM using specialized interfaces for defining inputs and outputs. The model created using the forward dosimetry interface in PLETHEM can be imported into the reverse dosimetry interface to estimate exposures

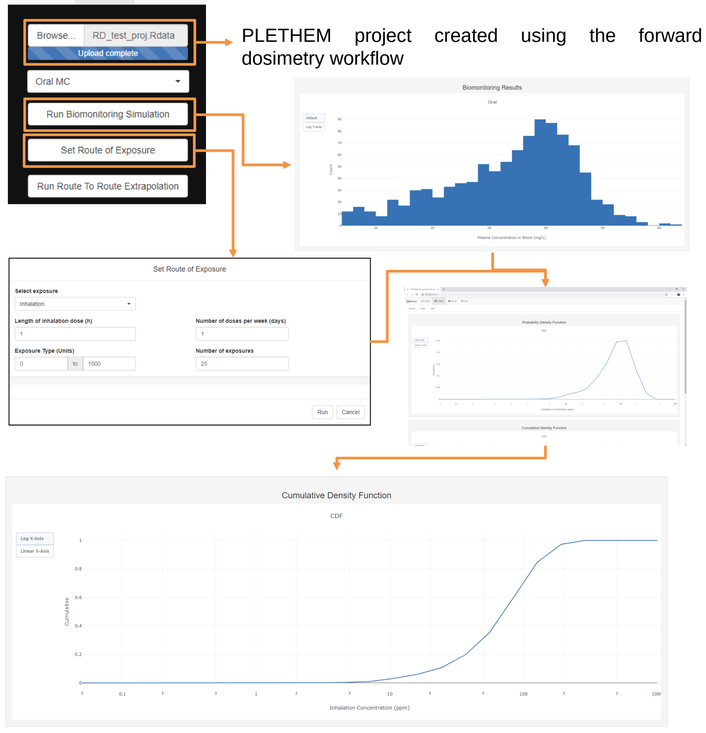


Route to Route Extrapolation

PBPK models can be used to extrapolate human or animal Pont of Departure (POD) from one route of exposure to another. Route to route extrapolation is useful in estimating hazard due do exposure from a route which was not explicitly tested in previous studies (like calculating the POD for a dermal exposure that leads to the same internal concentration following a known oral exposure-based POD). PLETHEM uses the forward and reverse dosimetry workflows internally to perform route to route extrapolation. The forward dosimetry workflow is used to estimate internal plasma concentration (Cmax) that corresponds to the external POD for a known route of exposure. The reverse dosimetry workflow is then used to estimate an external POD along a different route that would give the same internal plasma concentration. All of this is achieved through a series of interfaces that allow users to upload PLETHEM project files created using the forward dosimetry workflow interface.



PLETHEM uses interfaces shown below to run the workflow. This workflow uses the same DBA algorithm that is a part of the reverse dosimetry workflow to perform the estimation.

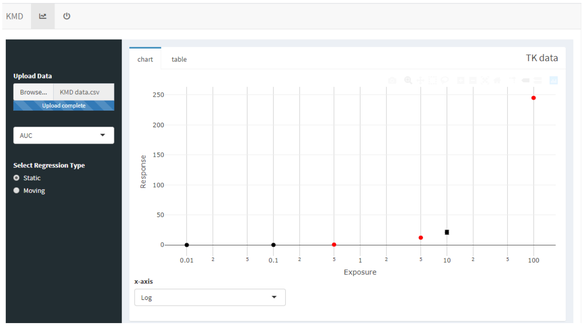


Kinetically Derived Maximum Tolerated Dose (KMD)

Kinetically derived maximum tolerated dose (KMD) is an important tool in understanding the non-linearities in a toxicokinetic study. These non-linearities can indicate inefficiencies in absorption and/or elimination of dose. We have implemented the workflow developed by McFadden et al. (2012) to determine the KMD in a toxicokinetic study. The workflow is implemented in PLETHEM through a series of interfaces that will be incorporated into the next release of PLETHEM in CRAN. The workflow is also available as a standalone web tool at https://scitovation.shinyapps.io/plethem-kmd

	A	B	C	D	E	F
1	Nominal E	Actual Exp	AUC	Cmax	Histopath	Reps
2	0	0	0	0	0	1
3	0	0	0	0	0	2
4	0	0	0	0	0	3
5	0.01	0.01	0.012602	0.030189	0.022402	1
6	0.01	0.01	0.012127	0.031382	0.030006	2
7	0.01	0.01	0.012373	0.04031	0.0322	3
8	0.1	0.1	0.12451	0.422081	0.205313	1
9	0.1	0.1	0.130754	0.330519	0.204716	2
10	0.1	0.1	0.124276	0.40334	0.210449	3
11	0.5	0.5	0.626542	2.023835	1.547637	1
12	0.5	0.5	0.636158	2.097046	1.589893	2
13	0.5	0.5	0.635538	2.077093	1.583088	3

Template excel file for uploading data for estimating maximum tolerated dose



Output from the maximum tolerated dose algorithm. The red circles indicate doses that have been identified as not being on a linear dose response relationship

Other improvements to PLETHEM in 2019

- Implemented trout PBPK model in PLETHEM developed by Krishnan et al (2009) to support ecotoxicology modeling
- A unified QSAR algorithm for predicting partition coefficients in highly lipophilic compounds
- API to connected to NIEHS's Integrated Chemical Dashboard (ICE)
- Interfaces to import physical-chemical predictions from OPERA QSAR models

References

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Krishnan, Kannan, and Thomas Peyret. "Physiologically based toxicokinetic (PBTK) modeling in ecotoxicology." *Ecotoxicology modeling*. Springer, Boston, MA, 2009. 145-175.

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Acknowledgements

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