Abstract #1791

Development of a Generalized Inhalation Model for Use with the High-Throughput Toxicokinetics (*httk*) Package in R

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Introduction

Currently, it is difficult to prospectively estimate human toxicokinetics (particularly for novel chemicals) in a high-throughput manner. The R software package *httk* was developed, in part, to address this deficiency through the use of physiologically-based toxicokinetic (PBTK) modeling. However, the PBTK model included in the *httk* package is currently limited to oral and intravenous exposure routes. The aim of this investigation was to develop a generalized inhalation model for *httk* and to evaluate the model using published exposure data.

Methods

- Model structure was based on published physiologically-based models
  - Jongeneelen *et al.* (2011) for calculation of blood:air partitioning based on chemical properties[i]
  - Clewell *et al.* (2001) for inhalation model parameters[ii]
- Evaluated 42 volatile organic chemicals (VOCs) with concentration-time data available in previously published studies
  - Physicochemical data (molecular weight, Henry's Law coefficient, log P) were obtained using EPA's CompTox Chemicals Dashboard with OPEn qsaR App predictions[iii]
  - Fraction unbound in plasma was calculated using Simulations Plus® ADMET Predictor™ v. 9
- Inputs for each exposure scenario included chemical concentration in the air, length of exposure to the chemical, and species. Michaelis-Menten liver metabolism was implemented for rats.
- Appropriateness of simulated concentrations for chemicals was determined by examining log-transformed observed vs. simulated:
  - Concentrations (blood, plasma, exhaled breath)
  - Max concentration (C_{max})
  - Area under the concentration-time curve (AUC)

Results

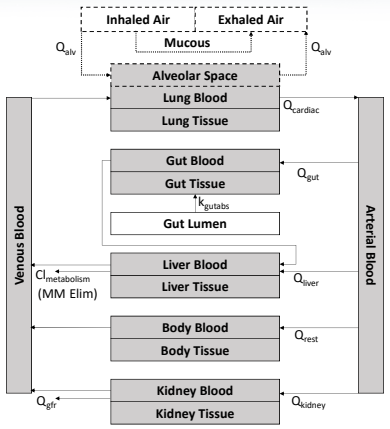

Figure 1: Physiological model structure, dotted lines indicate newly added inhalation components

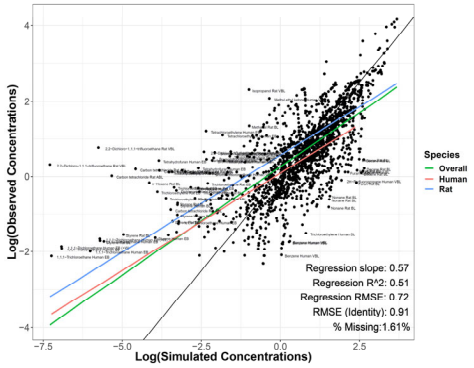

Figure 2: Log-transformed observed vs. simulated concentrations (blood and exhaled air). Regression measures of fit are related to the "Overall" regression. Black line is the line of identity (x = y). Labeled points are >2 log-orders different between observed and simulated values.

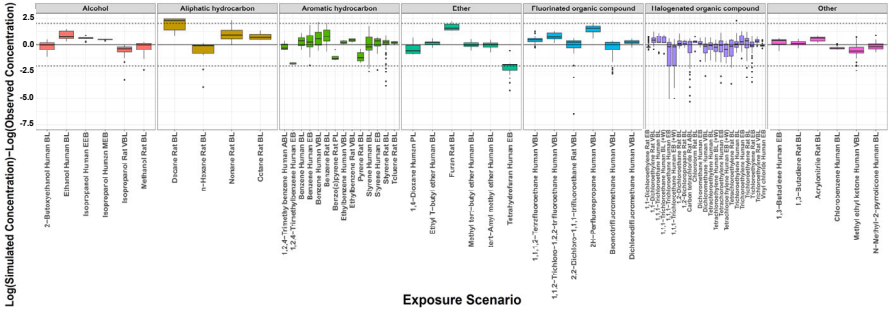

Figure 3 : Log-transformed simulated minus observed concentrations for each exposure scenario. Scenarios are grouped by chemical class. (BL, Blood; EEB, End-exhaled breath; MEB, Mixed exhaled breath; VBL, Venous blood; ABL, Arterial blood; EB, Exhaled breath; PL, Plasma; +W, with work/exercise)

Results (continued)

- In total, 143 exposure scenarios (77 in humans, 66 in rats) to 42 chemicals were included in the analysis
  - Included chemicals had mean molecular weight of 116.10 g/mol (range: 32.04-252.32 g/mol) and log P of 2.2 (range: -0.6-6.1)
- **Figure 1** shows the structure of the model utilized in the analysis with the added inhalation components
- Goodness-of-fit values for observed vs. simulated values are shown in **Figure 2** for log-transformed concentrations (blood and exhaled air)
  - C_{max} regression: slope = 0.83, r^2 = 0.72, RMSE (Identity) = 0.48
  - AUC regression: slope = 0.92, r^2 = 0.79, RMSE (Identity) = 0.50
- Approximately 3.5% of the observed concentration values were >2 log-orders different than the simulated concentrations (0.8% overpredicted, 2.7% underpredicted)
- About 1.6% of measured data points were censored because they were negligible values at t = 0
- **Figure 3** provides the distribution of the differences between log-transformed simulated and observed concentrations for each given chemical/species/matrix combination grouped by CAMEO chemical class

Conclusions and Future Directions

- Goodness-of-fit values indicate relatively reasonable simulation of the reported data
- Limitations include lack of accounting for ingestion, dermal absorption, and lung metabolism
- External evaluation will be pursued with concentration-time data not used in this analysis (see Sayre *et al.* Abstract 1766/Poster P142)
- Future efforts will be focused on identifying trends in model fit relative to chemical properties, inclusion of an aerosol inhalation component

References

[i]Jongeneelen FJ, Berge WF. *Ann Occup Hyg.* 2011. 55(8):841-864.
[ii]Clewell HJ 3rd, *et al. Toxicol Sci.* 2001. 63(2):160-172
[iii]Mansouri K, *et al. J. Cheminform.* 2018. 10(1): 10

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