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Introduction

Physiologically based pharmacokinetic modeling (PBPK) is a valuable tool to evaluate inhalation exposure of volatile organic compounds (VOCs). Many literature models are ad hoc, built for a single purpose/molecule, include small subset of tissues, and rely on experimental or fitted partition coefficients. In this work, a standardized PBPK modeling platform GastroPlus® (Simulations Plus, Inc.) is utilized to develop a PBPK model for vapor inhalation. Previously, the inhalation capability was focused on dry powder, nebulized, or solution formulations. The focus of this work is building a model to describe vapor inhalation and validating its usage.

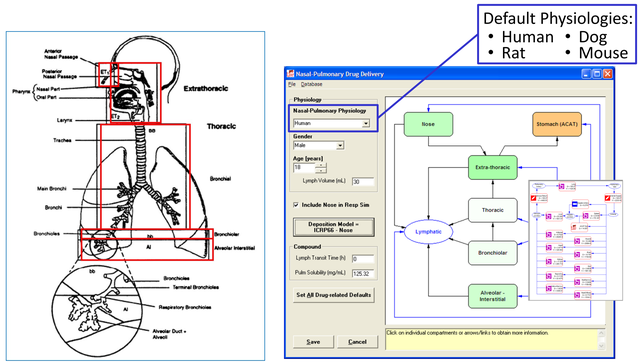

Figure 1: Compartmental representation of the lung model

References

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Methods

The VOC PBPK inhalation model was built using GastroPlus version 9.7. Mass balance equations that describe gas flow in/out of the system were developed to calculate the VOC in different lung sections. Drug partitions into mucus based on Henry's law and diffuses though the epithelial cells reaching systemic circulation. Mucus and epithelial cell layer thickness is location dependent in the lung. Figure 1 and 2 show the lung compartmental model framework and a detailed representation of a single compartment. Input values of gas diffusion coefficient and Henry's law constant were obtained from the EPA EPI Suite software. Physicochemical properties were calculated from ADMET® Predictor 9.5. Partition coefficients in the PBPK models were calculated from Lukacova method. Metabolic clearance (linear or non-linear) was fit in all cases to IV and/or oral PK data.

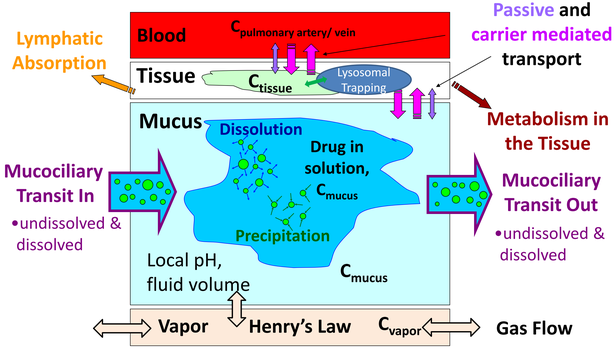

Figure 2: Pulmonary PBPK model diagram

Results and Conclusions

The model was tested on several available literature datasets including ethanol, methanol, acetone, and styrene [1-11]. Methanol plasma concentration (Cp) prediction after inhalation of 200 - 2000 ppm for 6 hours in rat is shown in Figure 3. The average Cmax and AUC % error for the 200 -2000 ppm dose was 22 and 23%. However, the error was largely dictated by the 2000 ppm formulation.

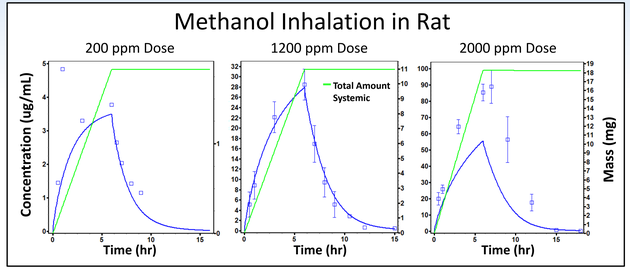

Figure 3: Cp-time prediction of 200-2000 ppm Methanol Inhalation in rat. PBPK model parameters determined from IV data used to predict inhalation.

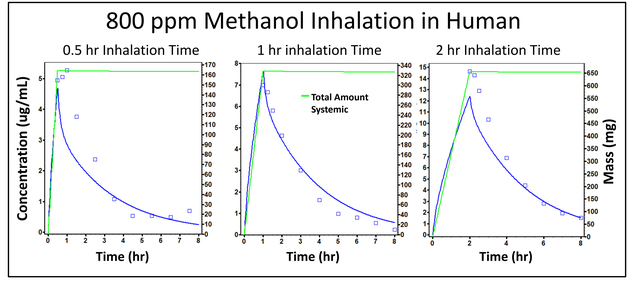

Figure 4: Model prediction of 800 ppm methanol inhalation in human with exposure times from 0.5-1 hr. PBPK model parameters scaled from rat used to predict inhalation.

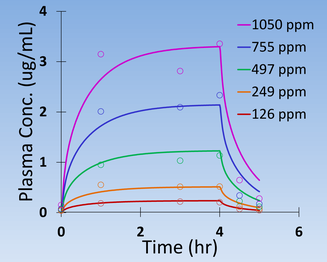

Figure 5: Predicted and observed ethanol Cp-time profile for human vapor exposure at 126-1050 ppm

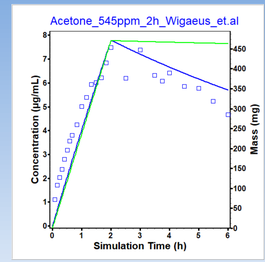

Figure 6: Predicted and observed Cp-time of acetone during vapor exposure in human at 545 ppm

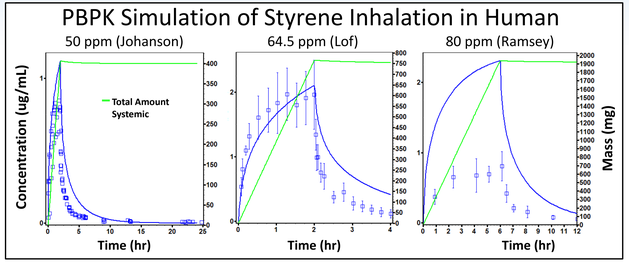

Figure 7: Predicted and observed styrene plasma concentration during vapor exposure at 50, 64.5, and 80 ppm in human. Note the amount in systemic circulation can decrease due to exhalation clearance.

The model was then applied to predict 800 ppm exposure in human with clearance from literature [5] with an average Cmax and AUC % error of 13.4% and 19.9%. Predictions of human VOC inhalation of ethanol, acetone and styrene are shown in Figure 5, 6, and 7. The same procedures were followed as the methanol model and similar error was achieved except for one outlier dataset for styrene [11]. Overall, the model was successful in predicting plasma concentrations for rat and human.

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