Abstract

Biofuel blends of 10% ethanol (EtOH) and gasoline are common in the United States, and higher EtOH concentrations are being considered (15-85%). Currently, no physiologically-based pharmacokinetic (PBPK) models are available to describe the kinetics of EtOH-based biofuels. PBPK models were developed to describe life-stage differences in the kinetics of EtOH alone in adult, pregnant, and neonatal rats for inhalation, oral, and intravenous routes of exposure, using data available in the open literature. Whereas ample gavage and intravenous data exist, kinetic data from inhalation exposures are limited, particularly at concentrations producing blood and target tissue concentrations associated with developmental neurotoxicity. Compared to available data, the three models reported in this paper accurately predicted the kinetics of EtOH, including the absorption, peak concentration, and clearance across multiple datasets. In general, model predictions for adult and pregnant animals matched inhalation and intravenous datasets better than gavage data. The adult model was initially better able to predict time-course blood concentration data than was the neonatal model. However, after accounting for age-related changes in gastric uptake using the calibrated neonate model, simulations consistently reproduced the early kinetic behavior in blood. This work provides comprehensive multi-route life-stage models of EtOH pharmacokinetics and represents a first step in development of models for use with gasoline-EtOH blends, with additional potential applicability in investigation of the pharmacokinetics of EtOH abuse, addiction, and toxicity.