PBPK Models for Gasoline-Ethanol Biofuels in Adult and Pregnant Rats

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As utilization of biofuels (BF) in the commercial marketplace has increased in recent years, so has the need for evaluation of exposure-related health effects, such as developmental neurotoxicity. This research describes the development of inhalation life-stage physiologically-based pharmacokinetic (PBPK) models for vapors of gasoline (E0) and two BF blends, E15 (15% EtOH) and E85 (85% EtOH). Time-course blood hydrocarbon concentration (BHC) data were collected from non-pregnant female rats exposed to E0, E15, and E85, at total hydrocarbon concentrations (THC) of 3K, 6K, and 9Kppm (≤6h exposure, 4-6 time points per dose). Peak (end-of-exposure) BHC data were also collected from pregnant dams exposed to 9Kppm (6.33h, GD9, 16, 20) of E0 or E15. These datasets were used to evaluate and refine PBPK models for each mixture and to compare estimates of BHCs across BF types at comparable THCs. PBPK models were constructed using a series of sub-models for prominent aromatic and aliphatic HCs representing ~45-66% of total vapor (depending on BF), while the remaining fractions were lumped. The overall modeling framework allowed for flexibility across blend compositions. The sub-models were parameterized with literature and structure-activity-based estimates; estimated physiochemical and metabolic parameters were used for the lumps. The models adequately simulated BHCs for most aromatic and aliphatic HCs across the various exposure scenarios. Specifically, HCs with robust calibration literature were usually well simulated, while clearance rates for the other aliphatics often did not adequately match model BHC predictions. Simulations for aromatics at high vapor concentrations were improved by including metabolic interactions; HCs at low concentrations were often better simulated without these interactions. The final models may be relevant for simulations of other blend ratios. Abstract does not reflect EPA policy.

Keywords: Gasoline, PBPK model, Mixtures