Abstract

Ethanol (EtOH) exposure induces a variety of concentration-dependent neurological and developmental effects in the rat. Physiologically-based pharmacokinetic (PBPK) models have been used to predict the inhalation exposure concentrations necessary to produce blood EtOH concentrations (BEC) in the range associated with these effects. Previous laboratory reports often lacked sufficient detail to adequately simulate reported exposure scenarios associated with BECs in this range, or lacked data on the time-course of EtOH in target tissues (e.g., brain, liver, eye, fetus). To address these data gaps, inhalation studies were performed at 5,000, 10,000, and 21,000 ppm (6 hr/d) in non-pregnant female Long-Evans (LE) rats and at 21,000 ppm (6.33 hr/d) for 12 days of gestation in pregnant LE rats to evaluate our previously published PBPK models at toxicologically-relevant blood and tissue concentrations. Additionally, nose-only and whole-body plethysmography studies were conducted to refine model descriptions of respiration and uptake within the respiratory tract. The resulting time-course and plethysmography data from these *in vivo* studies were compared to simulations from our previously published models, after which the models were recalibrated to improve descriptions of tissue dosimetry by accounting for dose-dependencies in pharmacokinetic behavior. Simulations using the recalibrated models reproduced these data from non-pregnant, pregnant, and fetal rats to within a factor of 2 or better across datasets, resulting in a suite of model structures suitable for simulation of a broad range of EtOH exposure scenarios.

Abbreviations: Ethanol (EtOH), BEC (blood EtOH concentration), BrEC (brain EtOH), LEC (liver EtOH), EEC (eye EtOH), fCEC (fetal carcass EtOH), fBEC (fetal blood EtOH), fBrEC (fetal brain EtOH), nose-only (N-O), whole-body (W-B), plethysmograph (PLY), gestation day (GD).