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Sweeney and Gargas Publish PBPK Model for Ethylbenzene

A. Nong, G. Charest-Tardif, R. Tardif, D. F. Lewis, L. M. Sweeney, M. L. Gargas, and K. Krishnan. Physiologically based modeling of the inhalation pharmacokinetics of ethylbenzene in B6C3F1 mice. *J Toxicol Environ Health A* 70 (21):1838-1848, 2007.

A physiologically based pharmacokinetic (PBPK) model was developed for inhaled ethylbenzene (EB) in B6C3F1 mice. The mouse physiological parameters were obtained from the literature, but the blood:air and tissue:air partition coefficients were determined by vial equilibration technique. The maximal velocity for hepatic metabolism (Vmax) obtained from a previously published rat study was increased by a factor of approximately 3 to account for enzyme induction during repeated exposures. The Michaelis affinity constant (Km) for hepatic metabolism of EB, obtained from a previously published rat PBPK modeling study, was kept unchanged during single and repeated exposure scenarios. Hepatic metabolism alone could not adequately describe the clearance of EB from mouse blood. Additional metabolism was assumed to be localized in the lung. The parameters for pulmonary metabolism were obtained by optimization of PBPK model fits to kinetic data collected following exposures to 75-1000 ppm. The PBPK model successfully predicted all available blood and tissue concentration data in mice exposed to 75 or 750 ppm EB. Overall, the results indicate that the rate of EB clearance is markedly higher in B6C3F1 mice than rats or humans and exceeds the hepatic metabolism capacity. Available biochemical evidence is consistent with a significant role for pulmonary metabolism; however, the extent to which the extrahepatic metabolism is localized in the lung is unclear. Overall, the PBPK model developed for the mouse adequately simulated the blood and tissue kinetics of EB by accounting for its high rate of clearance.

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