

Sapphire News

Estimation of Inter-Individual Variation in Oxidative Metabolism of Dichloromethane in Human Volunteers.

Sweeney LM, Kirman CR, Morgott DA, Gargas ML. *Toxicol Lett.* 2004 Dec 30;154(3):201-16. The Sapphire Group, 2661 Commons Boulevard, First Floor, Dayton, OH 45431, USA.

A modified version of the original physiologically based pharmacokinetic (PBPK) model by Andersen et al. (1987) has been developed and used in conjunction with previously published human kinetic data for dichloromethane (DCM) metabolism and to assess interindividual variability in the rate of oxidative metabolism. Time-course data for 13 volunteers (10 males, 3 females) exposed to one or more concentrations of DCM (50ppm, 100ppm, 150ppm, or 200ppm) for 7.5h were used to optimize the maximal rate of hepatic metabolism ($V(\max_C)$) through the cytochrome P450 pathway for each individual. DCM breath and blood concentrations were used, along with carboxyhemoglobin concentrations in blood and carbon monoxide (CO) concentrations in exhaled breath, to estimate the model parameters. Significant improvements in model fit were achieved when extrahepatic oxidative metabolism of DCM was added to the model structure. The 13 individual $V(\max_C)$ values ranged from 7.1 to 23.6mg/h/kg(0.7) and appeared to be bimodally distributed. The distribution was not sex related and may be related to differential CYP2E1 induction. A comparison of the observed variation in $V(\max_C)$ values to other estimates of variability in the rate of oxidative metabolism and human CYP2E1 activity suggest a relatively narrow range in human hepatic activity toward DCM.