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PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF DI - N - BUTYL PHTHALATE (DBP) IN PREGNANT RATS

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DBP is a phthalic acid ester widely used as a plasticizer and solvent and a known reproductive toxicant. PBPK models incorporate physiological and chemical specific parameters to make quantitative predictions of tissue concentrations over time. The objective of this study was to develop a PBPK model to predict fetal exposure to monobutylphthalate (MBP), the proposed toxic metabolite of DBP, during the critical window of reproductive development in rats (gestation days GD12-20). A flow-limited PBPK model for a pregnant rat was developed based on an existing model (O'Flaherty et al., 1992, Toxicol. Appl. Pharmacol. 112: 245-256). Physiological parameters were obtained from peer-reviewed published literature reports. Chemical specific parameters were obtained from or calculated using data available from literature. Specifically, DBP to MBP metabolism in the gastrointestinal (GI) tract was modeled using Michaelis-Menten kinetics, and MBP uptake from GI fluid was calculated using a first-order rate constant. MBP metabolism was assumed to follow Michaelis-Menten kinetics in the liver. We evaluated the ability of this PBPK model to predict MBP concentration by comparing model output with data on maternal plasma, placenta, and fetal plasma following oral administration of DBP (0.5 and 1.5 g/kg) in pregnant rats on GD14 (Saillenfait et al., 1998, Toxicol. Sci. 45: 212-224). Model simulations predicted the time course of MBP uptake, distribution, and elimination from maternal plasma, placenta, and fetal plasma. Experimental data were underpredicted but model outputs were consistent with the rapid clearance of DBP and MBP, greater than 90% excreted within 48 hours, seen experimentally. Sensitivity analysis indicated that model predictions depend strongly on the rate-function used for MBP absorption from the GI tract following oral administration of DBP. Targeted experimental data on pathways of oral absorption and metabolism parameters during pregnancy will be required to improve predictions of MBP concentrations in maternal and fetal tissues.

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