Development of a Physiologically Based Pharmacokinetic Model for Triadimefon and Triadimenol in Rats and Humans

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A physiologically based pharmacokinetic (PBPK) model was developed for the conazole fungicide triadimefon and its primary metabolite, triadimenol. Rat tissue:blood partition coefficients and metabolic constants were measured *in vitro* for both compounds. Kinetic time course data for parent and metabolite were collected from several tissues after intravenous administration of triadimefon to male Sprague Dawley rats. The model adequately simulated peak blood and tissue concentrations but failed to predict the observed slow terminal clearance of both triadimefon and triadimenol from blood and tissues. Low capacity protein binding of parent and metabolite in blood and tissues was speculated as a possible explanation of clearance patterns, and model predictions were significantly improved by the addition of optimized binding parameters. Human models with and without blood and tissue binding were constructed for triadimefon and triadimenol using human derived *in vitro* metabolic constants. Human equivalent doses (HEDs) were calculated for both models for a rat NOAEL dose of 11 µmol/kg/day using area under the concentration curve (AUC) in brain and blood for triadimefon and triadimenol as dosimetrics. All dosimetric-based HEDs were above the oral reference dose of 0.11 µmol triadimefon/kg/day.