

metabolism were found. Adipose blood flow was correlated with the measured fraction of adipose tissue. Body weight, adipose tissue fraction, and blood/air partition coefficient were correlated with terminal half-life, steady-state volume of distribution, and terminal volume of distribution. Extrahepatic metabolism was correlated with systemic clearance and terminal half-life. An increased adipose fraction led to lower blood concentrations up to 8 hr post-exposure. Use of subject-specific model parameters greatly improved model fit and demonstrated interindividual differences in toxicokinetics. Financial support was provided by the Superfund Basic Research program, NIEHS ES 04696.

1282 A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR INGESTION OF CHROMIUM (III and VI) IN DRINKING WATER: VALIDATION WITH HUMAN STUDIES

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A physiologically-based pharmacokinetic model (PB-PK) for trivalent and hexavalent chromium was developed using rodent data scaled up to human parameters for physiology and chromium kinetics. The model was calibrated with human ingestion data on trivalent chromium compounds and preliminary data from recent human volunteer studies of hexavalent chromium in drinking water. The substantial reducing capacities of gastric fluids and the blood demonstrated in recent studies suggests that drinking water exposures exceeding 10 mg Cr(VI)/day would be required to result in any measurable or substantial distribution of the hexavalent form beyond the stomach. At the Cr(VI) water concentrations examined in our human studies, the PB-PK model predicts systemic uptake and distribution of chromium only in the trivalent form. The model also predicts that high concentrations of Cr(VI) would be required in drinking water to overwhelm the reductive capacity of the stomach and the blood. Since Cr(VI) imparts a bright yellow color to drinking water even at 10 mg Cr(VI)/L, this model suggests that plausible long-term exposures to Cr(VI) in drinking water below this level are pharmacokinetically equivalent to uptake of the more bioavailable forms of trivalent chromium.

1283 A PHYSIOLOGICALLY-BASED PHARMACOKINETIC DESCRIPTION OF BROMODICHLOROMETHANE (BDCM) TISSUE DOSIMETRY AND METABOLISM

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BDCM is a by-product of water chlorination which is carcinogenic in rats and mice. The carcinogenic response induced by BDCM in rodents is likely due to the amount of compound reaching target tissues and the rate of BDCM metabolism to reactive intermediates. To estimate the delivery of BDCM to target tissues following oral gavage, we have developed a physiologically-based pharmacokinetic (PBPK) model for BDCM in the male F-344 rat. The model consists of six compartments (liver, kidney, slowly and rapid perfused tissues, fat and gut). The gut compartment consists of a number of sub-compartments, each described by an absorption constant (K_a; 1/hr), a bioavailability term (A; unitless) and a time of emptying (T; hours). Constants for BDCM metabolism were obtained from blood bromide determinations following constant concentration inhalation exposures (50–3200 ppm for 4 hr). Levels of BDCM in tissues and exhaled breath following oral gavage of 50 or 100 mg/kg in corn oil or 10% Emulphor were quantitated using gas chromatography techniques. Parameterization of the oral uptake of BDCM was accomplished by fitting blood and exhaled breath chamber BDCM concentration-time profiles by changing values of K_a, A, and T. BDCM metabolism, assessed by blood bromide production, was described using two saturable pathways (K_{m1} = 0.5 mg/l; K_{m2} = 5.0 mg/l; V_{max1} = 11.0 mg/hr/kg; V_{max2} = 2.0 mg/hr/kg). Model simulations were in good agreement with measured target tissue BDCM levels using oral uptake parameters obtained by fitting exhaled breath curves. This work increases the confidence in the present model structure and values for metabolic constants. This model will help reduce the uncertainties in extrapolations from animal bioassay results following oral gavage with BDCM to the human exposure situation. (This abstract does not reflect EPA policy).

1284 PHYSIOLOGICALLY-BASED PHARMACODYNAMIC MODELING OF ACUTE CARDIOVASCULAR RESPONSE TO REPEATED NICOTINE ADMINISTRATION IN HUMANS

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Tachyphylaxis is a well-characterized physiological response to the effects of many xenobiotics. To better understand this process, a physiologically-based pharmacodynamic (PB-PD) model which includes a negative feedback control system was applied to further describe the previously reported effects of nicotine on heart rate. The PB-PD model was linked to the tissue concentrations predicted from a physiologically-based pharmacokinetic (PB-PK) nicotine model which we have developed. The combined PB-PK/PD model was evaluated by fitting published PK and PD data obtained following two 30-min intravenous infusions of nicotine to humans (Porchet *et al.*, 1988). After simulating nicotine tissue concentration-effect proterisis, the arterial, heart and brain tissues were the apparent effect sites on heart rate. Another simulation for acute administration of nicotine was run using brain nicotine concentrations as input to the model. This approach helps eliminate apparent tachyphylaxis attributable to distribution delays in tissues. The negative feedback system was modeled to quantify the rate and extent of acute tolerance development and to consider homeostatic mechanisms. Simulation results for heart rate indicated different rates (0.40–0.79 hr⁻¹) of acute tolerance development following different intervals between successive intravenous infusions of nicotine. The combined PB-PK/PD model allowed adequate quantitative descriptions of heart rate changes based on more physiologically relevant mechanisms to predict both PK and PD responses to nicotine. Therefore, the nicotine PB-PK/PD model is a more useful tool to study nicotine's physiological and pharmacological effects.

1285 A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL FOR TOLUENE DISPOSITION IN RATS

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Toluene is an organic solvent widely used in many industries and commercial products. When inhaled, toluene exerts its main toxic effects on the central nervous system (CNS). The objective of this study was to develop and validate a PBPK model for toluene disposition in rat as a basis for correlating toluene concentration in the CNS to observed neurobehavioral effects. The model consisted of the following compartments: brain, liver, lung, adipose tissue, richly perfused tissues and slowly perfused tissues. Physiological parameters, metabolic rate constants and chemical specific parameters, such as solubility in blood and selected tissue (except for brain) were obtained for the literature. Brain to blood partition coefficient was measured in homogenates of brain Sprague Dawley rats using vial equilibration technique and was estimated to be 1.1 ± 0.38 (mean ± sd, n=8). Using these parameter values the model well predicted published data of toluene levels in brain and venous blood of rats after single acute exposure (75, 150, 225ppm, 5 hours; 500 ppm, 4 hours; 2000 and 10000 ppm, 0.5 hours) and after repetitive exposure (150 ppm, 5 hours for 9 days) to toluene by inhalation. This model appear useful for understanding the relationship between brain toluene concentration and toxicological effects and it represents a first step for developing a human model.

1286 PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING OF CARBON TETRACHLORIDE (CCl₄) TISSUE DISTRIBUTION IN RATS AFTER EXPOSURE BY INHALATION, ORAL GAVAGE AND INTRAGASTRIC INFUSION

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Although CCl₄ metabolism has been extensively studied, there is little information on CCl₄ tissue concentration. Previously, we have developed a single, consistently parameterized PBPK model for CCl₄ to describe arterial blood concentration time-course data in fasted, adult male Sprague-Dawley (SD) rats for three routes and two levels of exposure. The objective of the present study was to characterize CCl₄ pharmacokinetics in the liver and extrahepatic tissues following oral and inhalation exposures with the previously developed