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1267 DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL FOR TRICHLOROETHYLENE AND ITS METABOLITES IN B6C3F1 MICE

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In recent years, three carcinogenicity bioassays have indicated that the daily oral administration of TCE in corn oil lead to an increased incidence of hepatocellular carcinoma in B6C3F1 mice. To describe and predict the kinetics of TCE absorption, blood and tissue distribution, metabolism and excretion, and better understand its toxicity, a PBPK model was developed for TCE and its metabolites in mice. This model provides a detailed description of TCE kinetics that combined with relatively simple sub-models for metabolites. The model structure consisted of liver, kidney, lung, richly perfused tissues, slowly perfused tissues and fat that were interconnected by arterial and venous blood pools. Partition coefficients (PCs) for TCE were determined by vial equilibrium method, and PCs of non-volatile metabolites were determined using the methods of Jepson et al. (1994). B6C3F1 mice were given bolus oral doses of 300, 600, 1200 and 2000 mg/kg TCE dissolved in corn oil. At various time points, mice were sacrificed and blood, liver, kidney, lung and fat were collected. The blood and tissue samples were assayed for TCE and its metabolites, chloral hydrate (CH), trichloroethanol (TCOH), trichloroethanol glucuronide (TCOG), trichloroacetic acid (TCA) and dichloroacetic acid (DCA). This study demonstrated that DCA was formed in mice and its formation and kinetics appeared to be driven by TCA concentration. (Supported by SERDP grant CU-110).

1268 A DETAILED COMPARISON OF THE VARIOUS MODELS USED TO PREDICT BLOOD LEAD CONCENTRATIONS FOR A GIVEN EXPOSURE SCENARIO

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Lead has been and will continue to be a major concern as an environmental contaminant. The major concerns with lead poisoning are neurotoxic effects. The Center for Disease Control (CDC) has issued a benchmark for a safe blood lead concentration of 10 µg/dL. Since this criteria is an internal concentration and not an exposure concentration, models are needed to predict the blood lead concentration associated with a given exposure scenario when performing a site specific risk assessment. The USEPA recommends the Integrated Exposure Uptake BioKinetic (IEUBK) model for predicting blood lead concentrations in children less than 6 years of age but has not made any official recommendations as to which model should be used for predicting blood lead concentrations in adults and/or children older than 6 years of age. Three lead models (IEUBK, a physiologically-based pharmacokinetic (PBPK) model and an empirical kinetic model (Bowers)) were compared to determine which model is most appropriate for use in site specific risk assessments. These models were compared as to: 1) model structure, 2) model parameter values and sensitivity in affecting the model predictions, 3) extent and applicability of model validation, 4) differences in model predictions for the same exposure scenarios, and 5) the theoretical limits of application. The PBPK model was found to be the most fully validated, and was the only model applicable to predict blood lead concentrations associated with short-term exposures and for both children and adults. The IEUBK model was found to contain some highly sensitive model parameters which were empirically derived and was not valid for modeling short-term exposure scenarios. The Bowers model was found to be of limited scope and complexity and was only theoretically applicable for predicting blood lead concentrations in adults exposed to lead for long durations.

1269 EXTRAPOLATION OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL DESCRIBING 2-METHOXYACETIC ACID DISPOSITION AFTER 2-METHOXYETHANOL INHALATION AT 5 PPM FROM PREGNANT MICE TO RATS AND HUMANS

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Accurate prediction of embryo dosimetry in pregnant animals is an important step towards improved risk assessment for exposure to chemicals during human pregnancy. We have developed a PBPK model that describes the disposition of 2-methoxyacetic acid (2-MAA) in mice and their embryos during organogenesis (*TAP* 132, 103-114, 1995). This alkoxyacid is the

primary metabolite and proximate toxicant of 2-methoxyethanol (2-ME). The model was extrapolated to pregnant rats with pharmacokinetic data obtained from oral and iv bolus administrations of 2-ME (*Toxicologist* 15, 47A, 1995). Subsequently, the model accurately predicted maternal plasma levels of 2-MAA determined when mice inhaled 5 ppm 2-ME for 8 hr on gestation day 11. Inhalation exposures (5 ppm; 8 hr/day; 5 days/week) were simulated for rats and women during the first 3 weeks of pregnancy. Projected 2-MAA plasma levels were well below those causing grossly visible malformations in mouse fetuses. Based on animal studies, maternal plasma 2-MAA concentrations might be suitable surrogates for those in the embryo. The same model also reasonably fitted published 2-MAA urinary excretion data from men who had inhaled 5 ppm 2-ME for 4 hr. Taken together, the projections show that this PBPK gestation model provides an improved quantitative basis for extrapolations among species and from high to low dose, which are important components of the risk characterization process.

1270 APPLICATION OF NICOTINE PHARMACOKINETIC MODELING FOR DATA ANALYSIS

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Physiologically- (PBPK) and population-based nicotine pharmacokinetic / pharmacodynamic models have been applied to describe nicotine plasma kinetics and to estimate nicotine uptake in cigarette smokers. These models have also suggested optimal designs for pharmacokinetic experiments, and explained some of the physiological effects of nicotine. The selection of a model for data analysis depends upon the nature of the available data and the objective of the analysis. Current work seeks to evaluate modeling approaches for analyzing sparse data which were obtained as a supplement to another study. Both PBPK and population models described the plasma data reasonably well. Nicotine uptake from smoking a commercial cigarette was estimated in subjects by applying a validated PBPK model to plasma data. The model-estimated value of 0.95 mg/cigarette was in line with nicotine yields measured by the human mimic smoke machine (1.11 mg/cigarette) and the FTC method (0.71 mg/cigarette). Model estimates may have been impacted by interindividual differences in physiological or/and biological factors. However, the confidence in the model would be greatly strengthened if sampling times and data points were optimized. Although the interindividual variability in pharmacokinetic parameters was taken into account by a population modeling approach, uncertainty remains concerning the bioavailability of nicotine based on current data. This uncertainty results from the nature of the data and the fact that an IV reference data set is not available. Nevertheless, plasma kinetics as calculated by interpolation from a population model, previously derived from well balanced and controlled experiments, can be linked with response to nicotine to develop a pharmacodynamic model.

1271 PHARMACOKINETICS OF [¹⁴C]TRICHLOROACETATE IN MALE FISHER 344 RATS

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The pharmacokinetics of trichloroacetate (TCA) are being investigated experimentally and analyzed using a physiologically based pharmacokinetic (PBPK) model. TCA is a metabolite of both trichloroethylene and perchloroethylene as well as being a chlorination byproduct in drinking water. TCA causes liver cancer in mice, but not in rats. It also causes cardiac malformation in the offspring of rats exposed during pregnancy. TCA is poorly metabolized (<20%) and largely excreted in urine. It has a pKa of 0.9; it is fully charged at physiological pH, except in the stomach. Rats were dosed with 10 mg/kg by i.v. injection via the lateral tail vein. Blood and tissues were collected at 0.5, 1, 3, 6, 9, 24, and 48 hr post injection (n = 4 rats/time). Total radiolabel was determined in oxidized tissues, urine, and exhaled CO₂ (trapped in aqueous potassium hydroxide) by scintillation counting. In a separate series of experiments blood was sampled via a jugular canula to determine concentrations at early time (2, 6, 12, 18, 24, 30, 36, 46, 60 min). Radiolabel concentrations were highest in plasma until late times. Virtually all plasma radioactivity was TCA (determined by HPLC). Tissue concentrations at 0.5 hr: Plasma > Kidney > Red Blood Cells > Liver > Large Intestine > Skin > Small Intestine > Muscle > Fat. A parallel linear decrease occurred out to 9 hr in plasma, kidney, red blood cells, skin, muscle, and fat. Concentrations in liver and small and large intestine decreased more slowly. A PBPK model is being developed that includes compartments for plasma, red blood cells, liver, kidney, and other lumped tissues. The goal is to model the tissue