compartment including liver, brain, fat, kidney, placenta/foetus, blood and rest of the body. Parameters such as tissue volumes, blow flows, and partition coefficients were extracted from previously reported studies. Optimization was performed using mouse exposure data for adult female and neonates determined in our laboratory. The optimized model was extrapolated to rats and validated using data from the literature. The model validation used experimental data from acute and subchronic exposures prior to and during gestation. The simulations predict that BDE-47 tissue concentrations in the maternal compartments are within the standard deviation of the experimental data. This PBPK model presented here is the first reported for any PBDE. This model may provide a framework for the development of a human PBPK model to predict both adult and developmental PBDE concentrations for use in risk assessments. (This abstract does not reflect Agency policy. Supported in part by EPA cooperative agreements CR830756 and DESE CT 826513.)

1684 PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING OF INHALED MANGANESE IN RATS.

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Manganese (Mn) is an essential element found in food, water and air. Mn-containing fuel additives introduce small amounts of Mn particulates into the atmosphere after combustion. Symptoms of central nervous system toxicity from Mn are known to occur at high concentration inhalation exposures. However, Mn is an essential element, required for normal tissue growth and function. Tissue [Mn] is closely regulated to prevent accumulation to toxic levels. The purpose of this research is to develop a pharmacokinetic model to describe the regulation of tissue [Mn] in the face of increasing concentrations of inhaled manganese. We have developed a PBPK model to describe the tissue kinetics of Mn following inhalation of Mn by rats. Each tissue compartment had shallow and deep regions to describe discrete tissue Mn stores. The PBPK model parameters were calibrated using dietary data for tissue Mn in rats following 14 days of inhalation exposure to $MnSO_4$ at specific doses. The steady state levels of Mn predicted by the PBPK model were tested against rat tissue measurements at dietary intakes of 2, 10 and 100 ppm of Mn. Dose dependent hepatic biliary excretion, noted in other studies, was then necessary to regulate the tissue levels of Mn in rats measured following 14 days of inhaled exposure to 0.0, 0.03, 0.3 mg Mn/m^3. The hepatic controller in the model consisted of an empirical adjustment of biliary elimination rate constants of Mn based on net daily uptakes from ingestion and inhalation. At the highest inhalation exposure, the hepatic Mn controller increased the bile excretion rate constant in the PBPK model by a factor of 10 times the steady state rate. This PBPK model with the control by enhanced biliary excretion control was able to predict tissue regulated Mn levels in rats following inhalation. Multi-dose route PBPK models for Mn will provide support for the evaluation of tissue-dose based risk assessment of this essential metal.

1685 EVALUATION OF ADULT-NEONATE DIFFERENCE IN METABOLIC INTERACTIONS AMONG ALKYL BENZENES (ABS) USING A MIXTURE PBPK MODEL.

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A physiologically-based pharmacokinetic (PBPK) model for mixtures of ABs (toluene (T), m-xylene (X) and ethylbenzene (E)) has previously been developed and validated in rats and humans. This PBPK model, accounting for physiological and metabolic differences between rats and humans, provided simulations of the extent of metabolic interactions among the ABs. The objective of the present study was to evaluate adult-neonate differences in metabolic interactions among ABs using this mixture PBPK model. The approach involved the substitution of physiological parameters (cardiac output, breathing rate, tissue volumes and blood flows) in the previously validated adult PBPK model while considering physicochemical parameters as age-invariant, based on available data. The maximal velocity of metabolism of ABs was computed on the basis of the hepatic CYP2E1 protein content in neonates relative to adults. For this purpose, the subject-specific data on CYP2E1 in neonates (≤ 1 month old) were obtained from published literature. The mixture PBPK model, with the physiological and metabolic data for neonates, was used to simulate the inhalation kinetics of ABs previously evaluated in adults (1-17 ppm T, 1-33 ppm X and 1-33 ppm E; 7 hr). The simulated peak venous blood concentrations (Cmax) of ABs were greater in neonates compared to adults by a factor of <2. However, the additional change in Cmax during mixed exposures in neonates (upto a factor of 1.4 for a mixture of 17 ppm T + 33 ppm X + 33 ppm E; 7 hr) depended upon the subject-specific content of CYP. There was considerable interindividual variation in both neonates and adults such that the subject-specific magnitude of metabolic interaction was primarily influenced by the CYP content as well as the relative importance of perfusion and enzyme content in the hepatic clearance of ABs. Overall, this study showed that the extent of metabolic interactions can be predicted using PBPK models as a function of hepatic enzyme content and age-dependent physiological data.

1686 PHYSIOLOGICALLY BASED PHARMACOKINEITC (PBPK) MODELING OF METABOLIC INHIBITION FOR INTERACTION BETWEEN TRICHLOROETHYLENE AND CHLOROFORM.

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Trichloroethylene (TCE) and chloroform (CHCl3) are two of the most common environmental contaminants found in water. PBPK models have been increasingly used to predict target dose in internal tissues from available environmental exposure concentrations. A closed inhalation (or gas uptake) system was used to estimate metabolic parameters using male F344 rats at different initial concentrations. Individual chemicals were first tested separately using the following initial concentrations: 100, 500, 1000, and 3000 ppm. The decrease in chamber concentration reflecting metabolism was measured for up to 6 hours. A PBPK model was then used for each individual data set to obtain the metabolic parameters describing saturable metabolism, Vmax (maximum velocity of reaction) and Km (affinity constant). The next set of experiments described co-exposure of different binary combinations, including 500 ppm for both chemicals, 500 ppm TCE and 10 ppm of CHCl3, and 500 ppm TCE with 2000 ppm CHCl3. PBPK modeling was used to test three types of different metabolic inhibition: competitive, uncompetitive and noncompetitive. Results of the simulations suggest that competitive inhibition gives the closest agreement between the inhalation data and the simulations, resulting in an inhibition constant (Ki) of 0.33 mg/liter, which is similar to the Km value of 0.36 mg/liter. This interaction model was used to identify sensitive parameters for the design of future experiments. In summary, PBPK modeling results were consistent with competitive inhibition for TCE and CHCl3 co-exposure, leading to an overall decrease in metabolism when both chemicals are present simultaneously. (This abstract does not reflect EPA policy. Research support for Karen Yokley is provided by grants EPA T829472 and EPA CT833237.).

1687 ESTABLISHING CHANGES IN METABOLISM OF CARBON TETRACHLORIDE IN THE PRESENCE OF TRICHLOROETHYLENE IN THE RAT THROUGH THE USE OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING.

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Toxicological interactions of chemicals can affect metabolism, often decreasing overall associated metabolic rates; and changes in metabolism can be evaluated through the use of mathematical models. Trichloroethylene (TCE) and carbon tetrachloride (CCl_4) are common contaminants in water and at superfund sites. A closed inhalation (or gas uptake) system was used to collect metabolic data using F344 rats at various initial concentrations of TCE and CCl_4. The initial concentrations used for the exposures were: 25 ppm CCl_4 and 1000 ppm TCE, 25 ppm CCl_4 and 100 ppm TCE, 100 ppm CCl_4 and 500 ppm TCE, 100 ppm CCl_4 and 1000 ppm TCE, and 1000 ppm CCl_4 and 500 ppm TCE. This particular binary mixture pair is an example of metabolic synergy as opposed to the more common metabolic inhibition expected during exposure to multiple chemicals. A previously developed physiologically based pharmacokinetic (PBPK) model of carbon tetrachloride in the rat was verified to fit with gas uptake data for CCl_4 alone (with initial concentrations of 25 ppm, 100 ppm, 250 ppm, and 1000 ppm) and then used to simulate chamber concentration predictions for the aforementioned mixtures. In order to fit chamber concentration data for CCl_4 when administered with TCE, the parameter of the maximum rate of metabolism (V_{max}) was increased. An increase of 2.8 times the V_{max} value from the original model of carbon tetrachloride alone produced reasonable predictions for mixture data with higher concentrations (500 ppm or 1000 ppm) of TCE, and an increase of 1.4 times the original V_{max} worked well at predicting CCl_4 chamber concentration for mixtures with 100 ppm TCE. The increase in V_{max} suggests that metabolism of carbon tetrachloride is amplified by the presence of trichloroethylene and that this amplification is dose-dependant. (This abstract does not reflect EPA policy. Research support for Karen Yokley is provided by grants EPA T829472 and EPA CT833237.)

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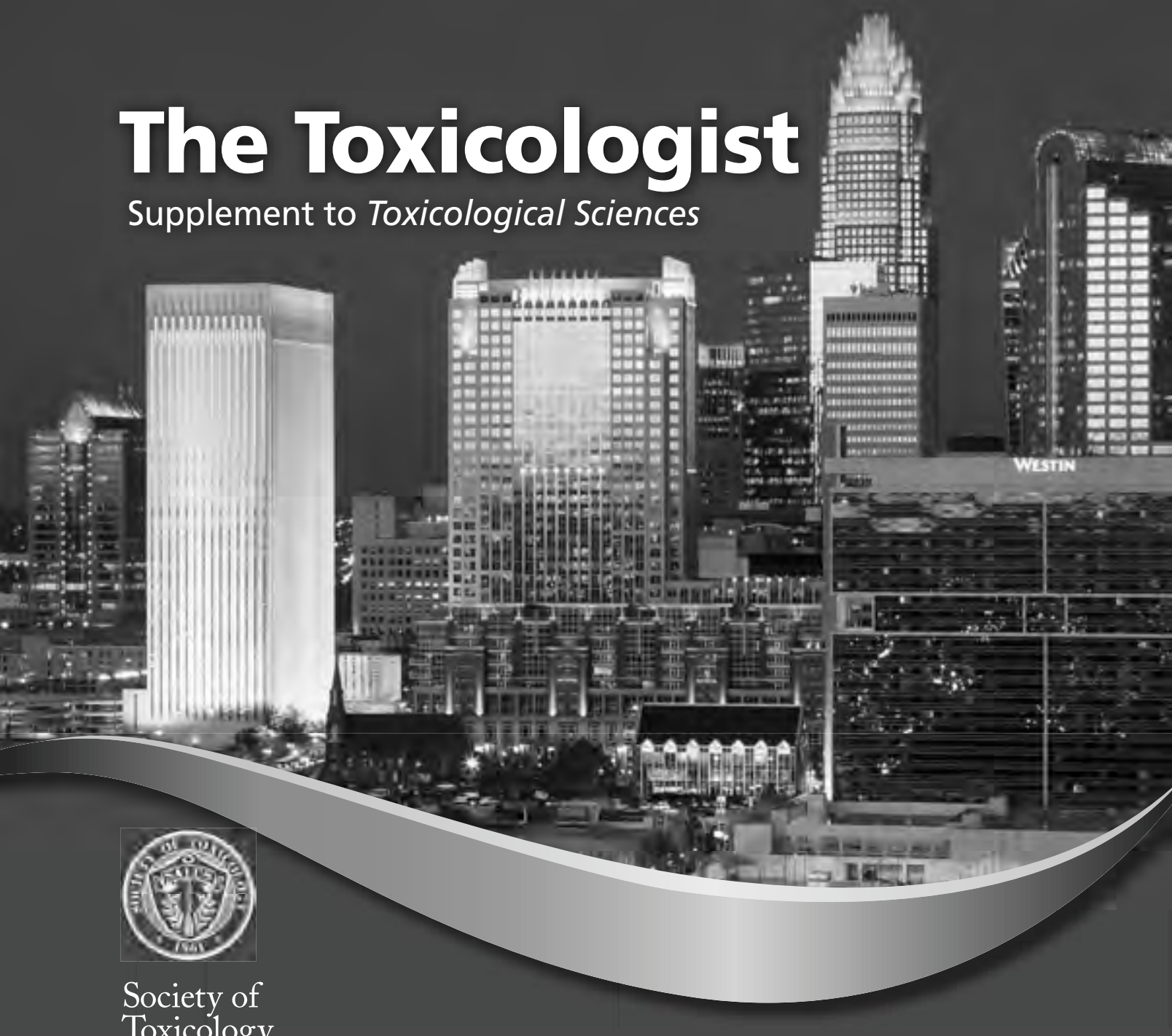

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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