PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING AS A TOOL FOR PREDICTING DOSE RESPONSE RELATIONSHIP FOR TCDD DURING DEVELOPMENT

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Introduction

TCDD (2,3,7,8-TCDD) can be transferred during gestation to the developing fetus or during the postnatal period from breast milk to the nursing infant. Developmental defects induced by dioxins are causing increasing concern since they occur at low dose levels and are usually irreversible. One important public health challenge includes the need to protect children's health. A number of legislative and regulatory changes have resulted in a re-examination of the developmental toxicity testing methods and the application of this data for risk assessment[1]. Children, infants and fetuses are thought to be more sensitive to the health effects of environmental chemicals, particularly for non-cancer effects because they are undergoing critical developmental processes[2]. In addition, altered sensitivity of developing organisms may be due to life stage specific differences in pharmacokinetics of xenobiotics. The development of PBPK models may provide insight into the pharmacokinetic and dispositional differences between life stages. Physiologically-based pharmacokinetic models (PBPK) have been published for TCDD in adult female, male, mice and rats[3-6]. While there are no developmental PBPK models in mammals for TCDD, one model does describe maternal transfer of TCDD in brook trout[7]. The development of a PBPK model for maternal transfer of TCDD in mammals is important for improving human health risk assessments for the developmental effects of TCDD.

Pharmacokinetic information has been published on the transfer of TCDD from the mother to the rat fetus[8-10]. The present research focuses on the extensions of the PBPK for dioxin in female rats to include a fetal compartment. In addition this report provides parameter descriptions of the model for the distribution of TCDD from the dam to the fetal compartment.

Methods and Materials

Model development, Parameterization and Validation

The model consisted of eight maternal compartments (blood, lung, kidney, skin, fat, liver, placenta, and rest of the body) and two fetal compartments (blood and whole fetus) (Figure 1). The maternal and fetal compartments have independent circulatory compartments. The placenta is considered a maternal compartment while receives systemic flow blood from the dam. Chemical transfer from the dam to the fetus was described as a fraction of clearance ($C_{placenta} * V_{placenta} * E_{transfer}$). Other physiological and biological processes included in this model were Ah receptor and CYP1A2 protein binding, and metabolism-excretion in the dam via urine and bile. The physiological parameters for the non-pregnant rat were obtained from Wang *et al.*[5]. Descriptions of tissue growth for placental and adipose compartments and changes in fetal cardiac output and placental blood flow were obtained from O'Flaherty [11,12]. The partition coefficient for the fetal blood:whole fetal body compartment was

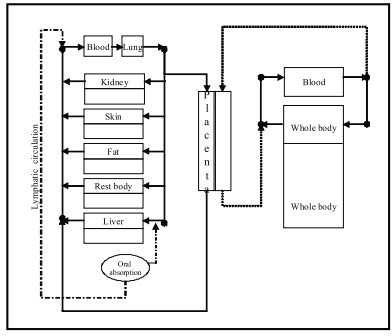

Figure 1. Conceptual representation of developmental PBPK model for rat.

assigned the same value as the partition coefficient for the maternal rest of the body compartment. The fetal blood compartment was assigned the same body weight fraction as for maternal blood. AhR parameters for placenta, such as binding capacity and affinity constant were assumed to be similar to the kidney. No enzyme induction process was described in the fetal compartment. The algebraic and differential equations describing the kinetics of TCDD were written and solved using a commercially available software, namely ACSL® (Advanced Continuous Simulation Language, AEgis Technologies Group, inc., Huntsville, AL)

Two sets of experimental data were used: Wang et al. (1997), exposed female rats to a single dose of 10 µg/kg of TCDD by gavage and measured TCDD concentrations in different tissues over a period of 900 hours[5]. In Hurst et al. (2000), pregnant Long Evans rats were exposed to a single dose of 0.05, 0.20, 0.80, 1.0 µg/kg on gestation day (GD) 15 followed by euthanasia at GD16 and GD21[8]. Optimizations were done with the Wang data and with a single dose level (0.2 ug/kg) from the data of Hurst et al. (2000)[8]. Model predictions were validated using the remaining data of Hurst et al. (2000)[8].

Results and Discussion

Figure 1 shows the conceptual representation of the developmental rat PBPK model used in this study. The left side of the figure represents the maternal compartment and the right side represents the fetal compartment. Following oral exposure, TCDD distribution occurs via lymphatic circulation and portal veins. The major contributors of excretion and metabolism are the liver and kidney. The transfer of TCDD to the fetal compartment was described as a passive diffusion of TCDD from the placental compartment to the fetus. Because the initial model of Wang et al.[8] was modified for this exercise (i.e. grouping the spleen in rest of the body compartment and addition of placenta and fetal compartments), the ability of the present model to predict the disposition of TCDD in non-pregnant rats was examined. The modified model predicts the TCDD pharmacokinetic and distribution data from Wang et al.(1997)[4] with similar accuracy as the original model (not shown).

The model adequately predicts the blood, hepatic, placental and fetal TCDD concentrations at 0.2 and 0.8 ug/kg presented in Hurst et al. (2000)[8] (Figure 2-3 respectively). These results suggest that the exchange of TCDD between the dam and fetus could occur by simple diffusion. The data of Hurst et al. (2000,1998)[8,9] demonstrate that the distributions of TCDD in different fetal tissues are similar. These results suggest that the lipid content of the different fetal tissues is similar, including blood, and that the partition coefficient would be close to unity for the different fetal tissues. This developmental PBPK

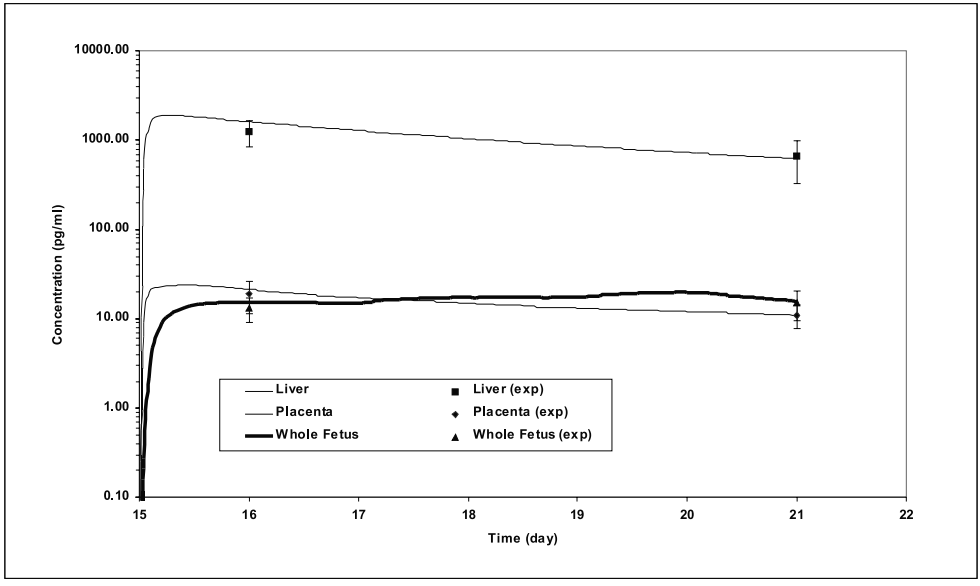

Figure 2. Pharmacokinetic distribution of 2,3,7,8-TCDD in liver (square), placenta (diamond) and whole fetus (triangle) at GD16 and GD21 after single exposure to 0.2 ug/kg by gavage at GD15. Each point represented a mean and ±Sd (n=4-5)

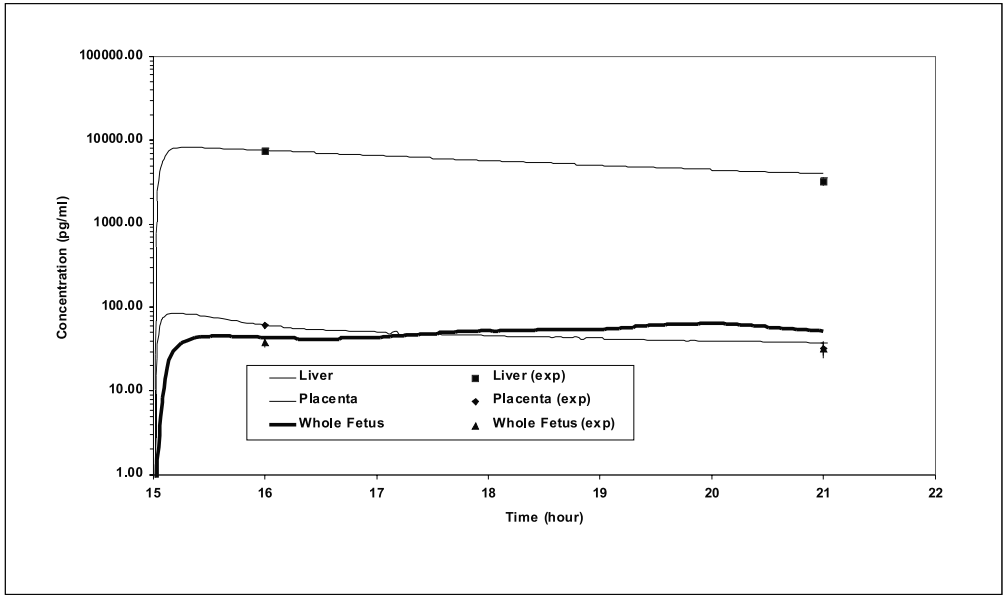

Figure 3. 2,3,7,8-TCDD distribution in liver (square), placenta (diamond) and whole fetus (triangle) at GD16 and GD21 after single exposure to 0.8ug/kg by gavage at GD15. Each point represented a mean and ±Sd (n=4-5)

model is a powerful tool for risk assessment as well as for understanding basic pharmacokinetic and pharmacodynamic processes during development. During fetal development there are critical windows in which important physiological and biochemical processes occur. Understanding the relationship between these critical windows and dose metric parameters are important determinants in developmental models of toxicity.

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