UTILIZATION OF A PBPK MODEL TO PREDICT THE DISTRIBUTION OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN HUMANS DURING CRITICAL WINDOWS OF DEVELOPMENT.

C Emond[1,2], LS Birnbaum[2] and MJ DeVito[2]

[1]National Research Council,[2] US EPA, ORD, NHEERL, ETD, PKB, RTP, NC, 27711, USA

Introduction

Tetrachlorodibenzo-p-dioxin (TCDD) is a ubiquitous environmental contaminant that induces a wide spectrum of toxic responses, including developmental toxicity. TCDD can be transferred during gestation into the developing fetus or during the postnatal period from breast milk to the nursing infant. Moreover, the different stages of fetal development have different critical windows of sensitivity. The duration of these sensitive windows is often several-fold shorter in experimental animals then in human[1]. Compared to rodents, humans eliminate TCDD much slower. Elimination half-lives of TCDD is approximately 25 days for rats and 5-11 years in humans. Because there is a continuous background exposure resulting in significant accumulation of TCDD in humans, all developing fetus are exposed to this chemical. Understanding the relationship between exposure, dose and response is important in estimating potential adverse health effects associated with background exposure to TCDD.

Physiologically based pharmacokinetic (PBPK) modeling involves simulation of absorption, distribution, metabolism and excretion of chemicals based on tissue solubility characteristics, metabolism rates and physiology of the test species [2]. Utilization of a PBPK model to predict maternal to fetal transfer of TCDD can be important for improving human health risk assessments for the developmental effects of TCDD. While PBPK models for TCDD have been published for different adult species including, rat, mice, fish and humans, no PBPK models have described the distribution of TCDD during pregnancy.

The aims of this work were to development of a PBPK model to predict the distribution and accumulation of TCDD between maternal and fetal compartments in humans. In addition, this model was used to simulate background and episodic gestational TCDD exposure in adult humans in order to predict TCDD concentrations in the fetus.

Methodology

a) Model description

The PBPK model for gestational exposure to TCDD used in this study was previously validated in the rat. This model consisted of 4 maternal compartments (liver, fat, placenta and, rest of the body) and 1 fetal compartment corresponding to the whole fetus (Figure 1). The PBPK model included mathematical descriptions of Ah receptor binding, TCDD induction and binding to CYP1A2, and physiological alterations occurring during gestation. All parameters for human came from the literature.

During gestation the changes in the mother's physiology include the appearance of the placenta and fetus as well as maternal changes in adipose tissue storage. Mathematical expressions describing these physiological changes were fit to data published in the literature to reproduce the

growth curves of these compartments. Increases in the blood flow to these compartments are also described mathematically to fit with the available data. The PBPK model assumes the distribution of TCDD occurs through diffusion limited processes for fat, liver, placenta and rest of the body. Absorption of TCDD was described similar to that used in the rat model. Biliary and urinary elimination rates were taken from the literature. This PBPK model describes oral exposures because dietary exposures represent over 95% of the daily intake of TCDD. The human parameters used came from the literature [3,4,5,6]. Parameters for induction of 1A2 and Ah receptor came from Wang et al. (1997). Partition coefficients were calculated by the ratio of TCDD concentrations in tissue: blood in neutral lipid equivalents [4].

The algebraic and differential equations describing the kinetics of TCDD were written as a program and solved using commercially available software (ACSL®; Advanced Continuous Simulation Language, Aegis corporation., Huntsville, AL)

b)- Exposure scenarios:

Simulation assumed exposures at a background level for 20 years followed by a gestation period of 40 weeks. The background exposure dose was 0.32 pg/kg/day representing estimated dietary intakes of TCDD. Experimental data for liver and fat came from Leung et al. 1990. Data for placenta, maternal and fetal blood came from Schecter et al. 1998 and Abraham et al.1998.

Results

The equations developed to follow the physiological changes in placenta, fat and fetus predict relatively well compared to the experimental data (not shown). All experimental physiological data used for the validation of these equations came from Hytten and Leitch (1971).

Different exposure scenarios were examined including chronic exposure and chronic exposure with intermittent periods of high exposures (i.e. meals containing higher than average concentration of TCDD). This model assumed a background exposure prior to the gestation period. Initial tests of the model compared the fit of the model to two different data sets. Leung et al (1990) presented data on liver and adipose tissue from humans with no known high exposures to TCDD and related chemicals. Schecter et al (1998) presented maternal and cords blood and placental concentrations of TCDD from maternal and infant pairs. The model predicts these data reasonably well assuming a daily intake of 0.32 pg/kg/d of TCDD for 20 years (Figure 2).

It should be noted that few data were available for placenta and cord blood. In the case of the fetal compartment, predicted fetal TCDD concentrations are assumed to be similar to cord blood concentrations (Figure 2). At the beginning of gestation the relative steady state was redistributed by incorporation of new compartments. Nevertheless, the initial testing of this model provided reasonable fits to human exposure data considering the limited data available for human fetal concentrations.

Figure 1:Conceptual PBPK model representation describes and used in this study for human.

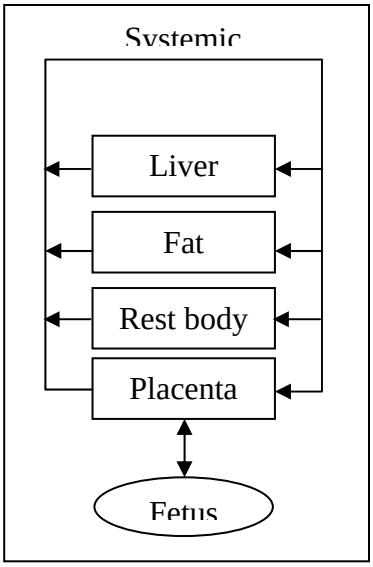
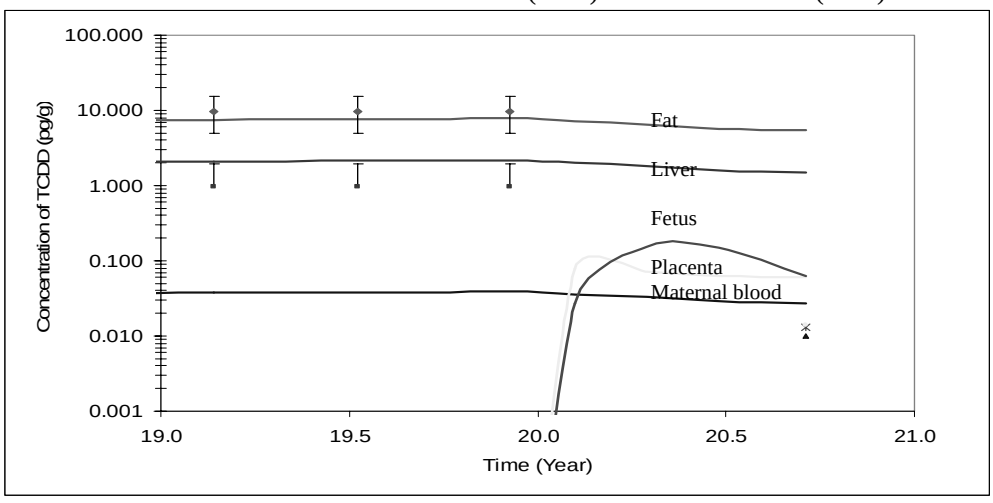


Figure 2: Distribution of TCDD in fat (oval), liver (square), blood (triangle), placenta (circle) and Fetus (star), following daily exposure to 0.32 pg/kg/day corresponding to background exposures during a period of 20 years following by a gestation period of 40 weeks. Concentrations are presented as of pg of 2,3,7,8-TCDD/g of tissue. Simulated values were compared to the human data for each compartment. Liver and fat concentration came from Leung et al. (1990) Maternal and fetal concentration came from Schecter et al. (1998) and Abraham et al. (1998)



Discussion

This study presents a PBPK model for estimating TCDD concentrations in the human placenta and fetus. This PBPK model framework developed for gestational exposure showed good reproducibility and relationship between simulated and human tissue concentration data.

In rodents, TCDD is sequestered in liver due to induction of hepatic CYP1A2. However, this typically occurs at exposure levels higher than those of background human exposure. The present model demonstrates that at background human exposures, hepatic sequestration of TCDD by CYP1A2 has little influence on the distribution of TCDD. At the current human background exposure, fat partitioning seems to have a higher impact on the distribution and elimination of TCDD in humans. This is consistent with the predicted minimal induction of CYP1A2 from the model.

The advantage of a PBPK model is that we can simulate alternative scenarios (acute or subchronic) and examine the role different metabolic pathway play in the pharmacokinetics of a chemical under realistic exposure scenarios. The model presented here has been reduced to four compartments in part because the adequate human data for the other tissues or compartments are limited.

Future efforts will focus on validating this model with additional human data sets. Also attempts to correlate fetal tissue dose with windows of sensitivity would be useful in understanding the relationship between exposure, dose and response. This model is a useful tool for use in risk assessment, as well as for understanding basic pharmacokinetic and pharmacodynamic processes during development.

References

1. Nau H (1991), *Fundam Appl Toxicol* **16**: pp 219-221.
2. Krishnan K and Andersen M E (2001) Physiologically based pharmacokinetic modeling in toxicology, in *Principles and Methods of Toxicology* (Hayes AW ed) Raven Press, New York.
3. Hytten FE and Leitch I (1971) *The Physiology of Human Pregnancy*. Blackwell Scientific Publications, Oxford London.
4. Emond (2001) Thesis University of Montreal
5. Lawrence GS and Gobas F A (1997), *Chemosphere* **35**: pp 427-452.
6. Wang X, et al. (1997),*Tox and Appl Pharmacol* **147**: pp 151-168.
7. Leung HW et al. (1990), *Toxicol Lett* **50** : pp 275-282.
8. Abraham K, et al. (1998) *Chemosphere* **37** : pp 1731-1741.
9. Schecter et al., (1998),*Chemosphere* **37**: pp 1817-1823.

Disclaimer:

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Approval does not signify that the content necessarily reflects the view and policies and the agency nor does mention of the trade names or commercial products constitutes endorsement or recommendation for use,

Acknowledgments

This project was funded by in part by a cooperative agreement (CR 828790) with NRC, NAS and performed at US EPA RTP, NC, USA. (This abstract does not represent US EPA policy).