Extrapolation of a Previous PBPK Model for TCDD across Routes of Exposure, Genders, and from Rats to Mice.

Xiaofeng Wang*^ , Michael J. Santostefano*, Michael J. DeVito#, and Linda S. Birnbaum#.
*Curriculum in Toxicology, UNC, Chapel Hill, NC; #USEPA, NHEERL, RTP, NC. ^Current Address: MGA Software, Concord, MA

Abstract

In our previous study[9], a PBPK model to describe the disposition of TCDD was developed based on a single oral dose of 10 μg TCDD/kg in female Sprague-Dawley (SD) rats. The objective of this study was to extrapolate the previous model across routes of exposure, genders of SD rats, as well as from rats to mice. The model predictions were compared with the experimental data obtained from female[7] and male SD rats[10], as well as C57BL/6J mice[6]. The doses range from 0.03 μg/kg to 10 μg/kg. The physiological differences between genders of SD rats, as well as between rats and mice were taken into account in the extrapolation. The results demonstrated that our previous PBPK model accurately described the TCDD distribution in the specified compartments of both female and male SD rats following an iv injection, and of mice following an ip dose. This study extends previous TCDD models by illustrating the validity of the previous model and providing further confirmation of the potential PBPK model in extrapolation across routes of exposure and genders, as well as future use of the model in humans. In addition, the results from the extrapolation to mice suggest the possible species dependent enzyme induction.

Introduction

2,3,7,8-Tetrachlorodibenzo-p-dixon (TCDD) and related environmental contaminants share a common Ah receptor (AhR)-mediated mechanism of transcriptional activation of a number of genes. Induced proteins such as CYP1A2 then interact with TCDD and leading to redistribution of TCDD to the liver. This saturable induction of CYP1A2 as well as the saturable binding of TCDD to CYP1A2 results in nonlinear dose-dependent tissue distribution. This phenomenon leads to the development of physiologically-based pharmacokinetic (PBPK) models for disposition of TCDD and related compounds. In a previous study, an improved PBPK model was developed for the time course tissue distribution data obtained following a single oral dose of 10 μg [3H]TCDD/kg to female Sprague-Dawley rats[9]. One ultimate goal for PBPK studies is to eventually predict tissue levels of environmental contaminants in humans exposed to TCDD and related compounds through model extrapolation. To validate the model and improve the reliability of such an extrapolation, it is useful to study the routes of exposure, genders and several species.

Method

The PBPK model developed based upon a single oral dose (10 μg TCDD/kg body weight) was reported previously[9]. In the present study, this model was used to predict the tissue concentration of TCDD following an iv dose in both female and male SD rats, as well as an ip dose in mice. The dose range covers the nonsignificant to significant liver sequestration.

The experimental data to validate the model were reported by Li[7], Weber[10], and Leung[6]. In Li's study, female SD rats weighting 190-200 g were used for an iv injection of 5.6 μg

TCDD/kg. The concentrations of TCDD in multiple tissues were measured. In Weber's study, male SD rats weighting 240-290 g were used for an iv injection of 9.25 μg TCDD/kg. The concentrations of TCDD in multiple tissues were measured. Both studies reported the serum concentration of TCDD. Therefore, the blood concentration of TCDD was obtained by dividing the serum data with the hematocrit (assuming that there is negligible TCDD in red blood cells). Assuming the weight ratio of white to brown fat is 0.165[8], the total TCDD concentration of the adipose tissue was obtained based on the values of the brown and white fat. In addition, the early time data points of tissue concentration reported in Weber's study were used to validate the previous results[9] in estimation of membrane permeability and the binding affinity of TCDD to CYP1A2 (see results below). In Leung's study, the mice were given an ip dose of 0.03 μg TCDD/kg.

The physiological parameters for female and male SD rats , as well as for mice were obtained from reference[5]. The growth of the female SD rats in Li's study were estimated from our previous results[9]. The urinary and biliary clearance for these female rats were obtained by allometric scale-up from previous results (Wang *et al.*, 1997). The growth of male SD rats and urinary clearance of the male rats were obtained from Roth[8]. Urinary clearance for mice was obtained from rats by allometric scale-up. Metabolism in the liver as well as biliary clearance of mice was estimated based on the fecal excretion in the mice[1,4]. All the other parameters were kept unchanged. A $\delta(t)$ function was employed to simulate the iv injection[2]. The ip injection was simulated by an iv injection followed by the transport from the injection site to the blood.

Model simulations were conducted using ACSL (MGA Software, 1997).

Results

Table 1shows those parameters whose values are either scaled up from previous study (first column),or estimated in this study. All the other parameters unchanged in this study were presented in previous work[9]. Several observations can be made regarding these parameters: 1) the ratio of membrane permeability to perfusion rate is the same for male/female SD rats and mice; 2) the tissue/blood equilibrium distribution ratio is approximately the same for male/female SD rats and mice; 3) the assumption that the basal level of CYP1A2, the AhR concentration, and the maximum induction fold in male/female SD rats and mice are the same appears to be reasonable; 4) male and female SD rats seems similar sensitive in CYP1A2 induction, while mice appears more sensitive than rats (the Hill coefficient of mice is greater than that of rats).

Figure 1 shows both the experimental data[10] and the model predictions for liver, adipose tissue, skin, blood of male SD rats. Highest concentrations of TCDD were found in liver, followed by the adipose tissue. Lowest concentrations were found in the blood. The model accurately predicts the TCDD concentration in multiple tissues (model predictions for kidney, lung, muscle, and spleen not shown). The model over predicts the blood concentration at the later time points by approximate 2-fold).

Figure 2 presents both the model predictions and the experimental data[7]. One day after the injection, the highest concentration of TCDD was found in liver, followed by the adipose tissue. Lowest concentrations were found in the blood. The model accurately predicts the time course tissue concentration of TCDD in multiple tissues.

In previous study[9], the values for membrane permeability were determined based on the early time points of tissue distribution. In Weber's study, the early time points of tissue distribution were obtained from an iv injection. These data provide better information for membrane permeability estimation than oral dose, since the influence on tissue uptake by the GI tract absorption is eliminated. The obtained from this study are agreement to the values previously reported[9].

As mentioned by the authors[10], the basal CYP1A2 concentration in the liver is 1.78 nmole/g liver based on the lethal dose of TCDD in male SD rats, which is consistent with reported value (=1.6 nmole/g liver) [3]. In the present study, the basal CYP1A2 concentration was chosen as 1.6 nmole/g liver. Once this value was determined, the binding affinity of TCDD to CYP1A2 was able to be uniquely determined based on the TCDD concentration in the liver before CYP1A2 induction occurs. Using early time points of the liver in Weber's study, the dissociation constant of TCDD binding to CYP1A2 is 30 nM. The result is also consistent with previous study[9].

Figure 3 shows the results of model prediction and the experimental data obtained from C57BL/6J mice. Highest concentrations of TCDD were found in the adipose tissue, followed by the liver. The reason for that is the insignificant induction of CYP1A2 at this low dose. The simulations demonstrated that choosing a value for Hill coefficient as 1.5 for CYP1A2 induction in mice provide a better description of TCDD distribution.

Discussion

This study validates the model developed in our previous work[9], in which estimation of the membrane permeability and the dissociation constant of TCDD bound to CYP1A2 were investigated. In addition, the accurate predictions of TCDD distribution in male and female SD rats with the same model suggests that the difference of the pharmacokinetic behavior as well as enzyme induction between genders in SD rats might be negligible. Furthermore, the larger Hill coefficient in mice than in rats implies that the induction of CYP1A2 in mice could be more sensitive.

The over prediction of blood and muscle concentration in Weber's study occurred at the later time points where the concentrations are very low. The concentrations of serum in Weber's study are smaller than in Li's study at the later time points, while the dosing concentration is larger in Weber's study than in Li's study. Therefore, the over prediction of the model may be caused by the limitation of the accuracy of the assay

In conclusion, this study not only provides the further confirmation of the potential PBPK model in extrapolation but also implies species dependent enzyme induction.

References

(1) Birnbaum L.S.; *Drug Metab. Dispos.***1986,** 14, 34-40
(2) Bischoff, K.B.; *Chemical Engineering in Medicine and Biology*, D. Hershey (ED.). New York: Plenum Press, **1967**
(3) Buckley-Kedderis I.; Diliberto, J.J.; Birnbaum, L.S.; *Toxicol. Appl. Pharmacol.*, **1991**, 108, 397-406
(4) Gasiewicz, T.H.; Geiger L.E.; Rucci G.; Neal, R.A.; *Drug Metab. Dispos.*,**1983**, 11, 397-403
(5) ILSI (1994), USEPA
(6) Leung H.; Poland A.; Paustenbach, D.J.; Murray, F. J.; Andersen, M.E.; *Toxicol. Appl. Pharmacol.*, **1990**, 103, 411-419
(7) Li, X; Weber, L.W.D.; Rozman, K.K.; *Fund. Appl. Toxicol.*, **1995**, 27,70-76
(8) Roth, W.L; Freeman, R.A.; Wilson, G.E.; *Risk. Analysis*, **1993**, 13, 531-543
(9) Wang, X.; Santostefano, M.J.; Evans, M.V.; Richardson, V.M.; Diliberto, J.J.; Birnbaum, L.S.; *Toxicol. Appl. Pharmacol.*, **1997**, (Submitted)
(10) Weber, L.W.D.; Ernst, S.W.; Stahl, B.U.; Rozman, K.K.; *Fund. Appl. Toxicol.*, **1993**, 21, 523-534

Table 1 Parameters for TCDD in female/male SD rats and mice

	female SD rats Wang, *et al.*, 1997	female SD rats Li, *et al.*, 1995	male SD rats Weber, *et al.*,1993	C57BJ/6J mice Leung, *et al*, 1990
Tissue/blood				
adipose	100	100	100	150
kidney	6	6	6	8
skin	10	10	10	30
muscle	1.5	1.5	1.5	3
liver	6	6	6	8
lung	6	6	6	8
spleen	5	5	5	6
Elimination				
urinary	1.0	0.83	$0.0064*Wt^{0.82}$ (mL/hr)	2.3
fecal (1/hr)	2.0	1.56	1.5	1.5
Hill Coe.	0.6	0.6	0.6	1.0

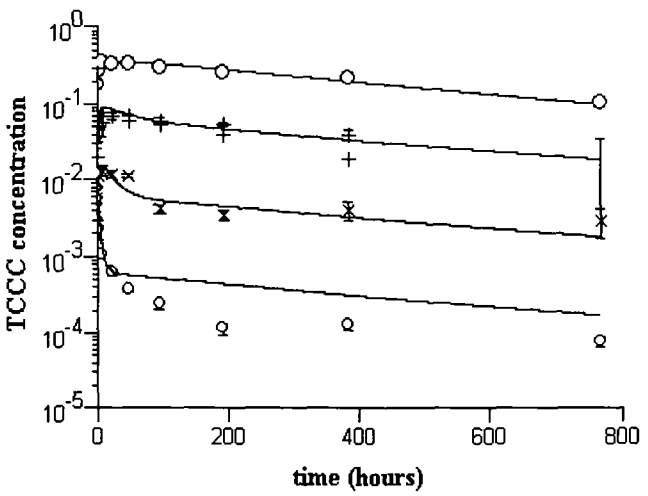

Figure 1 TCDD distribution in male SD rats
Line—model prediction; symbol—experimental data;
liver (O), adipose tissue (+), skin (x), blood (o)

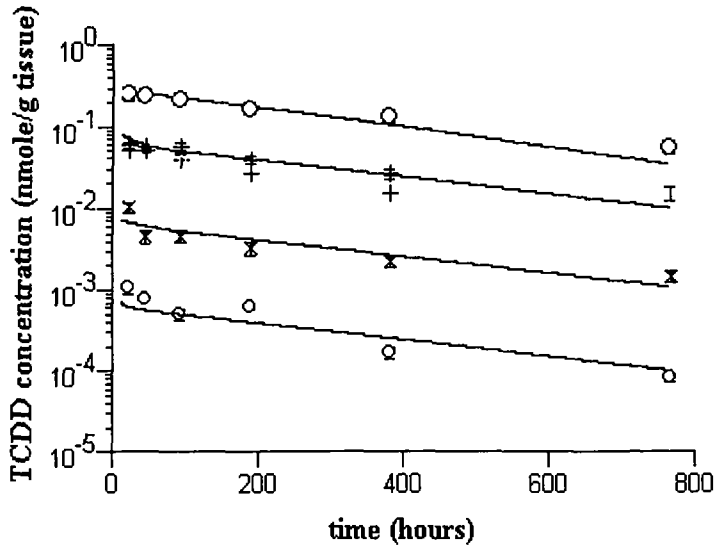

Figure 2 TCDD distribution in female SD rats
Line—model prediction; symbol—experimental data;
liver (O), adipose tissue (+), skin (x), blood (o)

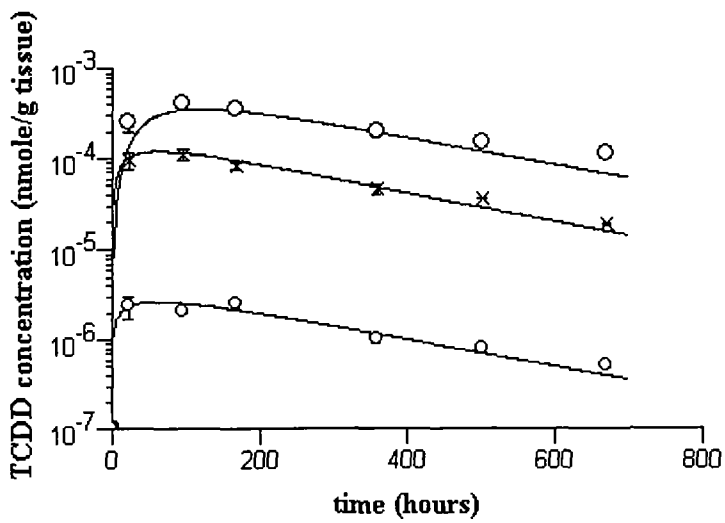

Figure 3 TCDD distribution in C57BL/6J mice
Line—model prediction; symbol—experimental data;
liver (O), adipose tissue (x), blood (o)