Receptor Incorporated Physiologically-Based Pharmacokinetic Model for TCDD Distribution in Rat

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1. INTRODUCTION

Recent physiologically-based pharmacokinetic (PBPK) and pharmacodynamic (PD) models for tissue distribution and enzyme-induction by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds have contributed to understanding the disposition of TCDD and related chemicals in a biological systems (Leung *et al.*, 1988; Leung *et al.*, 1990a; Leung *et al.*, 1990b; Andersen *et al.*, 1993; Buckley-Kedderis *et al.*, 1993; Kohn *et al.*, 1993; Eklund and Andersen, 1995). However, the reliability of these models is questionable because they were developed based on limited information. A general PBPK model includes a large number of parameters and equations. Without appropriate experimental data points the fitted parameters are not reliable. In addition, when compartments are correlated by adjusting different parameters, the same concentration distribution in a particular compartment could be obtained with multiple estimates for a specific parameters. Therefore, the values of the parameters estimated may not be unique. In this paper, we focused on how to simplify the PBPK model to reduce the number of equations/parameters, to find an appropriate approach to minimize the influence of correlation between those parameters, and to utilize the information on tissue concentration, excretion data, binding and induced enzyme data for parameter estimation. A new eight compartmental PBPK model was developed to analyze the time-dependent tissue distribution for TCDD in the blood, fat, skin, kidneys, liver, lungs, spleen and the rest of the body (mainly muscle) of female Sprague-Dawley rats treated with 10 μg [^{3}H]TCDD/kg for 30 min, 1, 3, 8 or 24 hours or 7, 14 or 35 days. The dose of TCDD and time-points were chosen for accurately assigning unique parameter values such as permeability and partition coefficents.

2. EXPERIMENTAL SECTION

Animals/Treatment/TCDD Determination. Eight week old female Sprague-Dawley rats (200-225 g) were administered a single oral dose of either a corn oil solution containing 10 μg (31 μmol, 5 μCi) [^{3}H]TCDD/kg or corn oil vehicle alone at 5 ml/kg bw. At 30 min, 1, 3, 8 or 24 hr or 7, 14 or 35 days after dosing, blood (10 cc) was removed via cardiac puncture, and the following tissues were isolated and weighed: liver, lungs, kidneys, spleen, skin, muscle, and adipose tissue. [^{3}H]TCDD concentrations were determined by combustion in a Packard 307 Sample Oxidizer (Packard, Downers Grove, IL) and analyzed by liquid scintillation counting. All data were presented as the mean ± standard deviation.

3. MODELING SECTION

Basis in PBPK model development. To describe the TCDD disposition in the rat, eight compartments were chosen based on TCDD-induced responses (Birnbaum, 1994) and

appeared to be more general than either flow-limited or membrane-limited. The body weight change was taken into account in the PBPK model since we are interested in long term exposures. The tissue weight change was assumed to be proportional to the total body change. The mathematical equations of the model were obtained by mass balance on each compartment according to different mass transport conditions. The total tissue concentration was contributed by partitioning, binding of TCDD to Ah receptor, and hepatic CYP1A2-induction. The induction of CYP1A2 was expressed by the induction rate and the degradation rate. Oral dose was assumed to be delivered to the blood circulation via the lymphatic system (Roth *et al.*, 1994).

Parameter estimation. Tissue weight and body weight were measured from these experiments. The blood flow rate and the tissue blood weight were obtained from reference data (ILSI, 1994). All the other parameters were obtained from the fitting of the data to the model. The fitting was conducted in two stages. At stage one, parameters were estimated by solving each compartment independently based on the arterial blood concentration. Therefore, the correlation between parameters was minimized. At stage two, the results obtained from stage one were evaluated by solving the entire system using oral dose as input. Rate constants for kidney clearance and liver excretion were estimated by combining the information on tissue TCDD concentration, urinary, and fecal excretion (Allen *et al.*, 1975; Diliberto *et al.*, 1995). Parameters related to TCDD binding to Ah receptor, to CYP1A2 induction, and to TCDD binding to CYP1A2 were obtained by using the enzyme data (Santostefano *et al.*, these proceedings).

4. RESULTS AND DISCUSSION

The results are presented in Table 1.

Flow-limited/Membrane-limited transport. Lung and spleen compartments were assumed to be flow-limited. This assumption was evaluated by examing the effect of permeability on TCDD distribution in these tissues. Fat, kidneys, and the rest of the body were assumed as membrane-limited. The fitted results (Table 1) showed that the ratios of the permeability to blood flow (PA/Q) were 0.08, 0.001, and 0.03 respectively. These values demonstrated that the membrane-limited assumption is applicable (Dedrick and Bischoff, 1968; Bischoff, 1975; Lutz *et al.*, 1980).

Binding/induction. The contribution of TCDD binding to the Ah receptor plays different roles in different tissues. In those tissues without CYP1A2 induction (i.e. skin, Figure 2), the Ah receptor does not play an important role in tissue uptake at this dose. However, for liver (Figure 3) which is CYP1A2 inducible, the Ah receptor concentration is essential in determining tissue uptake of the chemical.

Application of the model. The current model successfully simulated the time-course localization of TCDD in the blood (Figure 4) obtained by a different laboratory under different conditions (Li *et al.*, 1995).

5. CONCLUSIONS

The results demonstrate the importance of early time points to estimate PBPK parameters. The criteria to judge either flow-limited or membrane-limited condition (Q/PA) is useful for model simplification. In addition, the Ah receptor concentration does not play an important role in tissue uptake for those tissues without CYP1A2 induction at this dose. However, for the liver, the binding and the induction information is essential to estimate the TCDD level.

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7. NOMENCLATURE

PA:	permeability (g/hr)
Q:	blood flow rate (g/hr)
R:	partition coefficient
W:	weight (g)
K_d(Ah):	dissociation constant of TCDD binding to Ah receptor (nmole/g)
Ah_{tot}:	total Ah receptor concentration in the tissue (nmole/g)
K_d(A2):	dissociation constant of TCDD binding to CYP1A2 (nmole/g)
C_{A2base}:	CYP1A2 base level in the liver (nmole/g)
In_{A2}:	induction rate constant of CYP1A2 (nmole/g/hr)
IC_{A2}:	Michaelis-Menten constant of CYP1A2 induction (nmole/g)
K_2:	CYP1A2 degradation rate (nmole/g/hr)
V_{uri}:	urinary clearance (nmole/g/hr)
K_{Par}:	metabolite and parent compound excretion in the liver (nmole/g/hr)
av:	bioavailability
Qly:	absorption rate from lymph

Subscript

B:	blood
F:	fat
K:	kidney
Li:	liver
Lu:	lung
S:	skin
Sp:	spleen
Re:	the rest of the body
0:	initial value

Table 1 Results of parameter estimation

Tissue	Physiological parameters*	Parameters estimated**
fat membrane-limited	Q_{F0}=460g/hr W_{F0}=17.3g	R_F=100.0 PA_F/Q_F=0.08
kidney membrane-limited	Q_{K0}=930g/hr W_{K0}=1.95g	R_K=7.0 PA_K/Q_K=0.001 V_{uri}=2.0 (1/g/hr) K_d(Ah)=1.6x10^{-4}nmole/g*** Ah_{tot} =3.6x10^{-4}nmole/g
skin general case	Q_{S0}=383g/hr W_{S0}=45.8g	R_S=10.0, PA_S/Q_S=0.16 Ah_{tot} =5.4x10^{-4}nmole/g
liver general case	Q_{Li}=1208g/hr W_{Li}=11.46g	R_{Li}=5.0, PA_{Li}/Q_{Li}=0.4 K_{par} =3(nmole/g/hr) Ah_{tot} =5.4x10^{-4}nmole/g K_d(A2)=2.5x10^{-3}nmole/g C_{A2base}=0.1nmole/g, In_{A2}=6 nmole/g/hr K_2=0.07 nmole/g/hr, IC_{A2}=0.02 nmole/g
lung flow-limited	Q_{Lu}=6624g/hr W_{Lu}=1.27g	R_{Lu}=6.0 Ah_{tot} =5.4x10^{-4}nmole/g
spleen flow-limited	Q_{Sp}=112.2g/hr W_{Sp}=0.56g	R_{Sp}=5.0
Blood	W_B=18.9g	Qly=0.08 (nmole/hr), av=0.6
rest body membrane-limited	Q_{Re}=1900g/hr W_{Re}=87.6g	R_{re}=1.6 PA_{re}/Q_{re}=0.03

*blood flow rate and tissue blood volume are obtained from reference (ILSI, 1994)
body weight and tissue weight are obtained from experiment.
**adjusted by fitting.
***K_d(Ah) values are the same in different tissues.

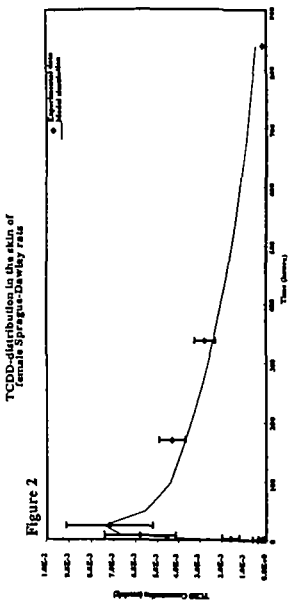

Figure 2

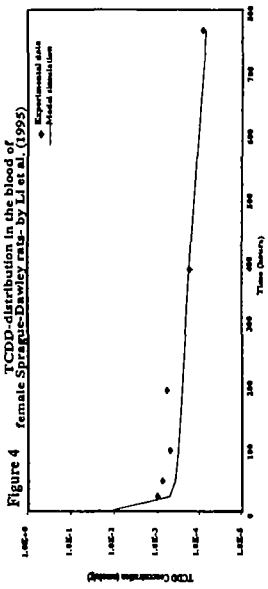

Figure 4

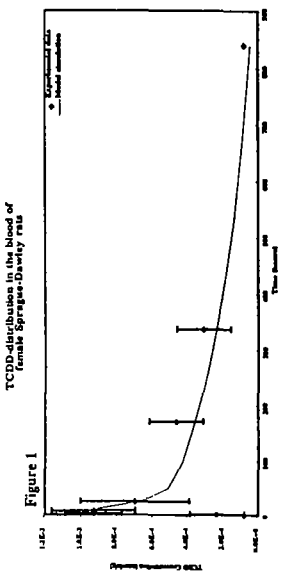

Figure 1

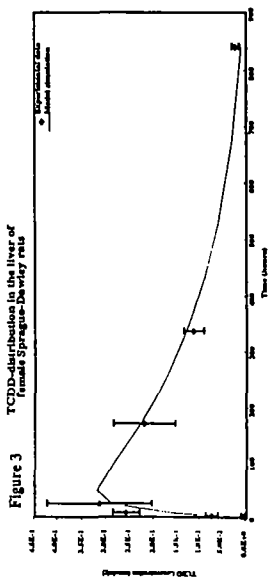

Figure 3