A Physiologically-Based Pharmacokinetic Model for 2,3,7,8-Tetrabromodibenzo-p-dioxin (TBDD) in the Rat

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Biologically-based models represent a useful way to integrate mechanistic pharmacokinetic data by explicitly defining important determinants of chemical disposition. The objective of the present work was to develop a physiologically-based pharmacokinetic model to describe the disposition of 2,3,7,8-tetrabromodibenzo-p-dioxin (TBDD) in the rat. The present model, which is based on previously developed physiologically-based models for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)[1,2], was used to analyze the tissue distibution and excretion of the brominated congener, TBDD, following single intravenous administration of 1 or 100 nmol/kg ^{3}H-TBDD.

The TBDD model consists of a blood compartment and five tissue compartments: liver, fat, skin, slowly perfused tissues, and richly perfused tissues (Fig. 1). As in previous dioxin models, tissue compartments are defined with specified volumes (V_T) and blood flows (Q_T). In the present model, each tissue has an associated tissue blood volume(V_{TB}), and uptake of chemical from tissue blood to tissue is proportional to a permeation coefficient -surface area cross product, PA_T [1]. Tissue uptake is diffusion-limited when $PA_T < Q_T$. Each tissue has a specified partition coefficient, P_T, which represents the intrinsic solubility of TBDD in that tissue. In addition, the liver compartment is modeled with equations to describe first order metabolic clearance and saturable binding of TBDD with the Ah receptor and an inducible binding species. As previously noted[3], CYP1A2 has been hypothesized to be the putative binding species. In the model, the hepatic induction of CYP1A2 is assumed to result directly from the formation of a ternary TBDD-Ah receptor-DNA complex. Induction is modeled as an increase in the production of protein, the increase being specified by a Hill binding relationship between the TBDD-Ah receptor complex and DNA.

Cardiac output and blood flow to liver, skin, slowly perfused and richly perfused tissues were estimated based on data obtained in unanesthetized rats using a radiolabeled microsphere technique[4]. The model allowed for growth of the animal over time. The volume of the fat compartment was described as a function of body weight using an algorithm based on data from our laboratory[5]. The ratios of tissue:blood concentrations of TBDD 56 days following a single iv dose[6] were used to provide initial estimates for tissue:blood partition coefficients. As in previous models[2], the renal tissue:blood concentration ratio was used to represent the liver partition coefficient. For fat, the partition coeffient was estimated based on that used for TCDD[1] with adjustment upwards to provide a reasonable fit with the fat concentrations following a single iv dose[6]. The model did not include induction of metabolism[7]. The transluminal excretion of parent directly to the gastrointestinal tract with subsequent excretion

into the feces occurred with a first order rate constant, Kp. This process whereby parent chemical is excreted following parenteral dosing has been described for TBDD and TCDD[6,8]. The basal and induced binding capacities used in the model are based on measured levels of CYP1A2 in the rat liver following TBDD treatment[7]. In accordance with the similar pharmacokinetic and pharmacodynamic properties of TBDD and TCDD, other model parameters were based on those used for TCDD[1]. Model parameters are tabulated in Table 1. The mass-balance differential equations for the model, which have been fully described elsewhere[1], were solved simultaneously using SimuSolv^R (Dow Chemical Company, Midland, Michigan).

The model was used to describe the time-dependent distribution of ^{3}H-TBDD to liver and fat following a single intravenous dose of 1 nmol/kg[6]. These experiments were conducted with male F-344 rats (225-290 kg; 3-4 months of age). Terminal tissue distribution and excretion of radioactivity following administration of a high dose (100 nmol/kg) of ^{3}H-TBDD were also modeled.

Liver and fat are the primary tissue depots following administration of TBDD. As illustrated by the data in Fig. 2, concentrations of TBDD in these tissues are highly time-dependent. At the low dose, liver concentrations exceed those in fat for approximately 2 weeks after which the liver:fat ratio declines to less than 1. In the model, accumulation in the liver is attributable to specific binding of TBDD with the inducible protein, CYP1A2. The model predictions, represented by the smooth curves in the figure, agree well with the time-dependent behavior of TBDD disposition in these tissues. However, extrahepatic tissue concentrations such as fat (and skin) are generally underpredicted at later time points.

As noted with TCDD, tissue distribution is dose-dependent. At the 100 nmol/kg dose, hepatic concentrations of TBDD remain higher than those for fat on Day 56 (117 ng/g vs. 45 ng/g), whereas the model would predict a liver:fat concentration ratio of 1. While hepatic, and consequently extrahepatic disposition of TBDD may be adjusted by varying the binding affinity (KB2) of TBDD for CYP1A2, KB2 is constrained by the observed differences in disposition at the high versus the low dose. Dose-dependent differences are also observed in the case of skin whereby the partition coefficient (PS) used to estimate concentrations in skin at low doses greatly overpredicts the 56-day skin concentration at the high dose.

Excretion of TBDD and TBDD metabolites in urine and feces at the low dose is shown in Fig. 3. The terminal portion of the data suggested a terminal half-life of approximately 18 days[6] which is reflected fairly well by the slope of the curve generated by the model, though the absolute amount excreted is overpredicted by the model. The large % dose excreted within the first few days is probably due to a rapidly excreted impurity in the radiolabeled TBDD. Previous studies with ^{3}H-TCDD have shown the presence of a tritiated impurity not discernable by conventional radio-HPLC (high pressure liquid chromatography) techniques (unpublished results from our laboratory).

The present study provides further validation of the model structure originally developed to describe important dispositional determinants for TCDD[1,2]. The TBDD model is currently being refined to improve predictability of the time- and dose-dependent behavior of TBDD disposition in hepatic and extrahepatic tissues. The model will also be expanded to incorporate environmentally relevant routes of exposure.

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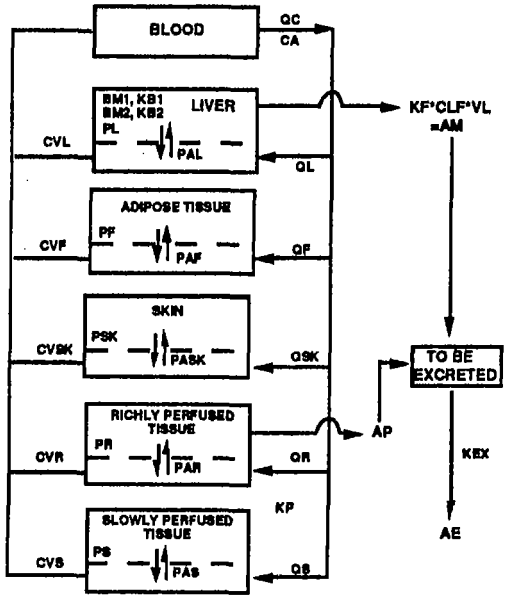

Fig 1. PBPK model of TBDD in the rat.

TABLE 1

Model Parameter	Abbrev-iation	F-344 Rat
Body weight (kg)	BW	0.23
Volumes (% BW)		
Liver	VLC	4
Richly perfused	VRC	5
Slowly perfused	VSC	55
Fat	VFC	11
Skin	VSKC	16
Blood	VLC	8
Cardiac Output	QC	6
Tissue blood flow (%QC)		
Liver	QLC	15
Richly perfused	QRC	32
Slowly perfused	QSC	38
Fat	QFC	9
Skin	QSC	6
Diffusional clearance (hr^{-1})		
Liver	PAL	2.5 * QL
Richly perfused	PAR	2.5 * QR
Slowly perfused	PAS	1.0 * QS
Fat	PAF	0.2 * QF
Skin	PASK	0.1 * QSK
Partition coefficients		
Liver/blood	PL	2
Richly perfused/blood	PR	2
Slowly perfused/blood	PS	4
Fat/blood	PF	1100
Skin/blood	PSK	100
Rate constants ($hr^{-1}kg^{-1}$)		
Metabolism	KFC	3.0
Excretion of parent	KPC	0.002
Excretion rate	KEX	0.1
Binding constants		
Ah maximum (pmol/liver)	BM1	3.75
Ah affinity (nM)	KB1	0.01
1A2 basal (nmol/liver)	BM2O	12
1A2 max (nmol/liver)	BM2I	120
1A2 affinity (nM)	KB2	8

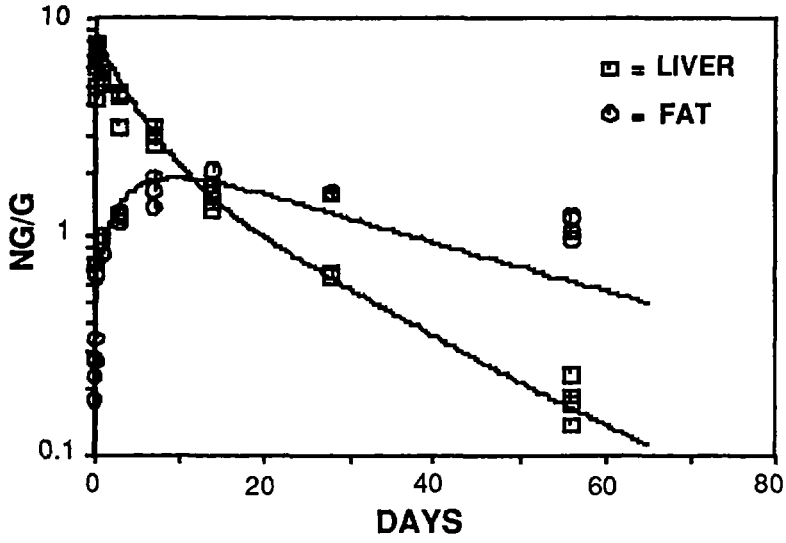

Fig 2. Tissue concentrations of ^{3}H-TBDD following a single iv dose of 1 nmol TBDD per kg body weight.

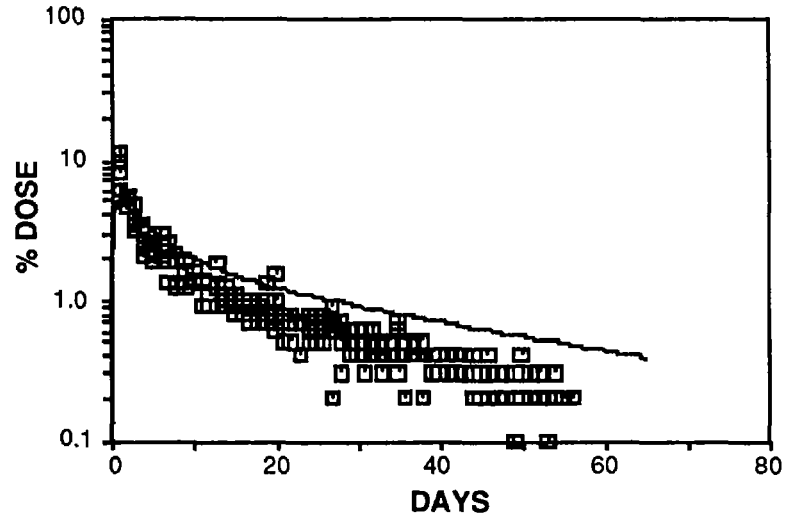

Fig. 3 Excretion of 3H-TBDD in urine and feces following a single iv dose of 1 nmol TBDD per kg body weight.