Toxicokinetics of 2,3,7,8-TCDD (dioxin) and related compounds

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Dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) is a potent carcinogen in both rats and mice[1,2]. Its carcinogenicity is thought to result from its action as a tumour promoter rather than as an initiator[3]. All of the toxic actions are believed to be mediated via the specific binding of TCDD to a cytosolic protein receptor, designated the *Ah* receptor. Following the formation of an *Ah* receptor-TCDD complex, and a cytosol-to-nucleus translocation, the complex binds with high specificity to DNA. This binding modifies the regulation of various genes, some involved in metabolic processes, and others with potential to alter cellular growth and differention[4]. Among the hepatic proteins induced by the interactions between the *Ah* receptor-TCDD complex and DNA is a cytochrome, CYP1A2, which readily binds dioxin[5]. The induction of this protein appears to lead to a dose-dependent sequestration of dioxin in the liver. Any comprehensive model of TCDD pharmacokinetics must include a description of the induction of hepatic binding proteins mediated by the interaction of the TCDD complex with DNA. In this paper we describe an extended physiologically-based pharmacokinetic (PB-PK) model that includes diffusion-limited distribution of TCDD into tissues and accounts for both physiological changes within the growing animal, and for induction of binding protein/enzymes by ternary interactions between the TCDD-*Ah* receptor complex and DNA binding sites.

The TCDD PB-PK model consists of five compartments: liver, fat, blood, slowly perfused and richly perfused tissues. The latter two compartments are representative of muscle/skin and kidney/visceral tissues, respectively. Each of the four tissue compartments has a specified tissue blood volume, taken from Bischoff and Brown[6], and a tissue compartment volume. The movement of the chemical into the tissue (t) from the tissue blood (tb) compartment is proportional to a permeation coefficient-surface area cross-product for the tissue.

Mass balance diffential equations are used to calculate amount of TCDD in each tissue or tissue blood compartment (A_t or A_{tb}), and TCDD concentrations (C_t) are calculated by dividing the amount by the compartmental tissue volume (V_t). Important parameters are displayed in Table1.

In the liver the total mass is apportioned between free (partitioned) and bound forms of TCDD. Partition coefficients, which describe the intrinsic solubility of TCDD for each tissue, are taken from Andersen and coworkers[7]. C_{lf} is the free concentration in the tissue.

$$A_l = P_l V_l C_{lf} + BM1\ C_{lf}/(KB1 + C_{lf}) + BM2T\ C_{lf}/(KB2 + C_{lf}) \quad (1)$$

The second term is the amount of the *Ah* receptor-TCDD complex (*Ah*-TCDD) and the third term represents the amount of the binding protein complex. BM2T, the concentration of binding protein sites at time t, is calculated from the concentration of the *Ah*-TCDD complex, a DNA dissociation constant, obtained by data fitting, and the basal and maximally induced concentrations.

$$BM2T = BM2O + BM2I\ (Ah\text{-TCDD})^n/((Ah\text{-TCDD})^n + Kd^n) \quad (2)$$

Induction of cytochrome P-4501A1 activity occurs with a half-life related to a 1A1 degradation rate constant (k_1). Eqn (3) below:

$$d1A1/dt = K0(1 + MAXIND(Ah\text{-TCDD})^{n1}/(Ah\text{-TCDD})^{n1} + Kd1^{n1}) - k_1 1A1 \quad (3)$$

The disposition of TCDD to the liver and fat is highly dose-dependent in the concentration range between 1 and 10,000 ng/kg bw. The model was used to examine the dosimetry of 2,3,7,8-TCDD in Wistar rats administered a single s.c. dose of [^{3}H]-TCDD[8]. The concentrations are expressed as %dose/gram tissue and would be horizontal lines if disposition was dose-independent (Fig. 1). The curvature is due to the induction of a high-affinity binding protein(s), modelled as CYP1A2. The smooth curves were obtained with the model based on the parameters shown in Table 1. The model as configured for the dose-response study was used to examine the time-course of TCDD disposition following a single s.c. dose[8].

The challenge in providing a biologically realistic kinetic model for dioxin is the need not only to account for the determinants of disposition (i.e., tissue partitioning, biotransformation rates, and protein binding constants), but also to describe the pharmacodynamic events related to the induction of TCDD binding protein species in the liver by TCDD. Knowledge of the molecular mechanisms of the interactions of the *Ah* receptor-TCDD complex with regulatory regions of specific genes is growing rapidly, but already clearly shows the role of ternary *Ah* receptor-TCDD-DNA complexes in regulating gene transcription.

The model of disposition in this paper is based on a ternary complex being obligatory for the pharmacodynamic action of TCDD at the genomic level. In describing these interactions we require estimates of binding constants between the *Ah* receptor and TCDD and between the *Ah* receptor-TCDD complex and sites on DNA[7]. These ternary interactions with DNA then enhance transcriptional processes, leading to increased amounts of specific dioxin-binding protein(s), presumably cytochrome CYP1A2.

The behavior of dose-dependent hepatic sequestration is a characteristic of many congeners of dioxin[9] and is observed in multiple species, including humans[10]. Thus, this basic model structure appears to be widely applicable with these various chemicals that act *via* the *Ah* receptor.

In conclusion, a generic PB-PK model has been developed to describe the disposition and enzyme-inducing properties of TCDD. Ternary interactions between the *Ah* receptor, TCDD and DNA binding sites lead to enhanced production of various proteins, including specific hepatic proteins that bind TCDD. Induction of these proteins leads to dose-dependent liver accumulation of TCDD. With this same model structure we can also describe; induction, multiple dosing, and time course tissue distribution over a 100-day period post-injection.

With appropriate values for partition coefficients, binding constants and metabolic rates, this model should also prove to be useful for describing the kinetics and dynamics of many xenobiotics that interact *via* the *Ah* receptor and affect gene expression.

References

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Table 1. Parameters for the physiological dosimetry model for TCDD - based on a 215g rat.

Model parameter	Abbreviation	Wistar Rat
Partition Coefficients		
Liver/blood	Pl	20
Fat/blood	Pf	375
Richly perfused/blood	Pr	20
Slowly perfused/blood	Ps	30
Protein Binding		
Ah maximum (pmoles/liver)	BM1	3.75
Ah affinity (pM)	KB1	35
1A2 basal level (nmoles/liver)	BM2O	10
1A2 maximum (nmoles/liver)	BM2I	85
1A2 affinity (nM)	KB2	6.5
Induction Characteristics		
1A2 - Hill term	n	1.0
1A2 - Hill binding constant	Kd	50
1A1 - Hill term	n1	2.3
1A1 - Hill binding constant	Kd1	210
1A1 basal synthesis rate (U/hr)	K0	0.7
1A1 degradation rate	k1	0.035
1A1 maximum fold induction	MAXIND	50

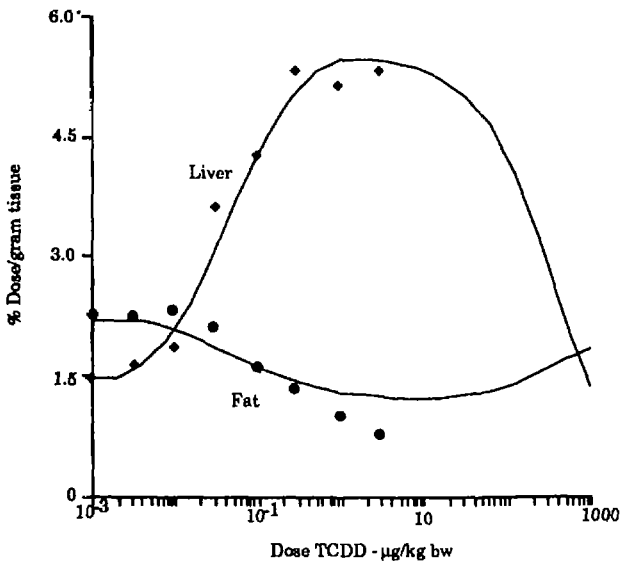

Fig 1. Dose-dependent disposition of 2,3,7,8-TCDD. Female Wistar rats were given a single s.c. dose of radiolabelled TCDD and sacrificed 7 days. Disposition was assessed in the liver and fat by liquid scintillation counting. Data are from Abraham and coworkers[8]. The smooth curves are the model simulations.