

A Dispersion Model for the Hepatic Uptake and Elimination of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin*

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Abstract

A convection-dispersion model for the uptake and elimination of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the liver is presented. The model is adapted from the general dispersion model of Roberts and Rowland and includes the dynamics of TCDD interaction with two intracellular proteins, the Ah receptor and cytochrome P450 IA2. A “well-mixed” compartment was added to describe the venous blood concentration of TCDD. The result is a nonlinear system of seven coupled partial and ordinary differential equations with time delays.

Keywords and phrases: Physiologically-based pharmacokinetic (PBPK) model, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), liver transport models, nonlinear partial differential equations, delay equations.

1 Introduction

The chemical compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is highly lipophilic and has been shown to accumulate in the fat and liver tissue of animals [1, 2]. Of particular interest is its ability to produce a wide range of effects in animals following exposure, including certain types of cancer [1]. Due to the presence and persistence of TCDD in the environment and its potential for bioaccumulation, the human health risk due to chronic, low level exposure is of global social concern.

While limited data is available on the effects of dioxin exposure in humans, knowledge of the mechanism of toxicity in animals may help us to better understand and possibly predict human TCDD endpoints. Animal

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studies of the mechanism of toxicity of TCDD have revealed that an intracellular hepatic protein, the aryl hydrocarbon (Ah) receptor, may play an important role [1, 2].

In rodents, TCDD is known to bind to two hepatic proteins: the non-inducible high-affinity, low capacity Ah receptor, and an inducible low-affinity, high-capacity microsomal protein, cytochrome P450 IA2 (CYP1A2) [3, 4, 5]. After administration of TCDD, the toxin binds to the Ah receptor protein which in turn produces a dose-related induction of CYP1A2 [4]. Therefore, this protein is present at both a basal (non-induced) level and an induced level in the presence of TCDD. Although the induced binding protein has been estimated to have a binding affinity 10^4 times less than the Ah receptor, its binding capacity is approximately 2×10^3 greater [4].

The liver appears to be a major target organ for chronic toxicity in rodents [1]. PBPK models which have attempted to describe the uptake, distribution, and elimination of TCDD in animals have generally used the “well-stirred” or “venous-equilibrium” model to describe events occurring in the liver [6, 7]. The basic assumption of this model, that the concentration of solute is uniform throughout the length of the liver acinus, does not describe the elimination of solutes with decreasing concentration gradients along the acinus following a bolus input. Although other models of hepatic elimination have been proposed which overcome this problem, a common concern is that they do not reflect the complex physiology of the human liver. In an attempt to develop a more physiologically realistic model as well as to generalize existing ones, a dispersion model for hepatic elimination was introduced in 1985 by Roberts and Rowland [8]. In this paper we show that this dispersion model can be adapted to describe the hepatic uptake and elimination of TCDD, including TCDD-binding to the Ah receptor protein and CYP1A2.

TCDD was the toxic contaminant in Agent Orange, the herbicide used by US forces during the Vietnam conflict. Time-course data is available on TCDD blood concentrations in US Air Force veterans who were exposed to Agent Orange during their service in Vietnam [9]. Anticipating the eventual use of this data in our numerical simulations, we added a “well-mixed” venous blood compartment to the liver model. This compartment includes a sink term to describe the rate of TCDD uptake by adipose (fat) tissue, a primary storage site for TCDD in the body [1, 2].

The organization of the paper is as follows. We begin in Section 2 with an overview of liver physiology with emphasis on microcirculation and discuss some of the general properties of the dispersion model. Section 3 deals with the development of the model from mass balance techniques, and it is in this section where TCDD-specific equations are incorporated into the general model. Venous blood concentrations are discussed in Section 4 and in Section 5 we discuss the boundary conditions. The complete model, including a discussion of its nonlinear aspects and a brief statement regarding well-posedness of solutions, is given in Section 6. Finally, Section 7 contains a summary of our work.

2 Liver Physiology and the Dispersion Model

2.1 The Physiology of the Human Liver

The liver receives blood from two sources: the portal vein which carries nutrient rich but oxygen poor blood from the alimentary tract, spleen, and pancreas and accounts for 75% of the liver’s total blood supply, and the hepatic artery which delivers oxygenated blood. The two blood supplies mix as they enter the smallest vessels, the sinusoids, which carry blood to the hepatic cells.

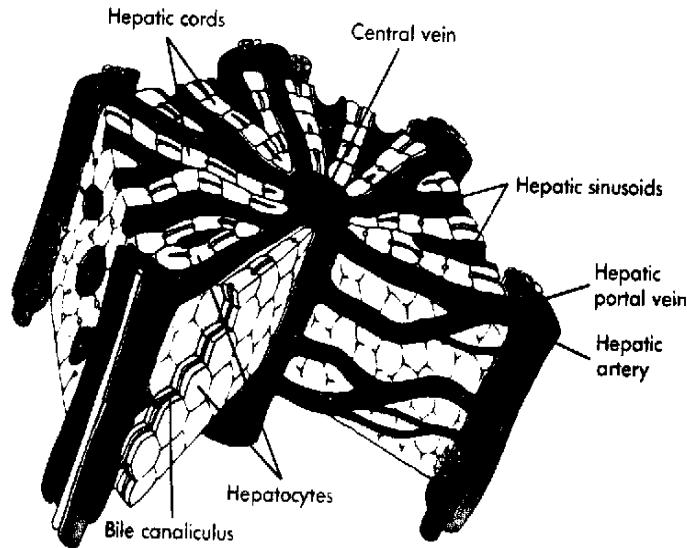


Figure 1: Schematic view of the classic hepatic lobule. Figure 22-3 from David F. Moffett, Stacia B. Moffett, and Charles L. Schauf, *Human Physiology: Foundations and Frontiers*, St. Louis: Mosby (1993). Reproduced with permission of The McGraw-Hill Companies.

The complex geometry of the liver and its effect on transport processes is best understood in terms of the smallest structural unit of the liver, the classic hepatic lobule (see Figure 1). There are approximately one million lobules in the human liver, with each lobule in cross-section roughly polyhedral in shape [10, 11]. Blood enters the lobule from each of six portal triads approximately equally spaced at its peripheral angles. The portal triad consists of a terminal branch of the portal vein, the hepatic artery, and bile duct. Each portal triad supplies blood to and transports bile from more than one lobule. The lobules are composed mainly of liver cells, called hepatocytes, which are interconnected and subdivided by spaces into plates (also called hepatic cords) generally one cell thick. Separating the cell plates and supplying blood to the cells are the hepatic sinusoids which interconnect and anastomose irregularly throughout the lobule, finally emptying into a central terminal hepatic venule (central vein). The lining of the sinusoids is a discontinuous layer of endothelial cells permitting exchange of elements in the blood with the Disse space, a small channel between the sinusoid and the hepatocytes. Each hepatocyte is exposed to the space of Disse and therefore is in contact with blood on one or more sides. Blood flows from the portal area at the periphery of the lobule to the center.

Each central vein drains only one lobule, and increases in size as it empties into a sublobular vein. The sinusoids open into and radiate from this central vein outward to the portal areas, varying in length from 220-480 μm and in caliber from 9-12 μm wide [11]. The central vein is much larger than the sinusoids, with an average diameter of 45 μm [11]. The blood is cleared from the liver by emptying into increasingly larger blood vessels until it reaches the hepatic vein and ultimately the inferior vena cava.

Bile is excreted by the hepatocytes into bile caniculi which have no discrete structure of their own but rather are formed by the plasma membranes of adjacent cells. The caniculi form a network which surrounds each cell in a hepatic plate, and eventually drain into the bile ductule located in the peripheral portal triad. Bile flows countercurrent to blood.

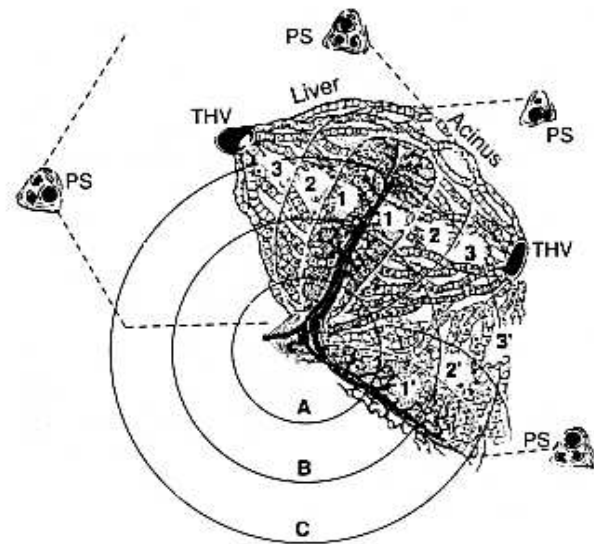


Figure 2: Zones 1, 2, and 3 of the liver acinus. Zones of an adjacent acinar unit are represented by 1', 2', and 3'. Circle A represents the periportal area whereas circles B and C represent areas peripheral to the portal space (PS). THV represents the terminal hepatic venule or central vein. Figure 1 from A.M. Rappaport, Z.J. Borowy, W.M. Lougheed, and W.N. Lotto, Subdivision of hexagonal liver lobules into a structural and functional unit; role in hepatic physiology and pathology, *Anat. Rec.* **119**(11) 11-27 (1954). Reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Three primary lobular schemes have been developed to describe the functional units of the liver: the classical, portal, and liver acinus.

- **Classical.** The classic functional unit is the classic hepatic lobule described above. Although this is regarded primarily as an anatomical structural unit of the liver, some changes (such as fat and glycogen deposition after a meal) within the liver originate and spread throughout the lobule from either the portal areas or the central areas producing concentric zones of change about the central vein [11].
- **Portal.** In the portal lobule, bile flows from the periphery of the lobule to a centrally located bile ductule and blood flows in the opposite direction. The portal lobule is used to describe the function of bile secretion in the liver.
- **Liver Acinus.** Introduced in 1969 by Rappaport, the liver acinus is described as the smallest functional unit of the liver [11]. The simple hepatic acinus is irregular in shape (roughly oval), and includes small sections of two adjacent classic lobules. The unit is bounded by two portal tracts and two central veins, with the branches between the portal tracts forming the central axis of the acinus. In this way the liver acinus portions the lobule into three concentric zones based on the richness of the blood supply to the cells (see Figure 2).

Zone 1, which surrounds the central axis, receives the blood which is richest in both nutrient and oxygen content. Zone 2 is a transitional zone between those cells which receive the richest blood supply and those cells in zone 3 which receive blood depleted of much of its nutrients and oxygen but

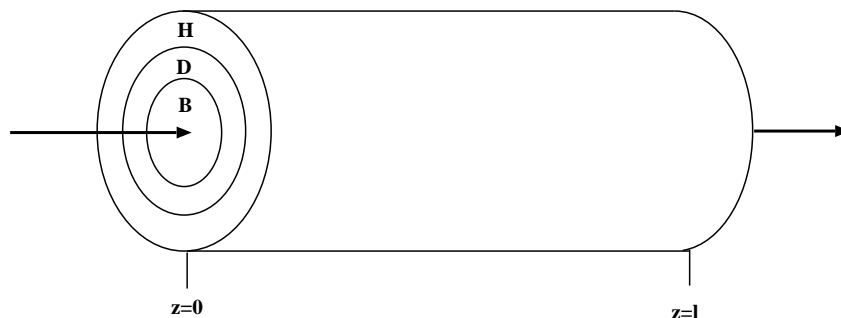


Figure 3: The liver represented as a cylinder: (B) blood or sinusoidal volume, (D) Disse space volume, (H) hepatocyte volume.

which are responsible for many metabolic processes of the liver. Zone 3 is the area which is closest to the central vein. In contrast to the classic hepatic lobule, in this scheme blood flows from the center to the periphery while bile flows from the periphery to the center of the lobule.

In zone 1, protein synthesis and formation of plasma protein occur [12]. In zone 3, cytochrome P-450 and NADPH-cytochrome P-450 reductase activity is higher than in the other zones and lipid synthesis is also greater [12].

2.2 The Dispersion Model

The sinusoids have varying lengths and widths and may branch or interconnect with other sinusoids before finally emptying into the central vein. Furthermore, blood elements travel down the sinusoids at different velocities, and evidence suggests that sinusoids in zone 1 of the hepatic acinus are highly anastomotic whereas those in zone 3 are relatively straight [13]. The net result is that blood elements taking different paths through the liver may require different lengths of time to pass through the liver. The variation in residence times is called the residence time distribution of the fluid.

The original model of Roberts and Rowland [8] was based on a model for nonideal flow in chemical reaction engineering [14]. In the model, the vessel under consideration is represented as a cylinder with constant cross-sectional area. As depicted in Figure 3, the sinusoidal regions and associated spaces of Disse and hepatocytes are treated in terms of three total volumes: the sinusoidal or blood volume (B) is the inner core of the cylinder and is surrounded by concentric regions consisting of the Disse space volume (D) and the hepatocyte volume (H). Fluid flow in the blood volume is modeled as plug flow upon which is superimposed some degree of backmixing or intermixing during flow [14]. The degree of backmixing is characterized by the axial dispersion coefficient, \mathcal{D} , which is used to quantify the variation in residence times of the fluid. The term “axial” is used to distinguish between mixing in the direction of flow and mixing in the radial direction (radial dispersion). In streamline flow, axial dispersion is primarily the result of differences in velocity gradients in the direction of flow whereas radial dispersion is mainly due to the process of molecular diffusion [14].

The process of axial dispersion is modeled in a manner analogous to molecular diffusion and is sometimes referred to as “turbulent diffusion” [15]. The higher the value of the axial dispersion coefficient, \mathcal{D} , the greater the degree of axial dispersion. It is important to note that the dispersion coefficient represents events

occurring in the liver at a global or macroscopic level; it represents the net effects of many factors influencing flow yet gives no information as to the specific factors affecting flow at any given physical location; i.e., it is a modeling artifact to handle backmixing.

3 A Preliminary Model

As discussed in Section 2.2, in the general dispersion model the liver is represented as a cylindrical vessel with constant cross-sectional area (Figure 3). The length of the cylinder is l : the distance from the entrance to the sinusoids at $z = 0$ (the portal area) to the exit from the sinusoids at $z = l$ (the central vein).

3.1 Assumptions

We derive our model under a number of standing assumptions. Of these, Assumptions 1.-4. and 8. are due to Roberts and Rowland. For a complete discussion of the anatomical/physiological justifications for these assumptions, the reader is referred to the original work [8].

1. Radial transport of solute is instantaneous.
2. Axial diffusion of solute can be ignored.
3. Only unbound solute can cross the cell membrane and be eliminated via metabolism or biliary excretion.
4. The ratio of the unbound to total solute concentration within blood and the Disse space are constant throughout the liver.
5. TCDD metabolism is a first-order process.
6. Elimination of TCDD is due to metabolism only. Unchanged TCDD is not eliminated in the bile.
7. All reactions occur at constant temperature.
8. Conditions do not vary across a section normal to flow.

Note that Assumption 8. reduces the problem to one dimension.

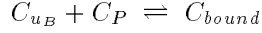
Assumption 4. guarantees that the amount of TCDD bound by blood proteins is proportional to the amount unbound. To see this, observe that the total concentration of TCDD within the blood, C_B , consists of both the bound and unbound pool; that is,

$$C_B = C_{u_B} + C_{bound}$$

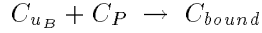
where C_{u_B} and C_{bound} are the concentrations of unbound and bound TCDD within the blood, respectively. From Assumption 4. we have that $f_{u_B} = \frac{C_{u_B}}{C_B}$ is constant, which then yields

$$C_{bound} = \left(\frac{1 - f_{u_B}}{f_{u_B}} \right) C_{u_B}.$$

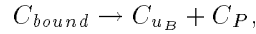
The basis of Assumption 4. is twofold; first, that TCDD binding to proteins in the blood is at steady state, and second, that the concentration of blood binding proteins remains constant. The standard model to describe the binding of unbound TCDD to blood lipoproteins is



where C_P is the concentration of blood binding protein. Let k^+ and k^- represent the rate constant for the forward reaction



and reverse reaction



respectively. Under steady state conditions and assuming C_P is constant, we have

$$C_{bound} = KC_{u_B}$$

where $K = \frac{k^+}{k^-}C_P$. Hence, under these conditions

$$f_{u_B} = \frac{1}{1 + K}$$

is constant.

3.2 Development of the General Dispersion Model

The development of the general equations is due to Roberts and Rowland and is presented here for completeness. The notation used is consistent with the original work [8].

We first consider an arbitrary volume element of thickness Δz at distance z along the length l of the cylinder (Figure 4). The volume of blood within this element is $V_B(z)$ which flows through a cross-sectional area A at a rate Q and velocity v . Let C_B represent the total concentration of TCDD in the blood (both free and bound) and C_{u_B} the concentration which is unbound.

The movement of TCDD in blood within this element is due to bulk flow (convection) and turbulent flow (dispersion) as well as transport of solute across the cell membrane. Elimination, via biliary excretion and/or metabolism, occurs in the hepatocytes. From the principle of mass balance we have

$$\left(\begin{array}{c} \text{Rate of change} \\ \text{of TCDD} \\ \text{within element} \end{array} \right) = \left(\begin{array}{c} \text{Net rate of flow} \\ \text{of TCDD} \\ \text{into element} \end{array} \right) - \left(\begin{array}{c} \text{Elimination rate} \\ \text{of TCDD} \\ \text{within element} \end{array} \right). \quad (1)$$

The net rate of flow into the element is the difference between the input and output rate. Let J_z denote the total mass flux across a plane normal to flow at location z . The net rate of flow of TCDD into the element is then $AJ_z - AJ_{z+\Delta z}$.

Since the transport of TCDD in the blood occurs by both convective and dispersive forces, the total mass flux is the sum of the convective and dispersive fluxes. The convective flow rate of TCDD is AvC_B ; therefore, the convective flux is given by

$$\text{Convective flux} = vC_B.$$

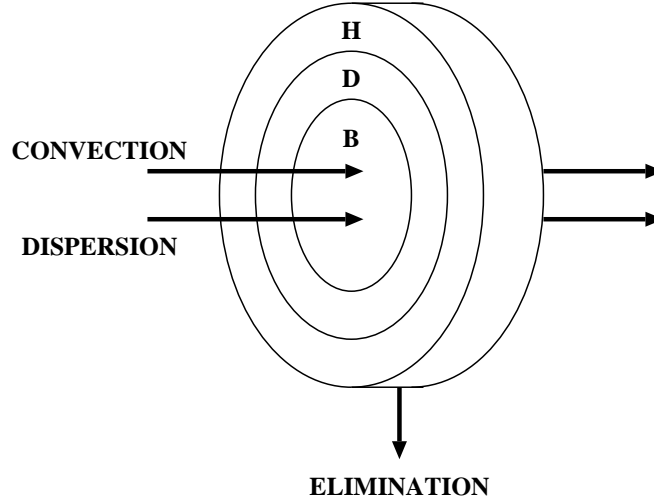


Figure 4: Schematic of events in a cross section of the liver, represented as a cylinder. (B) The blood or sinusoidal region, (D) the space of Disse region, (H) the hepatocyte region.

As discussed in Section 2.2, the dispersive flux is modeled in a manner analogous to Fick's law of diffusion:

$$\text{Dispersive flux} = -\mathcal{D} \frac{\partial C_B}{\partial z},$$

where the constant \mathcal{D} is the axial dispersion coefficient and is a measure of the degree of backmixing during flow. Combining these terms, we obtain

$$J_z = -\mathcal{D} \frac{\partial C_B}{\partial z} + v C_B.$$

Therefore,

$$\begin{aligned} \left(\begin{array}{c} \text{Net rate of flow} \\ \text{of TCDD} \\ \text{into the element} \end{array} \right) &= A \Delta z \left(\begin{array}{c} \text{Net rate of flow} \\ \text{of TCDD per} \\ \text{unit blood volume} \end{array} \right) \\ &= A \mathcal{D} \left[\frac{\partial C_B}{\partial z} \Big|_{z+\Delta z} - \frac{\partial C_B}{\partial z} \Big|_z \right] - A v [C_B \Big|_{z+\Delta z} - C_B \Big|_z]. \end{aligned}$$

Dividing both sides of the equation by the blood volume of the element, $A \Delta z$, and taking the limit as Δz approaches 0 from the right we have

$$\begin{aligned} \left(\begin{array}{c} \text{Net rate of flow} \\ \text{of TCDD per} \\ \text{unit blood volume} \end{array} \right) &= \lim_{\Delta z \rightarrow 0} \left[\frac{\mathcal{D} \frac{\partial C_B}{\partial z} \Big|_{z+\Delta z} - \mathcal{D} \frac{\partial C_B}{\partial z} \Big|_z}{\Delta z} \right] - \lim_{\Delta z \rightarrow 0} \left[\frac{v C_B \Big|_{z+\Delta z} - v C_B \Big|_z}{\Delta z} \right] \\ &= \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - v \frac{\partial C_B}{\partial z}. \end{aligned}$$

Multiplying both sides by the blood volume of the element, $V_B(z)$, we find

$$\left(\begin{array}{c} \text{Net rate of flow} \\ \text{of TCDD} \\ \text{into the element} \end{array} \right) = V_B(z) \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B(z) v \frac{\partial C_B}{\partial z}. \quad (2)$$

By Assumptions A5. and A6.,

$$\left(\begin{array}{c} \text{Elimination rate} \\ \text{of TCDD} \\ \text{within element} \end{array} \right) = V_H(z) k_3 C_{u_H}, \quad (3)$$

where $V_H(z)$ is the hepatocyte volume of the element, k_3 is the elimination rate constant, and C_{u_H} is the concentration of free TCDD in the hepatocyte volume. Substituting (2) and (3) into Equation (1) we have

$$\left(\begin{array}{c} \text{Rate of change} \\ \text{of TCDD} \\ \text{within the element} \end{array} \right) = V_B(z) \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B(z) v \frac{\partial C_B}{\partial z} - V_H(z) k_3 C_{u_H}. \quad (4)$$

Finally, assuming volumes do not vary along the length of the liver we find

$$\left(\begin{array}{c} \text{Rate of change} \\ \text{of TCDD} \\ \text{in the liver} \end{array} \right) = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} - V_H k_3 C_{u_H}.$$

We now consider the rate of change of TCDD in the liver in further detail. TCDD is present in the liver in the blood, Disse space, and hepatocytes. Let V_D and V_H represent the volumes of the space of Disse and hepatocytes, respectively, and C_D and C_H the total TCDD concentrations. The rate of change of TCDD in the liver can be expressed as the sum of the rates of change in each of the three compartments:

$$\left(\begin{array}{c} \text{Rate of change} \\ \text{of TCDD} \\ \text{in the liver} \end{array} \right) = V_B \frac{\partial C_B}{\partial t} + V_D \frac{\partial C_D}{\partial t} + V_H \frac{\partial C_H}{\partial t}. \quad (5)$$

Recall, by Assumption 4., the fraction of TCDD unbound within the blood and Disse space is constant throughout the length of the liver. The constant f_{u_B} was defined as the ratio C_{u_B}/C_B . We now define f_{u_D} as the ratio C_{u_D}/C_D ; that is, f_{u_D} is the fraction of solute unbound in the Disse space. We note that f_{u_D} is assumed constant but not necessarily equal to f_{u_B} . By Assumption 1., the distribution of solute between the blood and the space of Disse is instantaneous and therefore $C_{u_D} = C_{u_B}$. By substitution,

$$f_{u_B}/f_{u_D} = (C_{u_B}/C_B)/(C_{u_D}/C_D) = C_D/C_B,$$

or, equivalently, $C_D = \frac{f_{u_B}}{f_{u_D}} C_B$. The rate of change of TCDD in the space of Disse can therefore be expressed in terms of the rate of change of the total concentration of solute in the blood region:

$$V_D \frac{\partial C_D}{\partial t} = V_D \frac{\partial}{\partial t} \left(\frac{f_{u_B}}{f_{u_D}} C_B \right) = V_D \frac{f_{u_B}}{f_{u_D}} \frac{\partial C_B}{\partial t}.$$

Using this equality in (5), we find the rate of change of TCDD in the liver can be expressed in terms of the unknown variables C_B and C_H . Now equating (1) and (5) we obtain a general equation for the transport of TCDD in the blood region of the liver:

$$(V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} + V_H \frac{\partial C_H}{\partial t} = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} - V_H k_3 C_{u_H}.$$

As previously stated, the ideas presented to this point are primarily due to Roberts and Rowland and their equation describes in some generality solute transport in the liver. The remaining sections of this presentation deal with our development of model equations to specifically describe the hepatic uptake and elimination of TCDD with overall transport defined by the dispersion model.

3.3 Factors affecting cellular TCDD levels

3.3.1 Elimination

In general, hepatic elimination of drugs or toxins can occur due to metabolism as well as biliary excretion. Animal studies, such as those cited below, have revealed important information as to the mechanisms involved in the clearance of TCDD in the liver.

Rose *et al.* [16] examined the elimination of radioactively-labeled 2,3,7,8-TCDD in rats following both chronic, low-level exposure and a single oral dose. Overall elimination was found to be a first-order process with elimination rate constant $k = 0.023 \pm 0.006/\text{day}$ following a single oral dose of $1.0 \mu\text{g } [^{14}\text{C}]\text{TCDD}/\text{kg}$. Fecal excretion accounted for most if not all of the elimination of this compound, either as the parent compound or as metabolic products. In the chronic exposure study, rats were administered repeated oral doses of 0.01, 0.1, or $1.0 \mu\text{g}$ of $[^{14}\text{C}]\text{TCDD}/\text{kg}/\text{day}$ Monday through Friday for seven weeks. The body burden versus time data for each rat was fit to a one-compartment model assuming a first-order elimination rate. The elimination rate constant was found to be $k = 0.0293 \pm 0.0079/\text{day}$ by pooling the elimination constants for each rat. As in the single dose study, TCDD was excreted primarily in the feces although significant amounts were also detected in the urine.

In studies investigating the biliary excretion of TCDD products in treated rats, Ramsey *et al.* [17], and Poiger and Buser [18] found that only metabolites of TCDD were eliminated in the bile. An *in vivo* study by Kedderis *et al.* [19] using male F344 rats supports this finding. This is important since studies by Rose *et al.* [16] found no significant amount of metabolites of TCDD in extracts of rat liver. Similar observations have been made in the hamster [20]. As observed by Neal *et al.*, this would suggest that once these metabolites are formed, they are rapidly excreted [21].

Limited data is available on biliary excretion of TCDD in humans. Following a single dose of 1.14 ng of $[^3\text{H}]\text{TCDD}$ in a male volunteer, Poiger and Schlatter [22] found overall elimination of this substance in humans also followed apparent first-order kinetics, with a rate constant of elimination of 0.00327.

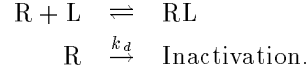
The study by Rose *et al.* [16] suggested that elimination of TCDD in the rat liver follows apparent first-order kinetics in the dose range studied. This, in addition to the finding that $[^{14}\text{C}]\text{TCDD}$ activity was predominantly metabolites of TCDD suggests metabolism in the rat liver is a first-order process [21]. The assumption of first-order enzyme kinetics was made by Leung *et al.* in their PBPK model [6].

3.3.2 Protein Binding

TCDD is known to bind to two intracellular hepatic proteins in rodents: the Ah receptor, and the inducible microsomal protein CYP1A2 [3, 4, 5]. Following the uptake of TCDD by the hepatocytes, the toxin binds to the Ah receptor which in turn produces a dose-related induction of CYP1A2 [4]. Hence, this protein is present at both a basal (non-induced) level and an induced level in the presence of TCDD.

Difficulty in extrapolating from animal to human models of dioxin action may be due in part to differences in properties of the Ah receptor between species [23]. In fact, the binding properties of the Ah receptor appear to be both species and ligand dependent [23, 24].

Bunce *et al.* [25], in an *in vitro* study involving Wistar rats, found that unbound Ah receptor rapidly loses its capacity to bind TCDD. It has been suggested that binding of TCDD to the receptor stabilizes the protein and that the bound complex is stable for many hours whereas free receptor is rapidly inactivated. One model which has been proposed [25] to account for the thermal inactivation of the receptor is



Several studies have attempted to estimate the binding parameters using this kinetic model [23, 24].

In developing a mathematical model which describes TCDD interaction with hepatic proteins one must also consider the natural process of intracellular protein turnover due to protein synthesis and degradation (proteolysis). Proteins are turned over with zero-order rates of synthesis and first-order rates of degradation [26]. In general, the rate of change in the amount of a protein assuming no other factors affecting turnover can be expressed

$$d[P]/dt = k_s - k_d[P],$$

where $[P]$ is the concentration of the protein, k_s is the rate constant of synthesis, and k_d is the rate constant of degradation [26]. In the presence of dioxin, the total concentration of certain proteins will include both the bound and unbound pools. We have previously noted that the binding of TCDD to the Ah receptor stabilizes the protein; therefore, we assume that only the free receptor is available for inactivation. We make this assumption for the degradation of CYP1A2 as well.

In regard to these studies on the kinetics of Ah receptor-TCDD binding, it should be noted that they are *in vitro* studies: whether the mechanisms which lead to the inactivation of the receptor *in vitro* are operative *in vivo* does not yet seem clear from a review of the literature [23, 24, 25, 27]. In the development of the model equations, we include an overall inactivation rate for the Ah receptor under the assumption that such a mechanism exists *in vivo*.

3.3.3 Model equations including TCDD-protein binding and elimination

We now apply mass balance techniques and the *law of mass action* to the transport and biochemical mechanisms represented in Figure 5 which affect the concentration of free TCDD in the hepatocyte volume. In the schematic, as in the dispersion model, P denotes the permeability coefficient of the hepatocyte to dioxin. By Assumptions A5. and A6., and further assuming that the rate constants are known, the following equation describes the rate of change of unbound or free dioxin in the cells:

$$\begin{aligned} \frac{\partial C_{uH}}{\partial t} & = \frac{P}{V_H}(C_{uD} - C_{uH}) - k_3 C_{uH} - k_{+1} C_{uH} C_{Ah} + k_{-1} C_{Ah-TCDD} \\ & \quad - k_{+2} C_{uH} C_{Pr} + k_{-2} C_{Pr-TCDD}, \\ & = \frac{P f_{uB}}{V_H} C_B - \left(\frac{P}{V_H} + k_3 \right) C_{uH} - k_{+1} C_{uH} C_{Ah} + k_{-1} C_{Ah-TCDD} \\ & \quad - k_{+2} C_{uH} C_{Pr} + k_{-2} C_{Pr-TCDD}, \end{aligned} \tag{6}$$

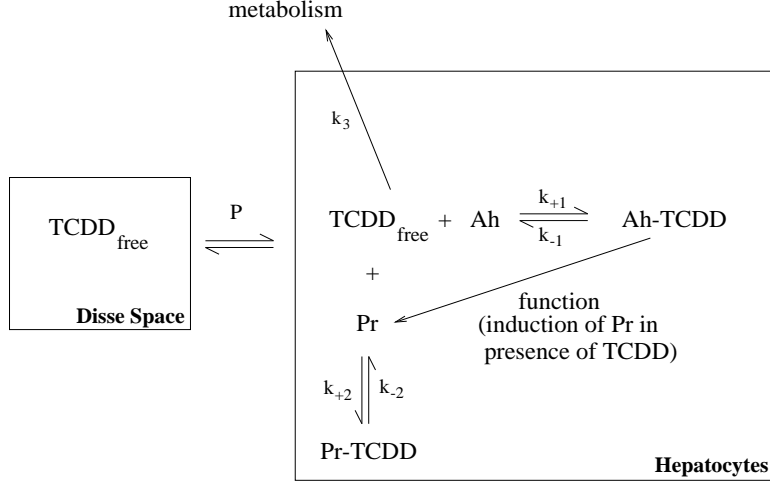


Figure 5: Schematic of TCDD interaction with cellular proteins, ignoring protein synthesis, degradation, and inactivation.

where C_{Ah} is the concentration of the Ah receptor, C_{Pr} is the concentration of CYP1A2, $C_{Ah-TCDD}$ is the concentration of the Ah receptor-TCDD complex, and $C_{Pr-TCDD}$ is the concentration of the CYP1A2-TCDD complex. By Assumption 1., $C_{u_D} = C_{u_B}$, and therefore

$$\begin{aligned}
 C_{u_D} &= \frac{C_{u_D}}{C_B} C_B \\
 &= \frac{C_{u_B}}{C_B} C_B \\
 &= f_{u_B} C_B.
 \end{aligned}$$

As illustrated in Figure 6, the mass balance equation for the rate of change of total TCDD in the cells, C_H , is

$$\begin{aligned}
 V_H \frac{\partial C_H}{\partial t} &= P(f_{u_B} C_B - C_{u_H}) - k_3 V_H C_{u_H} \\
 &= P f_{u_B} C_B - (k_3 V_H + P) C_{u_H}.
 \end{aligned} \tag{7}$$

In this model, net movement of TCDD into or out of the hepatocytes is determined solely by the processes of passive diffusion across the cell membrane or elimination via metabolic clearance, which are functions of the unbound species.

The time course of change of the remaining intracellular components are given below, and are based on Figures 7 and 8:

$$\frac{\partial C_{Ah-TCDD}}{\partial t} = k_{+1} C_{u_H} C_{Ah} - k_{-1} C_{Ah-TCDD}, \tag{8}$$

$$\frac{\partial C_{Ah}}{\partial t} = k_{-1} C_{Ah-TCDD} - k_{+1} C_{u_H} C_{Ah} - k_{d(Ah)} C_{Ah} + k_{s(Ah)}, \tag{9}$$

$$\frac{\partial C_{Pr-TCDD}}{\partial t} = k_{+2} C_{u_H} C_{Pr} - k_{-2} C_{Pr-TCDD}, \tag{10}$$

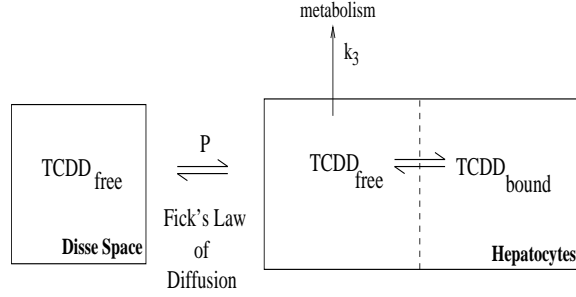


Figure 6: Schematic of the total concentration of TCDD in the hepatocytes.

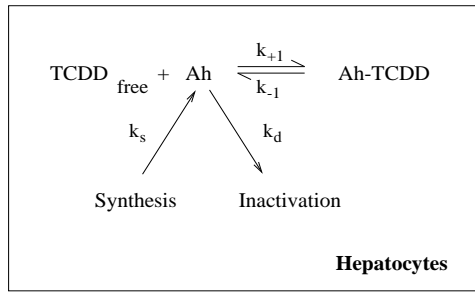


Figure 7: Schematic of Ah receptor protein interaction with TCDD in the hepatocytes.

$$\frac{\partial C_{Pr}}{\partial t} = k_{-2}C_{Pr-TCDD} - k_{+2}C_{uH}C_{Pr} - k_{d(Pr)}C_{Pr} + k_{s(Pr)} + \left(\frac{I_{Pr}}{V_H}\right) \frac{C_{Ah-TCDD}(t - \tau_r, z)}{C_{Ah}(t - \tau_r, z) + C_{Ah-TCDD}(t - \tau_r, z)}, \quad (11)$$

where $k_{d(Ah)}$ is the rate of inactivation of the Ah receptor, $k_{s(Pr)}$ and $k_{s(Ah)}$ represent the basal synthesis rate of CYP1A2 and the Ah receptor, respectively, and $k_{d(Pr)}$ is the degradation rate of CYP1A2. The rate of induction of the microsomal protein in the presence of TCDD is modeled as a function of the fractional occupancy of the Ah receptor at time $t - \tau_r$. The time delay, τ_r , accounts for the numerous intracellular processes which must occur between the time of TCDD binding to the Ah receptor and the time of synthesis of CYP1A2. A delay of six hours was incorporated into the mechanistic model of Kohn *et al.* [28] based on

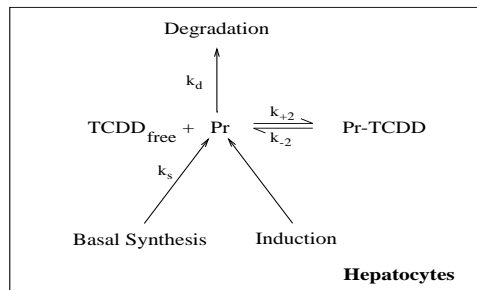


Figure 8: Schematic of CYP1A2 (Pr) interaction with TCDD in the hepatocytes.

the data of Sloop and Lucier [29]. I_{Pr} is the maximum rate of synthesis of CYP1A2. Thus, when the Ah receptor is fully occupied, the maximal amount of protein is synthesized. This model of CYP1A2 induction in the presence of TCDD in terms of the fractional occupancy of the Ah receptor is adapted from a model by Roth *et al.* [30].

3.4 A Preliminary Model System of Equations

From the development of the general equations in Section 3.2, we have

$$(V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} + V_H \frac{\partial C_H}{\partial t} = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} - V_H k_3 C_{u_H}.$$

Substituting (7) for $V_H \frac{\partial C_H}{\partial t}$ in the equation above we thereby eliminate C_H from the equation and obtain

$$(V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} + P(C_{u_H} - f_{u_B} C_B). \quad (12)$$

Equation (12) together with Equation (6) and Equations (8)-(11) yield a system of six partial differential equations in the six unknowns C_B , C_{u_H} , $C_{Ah-TCDD}$, $C_{Pr-TCDD}$, C_{Ah} , and C_{Pr} :

$$\begin{aligned} (V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} &= V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} + P(C_{u_H} - f_{u_B} C_B), \\ \frac{\partial C_{u_H}}{\partial t} &= \frac{P f_{u_B}}{V_H} C_B - (\frac{P}{V_H} + k_3) C_{u_H} - k_{+1} C_{u_H} C_{Ah} \\ &\quad + k_{-1} C_{Ah-TCDD} - k_{+2} C_{u_H} C_{Pr} + k_{-2} C_{Pr-TCDD}, \\ \frac{\partial C_{Ah-TCDD}}{\partial t} &= k_{+1} C_{u_H} C_{Ah} - k_{-1} C_{Ah-TCDD}, \\ \frac{\partial C_{Ah}}{\partial t} &= k_{-1} C_{Ah-TCDD} - k_{+1} C_{u_H} C_{Ah} - k_{d(Ah)} C_{Ah} + k_{s(Ah)}, \\ \frac{\partial C_{Pr-TCDD}}{\partial t} &= k_{+2} C_{u_H} C_{Pr} - k_{-2} C_{Pr-TCDD}, \\ \frac{\partial C_{Pr}}{\partial t} &= k_{-2} C_{Pr-TCDD} - k_{+2} C_{u_H} C_{Pr} - k_{d(Pr)} C_{Pr} + k_{s(Pr)} \\ &\quad + (\frac{I_{Pr}}{V_H}) \frac{C_{Ah-TCDD}(t - \tau_r, z)}{C_{Ah}(t - \tau_r, z) + C_{Ah-TCDD}(t - \tau_r, z)}. \end{aligned}$$

The first equation reflects the fact that the rate of change of TCDD in the blood and Disse space compartments is equal to the change in concentration due to dispersion and convection in the sinusoidal region plus the net rate of change of TCDD due to exchange with the surrounding tissue. This would be equivalent to a formulation of the problem by a mass balance on the blood and Disse compartments combined, where the sink/source term is taken as the passive diffusion of free TCDD across cell membranes.

4 Venous Blood Concentrations

We are primarily interested in gaining a better understanding of the uptake and elimination of TCDD in humans. Time-course data is available on serum TCDD levels in US Air Force veterans who were exposed

to the TCDD-contaminated herbicide Agent Orange during their service in Vietnam [9]. In order for us to utilize this data in future efforts, we introduce a compartment to describe the concentration of TCDD in venous blood.

Let C_{Vb} be the venous blood concentration of TCDD, Q_{Vb} the blood flow rate, and V_{Vb} the venous blood volume. Assuming a “well-mixed” compartment,

$$\frac{dC_{Vb}}{dt} = \frac{Q_{Vb}}{V_{Vb}}(C_B(t - \tau_c, l) - C_{Vb}) + I(t) - \dot{q}_3(t), \quad (13)$$

where $I(t)$ is the input rate of TCDD into the system, $\dot{q}_3(t)$ is the rate of uptake of TCDD by the adipose tissue compartment (taken as a sink), and τ_c is a circulatory time delay to account for the time lag from the exit of the liver at $z = l$ to the venous blood measurement location. The delay τ_c is on the order of seconds; in fact, the maximum time for blood elements to circulate through the body is about one minute [31]. Therefore, $\tau_c \ll \tau_r$.

5 Boundary Conditions

For the coupled venous blood-liver model, the boundary condition at the entrance to the liver is the TCDD concentration in the venous blood,

$$C_B(t, 0) = C_{Vb}(t). \quad (14)$$

Identifying the liver exit boundary condition, however, requires further discussion.

We assume, based on liver physiology, that no significant events occur which effect the concentration of solute in the liver outside the sinusoidal bed, by which we mean the region between the portal triads where blood enters the lobule at $z = 0$ and the central vein where it exits at $z = l$. This region consists of the sinusoidal blood and the surrounding Disse space and hepatocytes. We assume that the lining of the central vein is so thick as to be impermeable, and therefore that no exchange takes place between the blood in the central vein and the hepatocytes which surround it. We also assume a “closed vessel”; that is, once the blood exits the sinusoidal region at $z = l$, this blood does not reenter the sinusoid; i.e., we assume plug flow for $z > l$.

In Figure 9 we have taken a slice along the length of the “liver cylinder”. This schematic illustrates the processes which are represented in the mathematical model, where we assume plug flow in the blood stream prior to the entrance to and upon emergence from the cylinder. We define C_B^* and C_B^{**} to be the total concentration of TCDD in the entering and exiting blood stream, respectively.

Danckwerts boundary conditions [32] are often used in situations where one assumes a closed vessel. The Danckwerts exit boundary condition is

$$\frac{\partial C_B}{\partial z} = 0, \quad z = l,$$

and is based on a flux balance:

$$vC_B^{**} = vC_B - \mathcal{D}\frac{\partial C_B}{\partial z}, \quad z = l. \quad (15)$$

In his original paper [32], Danckwerts argues that for a tubular packed reactor if $\frac{\partial C_B}{\partial z} < 0$ at $z = l$ the concentration at the exit would be greater than that at the end of the vessel. This is observed by substitution

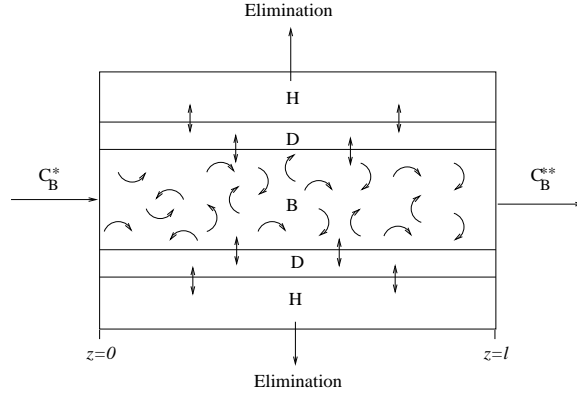


Figure 9: Schematic of the transport processes represented in the mathematical model, taken as a slice along the length of the “liver cylinder”. Arrows point in the direction of flow.

of the inequality into Equation (15). If $\frac{\partial C_B}{\partial z} > 0$, then the concentration is increasing towards the end of the vessel and therefore would have to pass through a minimum somewhere within the vessel and then increase. Danckwerts argued that intuitively neither of these cases make sense for the system governed by the equation

$$\mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - v \frac{\partial C_B}{\partial z} - k C_B = 0,$$

where k is the rate constant for the chemical reaction in the vessel. Hence, $\frac{\partial C_B}{\partial z}$ must be zero at the exit boundary.

We argue that Danckwerts’ intuitive argument for a tubular packed reactor does not apply to the more complicated model considered here; that is, as in the second scenario, we cannot preclude the possibility of a concentration-distance profile of TCDD in the blood compartment of the liver which increases toward $z = l$ due to the two way exchange between the sinusoids and hepatocytes.

For example, suppose the blood (and Disse space) concentration of free dioxin was less than the hepatocyte concentration of free dioxin in some region along the sinusoids. In this event, free dioxin in the hepatocytes would diffuse across the cell membrane and re-enter the blood supply thereby increasing the blood TCDD concentration. We argue that the possibility of such an event seems likely due to the binding of TCDD by intracellular proteins, and therefore conclude that Danckwerts’ argument *does not hold* in support of the exit boundary condition

$$\frac{\partial C_B}{\partial z} \Big|_{z=l} = 0.$$

In the physical situation, where blood is entering the central vein from sinusoids at different locations along its length, one would expect a dispersive effect in this area due to convective mixing. However, this situation does not occur in the mathematical model; the sinusoidal blood is treated as one volume, which empties into a blood compartment at $z = l$ from where it will eventually return to the general circulation. We have assumed plug flow in this region ($\mathcal{D} = 0$). Hence, we have $\lim_{z=l+} \frac{\partial C_B}{\partial z} = 0$.

We have argued that we cannot eliminate the possibility $\frac{\partial C_B}{\partial z} \Big|_{z=l} > 0$ and therefore cannot conclude, as is typically done in simpler models of this type, that $\frac{\partial C_B}{\partial z} = 0$ at $z = l$. In general, any combination of the following boundary conditions, one at $z = 0$ and one at $z = l$, will result in a well-posed initial-boundary

value problem for the hepatic dispersion model:

$$\text{BC at } z = 0 : \begin{cases} C_B(t, 0) = q_1(t) \\ \text{or} \\ vC_B(t, 0) - \mathcal{D}\frac{\partial C_B}{\partial t}(t, 0) = q_1(t) \end{cases}$$

$$\text{BC at } z = l : \begin{cases} C_B(t, l) = q_2(t) \\ \text{or} \\ vC_B(t, l) - \mathcal{D}\frac{\partial C_B}{\partial t}(t, l) = q_2(t). \end{cases}$$

For the Dirichlet boundary conditions, $q_1(t) = C_B^*(t)$ and $q_2(t) = C_B^{**}(t)$. The other boundary conditions are based on a flux balance, where $q_1(t)$ is the flux at $z = 0$ due to convective forces in the incoming stream; $q_1(t) \approx vC_B^*(t)$. Similarly, if $q_2(t)$ is the flux at $z = l$, $q_2(t) \approx vC_B^{**}(t)$.

If either q_1 or q_2 (or both) are unknown, we must be given some type of observations to be used in an inverse algorithm to estimate these (and possibly other) parameters in the initial-boundary value problem. Note that these observations do not necessarily have to be made at the boundary but can be given anywhere along the length of the cylinder.

For the model considered here, we take the flux exit boundary condition where $q_2(t)$ is treated as an unknown parameter:

$$vC_B(t, l) - \mathcal{D}\frac{\partial C_B}{\partial z}(t, l) = q_2(t). \quad (16)$$

The introduction of the new parameter q_2 yields a well-posed initial-boundary value problem but involves an unknown boundary term. We then must be given data (observations) on the solution to be used in an inverse problem to estimate q_2 as well as other unknown model parameters.

6 The Model System of Equations

The mathematical model presented thus far, including boundary conditions (14), (16), and the venous blood compartment (13), is as follows:

$$(V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} + P(C_{u_H} - f_{u_B} C_B), \quad (17a)$$

$$\begin{aligned} \frac{\partial C_{u_H}}{\partial t} &= \frac{P f_{u_B}}{V_H} C_B - \left(\frac{P}{V_H} + k_3 \right) C_{u_H} - k_{+1} C_{u_H} C_{Ah} \\ &\quad + k_{-1} C_{Ah-TCDD} - k_{+2} C_{u_H} C_{Pr} + k_{-2} C_{Pr-TCDD}, \end{aligned} \quad (17b)$$

$$\frac{\partial C_{Ah-TCDD}}{\partial t} = k_{+1} C_{u_H} C_{Ah} - k_{-1} C_{Ah-TCDD}, \quad (17c)$$

$$\frac{\partial C_{Ah}}{\partial t} = k_{-1} C_{Ah-TCDD} - k_{+1} C_{u_H} C_{Ah} - k_{d(Ah)} C_{Ah} + k_{s(Ah)}, \quad (17d)$$

$$\frac{\partial C_{Pr-TCDD}}{\partial t} = k_{+2} C_{u_H} C_{Pr} - k_{-2} C_{Pr-TCDD}, \quad (17e)$$

$$\frac{\partial C_{Pr}}{\partial t} = k_{-2} C_{Pr-TCDD} - k_{+2} C_{u_H} C_{Pr} - k_{d(Pr)} C_{Pr} + k_{s(Pr)} \quad (17f)$$

$$\begin{aligned}
& + \left(\frac{I_{Pr}}{V_H} \right) \frac{C_{Ah-TCDD}(t - \tau_r, z)}{C_{Ah}(t - \tau_r, z) + C_{Ah-TCDD}(t - \tau_r, z)}, \\
\frac{dC_{Vb}}{dt}(t) & = \frac{Q_{Vb}}{V_{Vb}}(C_B(t - \tau_c, l) - C_{Vb}(t)) + I(t) - q_3(t), \tag{17g}
\end{aligned}$$

$$\begin{aligned}
C_B(t, 0) & = C_{Vb}(t), \\
vC_B(t, l) - \mathcal{D} \frac{\partial C_B}{\partial z}(t, l) & = q_2(t). \tag{17h}
\end{aligned}$$

The product nonlinearities in (17) require further discussion. For $x, y \in \mathcal{R}$, we define \tilde{g}_{Ah} and \tilde{g}_{Pr} by

$$\tilde{g}_{Ah}(x, y) = k_{+1}xy, \tag{18}$$

$$\tilde{g}_{Pr}(x, y) = k_{+2}xy. \tag{19}$$

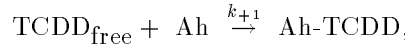
Both \tilde{g}_{Ah} and \tilde{g}_{Pr} are nonlinear continuous mappings from $\mathcal{R} \times \mathcal{R}$ into \mathcal{R} , but they are unbounded; that is, for any $N > 0$ there exist $x, y \in \mathcal{R}$ such that

$$|\tilde{g}_{Ah}(x, y)| > N, \quad |\tilde{g}_{Pr}(x, y)| > N.$$

The nonlinear terms (18) and (19) resulted from the *law of mass action* applied to the kinetic mechanisms proposed for TCDD-binding with intracellular proteins (see the discussion in Section 3.3). Specifically,

$$\tilde{g}_{Ah}(C_{u_H}(t, z), C_{Ah}(t, z)) = k_{+1}C_{u_H}(t, z)C_{Ah}(t, z)$$

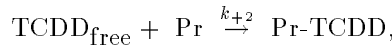
represents the rate of formation of the Ah-TCDD complex by the forward reaction



and

$$\tilde{g}_{Pr}(C_{u_H}(t, z), C_{Pr}(t, z)) = k_{+2}C_{u_H}(t, z)C_{Pr}(t, z)$$

represents the rate of formation of the CYP1A2-TCDD complex by the forward reaction



where C_{u_H} , C_{Ah} , and C_{Pr} represent the cellular volume concentrations of unbound TCDD, Ah receptor (Ah), and CYP1A2 (Pr), respectively.

For reversible bimolecular reactions (or interactions) of the form



the reaction rate will saturate with respect to one of the reactants [33]; that is, when the concentration of one of the reactants is high relative to the other, the reaction will exhibit zero order behavior [34] or constant rate of reaction. When saturable kinetics are operable, further increasing the concentration of the “excess” reactant will not result in an increased reaction rate, assuming all other conditions, such as temperature, remain fixed. Zero order behavior is common in biological systems [34] where, in general, the ligand is present in sufficiently high concentrations relative to the receptor or protein, as typically occurs in most enzyme-mediated reactions [33]. Thus, these types of reactions (20) are rate-limited *in vivo* due to saturation of the binding protein.

We therefore assume that within a certain range of concentrations the system behaves according to the nonlinearities prescribed by (18) and (19) but eventually saturates; i.e., the rates of formation of Ah-TCDD complex and CYP1A2-TCDD complex are limited, or bounded, due to the availability of binding species. In mathematical terms, this allows us to redefine the product nonlinearities in the mathematical model so as to be uniformly bounded in \mathcal{R} ; thus, we define $g_{Ah}, g_{Pr} : \mathcal{R} \times \mathcal{R} \rightarrow \mathcal{R}$ by

$$g_{Ah}(x, y) \equiv \begin{cases} \tilde{g}_{Ah}(x, y), & |x|, |y| \leq K_1, \\ M_1, & \text{otherwise,} \end{cases} \quad (21)$$

$$g_{Pr}(x, y) \equiv \begin{cases} \tilde{g}_{Pr}(x, y), & |x|, |y| \leq K_2, \\ M_2, & \text{otherwise,} \end{cases} \quad (22)$$

where the constants $K_1, M_1, K_2, M_2 > 0$ are *physiologically* determined.

Replacing the product nonlinearities in (17) with g_{Ah} and g_{Pr} as defined in (21) and (22), the mathematical model we consider is given by

$$(V_B + V_D \frac{f_{u_B}}{f_{u_D}}) \frac{\partial C_B}{\partial t} = V_B \mathcal{D} \frac{\partial^2 C_B}{\partial z^2} - V_B v \frac{\partial C_B}{\partial z} + P(C_{u_H} - f_{u_B} C_B), \quad (23a)$$

$$\begin{aligned} \frac{\partial C_{u_H}}{\partial t} &= \frac{P f_{u_B}}{V_H} C_B - \left(\frac{P}{V_H} + k_3 \right) C_{u_H} - g_{Ah}(C_{u_H}, C_{Ah}) \\ &\quad + k_{-1} C_{Ah-TCDD} - g_{Pr}(C_{u_H}, C_{Pr}) + k_{-2} C_{Pr-TCDD}, \end{aligned} \quad (23b)$$

$$\frac{\partial C_{Ah-TCDD}}{\partial t} = g_{Ah}(C_{u_H}, C_{Ah}) - k_{-1} C_{Ah-TCDD}, \quad (23c)$$

$$\frac{\partial C_{Ah}}{\partial t} = k_{-1} C_{Ah-TCDD} - g_{Ah}(C_{u_H}, C_{Ah}) - k_{d(Ah)} C_{Ah} + k_{s(Ah)}, \quad (23d)$$

$$\frac{\partial C_{Pr-TCDD}}{\partial t} = g_{Pr}(C_{u_H}, C_{Pr}) - k_{-2} C_{Pr-TCDD}, \quad (23e)$$

$$\begin{aligned} \frac{\partial C_{Pr}}{\partial t} &= k_{-2} C_{Pr-TCDD} - g_{Pr}(C_{u_H}, C_{Pr}) - k_{d(Pr)} C_{Pr} + k_{s(Pr)} \\ &\quad + \left(\frac{I_{Pr}}{V_H} \right) \frac{C_{Ah-TCDD}(t - \tau_r, z)}{C_{Ah}(t - \tau_r, z) + C_{Ah-TCDD}(t - \tau_r, z)}, \end{aligned} \quad (23f)$$

$$\frac{dC_{Vb}}{dt}(t) = \frac{Q_{Vb}}{V_{Vb}} (C_B(t - \tau_c, l) - C_{Vb}(t)) + I(t) - q_3(t), \quad (23g)$$

$$\begin{aligned} C_B(t, 0) &= C_{Vb}(t), \\ v C_B(t, l) - \mathcal{D} \frac{\partial C_B}{\partial z}(t, l) &= q_2(t). \end{aligned} \quad (23h)$$

The system (23) is a nonlinear system of partial differential equations with delay and questions of well-posedness are of interest. A detailed general theory of existence, uniqueness, and continuous dependence for systems which include the model above has been given in [35]. The results, obtained in the context of weak or variational forms, use ideas from the work of Banks *et al.* [36] for nonlinear hyperbolic systems.

7 Concluding Remarks

We have presented a model to describe the hepatic uptake and elimination of TCDD which includes the kinetics of TCDD-binding to the Ah receptor protein, induction of CYP1A2, and TCDD-binding to CYP1A2. The induction of CYP1A2 is based upon the fractional occupancy of the Ah receptor at a previous time to allow for the many intracellular processes which must occur before this Ah-receptor mediated activity is realized. Transport of solute in the blood region is described by a convection-dispersion equation to account for transport via bulk flow and turbulent diffusion. Uptake of TCDD by the hepatic tissue is due to diffusion of the solute across the cell membrane, with unbound TCDD the diffusing species. Metabolism of TCDD, which is considered to be a detoxifying step, is modeled as a first-order process. The resulting mathematical model is a nonlinear system of six partial differential equations with time delay.

In order to utilize available time data on human serum TCDD levels we introduced a “well-mixed” venous blood compartment. The model includes a sink term to describe the rate of TCDD uptake by adipose tissue, a primary storage site for TCDD in the body.

We have formulated boundary conditions which are consistent with the assumptions of the mathematical model and yield a well-posed initial-boundary value problem. The exit boundary condition contains an unknown boundary term. Hence, we must be given some observations of the system to be used in an inverse algorithm to estimate this and possibly other unknown parameters.

Current efforts involve the development of numerical methods for the system (17) to be used in model validation, simulation, and parameter estimation.

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A Notation

Let l denote a unit of length, m a unit of mass, and t a unit of time.

ABBR.	DESCRIPTION	UNITS
$V_B(z)$	volume of blood element of thickness dz	l^3
V_B	liver blood volume	l^3
V_D	Disse space volume	l^3
V_H	hepatocyte volume	l^3
A	cross-sectional area of blood component element	l^2
Q	blood volumetric flow rate in liver	l^3/t
v	average fluid flow velocity ($= Q/A$)	l/t
C_B	total concentration of TCDD in blood	m/l^3
C_{uB}	concentration of unbound TCDD in plasma	m/l^3
C_D	total concentration of TCDD in space of Disse	m/l^3
C_{uH}	concentration of unbound TCDD in hepatocytes	m/l^3
C_H	total concentration of TCDD in hepatocytes	m/l^3
C_{Ah}	total concentration of Ah receptor protein in hepatocytes	m/l^3
C_{Pr}	total concentration of CYP1A2 in hepatocytes	m/l^3
$C_{Ah-TCDD}$	concentration of Ah receptor-TCDD complex in hepatocytes	m/l^3
$C_{Pr-TCDD}$	concentration of CYP1A2-TCDD complex in hepatocytes	m/l^3
C_B^*	concentration of TCDD in entering blood stream ($z = 0$)	m/l^3
C_B^{**}	concentration of TCDD in effluent blood stream ($z = l$)	m/l^3
f_{uB}	fraction of TCDD unbound in the blood	
f_{uH}	fraction of TCDD unbound in the hepatocytes	
f_{uD}	fraction of TCDD unbound in space of Disse	
P	permeability coefficient of the hepatocyte to TCDD within the element	l^3/t
D	effective axial dispersion coefficient	l^2/t
$k_d(Ah)$	rate constant for thermal inactivation of Ah receptor protein	$/t$
$k_d(Pr)$	rate constant for degradation of CYP1A2	$/t$
k_{+1}	association rate constant of TCDD and Ah receptor	$l^3/(mt)$
k_{-1}	dissociation rate constant of Ah receptor-TCDD complex	$/t$
k_{+2}	association rate constant of TCDD and CYP1A2	$l^3/(mt)$
k_{-2}	dissociation rate constant of CYP1A2-TCDD complex	$/t$
k_3	apparent first-order metabolic clearance rate of TCDD	$/t$
$k_s(Ah)$	rate constant for synthesis of Ah receptor protein	$m/(l^3t)$
$k_s(Pr)$	rate constant for basal synthesis of CYP1A2	$m/(l^3t)$
I_{Pr}	rate constant for induction of CYP1A2 in presence of TCDD	m/t
τ_r	lag time between TCDD binding to Ah receptor and response	t
C_{Vb}	concentration of TCDD in venous blood	m/l^3
Q_{Vb}	venous blood volumetric flow rate	l^3/t
V_{Vb}	venous blood volume	l^3
$\dot{q}_3(t)$	rate of uptake of TCDD by adipose tissue	$m/(l^3t)$
$I(t)$	input concentration of TCDD in venous blood at time t	m/l^3
τ_c	lag time for circulation of venous blood	t

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