UTILIZATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL (PBPK) TO STUDY THE INFLUENCE OF BODY FAT MASS AND INDUCTION OF CYP1A2 ON THE PHARMACOKINETICS OF TCDD

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Introduction

2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD) is a ubiquitous environmental contaminant that induces a wide spectrum of toxic responses. In order to better characterize the potential adverse health effects of TCDD, an understanding of the pharmacokinetics of TCDD is important. Pharmacokinetics encompasses information on the absorption, distribution, metabolism and elimination (ADME) of a chemical in biological systems. Variations in physiological parameters such as age, obesity, disease or genetic polymorphisms can influence the distribution and elimination of xenobiotics[1,2]. Diliberto et al. found that CYP1A2 (-/-) knockout mice metabolize and eliminate TCDD slower than the C57BL/6N parental strains[3,4]. Studies in humans suggest that body fat composition plays an important role in the elimination of TCDD. However, no study has examined the interaction between these two parameters on the pharmacokinetics of TCDD. The objective of this work was to utilize a physiologically based pharmacokinetic model to characterize the influence of CYP1A2 induction and body fat mass on the half-life of elimination of TCDD.

Methods and Materials

A PBPK model has been developed to describe the ADME for TCDD in the rat (Figure 1). This PBPK model represents three compartments, liver, fat and rest of the body. Each compartment was described by a diffusion-limited distribution. These compartments are connected through systemic circulation. Parameters used for this description (i.e. tissue volume, cardiac output, organ blood, partition coefficient diffusion constant, or elimination constant) came from the literature [5]. This model is a reduced version of a PBPK model described by Wang et al and provides similar fits to data use to validate the Wang et al model[5]. In the present analysis, a comparison between body fat mass and elimination half-life was examined. Simulations using the PBPK model were done using a single oral dose of 10 μg TCDD/kg body weight, by gavage, administered at T=0. For each simulation, the fat fraction of body weight was varied from 0.069 to 0.7%. The elimination half-life of TCDD was determined in each of these simulations. In addition, these simulations were performed in the model with the CYP1A2 induction process either turned on or turned off. This analysis allows the examination of the influence of body fat mass alone on the elimination of TCDD in the presence or absence of CYP1A2 induction.

Results and Discussion

Figure 2 presents the influence of body fat mass on the elimination of TCDD in the presence of and absence of hepatic CYP1A2. As body fat mass increases, there is an increase in the half-life of TCDD. In the presence of CYP1A2 induction, body fat has less of an influence on the half-life of TCDD and the relationship between body fat mass and half-life is non-linear. When there is no induction of CYP1A2, the model predicts that the half-life of TCDD would increase linearly with increases in body fat mass. These observations could be explained in part by the fact that increasing body fat mass increases the storage volume for this highly lipophilic chemical. The influence of body fat mass on the half-life of TCDD plateaus at body fat mass of 45% or greater when CYP1A2 is inducible. There is no plateau effect observed in the absence of CYP1A2 induction.

This study provides further evidence that body fat composition and hepatic CYP1A2 induction are important parameters in the pharmacokinetics of TCDD. In addition, the model suggests that the fat fraction compartment could be in competition with CYP1A2 sequestration mechanism. When CYP1A2 concentrations are low, changes in body fat mass can have a large impact on the half-life of TCDD. However, when CYP1A2 is highly induced, body fat mass changes have little effect on the elimination of TCDD. In young adult rats, body fat mass is approximately 7% of body weight. Based on this PBPK model, when CYP1A2 is highly induced in young adult rats, increasing body fat mass would have almost no effect on the half-life.

There are several implications of this work for humans. In humans, average body fat mass is estimated at approximately 25% and is much higher in obese populations. In highly exposed populations, body fat mass would have little effect on the elimination of TCDD. However, in populations with no known high level of TCDD or dioxin exposure, body fat would have a large effect on the elimination of TCDD. Given the increasing proportion of medically obese patients in the US and other developed nations, the half-life of TCDD may be underestimated in these populations. Future studies examining the influence of body fat composition on TCDD elimination would allow for a better understanding of the pharmacokinetics of TCDD in background human populations.

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Figure 1: Conceptual representation of PBPK to simulate TCDD distribution model for rat

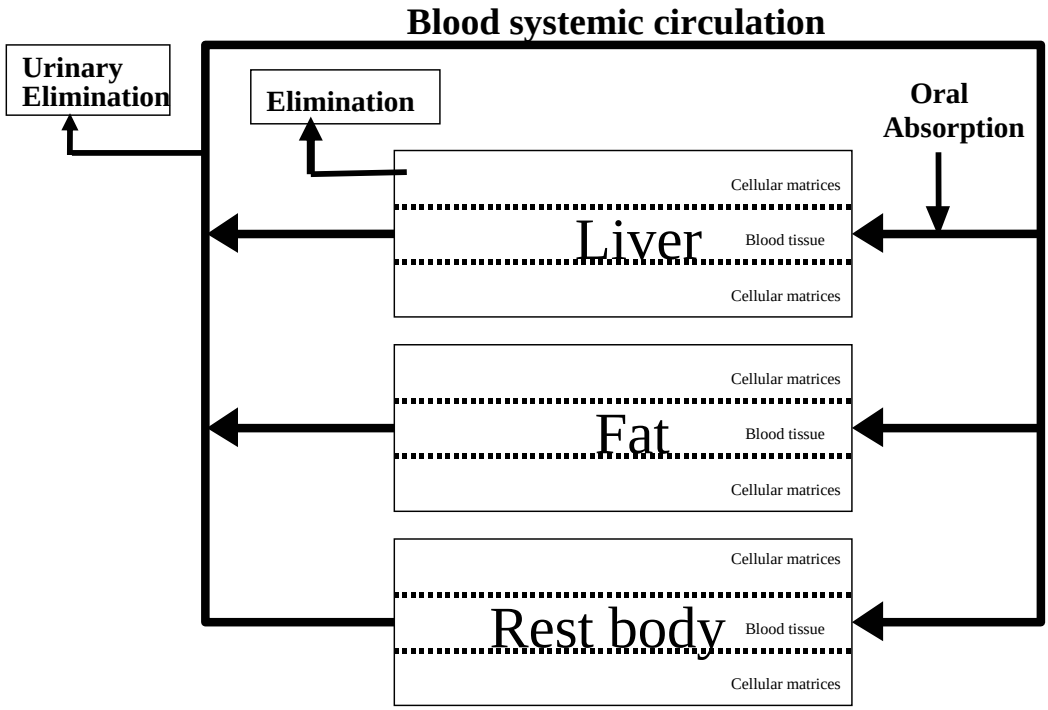

Figure 2: Relation between influence of fat fraction compartments with half life of elimination