APPLICATION OF A PHYSIOLOGOCIALLY BASED PHARMACOKINETIC (PBPK) MODEL TO AID IN UNDERSTANDING RELATIVE POTENCY FACTORS FOR DIOXIN-LIKE CHEMICALS

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Introduction

The TEF methodology is used to assess the potential adverse health effects following exposure to mixtures of dioxin-like chemicals. TEFs values are assigned to dioxin-like chemicals by an expert panel examining all the available data on the relative potency for a particular chemical compared to TCDD or PCB 126. The relative potency data comes from the peer-reviewed published literature. The WHO convened the last panel and the results from this panel have been published[1]. One of the difficulties in assessing these chemicals is that there is a large range in the relative potencies for some chemicals. For example, the range in relative potencies for the mono-ortho PCBs is 3-5 orders of magnitude. There are several possible reasons for this broad range of relative potencies. The studies included in the WHO database come from different laboratories that are examining different endpoints and species often using different exposure paradigms. Because of the small sample size (i.e., small number of studies examining the relative potency of a particular congener) it is difficult to quantitatively discern how much each of these factors accounts for the variability in the relative potency factors (RPFs).

The present study uses a PBPK model in an attempt to determine how study design could impact estimates of the relative potency for a particular congener. PBPK models are mathematical descriptions of the physiochemical, biochemical and physiological processes involved in the absorption, distribution, metabolism and elimination of a chemical. The PBPK models for TCDD describe both the pharmacokinetic properties as well as induction of CYP1A2. The mathematical description of CYP1A2 induction incorporates information on the Ah receptor affinity. By altering the affinity to the Ah receptor in the model we can predict the response of less potent ligands. In addition, we can also vary the elimination rate and predict the dose-response relationship for ligands with more rapid elimination compared to TCDD. We simulated responses of prototype ligands with different Ah receptor binding affinities and different elimination rates using the PBPK model. The results from these simulations were used to estimate the relative potency of these different prototype ligands under different exposure scenarios. These data demonstrate that for ligands with different elimination rates than TCDD, study designs can result in a range of RPFs of up to 2 orders of magnitude.

Methods

A PBPK model has been developed to describe the pharmacokinetics of TCDD in the rat. This model contained 3 compartments including liver, fat and rest of the body. These 3 compartments were linked together by the systemic circulation. The liver compartment describes Ah receptor binding, CYP1A2 induction and ligand binding to CYP1A2. This model is a reduced version of

the Wang et al[2] model and provides good fits to the experimental pharmacokinetic data for TCDD in rats. The parameters used in the model were initially optimized to fit the TCDD experimental pharmacokinetic data in rats.

Simulations of the model were run under acute and subchronic exposure conditions. In the acute simulations, the model was run for up to 14 days post exposure. In the subchronic simulations, the model was run for 90 days of daily exposure and responses were estimated at 3 days after the last exposure. In these simulations, the affinity to the AhR was varied from 10^{-1} nmol/ml to 10^{-4} nmol/ml. In addition we increased the elimination rate (Kel) by 10 and 20 fold compared to parameters optimized to the TCDD data. Simulations were run at dose levels ranging from 0.0001 to 10,000 ug/kg of chemical.

The induction of hepatic CYP1A2 was also simulated. RPF values were estimated by using the optimized model parameters that best fit the TCDD data as the standard. The ED50's were estimated for each simulation and the RPF was calculated by dividing the ED50 of the simulation by the ED50 of the TCDD standard simulation.

Results

When only the binding affinity to the Ah receptor is varied, the study design does not alter the estimate of the RPF with one exception (Table 1). When the binding affinity to the Ah receptor was decreased by 3 orders of magnitude, the study design slightly impacted the estimated RPF, with estimates ranging from 0.00075 to 0.001. It should be noted that the change in the RPF was proportional to the change in the binding affinity to the Ah receptor. For example, decreasing the binding affinity by an order of magnitude resulted in an order of magnitude decrease in the RPF.

Experimental design had a significant impact on the estimate of the RPF when the elimination rate was increased by 10- or 20-fold (Table 2). In the acute exposure simulations, the RPF is highest at the earlier time points and decreases as the simulation time is lengthened. For example, if the elimination rate is increased by a factor of 10, the RPF at 1 day is 0.4 and decreases to 0.005 at 14 days post exposure. When the elimination rate is increased by a factor of 20, the estimates of the RPF vary over 250 fold, from 0.17 to 0.00067. Estimates of the RPF in simulations of subchronic exposures are similar to the estimated RPFs in the acute exposures at the 7-day time point.

When both the elimination rate and the AhR binding affinity are changed, study design has a slightly greater influence on the estimate of the RPF. When the binding affinity to the AhR is changed by two orders of magnitude, study design has no effect on the RPF (Table 1). When the elimination rate is increased by 10-fold, the RPF decreases by 13-fold, comparing day 1 and day 7 in the acute simulations. When the binding affinity is changed by a two orders of magnitude and the elimination rate is increased 10-fold, the estimate of the RPF decreases 21-fold when comparing the day 1 and day 7 acute exposure simulations.

Discussion

The range of RPF values from the literature for some dioxin-like chemicals is over 3 orders of magnitude. Understanding the reasons for this large range will provide a better understanding of the uncertainties in the TEF methodology. There are a number of possibilities that may explain the large range in the RPFs. We have employed a PBPK model to provide insight into the

influence of study design on the estimates of the RPF. This exercise suggests that the if the only difference between the test chemical and TCDD is the binding affinity to the Ah receptor, then study design will not influence the estimate of the RPF. However, study design has a significant impact on chemicals that have elimination rates different from TCDD. The model estimates that for chemicals with elimination rates 20 times greater than TCDD, the RPFs can vary over 2 orders of magnitude depending on the study design. Thus, one reason for the large range in RPF values in the literature may be attributed to study design. However, for some chemicals the range in RPF values is greater than three orders of magnitude, demonstrating that other factors also contribute to this variability.

The present study also demonstrates the utility of PBPK models when applied to the TEF methodology. In this exercise we changed the AhR binding affinity and the elimination rate parameters in the model to mimic chemicals that do not bind as well or are eliminated faster than TCDD. It would also be possible to use measured values of AhR binding affinity and elimination rates and use the model to compare to experimentally derived RPF values. In addition, if sufficient data on binding to human AhR and human pharmacokinetics were available for a particular congener, it would be possible to use these models to estimate human TEF values. However, further validation of these models is required prior to such an exercise.

References

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Acknowledgments
This project was funded by in part by a cooperative agreement (CR 828790) with NRC, NAS and performed at US EPA RTP, NC, USA. (This abstract does not represent US EPA policy)

Table 1: Potency factors calculated in acute and subchronic exposure at different time points. RPFs were calculated by the ratio of ED_{50}s from simulations in which the AhR affinity constant was varied from 10^{-3} to 10^{-1} nmol/ml. For TCDD the affinity constant is 10^{-4} nmol/ml.

Day	Ahr-Kd =10^{-3}	Ahr-Kd =10^{-2}	AhR-Kd =10^{-1}
Acute (day)	Potency factor		
1	0.1	0.01	0.001
3	0.1	0.01	0.001
7	0.1	0.01	0.0009
14	0.1	0.01	0.00075
Subchronic 90days	Potency factor		
3 days post exposure	0.1	0.01	0.00085

1- AhR-Kd : Ah receptor affinity constant (nmol/ml)

Table 2: Potency factors calculated in acute and subchronic exposure at different time points. RPFs were calculated by the ratio of ED_{50}s from simulations in which the elimination rate was increased either 10 or 20 fold.

Day	Kel 10X	Kel 20X	Kel 10X and Ahr-Kd =10^{-2}
Acute (day)	Potency factor		
1	0.4	0.17	0.001
3	0.14	0.03	0.0002
7	0.03	0.006	0.000047
14	0.005	0.00067	-
Subchronic 90days	Potency factor		
3 days post exposure	0.03	0.001	0.000056

2- Kel : elimination constant (h-1)

3- AhR-Kd : Ah receptor affinity constant (nmol/ml)