# Use of a PBPK model with dose-dependent elimination rates predicts higher peak dioxin exposures than previously estimated

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**Introduction :**

Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is associated with increased risk for cancer, diabetes and reproductive toxicities in numerous epidemiological studies [(1)]. Several of these studies base exposure estimates on measurements of blood levels years after the accidental or occupational exposures. Peak exposures have been estimated in these studies assuming a mono or biphasic elimination rate for TCDD, with estimates of half-life ranging from 5 to 12 years. Recent clinical studies suggest that the elimination rate of TCDD is dose dependent. To address this question a physiologically based pharmacokinetic (PBPK) model can be used to predict the concentration of TCDD with a dose-dependent elimination rate. The aims of this study were to validate a dose-dependent elimination rate by using a PBPK model and to adequately predict the concentration of TCDD shortly after the exposure.

**Methods:**

A physiologically-based pharmacokinetic (PBPK) model was developed which describes the pharmacokinetics of TCDD in rodents and humans [(2)]. This approach is a mathematical description of the physiological, biochemical, and physico-chemical processes involved in the pharmacokinetics of TCDD. This model, originally validated in rodents, includes a mathematical description of the Ah receptor mediated induction of CYP1A2. Experimental evidence suggests that CYP1A2 is responsible for the metabolism and hepatic sequestration of TCDD [(3)]. In the model, the elimination rate of TCDD is dose dependent and is a function of CYP1A2 induction. Thus, at low exposures, there is minimal induction and the elimination of TCDD is very slow. However, at higher exposures, induction approaches a maximum and the elimination rate is much faster. Human physiological and biochemical parameters were incorporated into the rodent PBPK model for species extrapolation. Alls parameters in rodent and human came from the literature [(6)].

The initial evaluation of the human PBPK model used two data sets. The first data set comes from studies of United States Air Force Veterans from Operation Ranch Hand. Veterans involved in Operation Ranch Hand were responsible for the aerial spraying of Agent Orange and other herbicides contaminated with TCDD during the Vietnam War from 1961 to 1971. A subpopulation of 343 Ranch Hand veterans were randomly selected and TCDD concentrations were determined in blood samples collected every 5 years from 1982 to 1998 [(4)]. Optimization of the PBPK model used 20 randomly selected subjects. The validation of the model used an additional 10 randomly selected subjects from this cohort and showed a good correlation ($r^2$ =0.995) between predicted blood concentrations in 1982 and measured blood concentrations in 1982 (Table 1). The model was also validated with a second data set.

In the fall of 1997, two women presented clinical signs of TCDD intoxication [(5)]. Following presentation of chloracne, between the spring of 1998 through 2001, 25 and 20 blood samples were collected from patients 1 and 2, respectively. These women have the highest TCDD blood concentrations ever measured in adults.

**Results:**

In the veterans of Operation Ranch Hand, TCDD blood concentrations were first determined starting in 1982. The exposure occurred between 1961 and 1971, with a typical tour of duty lasting only a year. Peak blood concentrations were assumed to occur at the time of discharge from Vietnam. Estimates of peak blood concentrations were performed with the PBPK model and a classical one compartment pharmacokinetic model with a first order elimination using a half-life of 8.7 years (Table 1). In 1982, the range of blood concentrations from 10 randomly chosen subjects, shown in Table 1, was approximately 16 fold, from 12.7 to 209 ppt. Using the classical pharmacokinetic approach, peak blood concentrations range approximately 12 fold, from 53 to 640 ppt. Minor differences in the ranking and range of TCDD blood concentrations occur when comparing estimated peak concentrations using the one compartment pharmacokinetic model to blood concentrations measured in 1982. However, when using the PBPK model to estimate peak blood concentrations, a much larger range in exposures and a significant difference in the exposure rankings occur (Table 1). The PBPK model estimates that peak blood concentrations range over 250 fold, from 138 to approximately 40,000 ppt. This large difference is due to the inclusion of a dose dependent elimination rate in the PBPK model. At the lower exposures, the half-life of TCDD is over 10 years and at the higher exposures the half-life is only weeks.

The model predictions show good correlations with the measured blood concentrations in the two highly exposed women (Figure 1). The model predicts a rapid decrease in the blood concentrations during the distribution phase of the first few months of exposure, followed by an elimination that appears first order at these exposures, due to maximal induction of TCDD sequestration. The elimination rates in these women suggest that the overall half-life of TCDD during the first two years of exposure is less than three months. In the first blood samples collected from these women, the concentrations of TCDD were 144,000 and 26,000 ppt (lipid adjusted) in patient 1 and 2, respectively [(5)]. The PPBK model estimates that initial blood concentrations may have been as high as 507,000 ppt and 87,000 ppt (lipid adjusted) in patients 1 and 2, respectively.

## Discussion and conclusion

Studies on the elimination of TCDD have examined cohorts years after the exposures and suggest that the half-life approaches a decade. However, these studies did not examine the initial elimination of TCDD immediately following high level exposures. Recent studies which measured TCDD blood concentrations shortly after high level exposure indicate that the half-life is dose dependent [(5)]. The use of first order elimination of TCDD could significantly underestimate past exposures, resulting in exposure misclassifications in the epidemiological studies. Using a PBPK model that incorporates a dose-dependent elimination rate may provide a more accurate assessment of past exposures in the epidemiological studies. Further validation of such models is required prior to use in a quantitative exposure assessment.

Table 1: Comparison of initial blood concentration determination by first order elimination or by PBPK model in 10 Ranch Hand Veterans[1]

| Groups | $C_{blood}$ 1982 | $C_{blood}$ Sim. 1982 | C(0) TD | C(0) TD Sim. |
|---|---|---|---|---|
| Low | 12.7 | 13.7 | 53 | 138 |
| | 16.7 | 20.1 | 44 | 166 |
| | 23.5 | 26.9 | 72 | 277 |
| | 24.6 | 29.5 | 112 | 587 |
| | 25.0 | 19.4 | 83 | 168 |
| High | 33.7 | 37.8 | 103 | 492 |
| | 43.8 | 25.5 | 123 | 197 |
| | 115.5 | 132.3 | 381 | 6622 |
| | 182.3 | 198.3 | 602 | 40376 |
| | 209.7 | 234.6 | 640 | 35412 |

$C_{blood}$ 1982 :$C_{blood}$ in 1982 measured [ pg/g lipid adjusted]

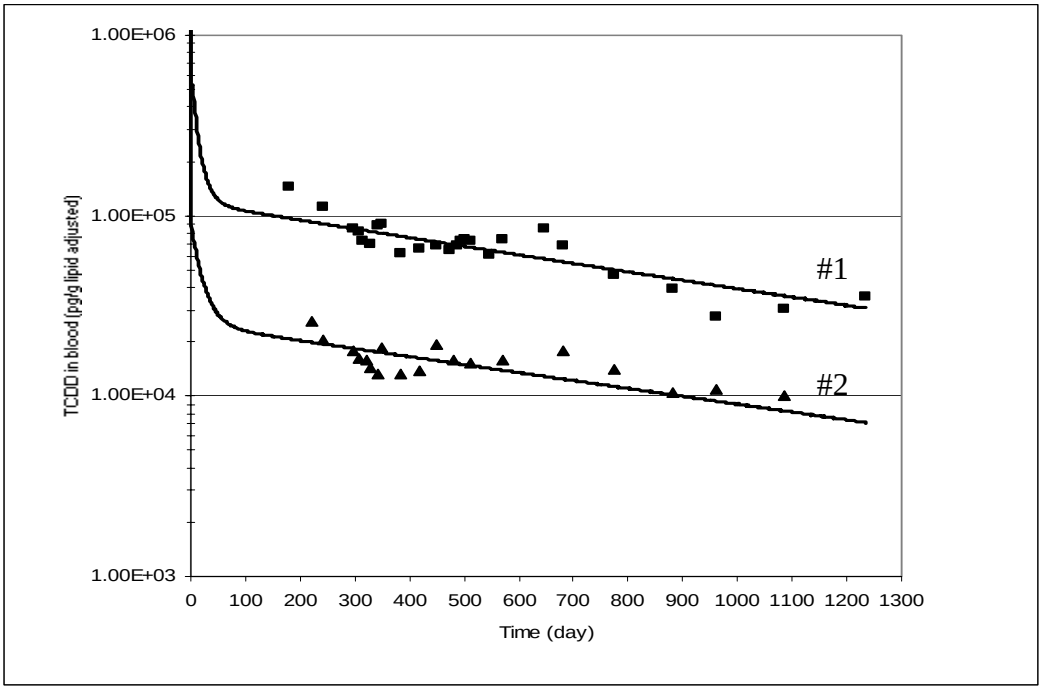
$C_{blood}$ Sim. 1982 : $C_{blood}$ in 1982 Predicted with PBPK model [ pg/g lipid adjusted]

C(0) TD : $C_{blood}$ at the time discharge from Vietnam estimated by using constant T½ to 8.7 years [pg/g lipid adjusted]

C(0) TD Sim.: $C_{blood}$ at the time discharge from Vietnam estimated by using a PBPK model [pg/g lipid adjusted]

[1]The model provides a good prediction of the measured blood concentrations in 1982 with a coefficient of determination of $R^2$ =0.995.

Figure1: Time course of TCDD in blood [pg/g lipid] for patients #1 and #2

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