Our assessment of the human PBPK model used an additional 10 randomly selected subjects from the Ranch Hand cohort and showed a good correlation ($r^2 = 0.995$) between predicted blood concentrations in 1982 and measured blood concentrations in 1982 (Table 1). We also assessed the human PBPK model with a second data set. In the fall of 1997, two women presented clinical signs of TCDD intoxication (Geusau et al. 2002). After presentation of chloracne, between the spring of 1998 through 2001, 25 and 20 blood samples were collected from patients 1 and 2, respectively (Geusau et al. 2002). These women are among those with 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 (Michalek et al. 1996, 2002). The exposure occurred between 1962 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. We documented the time of discharge for each veteran in the Ranch Hand cohort, and used these individual data in the back calculation for this study. TCDD blood concentrations were determined at four or five

---

Address correspondence to M. DeVito, Pharmacokinetic Branch, MD B143-01, Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA. Telephone: (919) 541-0061. Fax: (919) 541-4284. E-mail: devito.mike@epa.gov

*Current address: Department of Environmental and Occupational Health, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada. This project was funded in part by a cooperative agreement MIPR FQ7624-00-YA085 with the U.S. Air Force and cooperative agreement CR 828790 with the National Research Council, National Academy of Sciences, and performed at the U.S. Environmental Protection Agency (Research Triangle Park, NC, USA).

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Approval does not signify that the content necessarily reflects the view and policies of the agency, nor does mention of the trade names or commercial products constitute endorsement or recommendation for use.

The authors declare they have no competing financial interests.

Received 15 February 2005; accepted 25 August 2005.
time points for each Veteran starting in 1982. For each TCDD measurement we used data on body weight and height for each individual to estimate the body mass index for each veteran. We used the body mass index to estimate size of the adipose tissue compartment at the time of TCDD measurement for each individual based on the approach of Deurenberg et al. (1991). We estimated peak TCDD blood concentrations for each individual with the PBPK model using their individual data on blood concentrations, adipose tissue mass, and the time of discharge from Vietnam. We also estimated peak blood concentrations using a classical one compartment pharmacokinetic model with a first-order elimination. The classical model assumed a TCDD half-life of 8.7 years and used the TCDD blood concentrations at 1982 (Michalek et al. 1996) and the time of discharge as inputs into the model to estimate peak blood concentrations.

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. We used a classical pharmacokinetic approach; peak blood concentrations ranged approximately 12-fold, from 53 to 640 ppt (Table 1). Minor differences in the ranking and range of TCDD blood concentrations occur when comparing estimated peak concentrations using the one compartment classical pharmacokinetic model to blood concentrations measured in 1982. When using the PBPK model to estimate peak blood concentrations, we found a much larger range in exposures and a significant difference in the exposure rankings (Table 1). The PBPK model estimates that peak blood concentrations at the time of discharge range > 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 > 10 years, and at the higher exposures the half-life is only weeks. Models fits to these data are presented in Figure 1.

The model predictions show good correlations with the measured blood concentrations in the two highly exposed women (Figure 2). 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 because of maximal induction of TCDD sequestration metabolism. The elimination rates in these women suggest that the overall half-life of TCDD during the first 2 years of exposure is < 3 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 (Geusau et al. 2002). The PBPK 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. Based on this model, maximum CYP1A2 induction occurs at blood concentrations of approximately 1,250 ppt (lipid adjusted). Measured levels of TCDD in the women were approximately 20–100 folds higher than the blood concentrations that are predicted to be at maximal induction (Geusau et al. 2002).

### Discussion

Studies on the elimination of TCDD have examined cohorts many years after the exposures and suggest that the half-life approaches

Table 1. Comparison of initial blood concentration \(C_{\text{blood}}\) determination by first-order elimination or by PBPK model in 10 Ranch Hand veterans.

<table>
<thead>
<tr>
<th>Group</th>
<th>Measured (pg/g lipid adjusted)</th>
<th>Predicted with PBPK model (pg/g lipid adjusted)</th>
<th>Estimated with constant (T_1/2) of 8.7 years (pg/g lipid adjusted)</th>
<th>Estimated with a PBPK model (pg/g lipid adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.7</td>
<td>13.7</td>
<td>14.2</td>
<td>14.2</td>
<td>14.3</td>
</tr>
<tr>
<td>16.7</td>
<td>20.1</td>
<td>20.8</td>
<td>20.8</td>
<td>21.1</td>
</tr>
<tr>
<td>23.5</td>
<td>26.9</td>
<td>27.6</td>
<td>27.6</td>
<td>28.3</td>
</tr>
<tr>
<td>24.6</td>
<td>29.5</td>
<td>30.2</td>
<td>30.2</td>
<td>31.0</td>
</tr>
<tr>
<td>25.0</td>
<td>19.4</td>
<td>20.1</td>
<td>20.1</td>
<td>20.9</td>
</tr>
<tr>
<td>33.7</td>
<td>37.8</td>
<td>38.5</td>
<td>38.5</td>
<td>39.3</td>
</tr>
<tr>
<td>43.8</td>
<td>25.5</td>
<td>26.2</td>
<td>26.2</td>
<td>27.0</td>
</tr>
<tr>
<td>115.5</td>
<td>132.3</td>
<td>134.0</td>
<td>134.0</td>
<td>135.8</td>
</tr>
<tr>
<td>182.3</td>
<td>198.3</td>
<td>200.0</td>
<td>200.0</td>
<td>202.0</td>
</tr>
<tr>
<td>209.7</td>
<td>234.6</td>
<td>237.3</td>
<td>237.3</td>
<td>239.3</td>
</tr>
</tbody>
</table>

\(T_1/2\), half-life of TCDD in the blood.

*The model provides a good prediction of the measured blood concentrations in 1982 with a coefficient of determination of \(R^2 = 0.995\).
a decade. However, these studies did not examine the initial elimination of TCDD immediately after high-level exposures. The high concentration predicted with the model during the first 6 months is an extrapolation of what should be the concentration at the time of initial exposure. Limited data are available to validate the model for the initial exposure period. One data set is available from Poiger and Schlatter (1986). Although these data were used in the optimization of the model, the small sample size and only a single dose level do not provide confidence that the data from Poiger and Schlatter (1986) represent the wide range of potential exposures and populations at risk.

A number of pharmacokinetic models have incorporated dose-dependent elimination of TCDD. These models use a variety of approaches to describe the dose dependency. Andersen et al. (1993) use a hyperbolic function related to receptor occupancy to describe the dose-dependent elimination. This function is modified by a species specific “fold” factor that is used to adjust the elimination rate. In rats this factor is 1 and allows for a doubling of the elimination rate; other species would have different adjustment factors. Kohn et al. (2001) also use a Hill equation for the kinetics of the metabolizing enzyme with cytosolic TCDD concentrations as the substrate. The elimination of TCDD in these models is dose dependent because there is a dose-dependent sequestration of TCDD in the liver. In the present model we describe the elimination rate as a function of CYP1A2 induction. The different approaches used to describe the dose-dependent induction of TCDD elimination are due to a lack of understanding of the biologic basis of these phenomena. This uncertainty in our understanding of the elimination of TCDD indicates that caution should be used when applying any of these models to human epidemiologic studies. However, the use of dose-dependent elimination of TCDD is an important concept to consider when choosing and applying pharmacokinetic tools in exposure assessments for dioxin.

Recent studies that measured TCDD blood concentrations shortly after high-level exposure indicate that the half-life is dose dependent (Geusau et al. 2002), as do clinical studies of the Ranch Hand cohort (Michalek et al. 2002). The use of first-order elimination of TCDD could significantly underestimate past exposures, resulting in exposure misclassifications in the epidemiologic studies. Using a PBPK model that incorporates a dynamic elimination rate may provide a more accurate assessment of past exposures in the epidemiologic studies. A better understanding of the biologic basis of the dose-dependent elimination of TCDD would allow for the development of more biologically realistic PBPK models. Further validation of this model is required before use in a quantitative exposure assessment. However, a pharmacokinetic model that includes an inducible elimination should be applied when assessing past exposures to TCDD.

**Figure 2.** Time course of TCDD in blood (pg/g lipid adjusted) for two highly exposed women (patients 1 and 2). Symbols represent measured concentrations, and lines represent model predictions. These data were used as part of the model evaluation (Geusau et al. 2002).

**References**


