TCDD KINETICS IN AUSTRIAN PATIENTS: IMPLEMENTATION OF THE CARRIER ET AL. (1995) MODEL

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Introduction

The object of this paper is to apply a previously developed physiologically based model[1,2] to the observed elimination of TCDD in three patients from Austria with moderately to extremely high body burdens of TCDD.[3,4] Along with recent reports on the Seveso population,[5] these data indicate that at substantially elevated body burdens, elimination rates for TCDD are much higher than previous estimates that were based on data from persons with body burdens below 500 ppt [3-6]. A dependence of TCDD elimination rate on body burden has been observed in rodents (reviewed by Carrier et al.),[1] and a similar increased elimination rate at high concentrations was reported for polychlorinated dibenzofurans in humans.[7] The dose-dependence of elimination rate in rodents has been hypothesized to occur secondary to induction of the TCDD binding protein CYP1A2 in the liver, and data demonstrating CYP1A2 induction suggest a similar possibility in the Austrian patients.[3]

The Carrier et al. model postulates that TCDD elimination is directly proportional to the current concentration in the liver. However, the proportion of body burden in liver increases in a non-linear, saturable manner as body concentration increases (following a Michaelis-Menten relationship), theoretically as a result of the induction of the binding protein CYP1A2 in the liver. The model structure is described in more detail in a companion paper at this conference (Brunet et al.). The model has been implemented for elimination of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in a Yu-cheng patient[1] and for elimination of TCDD from several persons from Seveso.[6] This paper presents the results of the model for the Austrian patients and provides some information on the possible range of likely values for the key model parameters.

Materials and Methods

The dates of sampling, measured serum lipid TCDD levels, and body weight data for the Austrian patients were tabulated based on published reports[3,4] (no body weight data were available for Patient 3). Initial parameters for the elimination model were taken from the fits previously derived from data from laboratory studies and on selected Seveso patients[6] and are listed in the legend to Figure 1. The liver elimination rate, k_e, and the half-maximum concentration, K, were adjusted to improve the fits to the Austrian patient data. The model was implemented in a Microsoft Excel spreadsheet using numerical simulation methods.

Results

Figures 1A, 1B, and 1C present the measured data and model fits for the three Austrian patients. The figures illustrate the best-fit model results and compare them to the elimination predicted by a simple first-order model with a 7-year half-life where no adjustments for body weight changes are made. The initial value of *K*, 100 ng/kg, fit all three Austrian patients well. Best-fit values of hepatic elimination parameter k_e were 0.94, 0.63, and 0.77 yr^{-1} (Patients 1–3, respectively). These parameter values correspond to initial elimination rates with apparent half-lives (based on changes in serum lipid TCDD concentration) of between 1 and 2 years. This apparent half-life of elimination is, however, predicted to be concentration dependent and to increase as body concentrations decreases. Figure 2 illustrates the concentration dependence of the apparent half-life of elimination.

Discussion

These data confirm that, at elevated body burdens, the half-life for elimination of TCDD is much shorter than the conventional estimates of 7 to 9 years. Using parameters derived from animal studies and previous human data, the Carrier et al. toxicokinetic model, as modified in the accompanying paper (Brunet et al, this conference), reproduces the concentration dependence of elimination over a wide range of body burdens. The model structure is based on two key assumptions that are supported by animal data: metabolism and elimination at high body concentrations are mediated in the liver, and the proportion of body burden in liver increases in a non-linear, saturable manner as the binding protein CYP1A2 is induced. Depending on the specific value of k_e, the predicted apparent half-life based on changes in lipid concentration ranges from as little as about 1 year at lipid concentrations above 10,000 ppt to over 10 years at background body burdens, and the apparent elimination rate changes sharply as body concentration increases from background (Figure 2).

For the two female patients with extensive serial sampling data, the serial TCDD measurements often varied sharply from one measurement to another. Some of this variation was accounted for in the model by incorporating the changes in body weight, but not all. The blood samples analyzed from these patients were small (1 g), and analytical variability may have occurred. In addition, in an effort to increase TCDD elimination rate, these patients were ingesting a non-absorbed dietary fat substance (Olestra) at varying levels over the course of the three-year period. Measurements by the researchers indicate that this ingestion probably increased the total TCDD elimination over the period by 10% to 15%. Some of the variation in sample-to-sample levels may have been due to transient responses to changes in the level of Olestra ingestion. The total rate of elimination in the two female patients is higher than would have been observed in the absence of Olestra ingestion. This affects the degree to which the data from these two women are generalizable to the general population. However, while the additional elimination due to Olestra is significant, the overall elimination, even in the absence of Olestra administration, was still significantly greater than would be predicted by a first-order elimination with half-life of 7 years.

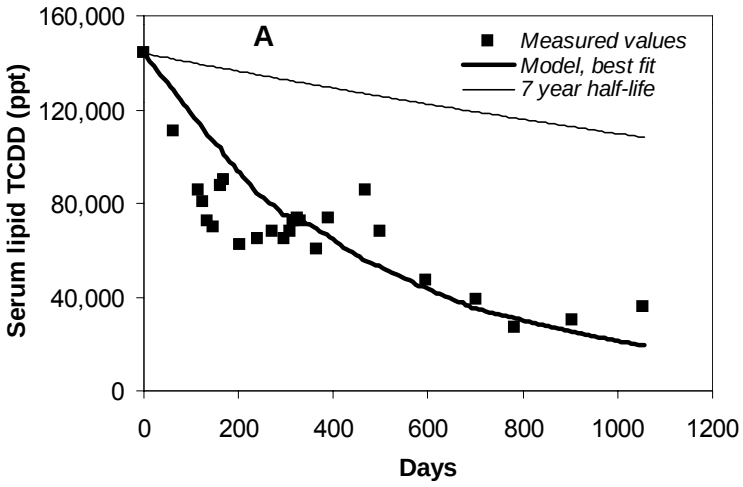
Good model fits could be obtained by varying only k_e, the liver elimination rate. The model fits for the two female patients (who had very high initial body burdens) were less sensitive to the other parameters, while for the male patient (with much lower initial body burden), the fit was also very sensitive to the value of *K*. The range of fitted values for the model parameter k_e is consistent with likely interindividual variability in elimination rate, the effect of variable rates of ingestion of

Olestra, uncertainties associated with body weight and body fat changes, and analytical variability. These data confirm the ability of the general form of the model to simulate the elimination behavior for TCDD over a wide range of concentrations. Model fits to these data and to sets of serial TCDD measurements from adults exposed in Seveso, Italy (Aylward et al., this conference), begin to suggest the range of variation in the model parameters that may exist in the general population. These data also indicate that a concentration-dependent rate of elimination for TCDD is a general phenomenon that is predictable over a wide range of concentrations.

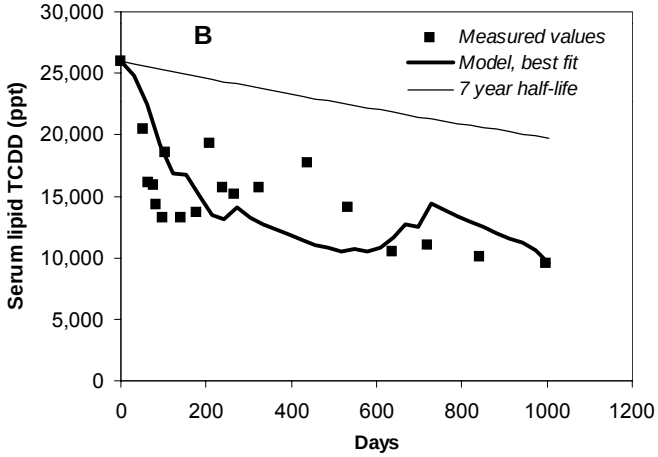
References

1. Carrier, G., Brunet, R.C. and Brodeur, J. (1995) Toxicol Appl Pharmacol, 131, 267.
2. Carrier, G., Brunet, R.C. and Brodeur, J. (1995) Toxicol Appl Pharmacol, 131, 253.
3. Abraham, K., Geusau, A., Tosun, Y., Helge, H., Bauer, S. and Brockmoller, J. (2002) Clin Pharmacol Ther, 72, 163.
4. Geusau, A., Schmaldienst, S., Derfler, K., Papke, O. and Abraham, K. (2002) Arch Toxicol, 76, 316.
5. Michalek, J.E., Pirkle, J.L., Needham, L.L., Patterson, D.G., Caudill, S.P., Tripathi, R.C. and Mocarelli, P. (2002) J Expo Anal Environ Epidemiol, 12, 44.
6. Carrier, G., Brunet, R.C., Mocarelli, P., Brambilla, G., Gerthoux, P.M., Needham, L.L. and Patterson, D.G. (1999) Organohalogen Compounds, 42, 159.
7. Ryan, J.J., Levesque, D., Panopio, L.G., Sun, W.F., Masuda, Y. and Kuroki, H. (1993) Arch Environ Contam Toxicol, 24, 504.
8. Moser, G.A. and McLachlan, M.S. (2002) Environ Sci Technol, 36, 3318.

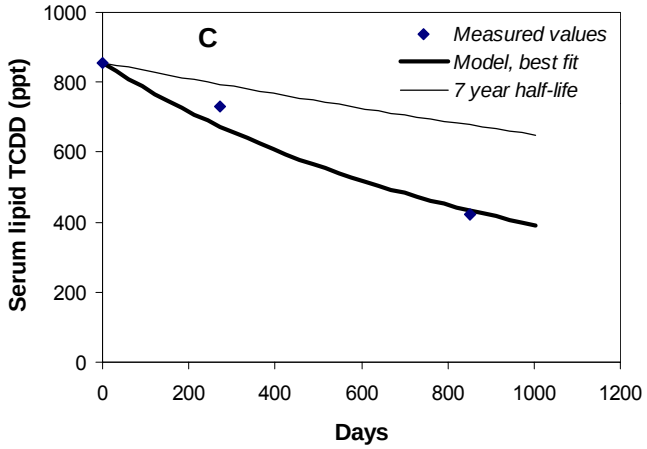
Figure 1: Measured and modeled serum lipid TCDD concentrations for Austrian patients. Model parameters, all fits: f_{min}=0.01; f_{max}=0.7; K=100 ng/kg; k_a=0.03 yr^{-1}.



A: Patient 1, female, initial age 30. Best fit k_e=0.94 yr^{-1}.



B: Patient 2, female, initial age 27. Best fit k_e=0.63 yr^{-1}.



C: Patient 3, male, initial age 26. Best fit k_e=0.77 yr^{-1}.

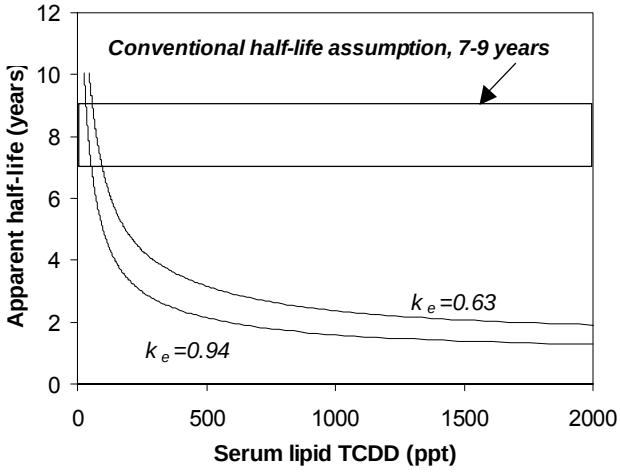


Figure 2: Apparent half-life for elimination based on changes in serum lipid TCDD concentration predicted by the modified Carrier model for the case of constant body weight, range of values for k_e from Austrian patients 1–3. Other model parameters as above.