TCDD ELIMINATION KINETICS: MODIFICATION OF THE CARRIER ET AL. (1995) MODEL TO INCLUDE AN ADDITIONAL ELIMINATION MECHANISM

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Introduction

The object of this paper is to present a modification to a previously developed physiologically based model[1,2] by Carrier and coworkers for simulating the metabolism and elimination of TCDD. Recent reports on three patients from Austria with moderate to extremely high body burdens of TCDD[3,4] and on the Seveso population[5] confirm the existence of a concentration dependence for the elimination of TCDD from the body. These data demonstrate that at substantially elevated body burdens, elimination rates for TCDD are much higher than previously estimated based on data from persons with body burdens below about 500 ppt. Average elimination half-lives of <1 to 3.6 years were observed in two women and one man exposed to very high or moderate levels of TCDD in Vienna, Austria, in 1997 (peak measured serum lipid levels of 144,000, 26,000, and 856 ppt)[3,4] and in adults exposed in Seveso, Italy, where multiple measurements of serum lipid TCDD levels were carried out beginning within two weeks after the accident (initial levels were over 2,000 ppt for many persons).[5,6]

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 original Carrier et al. model postulated that, at any moment, the amount of TCDD elimination is proportional to the current concentration in the liver. However, the proportion of body burden in liver was modeled to increase 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 key parameters for the model are k_e, the liver elimination rate; f_{min} and f_{max}, the minimum and maximum fractions of body burden that distribute to the liver; and K, the concentration at which the proportion distributing to liver reaches half-maximum. The model predicts the time-dependent TCDD concentrations in the body and in liver and fat tissue, and can incorporate changes in body weight and body composition, which can have significant effects on tissue concentrations.

However, recent data on the elimination of unchanged TCDD in feces, and the increase in such elimination after administration of Olestra, a non-absorbed dietary fat, suggests that, in addition to hepatic-mediated elimination, lipid-based partitioning across the intestinal lumen into the contents of the large intestine accounts for elimination of unchanged TCDD.[8] This paper presents a simple modification of the Carrier et al. model to account for this additional elimination mechanism and demonstrates the effect of the modification on the apparent elimination half-life for TCDD as a function of serum lipid TCDD concentration.

Methods

The structure of the Carrier et al. model was altered to account for an elimination mechanism due to lipid partitioning into intestinal contents by adding a term accounting for the amount of TCDD partitioning from circulating lipids across the intestinal lumen in the large intestine into the fecal content. The change in body quantity of TCDD as a function of time in the modified model is of the general form:

$$\frac{dQ_b(t)}{dt} = \frac{dQ_a(t)}{dt} + \frac{dQ_h(t)}{dt} \qquad (1)$$

where $dQ_h(t)/dt$ is the hepatic elimination as modeled in the original construction of the Carrier et al. model.[1] The change in quantity in adipose (and lipid) tissue is represented by a first-order elimination function operating on the amount of TCDD in lipid tissue $Q_a(t)$ with rate k_a:

$$\frac{dQ_a(t)}{dt} = -k_a * Q_a(t) \qquad (2)$$

and

$$Q_a(t) = BW(t) * w_a(t) * C_a(t) \qquad (3)$$

where the body weight *BW*, the percentage body fat w_a, and the adipose TCCD concentration C_a may all vary with time. The original structure of the model predicting distribution between adipose (or lipid) tissue and hepatic tissue as a function of body concentration remains unchanged, as does the structure of the model representation of hepatic elimination rate.

Data on intake and excretion of unchanged TCDD for 15 individuals from four studies [4,9-11] were used to evaluate k_a. Assuming that all fecal elimination of unchanged TCDD is due to this lipid-based elimination plus elimination of unabsorbed TCDD from dietary intake, mass balance yields:

$$k_a = \frac{F - [I * (1 - f_{abs})]}{Q_a} \qquad (4)$$

where F is the amount of unchanged TCDD eliminated in feces in pg/day, I is the amount of TCDD intake in diet in pg/day, and f_{abs} is the absorption fraction for TCDD in food in the small intestine. Data from Moser and McLachlan (2001) from experiments comparing fecal elimination of unchanged TCDD after high daily intakes to excretion after low daily intakes (four individuals) were used to estimate the absorption efficiency from food in the small intestine. The average absorption fraction, f_{abs} = 0.97, from these four individuals was applied to the intake and excretion data for the remaining individuals. The model was implemented in Microsoft Excel using numerical simulation methods.

Results

Based on the intake and excretion data from the 15 individuals and four studies, a value for k_a was estimated at 0.03 yr^{-1} (mean; S.D.=0.014). Figure 1 presents a comparison of the concentration dependence of the predicted elimination of TCDD using the original and modified model. The apparent half-life for elimination is estimated based on the instantaneous change in lipid TCDD concentration predicted by the model. The model parameters were set in a range observed in fits to serial serum lipid TCDD measurements in highly and moderately exposed persons and assumes constant body weight and body fat levels, although the effects of changes in these parameters can also be simulated using the model. The model modification has little impact on the predicted elimination rate at higher body concentrations, but as the body concentrations decrease toward background, the lipid-based elimination mechanism contributes more substantially to the total elimination rate.

Discussion

The original model described well high and moderate dose distribution and elimination of TCDD in both rodents and humans.[1,6] However, the original model structure predicts increasingly longer half-lives for elimination of TCDD as body and lipid concentrations approach background. The original model predicts half-lives in the range of 6 to 9 years for lipid concentrations around 100 ppt, but its predicted half-lives (more than 20 years, depending on model parameters) for concentrations about 10 ppt exceed substantially the observed half-lives (range of about 6 to 9 years[12,13]). This divergence of the original model from observed elimination behavior in humans may be explained by the omission of the mechanism of fecal elimination of highly lipid soluble persistent organochlorines, including TCDD, due to simple lipid partitioning from the circulation across the intestinal lumen into fecal contents (reviewed by Moser and McLachlan 2002). The modified model introduces the latter phenomena and more closely approximates the observed elimination rates at background concentrations, although additional data for estimating k_a might improve the performance further.

The original formulation of the model did not specify whether the elimination mediated in the liver occurred as a result of elimination of the unchanged compound or through its metabolism. However, recent data from human populations[4,8,10] suggest that the amount of unchanged TCDD eliminated cannot account for the rate of disappearance of TCDD in moderately to highly exposed populations. In combination with data that show inducible hepatic metabolism of TCDD in animals (Olson et al. 1994; Hu and Bunce 1999), these data suggest that the hepatic elimination of TCDD predicted in the Carrier et al. (1995) model represents metabolized compound and not elimination of the unchanged parent compound.

The modified model provides a useful framework for quantifying the concentration dependence of elimination rate for TCDD in humans. Modeling of 57 data sets of serial measurements of TCDD levels for moderately to highly exposed persons demonstrates the ability of the model to simulate the observed concentration dependence of elimination rate (other presentations by our group, this meeting). The model also allows a re-examination of the dose estimates made previously for occupationally exposed cohorts based on single serum lipid TCDD measurements made decades after last exposure. As noted by Geusau et al. (2002), a concentration-dependent elimination rate, with substantially faster elimination at elevated body burdens, indicates that previous estimates of

exposure in these cohorts, relying on constant elimination half-lives of 7 to 9 years, may have greatly underestimated the actual exposure in these cohorts.

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Figure 1:
Demonstration of concentration dependence of elimination rate for TCDD predicted by the original and modified model. Model parameters were set to values derived from fits to serial serum lipid TCDD measurements from moderately and highly exposed Seveso and Austrian patients. In this illustration, body weight and body fat levels were assumed constant.