IMPACT OF A CONCENTRATION-DEPENDENT ELIMINATION RATE FOR TCDD ON DOSE ESTIMATES FOR THE NIOSH COHORT

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Introduction

Two recent reports providing data on elimination rates for TCDD suggest that at substantially elevated body burdens, elimination rates are much higher than previously estimated based on data from persons with body burdens below 500 ppt. Elimination half-lives of <1 to 3.6 years have been observed in two women and one man exposed to moderate to very high levels of TCDD in Vienna, Austria, in 1997 (peak measured serum lipid levels of 144,000, 26,000, and 856 ppt)[1,2] and in adults exposed in Seveso, Italy, with multiple measurements of serum lipid TCDD levels beginning within days after the accident (initial levels over 2,000 ppt)[3,4]. A dependence of TCDD elimination rate on body burden has been observed in rodents (reviewed by Carrier et al),[5] and a similar increased elimination rate at high concentrations was reported for polychlorinated dibenzofurans in humans.[6] The dose dependence of elimination rate in rodents has been hypothesized to occur secondary to induction of CYP1A2 in the liver, and data demonstrating CYP1A2 induction suggest a similar possibility in the Austrian patients.[1]

An increased rate of elimination of TCDD in persons with elevated body burdens could have a significant impact on current estimates of exposure for the cohorts of industrial workers who were exposed to TCDD during the manufacture of herbicides. Until now, estimates of exposure for these workers have been based on serum lipid levels of TCDD measured a decade or more after last industrial exposure, which were back-calculated to estimated peak levels at time of last exposure, assuming a simple first-order elimination rate with a fixed half-life (ranging from 7.1 to 8.7 years).[7-9] Here, we back-calculate the exposures of the NIOSH cohorts using a modified version of the concentration-dependent elimination model of Carrier et al. (1995)[5]. The parameters used come from fits to serial sampling for serum lipid TCDD in 19 adult males who were highly exposed at Seveso. We compared the dose estimates to evaluate the potential impact of a concentration-dependent elimination rate on estimates of carcinogenic dose-response based on these populations.

Materials and Methods

We used a modified version of a model of the elimination kinetics of TCDD in humans developed by Carrier and coworkers[5] to estimate the occupational exposures in the NIOSH cohort. The Carrier et al. model[5] postulates a simple first-order elimination for TCDD based on 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 key parameters for the model are described in Table 1. A modification of the original model adds an elimination mechanism to account for elimination of unchanged compound from the circulation through lipid-based partitioning into the large intestine (mechanism reviewed by Moser and McLachlan 2002[10]; model modification is described in detail in other presentations, this meeting). The model predicts the time-dependent TCDD concentration 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.

The impact of the concentration-dependent elimination rate on dose estimates for the NIOSH cohort was assessed for three values of the hepatic elimination rate parameter, k_e (corresponding to the mean k_e and the lower and upper 95 percent confidence interval on the mean found in fits of serial TCDD measurements in 19 adult males from Seveso; work presented in other papers at this meeting). A concentration-vs.-time profile was obtained for each of the 250 workers by first back-calculating from date of sampling to a peak exposure on the date of last employment (a minimum of 15 years) and then estimating the constant exposure rate during employment that is necessary to result in the estimated peak on date of last employment. Both steps employed either the concentration-dependent functions for elimination or a constant elimination rate corresponding to half-lives of 7.5 or 8.7 years, as described above.

Results

Exposure estimates derived using a concentration-dependent rate of elimination are somewhat lower than the constant-rate estimates for the NIOSH workers with the shortest exposure duration, but are 7 to nearly 100 times higher (depending on model parameters) for the longest exposure duration group (Table 2). Estimates of other dose metrics (peak concentration in serum lipid and cumulative area under the curve, or AUC) are similarly increased using a concentration-dependent elimination rate (results not shown).

Figure 1 illustrates the concentration dependence of the apparent elimination half-life (based on instantaneous rates of change in serum lipid TCDD concentration) predicted by the model for the range of values of k_e used in modeling the NIOSH cohort data. Figure 2 presents the estimated concentration-vs.-time curves for a single individual calculated using constant 7.5- or 8.7-year half-lives (as relied upon in the USEPA 2000 cancer dose-response assessment[11] and in the most recent NIOSH cohort mortality update,[9] respectively) or using the concentration-dependent elimination rate function with the lower 95th confidence interval on the mean and the mean value for the hepatic elimination rate parameter.

Based on observed inter-individual variability in elimination rates in the sampling data from Seveso adults, back-calculated peak exposure levels for an individual using the mean hepatic elimination rate parameter may either greatly over- or under-estimate actual exposure levels for that individual. For an individual, a high measured concentration of TCDD (hundreds of ppt or higher) decades after last exposure may have resulted from either very high exposure during employment, slow elimination kinetics in that individual, or (most likely) a combination of these two factors. Use of the lower 95th confidence interval on the mean hepatic elimination rate parameter (derived from fits to the serial sampling data from adult males exposed in Seveso) in the model to assess the exposure of the NIOSH cohort presents a conservative estimate of exposure levels in this cohort (likely to underestimate).

Discussion

Several recent reports have established that, at high body burdens, humans eliminate TCDD much more rapidly than at lower body burdens, and more rapidly than has been conventionally

assumed.[2,4] Dose estimates for the NIOSH subcohort with the longest exposure duration obtained using a concentration-dependent elimination rate function were 7 to almost 100 times higher (depending on model parameters) than the dose estimates obtained using constant first-order elimination kinetics with half-lives of 7.5 or 8.7 years. These increased dose estimates suggest that the cancer potency estimates based on this and other occupational cohorts presented in the USEPA Draft Reassessment[11] and in more recent analyses[9] may overestimate the carcinogenic potency in these cohorts by nearly an order of magnitude or more. This analysis also suggests that the margin of exposure between highly exposed industrial cohorts and current background general-population exposures is probably much greater than previously estimated. The actual levels of exposure experienced by individuals in this cohort are highly uncertain due to the long back-calculation period and likely inter-individual variability in elimination kinetics.

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Table 1: Modified Carrier et al. (1995) model parameters and values based on fits to serial TCDD sampling from 19 adult males exposed in Seveso, Italy (other papers, this meeting)

Model Parameter	Description	Value
f_{min}	Minimum proportion of body burden distributed to liver	0.01 (unitless)
f_{max}	Maximum proportion of body burden distributed to liver	0.7 (unitless)
K	Body concentration for half-maximum increase in liver distribution proportion	100 ng/kg
k_a	Rate constant for elimination based on partitioning from circulating lipids into large intestine	0.03 yr^{-1}
k_e	Mean rate constant for hepatic elimination (based on fits to serial sampling from 19 Seveso adult males)	0.42 yr^{-1} (95% C.I.: 0.31- 0.53)

Table 2: Estimates of group median C_{avg} (calculated for each individual by dividing cumulative AUC in ppt-years by age in years at time of sampling) for exposure duration subcohorts of 250 NIOSH workers

	Median C_{avg}, ppt				
			Carrier modeled elimination (model parameters as in Table 1)		
Exposure duration (years)	Constant 8.7-yr half-life	Constant 7.5-yr half-life	k_e=0.31 yr^{-1}	k_e=0.42 yr^{-1}	k_e=0.53 yr^{-1}
<1 (n=126)	43	50	24	27	32
1 to <5 (n=87)	190	230	250	620	2,000
5 to <15 (n=25)	390	480	1,400	5,800	21,000
15+ (n=12)	1,700	2,100	14,000	51,000	190,000

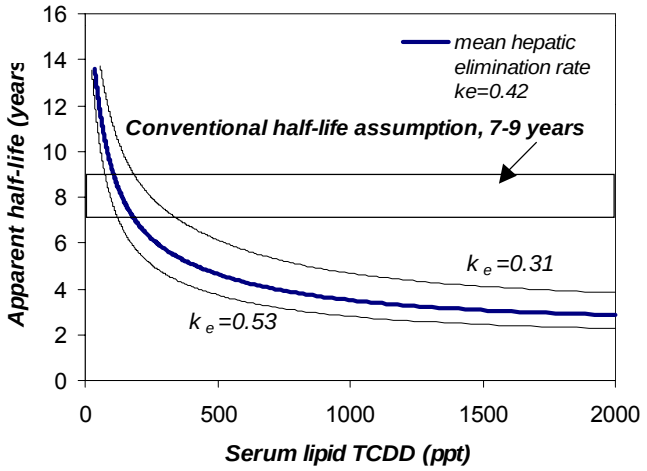

Figure 1: Apparent elimination half-life as a function of serum lipid TCDD concentration predicted by the model for the range of model parameters described in Table 1. Body weight and fat levels were held constant. Model values for the hepatic elimination rate k_e represent the mean and 95 percent confidence interval on the mean based on fits to serial serum lipid TCDD sampling data from 19 adult males exposed at Seveso.

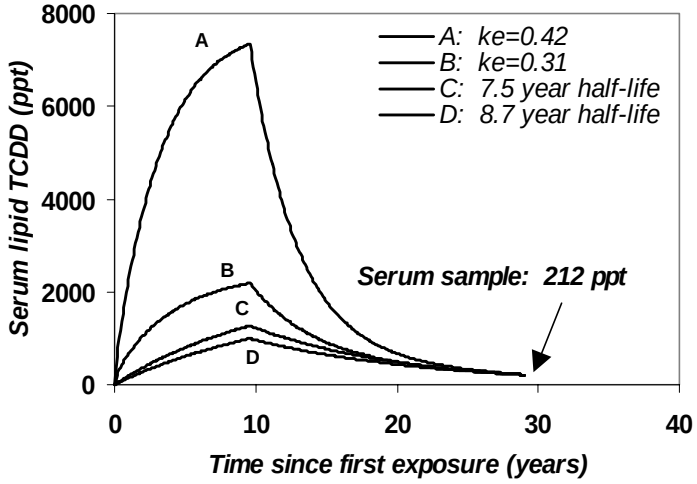

Figure 2: Effect of different elimination rate functions on the estimated historical TCDD concentration-vs.-time profile for a sample worker from the NIOSH cohort. Small changes in hepatic elimination rate constant produce large variations in estimated peak exposure levels.