Age- and Concentration-Dependent TCDD Elimination Half Life in Seveso Children

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Introduction

Shorter elimination half lives for TCDD and other PCDD/Fs have been reported in human infants [1,2] and in highly exposed adults[3,4] compared with those in the general population, but there are no half life data available for young children and adolescents (i.e., ages 1-18). These data for children are needed to further validate the two age-dependent PCDD/F half life models that have been proposed for estimating childhood body burdens and any associated risks[2,5]. Accordingly, this study examines a database of longitudinal TCDD measurements in the blood lipids of children (ages 0.5 to 18 years) exposed during the 1976 trichlorophenol reactor explosion incident in Seveso, Italy. As many as ten sequential measurements were made on some children. We evaluate the changes in the elimination rate as it is influenced by age, TCDD concentration in the body, chloracne status, and other parameters potentially influencing the elimination half life in children, adolescents and young adults. Our goal was to identify appropriate age versus half life relationships which could be used to estimate childhood body burdens, particularly for ages 1-8 years. These data could then be used when conducting health risk assessments.

Methods

Data from the Seveso incident include fairly complete information on longitudinal blood TCDD measurements, sampling date, exposure zone, severity of chloracne, and subject age, height, and weight at the time of sampling (up to 16 years after the incident). Persons under age 18 in July of 1976 with at least two blood TCDD measurements were included in the data evaluation which comprised a total of 27 females and 20 males within Zone A. The analytical method for lipid TCDD and some clinical correlations were reported by Mocarelli and colleagues[6].

The half life of TCDD was calculated based on one or more data pairs for each individual. The initial peak TCDD concentration in several cases was observed in samples taken several months after July of 1976, indicating that continuing absorption or equilibration was probably occurring. Half life was calculated using the standard equation [$T_{1/2}$ = -.693*(delta time)/Ln(TCDD Conc. @ time T/Conc. @ Initial Peak)]. We utilized the peak TCDD measurement between July of 1976 and 1977 as the initial value (A) of two or more blood samples in chronological sequence (e.g., A – B – C – D), and data pairs (e.g., A-B, A-C, A-D) were used to calculate half life. Nondetect values were included in the analysis as if present at the stated detection limit.

Some of the analyses utilized estimated values for body mass index (BMI) and Body Fat Mass (BFM) relevant to the sampling time and individual. BMI was calculated using the metric height and weight measurements and the standard equation (BMI = 1000*H/W/W) and BFM was calculated by estimating the body fat fraction (BMI*1.5*.01 for females, BMI * 1.2*.01 for males) and multiplying by body weight to obtain total kg of body fat.

Preliminary analysis of data correlations indicated the expected data scatter from typical laboratory analytical error (e.g., $\pm$ 10-30%) plus more substantial outliers that skewed the central tendency trends. Many of the extreme high and low half life values were observed in the first five years of measurements, which likely represent additional environmental exposures and/or slow equilibration of the body TCDD dose, both of which would make half life calculations less reliable for that period. Thus, all data pairs occurring prior to July of 1977 were excluded (9 half lives excluded: 0.1, 0.2, 0.3, 0.4, 0.6, 0.6, 0.8, 7.4 and 23.8 yrs). In other cases, outlier values occurred as unusually high

or low measurements within the first five years of data (through 1981). We excluded data pairs in this time period only if they were more than 2-fold higher or lower than the median of the values for that individual and/or for others within a ±3-year age span (8 half lives excluded: 0.7, 7, 8.1, 14.8, 18.5, 19.4, 27.9, and 30.7).

All data groupings were analyzed by linear regression using the algorithms in Microsoft Excel 2000. Selected subsets were defined according to age, body fat parameters, chloracne grade/status, and gender. Each data grouping was evaluated for age-dependent and concentration-dependent effects on TCDD elimination half life.

Results and Discussion

The study population under the age of 18 at the time of the Seveso incident included 20 male and 27 female children with 2 or more blood TCDD measurements (expressed as parts per trillion (ppt) in blood lipid). At the first sampling in 1976, the males ranged from 2.8 to 12.1 years of age and they had peak TCDD levels from 173 to 26,400 ppt. The females ranged from 0.5 to 16.6 years old and they had peak TCDD levels from 54 to 56,000 ppt. Table 1 presents summary statistics from linear regression analysis of the age versus TCDD half life plots. Table 2 presents regression results for body fat variables.

Table 1. Linear Regression Results for Age vs. Cumulative TCDD Half Life for Selected Subgroups

Subgroup	Slope	Intercept	R^2
Under Age 18 in 1976	0.12	0.18	0.46
With BMI < 25	0.11	0.39	0.42
With BMI < 20	0.12	0.12	0.39
With Chloracne	0.13	-0.24	0.67
With High Grade Chloracne (grade 3 or 4)	0.14	-0.37	0.64
With Low Grade Chloracne (grade 1 or 2)	0.12	-0.24	0.68
With No Chloracne	0.15	0.49	0.53
Males Only	0.12	0.47	0.49
Females Only	0.13	-0.05	0.50
Under Age 12 Only	0.00	1.50	<0.01

Table 1 illustrates that the slope or rate of increase in TCDD half life with increasing age varies within a limited range (0.11 to 0.15) for the whole study group and for subgroups defined based on body mass index, chloracne response, and gender. Unfortunately, there are insufficient data for individuals under age 12 to derive a meaningful regression analysis; however, the available data indicate a more gradual or flat slope for the youngest members in this cohort, centering on a TCDD half life of 1.5 years.

Table 2 illustrates the expected correlations between age and increasing body fat mass in children, as well as increasing TCDD half life with body fat mass or body mass index. Higher body fat or BMI generally correlates with a slower rate of increase in half life that is likely due to dilution of the existing TCDD mass in the growing lipid volume. Selection of only the leaner individuals (i.e., BMI < 20) leads to higher calculated slopes.

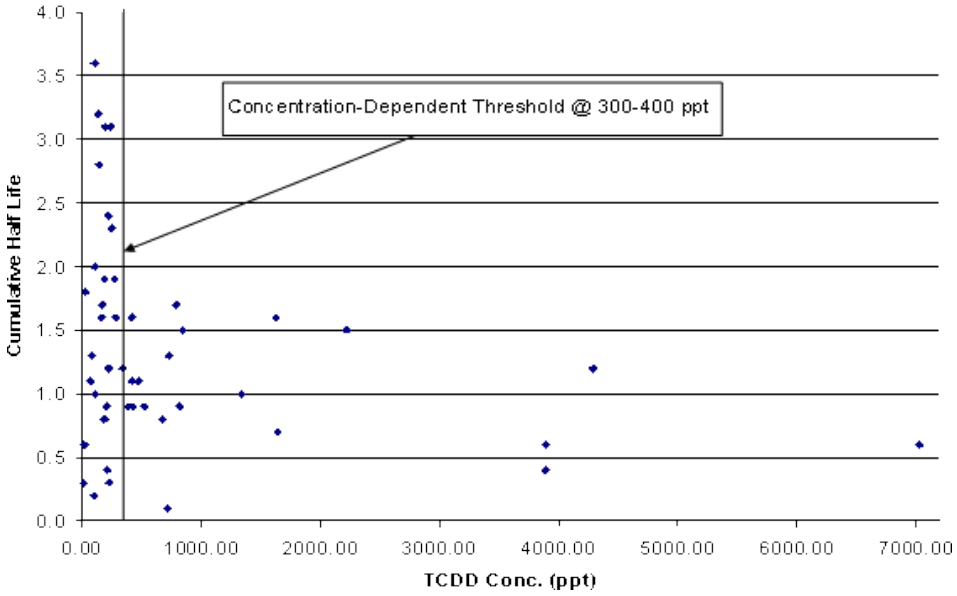
Table 2. Linear Regression Results for Selected Body Fat Indices, Age, and TCDD Half Life

Subgroup	Slope	Intercept	R^2
Under Age 18 in 1976, Age vs. Body Fat Mass (kg)	0.65	2.85	0.52
Body Fat Mass (kg) vs. TCDD Half Life	0.11	0.81	0.30
With BMI < 25	0.09	0.95	0.17
With BMI < 20	0.15	0.57	0.18
Body Mass Index vs. TCDD Half Life	0.19	-1.36	0.24
With BMI < 25	0.12	-0.18	0.08
With BMI < 20	0.13	-0.42	0.04

Figure 1 presents the (depleted) TCDD blood lipid concentration vs. half life relationship for children under age 12 (i.e., data pairs for higher ages were excluded; and TCDD values are the depleted [not initial] concentrations). An apparent threshold for shorter half lives around 300-400 ppt can be visualized, with the highest half life in males at 1.2 years and in females at 1.7 years based on the depleted TCDD concentration. Similar analysis of the entire

cohort showed no half lives above 2 years in those with > 2000 ppt, and only 2 half life values above 2.2 years at > 500 ppt (data not shown).

Figure 1. Seveso Children Under Age 12 (n = 24), TCDD Concentration vs. Half Life



These findings of age-dependent and concentration-dependent effects on TCDD half lives in Seveso children are consistent with findings reported in a companion paper[4] showing PeCDF and HxCDF half lives in people (ages 18-80) exposed during the Yusho and Yucheng poisoning incidents in Japan and Taiwan, respectively. The age-related increases in half life reported for PeCDF and HxCDF (0.18 and 0.12 yr/yr) are similar to that reported here for TCDD (0.11-0.15 yr/yr). Leung et al. (2005) also identified distinctly shorter half lives for those individuals with the highest tissue concentrations (e.g. > 3000 ppt), similar to that seen for the entire Seveso child cohort.

With respect to children under age 12, the available data indicate short PCDD/F half lives for infants (age 0-1 yr; Leung et al.[1]) and a consistent rate of half life increase starting in at least early adolescence based on the current study and other data[4]. Although the half life data on the 1-12 age group are limited, a slower or flat rate of increase is suggested here. Therefore, use of the higher age vs. half life slope relevant to early adolescence through adulthood (e.g., 0.12 yr/yr) is suggested as a conservative yet appropriate assumption for modeling body burdens for younger children (ages 1-12).

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