HALF-LIVES OF DIOXINS, FURANS, AND PCBS AS A FUNCTION OF AGE, BODY FAT, BREASTFEEDING, AND SMOKING STATUS

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Abstract

The half-lives of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) exhibit inter-individual variation based on different individual characteristics. Measured and modeled data from the literature were compared to examine the effects of age, percent body fat, and total body fat on the half-lives of 29 different congeners. Two strategies are proposed for adjusting half-lives for an individual based on a predefined reference value. An equation based on a linear relationship with age that is corrected for percent body fat, smoking status, and time spent breastfeeding a child provides results that are consistent with previously reported observations. Alternatively, an equation based on a linear relationship between half-life and total body fat adjusted for smoking status and time spent breastfeeding a child is proposed. This method requires further testing and validation against individual measurements.

Introduction

The main goal of the University of Michigan Dioxin Exposure Study (UMDES) is to determine the factors that affect the current serum concentrations of 29 congeners of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs). To understand and adjust the effects of past intake on current serum concentration of individuals[1], it is necessary to know the half-life of each congener at each age of their lives. Inter-individual half-life variability can partially be attributed to certain individual characteristics. Previous studies examine the effects of some of these factors on the half-lives of selected congeners, but a comprehensive study of all crucial factors and multiple congeners is currently nonexistent, according to the authors' knowledge. This study provides an adaptive method of personalized half-life calculation, incorporating all of the crucial factors that are applicable to the 29 PCDD, PCDF, and PCB congeners[2].

Materials and Methods

A literature review was conducted to identify the most important factors that affect the half-lives of dioxins and dioxin-like compounds in the human body. Measured and modeled data in the literature were used to examine the relationship between half-lives and these factors. Half-life values for a reference adult male and a reference infant were used to produce a continuous interpolation of the half-life as a function of age, percent body fat, and total body fat. When percent body fat or total body fat information was not available, the mean body mass index (BMI) given by the NHANES data[3] for each age was converted to a percent body fat using the approach proposed by Deurenberg et al[4]. Three models are tested to determine the best method to predict half-life: a model based on age, on percent body fat, and on total body fat. The differences between these models are illustrated using 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) is used as an example. The smoking adjustment factor was derived from Flesh-Janys et al.[5]. For congeners for which this information was not available, a mean value of the available congeners was assumed. A correction for breast feeding can introduced that accounts for the mother's drop in concentrations of dioxins, furans, and PCBs during breast feeding.

Results and Discussion

The main factors that influence the half-lives of PCDDs, PCDFs, and PCBs are a high body burden of dioxin like compounds, smoking status, age, body fat, and time spent breastfeeding a child. Both smoking and having high body burden appear to increase the metabolism of dioxin and dioxin-like compounds through the induction of the cytochrome P450 enzyme[6]. Kerger et al.[7] observe a concentration-dependent half-life, with shorter half-lives above a transition value of 700ppt in blood serum. Blood concentrations in the UMDES cohort are all below this level, thus it was not necessary to adjust half-lives for high body burdens. To ensure consistency, data from the literature for high body burdens were not considered in determining points of departure[8]. The effect of metabolism induction is accounted for in smokers, however, as they a exhibit a significant increase in decay rate for numerous congeners[5].

As shown if figure 1 there is a positive nearly linear association between age and half-life. This may indicate a direct relationship between age and half-life, or age may incorporate the effect of other parameters, such as the change in percent body fat with age. The short half-life in children may be partially attributed to dilution caused by rapid growth at young ages[9]. As children age, their rate of growth slows and the effect of metabolism on apparent half-life becomes more important than dilution.

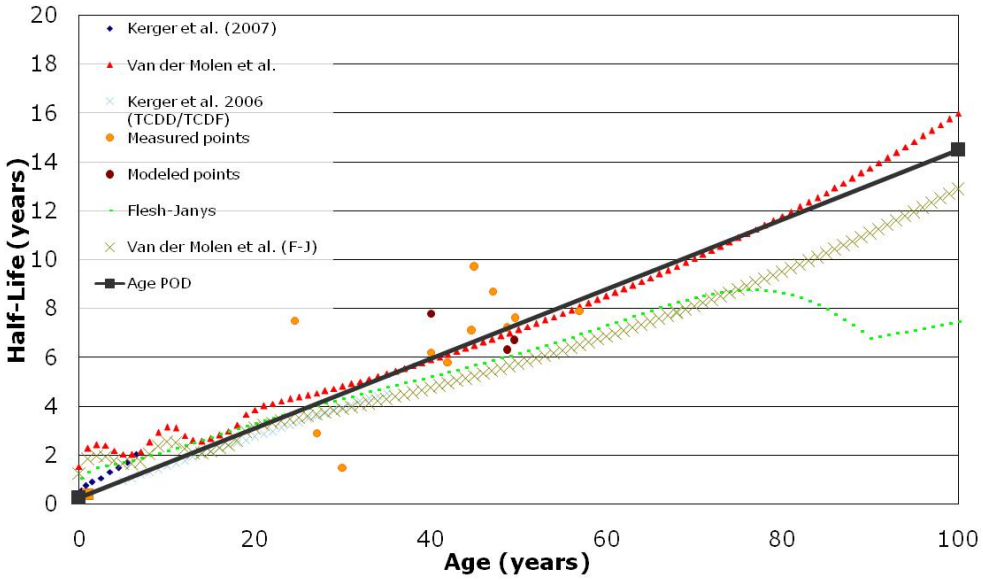

Figure 1. 2,3,7,8 TCDD: Half-Life (years) as a function of age in years: modeled and measured data as reported in Milbrath et al.[5,7,8,10,11]. The Kerger 2006 data is for children <700 ppt only[7]. The two measured points below the curve between 25 and 30 years correspond to acute poisoning of two females with extremely high concentrations of TCDD (26,000 ppt and 144,000 ppt)[12]. The solid line connects the two point of departure values given in Table 1. Van Der Molen et al. (F-J) refers to the application of the model presented by Van der Molen et al to the Flesh-Janys data[13].

The half-lives of PCDDs, PCDFs, and PCBs can also be partially correlated with percent body fat[14]. Figure 2 presents the same data as in figure 1, but with half-life expressed as a function of percent body fat. It appears that half-life increases as percent body fat increases. While this relationship holds well at older ages, it does not appear appropriate at younger ages (as shown by the arrow on figure 2). Because of this, the relationship between percent body fat and half-life could be useful for correcting the half-life for a given age, but should not be used to represent every stage of an individual's life.

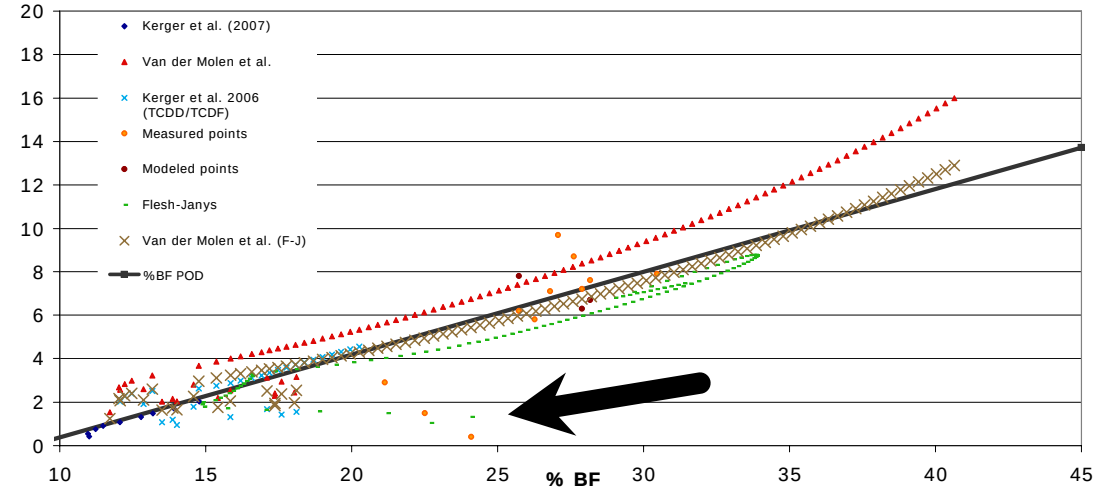

Figure 2. 2,3,7,8-TCDD Half-life as a function of percent body fat. Arrow shows area where the relationship of increased half-life with increase body fat does not hold. These values represent young subjects.

The results for the third model are shown in figure 3. This model plots half-life as a function of total body fat. Using absolute body fat rather than percent body fat better accounts for the effect of dilution found in children.

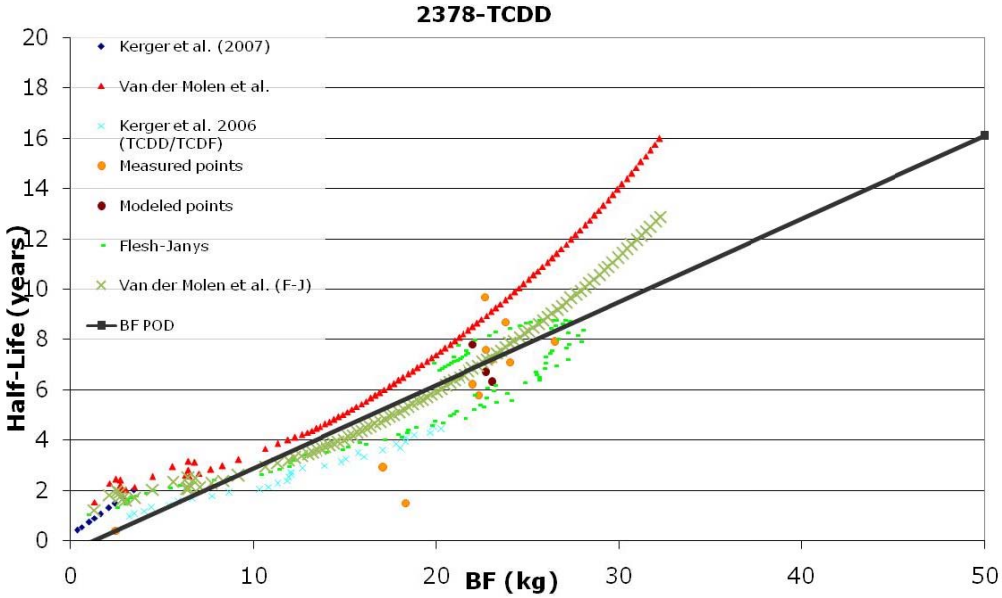

Figure 3. 2,3,7,8-TCDD Half-life in years as a function of total body fat (in kg). Once again, the two points below the curve correspond to acute poisoning of two females with extremely high concentrations of TCDD (26,000 ppt and 144,000 ppt)[12].

Based on the models presented above, two strategies are proposed for determining the half-lives of dioxins, furans, and PCBs in an individual. The first strategy is to use a linear relationship with age, using the reference values for an infant and for an adult male defined by Milbrath et al[8] as points of departure. These reference values and corresponding intercepts and slope parameters for 29 congeners are given in Table 1.

Chemical	age Low PoD	age high PoD	BF low PoD (kg)	BF high PoD (kg)	Half life Low PoD (year)	Half life PoD (year)	Chemical	age intercept (year)	age slope (year/year)	BF intercept (year)	BF slope (year/kg)	Smoke factor
2378 TCDD	1	48.7	2.49	23.09	0.400	7.200	2378 TCDD	0.257	0.145	-0.423	0.322	0.739
12378 PeCDD	1	48.7	2.49	23.09	0.320	11.180	12378 PeCDD	0.092	0.229	-0.995	0.507	0.683
123478 HxCDD	1	48.7	2.49	23.09	0.542	9.763	123478 HxCDD	0.349	0.197	-0.574	0.436	0.509
123678 HxCDD	1	48.7	2.49	23.09	0.390	13.078	123678 HxCDD	0.124	0.267	-1.146	0.593	0.635
123789 HxCDD	1	48.7	2.49	23.09	0.283	5.097	123789 HxCDD	0.182	0.103	-0.300	0.228	0.665
1234678 HpCDD	1	48.7	2.49	23.09	0.320	4.916	1234678 HpCDD	0.224	0.099	-0.236	0.218	0.525
OCDD	1	48.7	2.49	23.09	0.460	6.730	OCDD	0.329	0.135	-0.299	0.298	0.551
2378 TCDF	1	48.7	2.49	23.09	0.119	2.134	2378 TCDF	0.076	0.043	-0.125	0.095	0.648
12378 PeCDF	1	48.7	2.49	23.09	0.195	3.501	12378 PeCDF	0.125	0.071	-0.206	0.156	0.648
23478 PeCDF	1	48.7	2.49	23.09	0.270	7.002	23478 PeCDF	0.129	0.142	-0.545	0.316	0.648
123478 HxCDF	1	48.7	2.49	23.09	0.357	6.418	123478 HxCDF	0.229	0.129	-0.377	0.287	0.692
123678 HxCDF	1	48.7	2.49	23.09	0.401	7.220	123678 HxCDF	0.258	0.146	-0.424	0.323	0.695
123789 HxCDF	1	40	2.49	22.00	0.344	6.200	123789 HxCDF	0.194	0.152	-0.404	0.292	0.648
234678 HxCDF	1	48.7	2.49	23.09	0.155	2.794	234678 HxCDF	0.100	0.056	-0.164	0.125	0.648
1234678 HpCDF	1	48.7	2.49	23.09	0.172	3.094	1234678 HpCDF	0.111	0.062	-0.182	0.138	0.832
1234789 HpCDF	1	48.7	2.49	23.09	0.256	4.613	1234789 HpCDF	0.165	0.093	-0.271	0.206	0.648
OCDF	1	48.7	2.49	23.09	0.078	1.398	OCDF	0.050	0.028	-0.082	0.062	0.648
s_PCB_77	1	49.5	2.49	22.75	0.004	0.070	s_PCB_77	0.003	0.001	-0.004	0.003	0.648
s_PCB_81	1	49.5	2.49	22.75	0.041	0.730	s_PCB_81	0.026	0.014	-0.044	0.033	0.648
s_PCB_126	1	42.5	2.49	22.34	0.089	1.600	s_PCB_126	0.052	0.037	-0.101	0.074	0.648
s_PCB_169	1	42.5	2.49	22.34	0.406	7.300	s_PCB_169	0.239	0.169	-0.461	0.338	0.648
s_PCB_105	1	42.5	2.49	22.34	0.133	2.400	s_PCB_105	0.079	0.055	-0.151	0.111	0.648
s_PCB_114	1	42.5	2.49	22.34	0.556	10.000	s_PCB_114	0.328	0.231	-0.631	0.463	0.648
s_PCB_118	1	42.5	2.49	22.34	0.211	3.800	s_PCB_118	0.125	0.088	-0.240	0.176	0.648
s_PCB_123	1	42.5	2.49	22.34	0.411	7.400	s_PCB_123	0.243	0.171	-0.467	0.343	0.648
s_PCB_156	1	42.5	2.49	22.34	0.889	16.000	s_PCB_156	0.525	0.369	-1.010	0.741	0.648
s_PCB_157	1	42.5	2.49	22.34	1.000	18.000	s_PCB_157	0.590	0.416	-1.136	0.834	0.648
s_PCB_167	1	42.5	2.49	22.34	0.667	12.000	s_PCB_167	0.394	0.277	-0.757	0.556	0.648
s_PCB_189	1	42.5	2.49	22.34	1.222	22.000	s_PCB_189	0.722	0.508	-1.388	1.019	0.648

Table 1. Parameter values for equations 1-3 (given below).

Correction factors are introduced for the percent body fat and smoking status of an individual at a given age.

$$\tau_{1/2}(age_i, smoke_i, \%bf_i)_i = \left(\beta_{0(age)} + \beta_{age} \cdot age_i\right) \cdot SF_i \cdot \frac{\%bf_i^{2005}}{\%bf_{ref(age_i)}^{2005}} \quad (1)$$

Equation 1. Corrected half-life for an individual, where %BF is percent body fat, SF is smoking factor.

Gender differences are not explicitly accounted for in the below equations, but are indirectly included through different specified percent body fat values for each age. The decay rate is calculated as a function of half-life and the number of months spent breastfeeding a child during the considered year.

$$k_i = \frac{ln(2)}{\tau_{1/2}} + k_{breast} \cdot t_{breast} \quad (2)$$

Equation 2. Corrected decay rate for an individual, where *k breastfeeding* is the rate constant for breastfeeding in 1/year.

The alternative strategy is a linear relationship with absolute body fat (kg) (equation 3). The same corrections for smoking status and breastfeeding are used as in equations 1 and 2, and intercept and slope parameters are based on the same points of departure (reported in Table 1).

$$\tau_{1/2}(smoke_i, bf_i)_i = \left(\beta_{0(bf)} + \beta_{bf} \cdot bf_i\right) \cdot SF_i \quad (3)$$

Equation 3. Corrected half-life for an individual based on total body fat and smoking status.

When equation 1 was tested against the Flesh-Janys regression, a similar response was obtained over a wide age and percent body fat. There is not sufficient data to test the equation based on total body fat (equation 3), and this approach requires further validation. However, the described equations represent a simple and relatively consistent approach that can be used to determine individual half-lives for numerous dioxin, furan, and PCB congeners.

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