Age- and Concentration-Dependent Elimination Half Lives of Chlorinated Dibenzofurans in Yusho and Yucheng Patients

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Introduction

From 1980-1990, Ryan et al.[1] measured the PCDF concentrations in the blood fat of persons who ingested contaminated rice oil in Japan (Yusho) in 1968 and in Taiwan (Yucheng) in 1979. They observed that the clearance of PCDFs was faster in the Yucheng patients who had higher concentrations than those in Yusho. Since then, seven additional years of blood monitoring data have been obtained. This paper describes the results of our analyses of the complete 15-year sampling dataset in an attempt to better delineate the concentrations of PCDFs that elicited non-linear clearance kinetic behavior. We also explore the relationship between the clearance half-lives and the subjects' age.

Materials and Methods

Serial whole blood samples were collected annually from affected individuals during the period from 1982-1997 for Yusho and 1980-1999 for Yucheng[2]. The methods of blood collection and determination for PCDF concentrations have been described elsewhere[1].

Subject	Sex	Age during sampling[a]	2,3,4,7,8-PentaCDF	1,2,3,4,7,8-HexaCDF	1,2,3,4,6,7,8-HeptaCDF
			Range of concentration (ng/g blood fat or ppb)		
Yucheng					
BS	M	18-33	0.42-18.1	1.09-48.0	0.064-4.43
SS	M	26-41	0.90-17.9	2.06-42.4	0.037-5.07
RK	F	33-49	0.39-13.2	2.05-43.4	0.055-5.01
Yusho					
KK	F	59-74	1.05-3.04	0.54-2.55	0.014-0.31
TS	F	55-69	0.41-1.42	0.13-1.04	0.017-0.14
YUM	F	47-61	0.67-3.61	0.36-5.20	0.017-0.71
TH	F	61-76	0.62-2.35	0.17-1.65	0.007-0.23
HH	F	65-80	1.23-3.45	0.51-2.30	0.015-0.33

A total of 68 data pairs were collected, 22 from Yucheng and 46 from Yusho. The data from Yucheng were stable; while that from Yusho were quite erratic, with many samples showing unexpected higher concentrations than previous ones. This might be due to the greater influence from continuing background exposures for the lower PCDF blood levels observed in the Yusho patients.

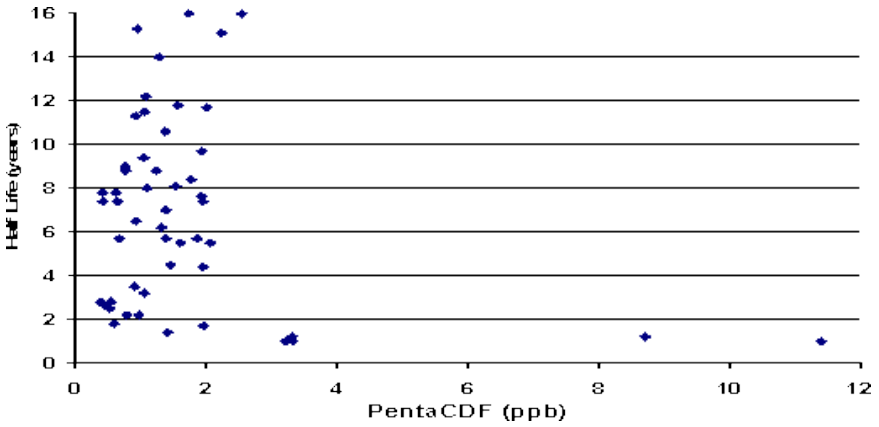
Exclusion criteria were established to improve the usability of the datasets. First, all concentrations below the detection limit were deleted. This removed 12 for heptaCDF. Second, any subsequent data points collected long after the initial measurement that showed a concentration >90% of the initial peak level were deleted. This excluded 5 for penta- (all for 1 person), 2 for hexa-, and 1 for heptaCDF. Third, any outlier with a calculated half-life >2-times higher than the median half-life value was deleted from further analysis. This excluded 1, 3 and 1 data point for penta-, hexa-, and heptaCDF, respectively. Half-lives were calculated from the remaining data pairs by assuming a one-

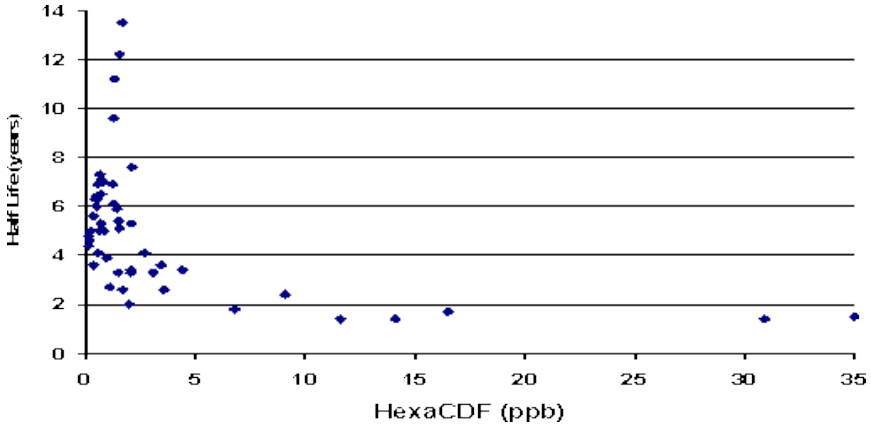
compartment model obeying first-order kinetics. Half-life estimates for each PCDF were grouped with respect to low and high concentrations, and were compared for differences using the Wilcoxon Rank Sum test, with the criterion for significance set at $p<0.05$. Half-lives were also examined for relationship to the subjects' age at the time of sampling by conducting linear regression analyses.

Results and Discussion

Figure 1 shows that the half-lives of penta- and hexaCDF displayed marked concentration dependency. For pentaCDF, the average half-life (±S.D.) of 1.1±0.1 y (n=5) at concentrations >3 ppb was 6.9 times shorter than that at <3 ppb (7.5±4.0 y, n=47, $p<0.0001$). For hexaCDF, the half-life of 2.3±0.8 y (n=12) at concentrations >3 ppb was 2.6 times shorter than that at <3 ppb (5.9±2.5 y, n=39, $p<0.0001$). Similar trends, but at a lower breakpoint of 1 ppb, were observed for heptaCDF (1.5±0.5 y, n=7 and 3.6 ± 2.0 y, n = 33, $p<0.0001$, data not shown).

Figure 1. Correlation of clearance half-lives versus concentrations of penta- and hexaCDF in the blood fat of Yucheng and Yusho patients.





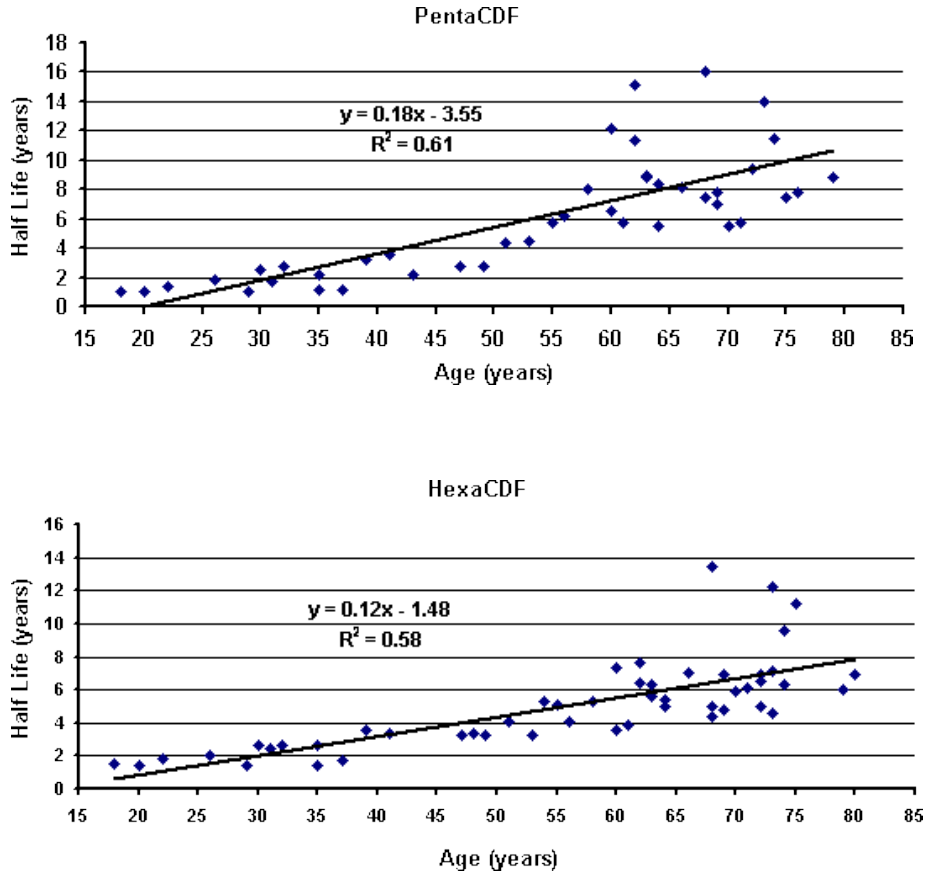
Our analyses extended the observation of Ryan et al.[1] that the clearance of PCDFs in humans was concentration-dependent. The reason for the faster clearance of PCDFs at high body burden may be related to Ah receptor-mediated induction of the CYP 1A1 and 1A2 subfamily of isozymes[3]. In addition to enhancing metabolic capacity, enzyme induction can affect the tissue distribution of PCDFs via specific and non-specific protein binding[4]. While enhanced metabolism is a consistent explanation for the increased clearance, the principal cause is believed to stem from differences in partitioning between the liver and adipose tissue, which together constitute >96% of the total body burden of PCDFs. At low concentrations, the portion of total body burden in the liver is low (< 1%), but at high concentrations when induction of the binding proteins is maximal, the hepatic fraction can be as high as 70%, and the liver concentration >15 times that in fat[5]. Thus, at high body concentrations corresponding to saturation of hepatic binding proteins, the liver provides a hugely expanded volume of distribution for PCDFs. The selective hepatic

sequestration leads to an effective dilution of the concentration in adipose compartment. The apparent decline in fat concentration translates to faster clearance rates and shorter half-live estimates. In fact, differences in PCDF clearance half-lives have also been observed between the human infant and adult[6], and the reason for this has been attributed to the rapid growth of adipose mass in the infant.

Our analysis indicates that transition to nonlinear kinetics occurs at about 1-3 ppb. This compares well with the concentration at half maximal hepatic fraction of body burden (300 ng/kg or 0.3 ppb body weight basis or 1.4 ppb fat basis, assuming that the weights of body and adipose are 70 and 15 kg, respectively) predicted by the model of Carrier et al[5]. Our observation of a decreasing trend in concentration-dependent differences in half-lives with respect to the PCDF's degree of chlorination probably reflects the different affinities and capacities of the hepatic binding proteins for the specific PCDFs

Figure 2 shows that the half-lives of penta- and hexaCDF had a positive linear correlation with respect to age of the subjects, with a rate of increase at 0.12 to 0.18 years of half life per year of age. A lesser rising trend was detected for heptaCDF ($y = 0.05x + 0.14$; $r^2 = 0.28$; data not shown).

Figure 2. Correlation of clearance half-lives of penta- and hexaCDF versus the age of Yucheng and Yusho patients.



The factors responsible for the gradual increase in half-lives of PCDFs with age are unclear. Again, it may be related to changes in the body composition that result in a reduced storage capacity for the distribution of PCDFs. Another consistent but less likely explanation may be a deterioration in capability to metabolize PCDFs with advancing age.

Our observations of the concentration- and age-dependence of half-life for the PCDFs are consistent with those reported for 2,3,7,8-tetraCDD[7]. These findings may have important implications for risk assessment. Failure to take these differences into account may grossly underestimate the peak body burden for individuals with high past exposures. This may result in a distorted dose-response relationship that can lead to erroneous risk calculations.

References

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