

LONG TERM HUMAN ELIMINATION AND HALF LIVES OF PCDFs IN YU-CHENG INDIVIDUALS

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Introduction

Pharmacokinetic information on persistent organic pollutants (POPs) including PCDDs, PCDFs and PCBs in humans is essential in order to evaluate the risk of these compounds. Such information is essential in order to estimate both previous and expected exposure and equate this with health effects. This scenario is particularly important for those individuals conspicuously exposed to dioxins, furans, and PCBs whether accidentally or occupationally. The pharmacokinetics of POPs either as commercial mixtures or as individual congeners is relatively well known in laboratory animals. However, data on absorption, distribution, metabolism, and elimination of these contaminants in human subjects is not nearly as well documented.

Using blood concentrations, we previously reported¹ on the elimination and half-lives of PCDFs and PCBs for 16 Yusho individuals from samples collected 14 to 22 years after rice oil consumption in Japan in 1968. The same information was given for 3 Yucheng individuals from blood samples collected 1 to 10 years after rice oil exposure in Taiwan in 1979. For the Yusho case, those results showed that body burdens of the toxic PCDF congeners, 2,3,4,7,8-pentachlorodibenzofuran (PnCDF) and 1,2,3,4,7,8-hexachlorodibenzofuran (HxCDF), were lower than for Yucheng at the stated times of sampling. Half-lives for the two PCDF congeners for Yusho were about 10 years while those for the higher exposed Yucheng group were between 2 and 3 years. The study also indicated that elimination was not linear with higher losses initially followed by slower clearance at lower exposure. We now report a follow up of the elimination of these compounds from the 3 Yucheng individuals with three additional blood sampling times in the last ten years for a total sampling of up to nine points per individual over 20 years. In addition, using blood lipid concentrations from samples taken in 1992, we described² the exposure of 50 Yucheng mothers from a mother/child cohort³. This study showed that PCDFs and PCBs were transplacentally transferred to their offspring with toxic effects. We have re-sampled 12 of these same Yucheng mothers in 1998 and now report for the first time on the elimination of PCDFs from that cohort.

Methods

Original three Yucheng people¹ Whole blood was collected from the three individuals in August 1993 (5 g each), in May 1995 (10-20 g) and in October 1999 (9 g each). Whole blood was the matrix originally used in May 1980 just after the Yucheng outbreak in Taiwan and for consistency was kept the same for all subsequent sampling.

Yucheng mothers^{2,3} Serum (about 2 g) was obtained from twelve mothers in early 1998. Sera

HUMAN EXPERIENCE

were used here since all previous work with the mother/child cohort used this matrix. Serum is preferred to whole blood for analysis as it is easier to handle and lipid determinations can be made using clinical methods. The small amounts of blood available in both exposed groups meant that measurable concentrations of PCDFs and PCBs could only be found in those individuals with high exposure. A pooled sample of 60 mL of serum from Taiwan taken in 1999 was also available for estimation of background or normal population exposure. For the pooled sample of large volume, most PCDD, PCDFs, and PCBs could be measured.

Determination of PCDFs and PCBs Analysis of bloods was carried out by a multi-stage cleanup process followed by determination using gas chromatography-mass spectrometry (GC-MS) as described⁴. In summary, this involved adding carbon-13 surrogate standards for isotope dilution MS, denaturing with specific amounts of ethanol and ammonium sulfate, and extraction with hexane. Lipid determination was performed gravimetrically on the hexane residue. Fat removal was carried out with sulfuric acid followed by separation into a PCB fraction (to be reported later) and a dioxin fraction (PCDDs and PCDFs). The analytes in the latter fraction were measured using GC-MS at 10K on a non-polar column. Although all congeners of the PCDD, PCDF, and PCB classes were determined including those 29 with toxic equivalency factors (TEFs), this report focuses on the two PCDF congeners, PnCDF and HxCDF, which are the hallmark of the rice oil poisoning.

Calculations Half-life estimations were made assuming first order kinetics with logarithmic clearance. Because of the relatively small amounts and different fractions of blood, calculations were made on both a lipid weight and a whole weight basis.

Results and Discussion

Three long term YC individuals The blood concentrations of 2,3,4,7,8-PnCDF, one of the two most important congeners, on a log lipid/time scale are shown in the chart. Even in 1999 more than 20 years after first ingestion of the rice oil, the concentrations of these congeners are still 30-100 times greater than those from contemporary Taiwanese who did not consume the oil. At first inspection it would appear that the clearance is more or less linear. However, when the overall half-lives are divided between the first and last ten years as shown in table 1, it is obvious that elimination was faster in the 1980's (2-3 yr) when exposure was higher (more than about 1-5 ppb) than it was in the 1990's (5-8 yr) at lower exposure (less than about 1 ppb). This result supports previous work that the clearance of these compounds in humans is multiphasic¹.

Yucheng mothers from cohort

Median blood lipid concentrations for PnCDF and HxCDF and corresponding half-lives are shown in table 2 for 10 of the 12 Yu-cheng mothers (2 were excluded due to uncertainties with the lipid content). The median values of the individual half-lives for the two congeners of about five years are similar to those of the three yu-cheng individuals in the second ten years after initial exposure. At that time post exposure, the blood lipid levels of the two groups were similar.

This study in Yu-cheng exposed people has followed the elimination of the toxic PCDF congeners for more than two decades with up to nine blood samplings per individual. It has shown that significant exposure continues to occur and that clearance is slower at lower exposure.

Examination of mothers from a mother/child Yu-cheng cohort more than 10 years post exposure has indicated that the half-lives for elimination are similar to those of the more studied first group

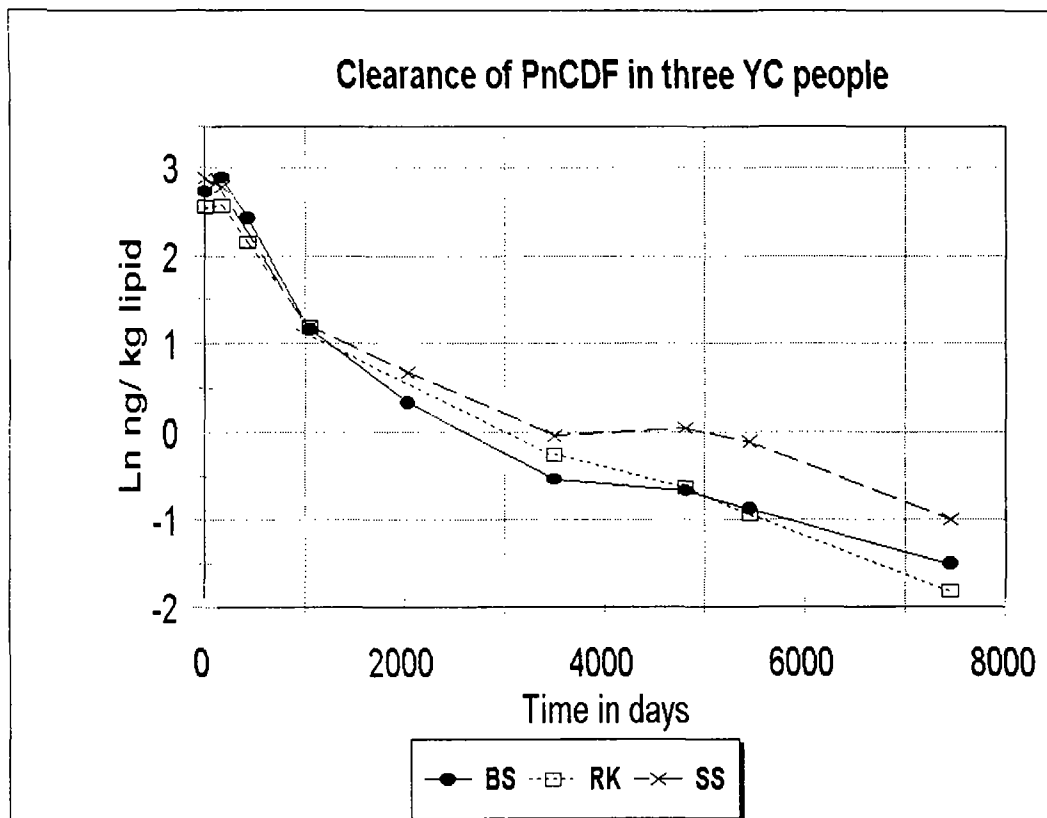
ORGANOHALOGEN COMPOUNDS

HUMAN EXPERIENCE

when blood lipid concentrations were also in the same order of magnitude.

Table 1. Half-lives ($t_{1/2}$ in years) for elimination of PCDFs in three Yucheng individuals						
Individual	BS		RK		SS	
	2,3,4,7,8-PnCDF					
	Number of points	$t_{1/2}$	Number of points	$t_{1/2}$	Number of points	$t_{1/2}$
All Values 1980-1999	9	3.18	8	3.18	8	3.95
First ten years	6	1.87	5	2.33	5	2.24
Last ten years	4	7.48	4	4.70	4	7.30
	1,2,3,4,7,8-HxCDF					
All Values 1980-1999	9	3.19	8	3.86	8	4.01
First ten years	6	2.11	5	2.85	5	2.71
Last ten years	4	6.89	4	6.11	4	6.10

Table 2. Blood lipid PCDF median concentrations (ng/kg) and half-lives of 10 Yu-cheng mothers			
	1992 blood	1998 blood	$t_{1/2}$ years
2,3,4,7,8-HxCDF	1.27	0.53	5.03
1,2,3,4,7,8-HxCDF	3.33	1.87	4.82



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