Fecal Clearance of PCDD/Fs in Occupationally Exposed Persons

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Abstract

A mass balance study was performed on six men with very high body burdens of PCDD/Fs in order to estimate the contribution of fecal excretion to the overall elimination of these compounds. The results showed good correlations between the PCDD/F concentrations in blood and feces. The fecal clearance of the native compounds contributed on average between 37 % (2,3,7,8-Cl_4DD) and 90 % (Cl_8DD) to the total elimination. It is suggested that the ingestion of non-absorbable fat could increase the fecal excretion rate and perhaps shorten the elimination half-lives significantly.

Introduction

One of the most problematic aspects of PCDD/Fs is their very high persistence in humans. Half-lives for the elimination of most of the 2,3,7,8-substituted congeners have been estimated to lie between 3 and 15 years[1)]. Given the high lipophilicity of these compounds, physical loss of body lipids can be expected to be the dominant mechanism for the elimination of native PCDD/Fs. The most important pathway for physical loss of body lipid is excretion with the feces, with fluxes of 5-7 g fat per day[2)]. Measurements of fecal excretion of 2,3,4,7,8-Cl_5DF and 1,2,3,4,7,8-Cl_6DF have yielded half-lives due to this mechanism alone[3)] which were comparable with the estimated total elimination half-lives of the congeners. This suggests that fecal excretion may be responsible for a large part of the overall elimination of 2,3,7,8-substituted PCDD/Fs.

In order to further investigate this hypothesis we studied the fecal excretion of PCDD/Fs in six highly contaminated persons. To clearly separate the fecal clearance of the body burden from excretion of non-absorbed PCDD/Fs taken up with food, both the intake and the excretion of PCDD/Fs were quantified. Fresh blood samples were taken and analyzed to allow calculation of the current body burden. The half-lives and rate constants for fecal clearance were calculated from the body burden and the fecal excretion rates. The overall clearance half-lives were calculated from the change in blood levels between the fresh samples analyzed and data available from samples collected about 5 years previously. By comparing the two elimination rates the contribution of feces excretion to the whole elimination process was estimated.

Experimental Methods

The study was performed in Hamburg with six men aged 41 to 73. The volunteers were former employers of the Boehringer chemical plant. From samples analysed by the ERG in the early nineties they were known to have high PCDD/F blood levels, especially for 2,3,7,8-Cl_4DD, but also for most of the other congeners. They had no intestinal diseases nor other abnormalities concerning eating habits, digestion, or fecal excretion. Table 1 gives information about the volunteers.

Table 1: Age, bodymass index (BMI), present and old blood levels of the volunteers

Volunteer	1	2	3	4	5	6
Age	41	73	62	59	68	59
BMI [kg/m²]	27.8	30.9	30.4	26.8	30.7	28.0
Blood Level [pg I-TEq/g fat] in 1996	272	720	550	300	650	320
varying dates in the years 1990-92	440	1103	1211	714	902	683

Food and feces were collected during two weeks in February 1996. The samples from three days were pooled to give four consecutive periods of three days each. The collection of the feces samples lagged one day behind the food sampling in order to account for the digestive passage. Measurement of PCDD/F uptake was performed using the duplicate method[4]: Duplicate portions of all food and all milk-containing beverages consumed by the volunteers were collected in precleaned glass bottles. After homogenizing with a mixer the samples were divided and one third was frozen for later analysis. All feces produced over the two weeks were collected using vessels lined with aluminium foil. Two blood samples of 40 ml were taken from each volunteer in precleaned glass bottles prepared with heparin. All samples were stored at -20 °C until further processing.

The food and feces samples were freeze dried and homogenized. 80 g of food and 15 g of feces, respectively, were soxhlet-extracted for 20 hours with toluene containing 12 ^{13}C-labelled internal standards. The extraction of the blood samples was performed using the method of PÄPKE ET AL.[5]. The clean up procedure included treatment with H_2SO_4-silica and chromatography on Alumina B Super 1.

The HRGC/HRMS analysis was performed on a VG-Autospec Ultima mass spectrometer, employing a DB5MS column for the hepta- and octa-congeners and a RTX2330 column for the lower chlorinated PCDD/Fs. Recoveries for 2,3,7,8-Cl_4-DD ranged from 80 to 96 %. A comparison of the standards used by ERGO and by the University of Bayreuth was conducted to insure the comparability of the concentrations in the new and old blood samples.

Results and Discussion

Table 2 shows the food uptake and feces excretion on a dry mass basis and a selection of the detected concentrations compared to the results of a background study with 14 adults of 24 to 64 years in North Rhine Westphalia[6]. The dry mass uptake and excretion lie within the range given in the background study. The concentrations of the PCDD/Fs found in food are comparable with levels reported elsewhere for Germany in the mid-nineties[4,6] with one exception: The PCDD/F

levels in Volunteer 5's food were ten times higher. This was traced to contaminated eggs from home-farmed free ranging chickens. These values have been excluded in Table 2. Compared to background the analyzed feces samples showed significantly higher levels of contaminants with very high blood levels, i.e. 2,3,7,8-Cl_4DD, but similar values for compounds with only slightly elevated blood levels, i.e. 2,3,4,7,8-Cl_5DF.

Table 2: Daily intake and excretion compared to a background study[6)]
(concentrations on a dose basis)

		Food Intake		Feces Excretion	
		this study	SCHREY ET AL.[6)]	this study	SCHREY ET AL.[6)]
Dry Mass	[g/d]	340 - 520	330 - 610	25 - 40	28 - 71
I-TEq	[pg/kg·d]	0.33 - 1.1	0.18 - 1.7	6.6 - 16	0.62 - 2.4
2,3,7,8-Cl_4DD	[pg/kg·d]	0.035 - 0.16	0.026 - 0.26	1.6 - 8.5	0.048 - 0.27
2,3,4,7,8-Cl_5DF	[pg/kg·d]	0.24 - 0.82	0.059 - 1.5	0.51 - 2.0	0.48 - 1.7
Cl_8DD	[pg/kg·d]	4.8 - 26	2.4 -17	49 - 475	14 - 68

For the discussion of the fecal clearance behaviour we considered only congeners showing "significant fecal clearance". This was defined as a fecal excretion in a given period at least four times higher than the corresponding food intake. Moreover, all excretion fluxes were corrected for contaminant intake to obtain the fecal excretion attributable to clearance from the body.

As expected, the blood analysis yielded lower levels than had been measured several years previously (Table 1). Nevertheless, the concentrations by far exceeded typical background levels. The blood samples showed an uncommon isomer pattern with unusually high levels of 2,3,7,8-Cl_4DD. This pattern is clearly distinct from regular blood and food patterns. The pattern found in feces was very similar to that in blood for the lower chlorinated congeners, with high concentrations of 2,3,7,8-Cl_4DD (Figure 1). A fairly constant ratio of the lipid based concentrations between blood and feces of about 3 was observed for those congeners. For the higher chlorinated congeners ratios as low as 1 were obtained. This shows that the concentrations in feces are qualitatively dependent on blood concentrations. Additionally, using linear regression we found a quantitative relationship between the concentrations in blood lipid and in feces resulting in good correlation coefficients for most of the congeners with a significant fecal clearance (Table 3).

The overall elimination half-lives were calculated from the concentrations in the two different blood samples assuming first order kinetics. Because a change in the amount of body fat affects blood concentrations and therefore the elimination kinetics, the half-lives were corrected for alterations in body weight. The results ranged from 3.5 years for 1,2,3,4,6,7,8-Cl_7DF to 7.9 years for 2,3,7,8-Cl_4DD and 15 years for 1,2,3,4,7,8-Cl_6DD. These half-lives are very similar to those found in other studies[1)]. No dependence of the overall half-lives on the degree of chlorination was observed. As metabolism is strongly dependent on the number of chlorene substituents[7)], this is an indication that metabolism is not the only clearance pathway.

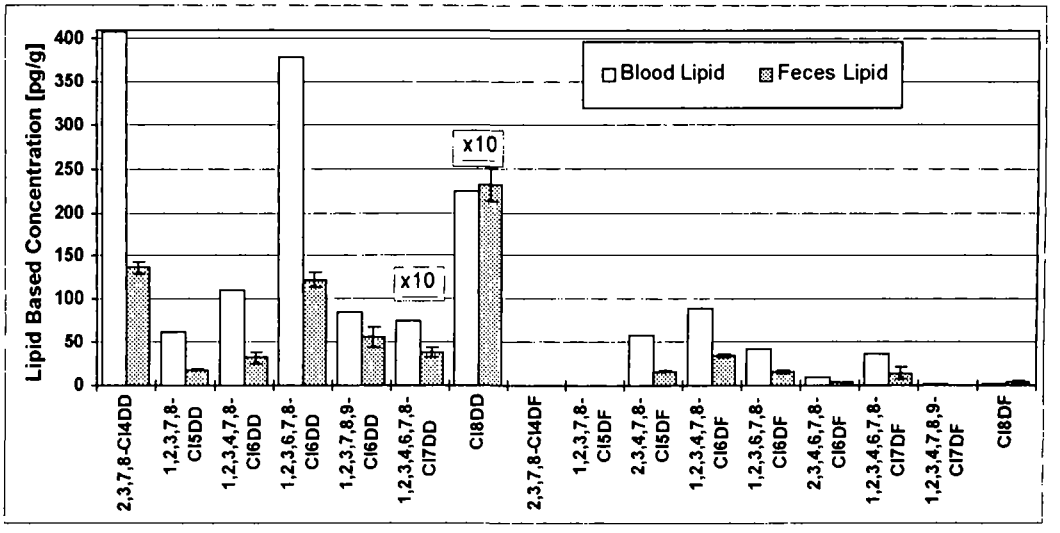

Figure 1: Lipid based concentrations in blood and feces of Volunteer 3
(feces: means and standard deviations of the four sampling periods)

Table 3: Correlation coefficients between blood and feces concentrations
(for all congeners with a significant fecal clearance)

	n	r
2,3,7,8-Cl_4DD	24	0.95
1,2,3,7,8-Cl_5DD	20	0.86
1,2,3,4,7,8-Cl_6DD	20	0.79
1,2,3,6,7,8-Cl_6DD	20	0.89
1,2,3,7,8,9-Cl_6DD	20	0.95
1,2,3,4,6,7,8-Cl_7DD	17	1.00
Cl_8DD	18	0.81
1,2,3,4,7,8-Cl_6DF	20	0.98
1,2,3,6,7,8-Cl_6DF	19	0.99
1,2,3,4,6,7,8-Cl_7DF	10	0.93

n: number of periods with significant fecal clearance

The good correlations between the fecal and blood concentrations indicate that fecal clearance can also be described with a first order kinetic model. The first order rate constant equals the measured daily excretion rate divided by the body burden of the contaminant. To get the body burden we assumed the concentration of PCDD/Fs in body fat to equal that in blood lipids and estimated the body fat content from the body mass index using the empirical equation from KNAPIK ET AL.[8]. The resulting half-lives for elimination due only to fecal excretion ranged from 10 years for Cl_8DD to 22 years for 2,3,7,8-Cl_4DD and 27 years for 1,2,3,7,8-Cl_5DD. Figure 2 shows the first order rate constants for the overall elimination (from the decrease of the blood

levels) and the fecal elimination (from daily excretion) for all compounds with a significant fecal clearance. As the calculation of the fecal elimination rate constants is based on two rather rough assumptions concerning the distribution of PCDD/Fs between blood and body fat and the complete body fat supply, the results should be viewed as approximations.

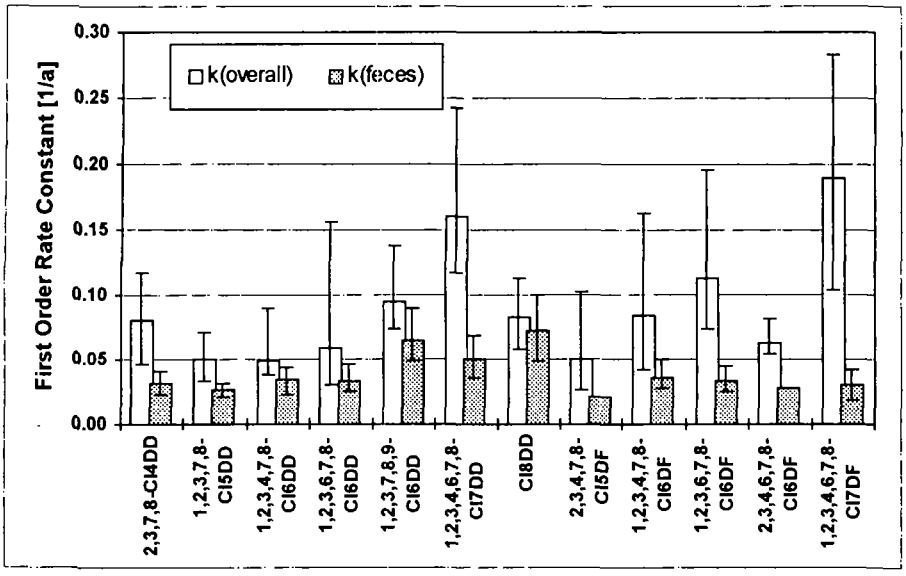

Figure 2: First order rate constants for overall elimination compared to fecal excretion (means with minima and maxima of all cases with significant fecal clearance)

The contribution of the fecal excretion to the overall elimination averages between 37 % (2,3,7,8-Cl_4DD) and 90 % (Cl_8DD) for most of the congeners. Only a few PCDFs show lower results. The relevance of the feces output to the overall elimination seems to increase with increasing chlorination, at least for the PCDDs. On the whole, fecal excretion can probably not explain the total PCDD/F elimination from the human body. Especially for the lower chlorinated congeners there appear to be other important loss pathways such as metabolism and loss of skin lipids.

An important implication of this finding lies in the potential for therapeutical treatments to increase the elimination rate. Assuming that the fecal excretion rate is limited by the fat content of the feces, one could attempt to increase the fat content by ingesting non-absorbable lipids. If the normal feces excretion of 5 g fat per day was quadrupled and the lipid based distribution of PCDD/Fs between the body and the intestine stayed the same, the overall elimination rate would at least be doubled. We feel this hypothesis is worthy of further investigation.

Acknowledgments

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