Studies on the elimination and distribution of individual polychlorinated dibenzofurans (PCDFs) in the liver and adipose tissue of different species

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Introduction

Several studies have been performed in different species on the toxicokinetics of either single PCDFs or mixtures extracted from various sources[1,2]. In general, most of these studies have been performed at a dosage high enough to cause biological effects (e.g. pronounced enzyme induction) in the exposed animals. Many studies did not examine if such effects occurred. In some of the early studies dosage high enough to induce a moribund status were used[3]. Analytical techniches today allow the performance of such studies at dosages low enough to avoid the induction of possibly disturbing biological effects. The intent of the present study was to compare the kinetics in the liver and adipose tissue of a synthetic mixture of PCDFs in several species at a dose where no pronounced biological effects would be expected to occur.

Experimental design

A mixture of nineteen PCDF congeners (Table 1) was given as a single oral dose (0.1 μg of each congener/kg body weight) to male Sprague-Dawley rats, male Hartley guinea pigs and male Golden Syrian hamsters. Postadministration levels of PCDFs in the liver and adipose tissue were determined at 0, 6 and 12 hours as well as 1, 2, 5, 10, 30 and 90 days after the administration. Clean-up of the liver and adipose tissues was performed using basic and acidic silica-, alox and Carbopack C columns. The high resolution GC/MS analyses were done at a mass resolution of 10.000 and the detection limit was 0.1-0.5 pg. The detection level was 0.1-1 ppt depending on isomer and sample measured. Tissue elimination data were analyzed by linear regression analysis using the linear form of the first order equation, i.e. $\ln A = \ln A_0 - k_e \cdot t$. Half-life was calculated based on fat and liver tissue concentrations.

Results
In rats and hamsters, primarily 2,3,7,8-substituted congeners were detected in liver. In contrast, the guinea pig retained most of the congeners administered. In adipose tissue of all three species, both 2,3,7,8- and non-2,3,7,8-substituted congeners were retained. Elimination of the retained congeners followed first order kinetics.

Elimination of individual PCDFs in the liver and adipose tissue of the rat
Only 2,3,7,8-substituted congeners had calculable half-lives in the liver tissue at either timepoint investigated. In adipose tissue half-lives for other congeners were also calculable. The levels of the individual congeners based on group means were in the range 14-2500 pg/g liver and 1-101 pg/g adipose tissue over the course of the study. Elimination of the retained congeners followed first order kinetics with elimination half-lives in the liver in the range 2-52 days and in the adipose tissue in the range 1-125 days. Some of the congeners showed a clear bi-phasic course of elimination.

Elimination of individual PCDFs in the liver and adipose tissue of the hamster
With the exception of 2,3,4,6,7-PeCDF (which had a very short half-life) only 2,3,7,8-substituted congeners had calculable half-lives in the liver tissue at either timepoint investigated. In adipose tissue half-lives for other congeners were also calculable. The levels of the individual congeners based on group means were in the range 3-1700 pg/g liver and 1-65 pg/g adipose tissue over the course of the study. Elimination of the retained congeners followed first order kinetics with elimination half-lives in the liver in the range 2-107 days and in the adipose tissue in the range 3-54 days.

Elimination of individual PCDFs in the liver and adipose tissue of the guinea pig
Out of the 15 congeners for which the half-lives were calculable in the liver, 7 were non-2,3,7,8-substituted congeners. The level of the individual congeners based on group means were in the range 1-270 pg/g liver and 1-170 pg/g adipose tissue over the course of the study. Elimination of the retained congeners followed first order kinetics with elimination half-lives in the liver in the range 1-19 days and in the adipose tissue in the range 3-38 days.

Ratios between liver and adipose tissue concentrations of single PCDF congeners
Only the ratios for 2,3,7,8-substituted congeners have been compared between the three different species. The ratios were noticeably higher in rats and hamsters compared to guinea pigs at Day 1 of the study but became more similar towards the end of the study.

2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF showed significantly longer hepatic retention times than 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF.

Conclusions

Clear differences in retention times were observed between the different species. In the liver of rats and hamsters, half-lives for only 2,3,7,8-substituted congeners were calculable (except for 2,3,4,6,7-PeCDF in hamsters), while in guinea pigs several non-2,3,7,8-substituted PCDFs had calculable half-lives. Lower chlorinated congeners were eliminated relatively fast from the liver tissue of rats and hamsters compared to higher chlorinated congeners. In liver tissue of guinea pig and in adipose tissue of all three species, the number of chlorine atoms did not seem to affect the retention times to the same extent. In adipose tissue, both 2,3,7,8- and non-2,3,7,8-substituted congeners were detected in all three species. 2,3,4,7,8-PeCDF proved to have a much longer retention time in the liver and adipose tissue of rats and hamsters when compared to 1,2,3,7,8-PeCDF while in guinea pigs the hepatic retention times for the two congeners were practically the same.

The fate of the 19 congeners was found to be species and congener dependent. Besides differences in metabolism between various species, other factors such as the relative degree of absorption and structural specific bindings, might also be responsible for a selective liver and adipose tissue retention.

References

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Table 1. The mixture of PCDF congeners administered.

Tetrachlorodibenzofuran	1,3,6,8
	1,3,7,8
	1,2,7,8
	1,4,6,9
	2,3,7,8
	2,3,4,7
	3,4,6,7
Pentachlorodibenzofuran	1,2,4,7,8
	1,2,3,7,8
	2,3,4,8,9
	2,3,4,7,8
	2,3,4,6,7
Hexachlorodibenzofuran	1,2,3,4,7,8
	1,2,3,6,7,8
	1,2,3,4,6,9
	2,3,4,6,7,8
	1,2,3,7,8,9
Heptachlorodibenzofuran	1,2,3,4,6,7,8
Octachlorodibenzofuran	1,2,3,4,5,6,7,8