Distribution and elimination of individual polychlorinated dibenzofurans (PCDFs) in the liver and adipose tissue of rat, hamster, guinea pig and mouse

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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. Since the toxicity of PCDDs and PCDFs is produced by the parent compound rather than the metabolites (1,2,3), metabolism and excretion of these compounds compose a detoxification process. In this regard, toxicokinetics as well as metabolism plays a significant role in determining the overall toxicity of these compounds (4). Most of the earlier studies have been performed at dosages high enough to cause biological effects (e.g.pronounced enzyme induction) in the exposed animals. Many studies did not examine if such effects occurred, and the time course studied was not always long enough, in order to get reliable elimination data. 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 biological effects were expected to occur.

Material and Methods

A mixture of nineteen individual PCDF (Table 1) congeners was given as a single oral dose (0.1 μg of each congener/kg body weight) to male Sprague-Dawley rats, Golden Syrian hamsters, Hartley guinea pigs, and C57Bl/6 mice. Postadministration levels of PCDFs in the liver and adipose tissue were determined at 0, 6 and 12 hours as well as at 1, 2, 5, 10, 30 and 90 days after administration. Clean-up of the liver and adipose tissues was done by open column chromatography. Disposable columns of acidic and basic silica, AlOx and Carbopac C were used. The HRGC-HRMS (VG 70-250S) analyses were done at a mass resolution of R = 10 000 and a detection limit of 0.1-0.5 pg. The detection level was 0.1 - 1 ppt depending on sample and congener 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.

Table 1. The mixture of PCDF congeners administered.

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

Results and Discussion

In rats, mice and hamsters, primarily 2,3,7,8-substituted congeners were retained in liver. In contrast, the guinea pig retained most of the congeners administered. In adipose tissue of all four 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 congeners in the liver and adipose tissue of the rat

The levels of the individual congeners, based on group means, were in the range 1-2500 pg/g liver and 1-105 pg/g adipose tissue over the course of the study. Elimination of the retained congeners followed first order kinetics with half-lives in the liver in the range 2-52 days and in the adipose tissue in the range 2-33 days. The congeners that showed a clear bi-phasic course of elimination in the liver and also the longest half-lives were 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDF and 2,3,4,6,7,8-HxCDF. The ranges of the half-lives for the two phases were 1-9 and 40-52 days, respectively.). The congeners that showed the longest half-lives in adipose tissue were 2,3,4,6,7-PeCDF and 1,2,3,7,8,9-HxCDF.

Elimination of individual congeners in the liver and adipose tissue of the hamster

The levels of the individual congeners, based on group means, were in the range 1-1741 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 1-86 days and in the adipose tissue in the range 2-13 days. The congeners that showed a clear bi-

phasic course of elimination in the liver and also the longest half-lives were all 2,3,7,8-substituted congeners. The ranges for the two phases were 1-2 days and 20-86 days, respectively. All congeners with calculable half-lives showed clear bi-phasic courses of elimination in adipose tissue, except 3,4,6,7-TCDF.

Elimination of individual congeners in the liver and adipose tissue of the guinea pig
The levels of the individual congeners, based on group means, were in the range 1-398 pg/g liver and 1-162 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 1-32 days and in the adipose tissue in the range 6-42 days. The congeners that showed a clear bi-phasic course of elimination in the liver were 1,2,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF and 2,3,4,6,7,8-HxCDF and the longest half-life (32 days) was observed for 2,3,4,6,7-PeCDF. The congeners that showed a clear bi-pasic course of elimination in adipose tissue were 1,2,7,8-TCDF, 1,3,6,8-TCDF and 1,2,4,7,8-PeCDF. The congeners that showed the longest half-lives were 2,3,4,6,7-PeCDF and 1,2,3,4,7,8-HxCDF.

Elimination of individual congeners in the liver and adipose tissue of the mouse
The levels of the individual congeners, based on group means, were in the range 1-587 pg/g liver and 1-276 pg/g adipose tissue over the course of the study. Elimination of the retained congeners followed first order kinetics, with elimination half-lives of the liver in the range 1-47 days and in the adipose tissue in the range 4-51 days. The only congener that showed a clear bi-phasic course of elimination in the liver was 2,3,7,8-TCDF. The ranges for the two phases of all congeners were 1-3 days and 18-47 days, respectively. Three congeners, 2,3,7,8-TCDF, 2,3,4,6,7-PeCDF and 2,3,4,6,7,8-HxCDF showed a clear bi-phasic course of elimination in adipose tissue.

Ratios between liver and adipose tissue concentrations of single PCDF congeners
The liver/adipose tissue concentration ratio was decreasing over the course of the study, for all congeners in rat and most congeners in hamster, while several congeners showed increasing ratios in guinea pig and mouse. The ratios in hamster and rat were noticeably higher for 2,3,4,7,8-PeCDF as well as for some of the hexa-chlorinated congeners as compared to other congeners. In guinea pig and mouse, the concentration ratios tended to be in the same order of magnitude, independent of the chlorination pattern.

Conclusions
Clear differences in retention times were observed between the different species. In the liver of rats, mice and hamsters, half-lives for only 2,3,7,8-substituted congeners were calculable (except for 2,3,4,6,7-PeCDF in mice and 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 of rats, hamsters and mice compared to higher chlorinated congeners. In liver tissue of guinea pig and in adipose tissue of all four species, the chlorination number 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 four species.

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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