Levels of PCDDs, PCDFs and Non-ortho PCBs in Various Human Tumour Tissues

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Introduction

2,3,7,8-substituted polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) as well as various polychlorinated biphenyls (PCBs) are potent tumour promoters in mammalians [1, 2]. Because of their ubiquitous occurrence in the environment and accumulation in the food chain these compounds could also present a risk factor for different types of human cancer. So far little data on PCDD/PCDF concentrations in cancer patients are available. Zober and Päpke [3] examined autopsy material from an eighty-year old man with a high accidental dioxin contamination and found that PCDDs and PCDFs were accumulated in a pancreatic carcinoma twofold beyond the concentrations in blood fat. However, in a recent study we could not detect any accumulation of PCDD or PCDF congeners in mammary carcinoma tissue beyond concentrations in adjacent tumour-free breast tissue [4]. Up to now, data on non-ortho PCBs in cancer patients are unavailable, either in tumour or in tumour-free tissues.

Here we present data on concentrations of PCDDs, PCDFs and non-ortho PCBs in five different tumour tissues from living cancer patients. Additionally, non-ortho PCBs were determined in mammary carcinoma tissue, adjacent tumour-free axillary adipose tissue and in healthy breast tissue. The TEQ values of the non-ortho PCB congeners were compared with the I-TEQ values of PCDDs/PCDFs using the present interim WHO/IPCS TEFs for PCBs [5].

Materials and Methods

Fresh tissue sections from malignant tumours and axillary adipose tissue not needed for histological evaluation or staging were obtained after surgical excision at the University Hospital, Tübingen. Normal breast tissue was obtained from autopsy material of patients deceased from causes other than mammary carcinomas. Tissue samples were frozen at -20 °C until processed. The analytical procedure applied for the determination of PCDDs/PCDFs already has been described in detail elsewhere [4]. The non-ortho PCBs were first separated from other PCBs on a column with 2.5 g Alumina B Super I and further from the PCDDs/PCDFs by chromatography on Florisil (1.8 g) by elution with 40 ml n-heptane/dichloromethane-(98:2). After addition of the non-ortho PCB congeners as $^{13}C_{12}$-labeled standards (6 ng each) the fractions were concentrated and purified on a small column with 0.1 g silica gel and 0.65 g silica gel/44 % conc. H_2SO_4. Analysis was performed by HRGC/HRMS (resolution = 5000) using a 60 m DB-5MS and/or a 30 m DB-Dioxin column.

Results

PCDDs/PCDFs. The PCDD/PCDF concentrations (in pg/g extractable fat) of six carcinoma tissue samples are shown in Table 1. Considering the age of the respective patients, the concentrations of five samples were in good agreement with data from human adipose tissue from Germany [6]. The congener profiles were also very similar (not demonstrated).
The PCDD/PCDF concentrations in the one analyzed hepatic carcinoma were four- to sixteenfold higher than could be expected from the data of non-cancerous human liver tissue [6]. The I-TEQ value was nearly five times higher (Table 3). The accumulation could not be linked with the degree of chlorination. The young female patient had no known occupational exposure to dioxins.

Non-ortho PCBs

The three non-ortho PCB congeners 77, 126 and 169 could be detected in all tumour and healthy breast tissue samples examined (Table 1 and 2). PCB 126 showed the highest levels in almost all samples. However, in the liver tumour the highest concentration was found for PCB 77 and a concentration decrease with increasing degree of chlorination was observed. In the soft tissue sarcoma low levels for all three congeners were detected. The pooled mammary carcinoma sample (n = 2) showed similar values as the corresponding tumour-free axillary adipose tissue samples suggesting that there is no significant accumulation of non-ortho PCBs in mammary tumour tissue. All these three breast tissue samples had high concentrations of non-ortho PCBs (Table 2)

Tumour tissue	liver*	soft tiss. sarcoma	kidney**	kidney	colon	ovar	**mean** (2 - 6)	adip. tiss. (Ref. 6)
Age (years)	27	unknown	72	37	23	44	44	57.7
Fat content (%)	1.3	27.0	14.5	19.2	12.8	0.70	14.8	
2,3,7,8-TCDD	8.8	6.1	4.5	2.0	3.5	4.7	4.2	3.2
1,2,3,7,8-PeCDD	11.7	9.4	12.9	6.3	8.0	23.2	12.0	19.5
Total HxCDDs	73.3	54.5	65.8	40.1	21.4	71.1	50.6	122
1,2,3,4,6,7,8-HpCDD	287	29.6	59.1	32.7	49.8	207	75.5	132
OCDD	1260	60	164	171	337	652	277	642
2,3,7,8-TCDF	5.9	1.3	1.5	0.80	1.1	7.8	2.5	3.1
1,2,3,7,8-PeCDF	4.6	1.1	1.3	0.15	0.59	2.9	1.2	-
2,3,4,7,8-PeCDF	43.3	41.7	43.0	19.3	19.9	44.5	33.7	50.1
Total HxCDFs	100	17.3	22.4	12.1	13.2	45.9	22.2	48.8
1,2,3,4,6,7,8-HpCDF	129	6.2	11.4	5.4	9.0	14.9	9.4	21.4
1,2,3,4,7,8,9-HpCDF	8.5	(<1.2)	(<0.93)	0.49	0.53	(<9.1)	0.51	-
OCDF	34.5	n.n.	8.7	1.2	2.8	11.5	6.0	5.4
I-TEQ for PCDD/PCDF	**60.0**	**39.4**	**42.4**	**20.7**	**21.9**	**54.1**	**35.7**	**57.6**
PCB 77	329	3.8	35.0					
PCB 126	106	13.2	230					
PCB 169	73.5	10.3	141					
TEQ for non-o PCBs	**11.5**	**1.4**	**24.4**					
TEQ non-o PCBs in % I-TEQ PCDD/PCDF	**19**	**3.6**	**58**					

* PCDD/PCDF values: mean of two repetitive analyses

** PCB values: mean of two repetitive analyses
Figures given in brackets are detection limits

Table 1. Concentrations of PCDDs, PCDFs and non-ortho PCBs in various human tumour tissues in pg/g extractable fat

Mammary tissue	breast glandular tissue	breast glandular tissue**	mammary carcinoma (n = 2)**	axillary adipose tissue	axillary adipose tissue	concentration ratio tumour/ axillary adipose tis.
Age (years)	70	40	81	80	81	
Fat content (%)	83.8	39.5	20.0	71.7	73.0	
PCB 77	28.3	45.9	331	504	444	0.70
PCB 126	427	417	733	1117	769	0.78
PCB 169	170	142	291	290	208	1.17
TEQ for non-o PCBs	**44.4**	**43.1**	**76.4**	**114.8**	**79.2**	**0.79**
I-TEQ for PCDD/PCDF*	51.1	29.1	67.9	50.3	43.6	1.45
TEQ non-o PCBs in % I-TEQ PCDD/PCDF	**87**	**148**	**113**	**228**	**182**	

* Ref. 4 ** mean of two repetitive analyses

Table 2. Concentrations of non-ortho PCBs in healthy breast tissue, mammary carcinoma tissue and corresponding axillary adipose tissue, compared with PCDD/PCDF concentrations (in pg/g extractable fat)

Sample	hepatic carcinoma	liver tissue (Ref. 6) (n = 25)	concentration ratio tumour/ liver tissue
Age (years)	27	56.8	
2,3,7,8-TCDD	8.8	1.1	**8.0**
1,2,3,7,8-PeCDD	11.7	1.6	**7.3**
Total HxCDDs	73.3	14.6	**5.0**
1,2,3,4,6,7,8-HpCDD	287	65.5	**4.4**
OctaCDD	1260	363	**3.5**
2,3,7,8-TCDF	5.9	0.5	**11.8**
2,3,4,7,8-PeCDF	43.3	11.7	**3.7**
Total HxCDFs	100	22.1	**4.5**
1,2,3,4,6,7,8-HpCDF	129	13.9	**9.3**
OctaCDF	34.5	2.2	**15.7**
I-TEQ PCDD/PCDF	**60.0**	**12.6**	**4.7**

Table 3. Comparison of the PCDD/PCDF concentrations in a hepatic carcinoma with those found on average in non-cancerous liver tissue from adults in the south of Germany [6)]

Figure 1 demonstrates that in all samples PCB 126 was responsible for almost the entire TEQ value of the non-ortho PCBs. In most samples the TEQ value of the non-ortho PCBs was similar to the I-TEQ value of PCDDs/PCDFs. In some of these samples (axillary adipose tissue) the TEQ-value of the PCBs was even twice as high as compared to the I-TEQ of PCDDs/PCDFs. However, in the hepatic carcinoma and especially in the soft tissue sarcoma the contribution of the non-ortho PCBs to the total dioxin-like TEQ value was much lower.

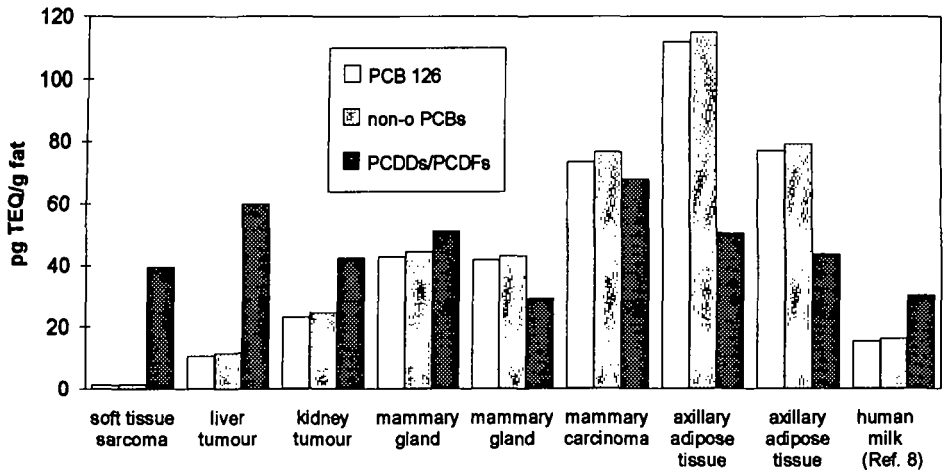

Figure 1. Comparison of the TEQ values of PCB 126, non-ortho PCBs and PCDDs/PCDFs in various human malignant tumour tissues and tumour-free axillary adipose tissue

Discussion

Our analytical data from five different tumour tissues (soft tissue, kidney, colon, ovary and breast) from living cancer patients without known occupational exposure to PCDDs, PCDFs or PCBs do not show any relevant accumulation of PCDD, PCDF or non-ortho PCB congeners beyond concentrations in tumour-free tissue. However, in the one hepatic carcinoma we found an accumulation of all 2,3,7,8-substituted PCDD/PCDF congeners which was on average nearly fivefold beyond concentrations in tumour-free liver tissue. In this sample the non-ortho PCBs showed a different congener distribution than that found by Myata et al. in liver tissue from two victims of fatal accidents [7].

Since the sources for PCDDs/PCDFs and PCBs are not necessarily identical we must not expect any correlation of PCDD/PCDF and PCB levels in human tissues. Further, the unusual congener distribution in the one hepatic carcinoma sample and comparatively low levels for non-ortho PCBs in the soft tissue sarcoma sample suggest that there are some differences in the toxicokinetics of PCDDs/PCDFs and non-ortho PCBs in humans. This is supported by the fact that unexpectedly low PCDD/PCDF concentrations found in tumour-free breast adipose tissue from four mammary cancer patients [4] were not observed for the non-ortho PCBs in two of these patients. The analysis of further samples is underway. Patterns of non-ortho PCBs similar to the ones in our samples also were found in human milk from the Netherlands [8], Sweden [9], and from Canada [10] as well as in blood fat from Finnish people [11] and Vietnam veterans [12].

Our data demonstrate that, according to the present TEF-concept, the non-ortho PCBs could have the same or even higher toxic relevance for the human body burden than PCDDs/PCDFs. In human milk the TEQ value of non-ortho PCBs amounts to about one half of the I-TEQ value of PCDDs/PCDFs [5, 8, 10] while the other half is contributed by the mono-ortho PCBs [5, 8]. Together these congeners even slightly exceed the TEQ contribution of PCDDs/PCDFs. However, widely applied procedures of PCB analysis still ignore the relevance of non- and mono-ortho PCBs. These procedures only analyze for the di-ortho congeners disregarding the fact that these congeners contribute only little to the TEQ value in spite of their relatively high tissue levels.

Since some PCBs and especially their monohydroxy metabolites display estrogenic properties they might function as promoters in the pathogenesis of breast cancer [2]. The relevance

of the three existing studies investigating the role of PCBs as a possible risk factor for breast cancer [13, 14, 15] is again limited by the fact that PCBs were only quantified in total and calculated as Aroclor 1260. This procedure does not take into account the large differences in toxic potency and in the mechanisms of action of the various PCB congeners and their metabolites. Therefore, the relevance of PCBs in the pathogenesis of breast cancer will only be elucidated if further investigations include an isomer-specific determination of the different non-, mono-, and diortho-substituted PCB congeners and their monohydroxy metabolites in mammary carcinoma and healthy breast tissue.

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