

Six measurements of PCDD/PCDF and five measurements of brain function with Single Photon Emission Computed Tomography (SPECT) in one individual. A case-study.

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Abstract

Six repeated measurements of PCDD/F in blood lipids and five repeated semiquantitative measurements of the regional cerebral blood flow (rCBF) with SPECT (^{99m}Tc -HMPAO) between 1990 and 1997 in one individual with moderate exposure to PCDD/F lead to three conclusions:

1. There is no influence of ageing on PCDD/F in this subject.
2. Loss of lipids and body mass index elevate the body burden of PCDD/F.
3. The reduction of the rCBF is related to the body burden of the most toxic congeners of PCDD/F.

Introduction

PCDD/F concentrations have been analyzed in exposed and unexposed populations. The background body burden and increased internal doses can be distinguished. Data show an age-dependency of the PCDD/F-body burden ¹⁾ and a secular trend toward lower internal doses. ^{2,3)}

The patient was born 1927 in Hamburg and emigrated to the USA. He operated a special wood factory in Pennsylvania from 1950 to 1990. In 1973 the factory buildings were treated with wood preservatives like pentachlorophenol, which were imported from Germany. The patient sought medical help in Germany. After recognizing the problem first step was to stop exposure in 1990. In Jan. 1991 PCP in his serum was 8.0 µg/l.

The wife of the patient was born 1920 in the USA. She never had any exposure to PCDD/F. Therefore she was taken as background control with two measurements of PCDD/F. The exposed husband became ill in the years before 1990. Colitis and other diseases arise. The most symptoms were neuropsychological like vertigo, cephalgia, loss of concentration, energy and spontaneous doing, neurasthenia. The highest stage of these symptoms were in 1993 to 1994, after loss of weight due to a serious infection, which was not caused from PCDD/F.

The objectives of these symptoms were analyzed with SPECT of brain.

This case study was driven by two hypotheses:

1. PCDD/F are stored in adipose tissue, and would be liberated into serum, and thus increase in concentration, upon weight loss.
2. CYP1A1 is known to be induced by PCDD/PCDF and found in the pyramidal cells of the neopallium and in the neurones of the central thalamic nuclei of the rat ⁴⁾. There may be similar conditions in humans. Then different body burden with TCDD (and other congeners) would result to different findings in measurements of brain function with SPECT.

Methods

PCDD/F in blood lipid of the exposed man were analyzed six times, PCDD/F of the unexposed woman were analyzed two times since 1990. Blood samples were determined by the ERGO Company, Hamburg. Dioxins were extracted from 40 to 60 g samples of whole blood and measured by gas chromatography/mass spectroscopy ⁵⁾. The findings are expressed in pg/g extractable lipids, i.e., part-per-trillion (ppt) concentration on lipid basis. The sum of PCDD/F is expressed as International TEQ ⁶⁾.

Lipid concentration was determined as the sum of cholesterol and triglycerides. The body-mass index was defined as the body weight in kg divided by the height*height in m².

The regional cerebral blood flow (rCBF) of the exposed man was analyzed five times since 1990. The Nuclear-Radiologist Dr. E.-U.Bieler, Hamburg, performed the Single Photon Emission Computed Tomographies. Tracer of these SPECT was the high lipophilic substance 99^m-Tc-HMPAO^{7,8)}. The measurements in this SPECT follow the otherwise described method of "region of interest"(ROI)⁹⁾. The regional cerebral blood flow is expressed in percent (semiquantitative). A reduction of rCBF³ 10 percent in a cortex area of 3 x 3 cm around is commonly a sign of disease.

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Results and Discussion

Changes in PCDD/F concentration, body mass index and lipids of the exposed man and changes in PCDD/F of the unexposed women, which is seven years older than he, are shown in table 1.

Table 1

PCDD/F concentration of control and the exposed individual (with body mass index and lipids)

exposure	date of	Age	ITEQ	2,3,7,8-Tetra-	1,2,3,7,8-Penta-	BMI	Cholesterol +
	sample		(pg/g)	CDD (pg/g)	CDD (pg/g)	(kg/m ²)	Trigl. (mg/dl)
PCDD/F	10.09.90	63.1	34.3	4.9	9.7	26.00	405
background	01.11.91	71.3	20.9	5.7	6.5		
PCDD/F	13.10.92	65.2	29.7	4.6	9.0	24.84	410
PCDD/F	12.06.94	66.9	56.2	6.9	17.2	19.98	291
background	02.03.95	74.6	18.0	2.9	6.1		
PCDD/F	16.04.95	67.7	30.1	4.2	9.8	23.33	415
PCDD/F	02.04.96	68.7	32.5	4.6	10.6	21.86	380
PCDD/F	22.04.97	69.7	29.6	4.8	10.0	22.15	308

ITEQ of exposed was found significant higher than ITEQ of unexposed (Mann-Whitney test, p < 0,02).

A reduction in the body burden in both over calendar time could not be detected (figure 1).

Figure 1: Calendar year and ITEQ between 1990 and 1997

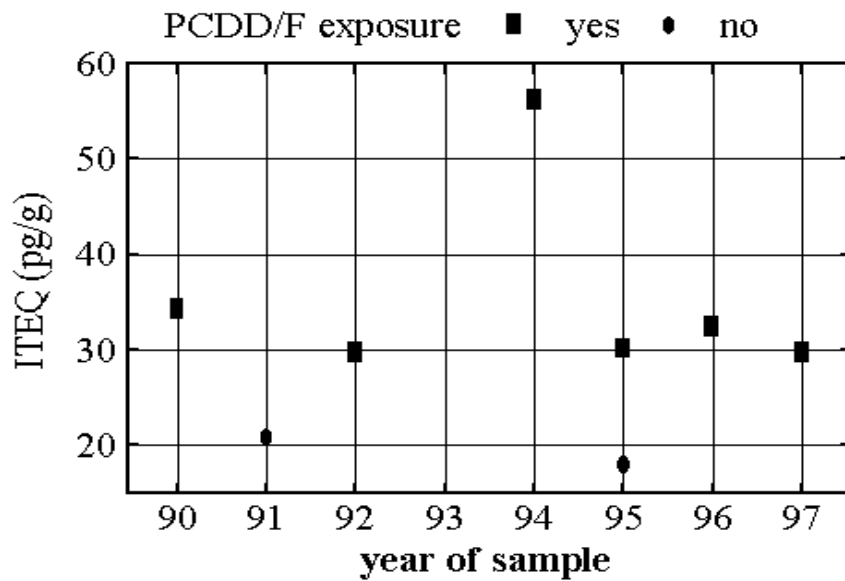


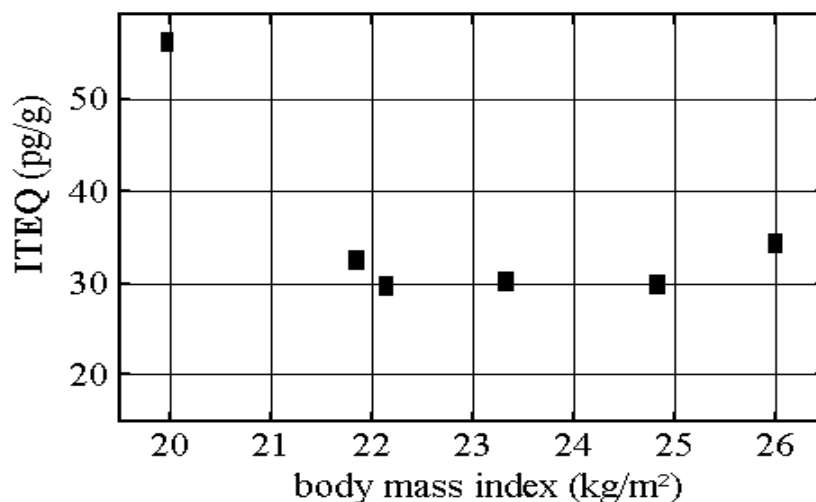
Figure 1 did not indicate an increasing level of ITEQ in ageing of both exposed or not exposed.

However figure 2 shows that reduction in body mass index (also in the sum of cholesterol and triglycerides) of about 25 % in the exposed man is related to an increase in ITEQ of 90 %. The secular trend might be masked by the change of lipid concentration in 1994.

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Figure 2. I-TEQ (NATO/CCMS) and body mass index



Excluding the one increased concentration, then PCDD/F plotted over the body mass index (figure 2) does not show a diluting effect as supposed by Pless et al. 1993¹⁰. A loss of weight seems to be associated with redistribution of PCDD/F and a higher lipid concentration. A moderate exposed person can during his life be exposed to higher concentration when losing weight. The increase can also trigger the development of new and the worsening of existing symptoms. Backward estimation of

PCDD/F is applied to calculate the potential risk of disease for past exposures ¹¹⁾. It is often assumed a one compartment model and a long elimination half-life of most of the 2,3,7,8-substituted PCDD/F congeners. Factors associated with lipid mobilisation may modify the body burden. The data suggest a need to take changes in body fat along with other indices of exposure into account when attempting to determine past exposures as risk factors for disorders/diseases.

Table 2 lists age at sample, age at SPECT and reduced rCBF (in prefrontal and premotoric regions of brain). The SPECT findings in 1993 (age 66,2) include the opercula fronto-parietale and fronto-temporale. The most significant reduction of rCBF was 24 percent.

Table 2

Age at sample, age at SPECT and reduction of rCBF

age at sample	age at SPECT brain	Reduced rCBF
65.2	63.8	8%
66.9	66.2	24%
67.7	67.3	14%
68.7	68.7	15%
69.7	69.8	13%

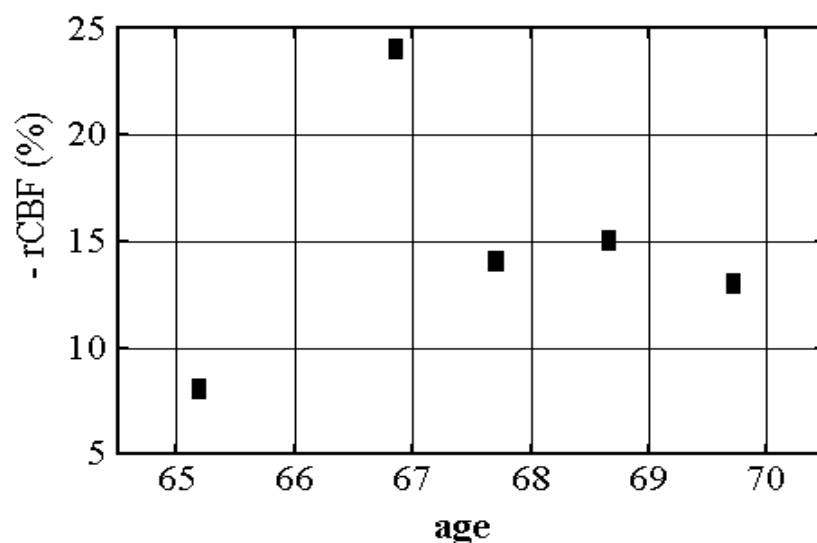
Ageing is often an important confounder of physiological or medical findings. A reduction of rCBF in SPECT is seen in pathological ageing.

However reduction of rCBF in relationship of ageing is not seen in figure 3.

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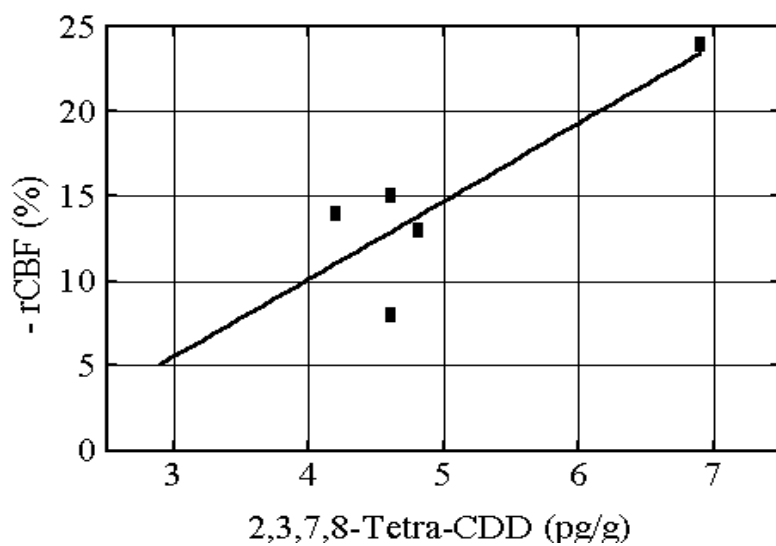
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Figure 3 Reduction of rCBF and age



The both most toxic PCDD/F-Isomers were plotted against rCBF (figure 4 and figure 5).

Figure 4. Reduction of rCBF and 2,3,7,8-Tetra-CDD



Linear regression gives the following equation:

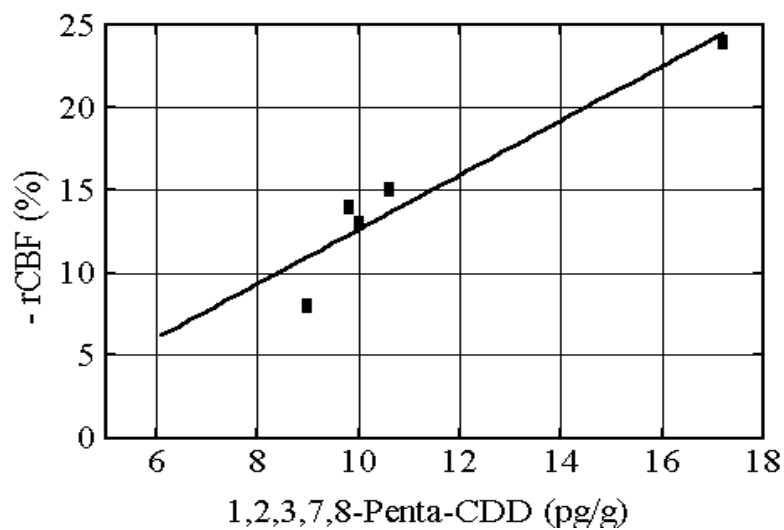
$$-rCBF = -8.0 + 4.6 \cdot (2,3,7,8\text{-Tetra-CDD}) \quad (R=0.85).$$

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Figure 5

Reduction of rCBF and 1,2,3,7,8-Penta-CDD



Linear regression gives the following equation:

$$-rCBF = -3.8 + 1.6 \cdot (1,2,3,7,8\text{-Penta-CDD}) \quad (R=0.94)$$

The neuropsychological symptoms were most seriously at the age of 66, when reduction of rCBF was the highest. The symptoms of toxic encephalopathy ¹²⁾ increased in time of the highest levels of 2,3,7,8-Tetra-CDD and 1,2,3,7,8-Penta-CDD. In 1993 Zober and Paepke ¹³⁾ published levels of 2,3,7,8-Tetra-CDD in premortal blood and in postmortal brain of three workers from BASF company. Case 3 in table 3 is a worker, who lost extremely body mass before he died. The loss of weight caused a higher level of 2,3,7,8-TCDD in blood lipid (7482 pg/g). 25 percent of this concentration in blood was concentrated in brain.

Table 3

2,3,7,8-Tetra-CDD in blood lipid and in brain (pg/g) of three BASF workers ¹³⁾

case	2,3,7,8-TCDD blood	2,3,7,8-TCDD brain	ratio brain/blood
1	255	36	0.14
2	32	7	0.22
3	7482	2457	0.33

After losing weight weight PCDD/F from adipose tissue will be found in blood lipids. 12-15 percent of this blood enter normally the blood-brain barrier (BBB) via arterial blood flow. High lipophilic molecules like 2,3,7,8-Tetra-CDD and 1,2,3,7,8-Penta-CDD (molecular weight smaller than 400 Dalton) are perfectly able to diffuse through the "tight epithelium"¹⁴⁾ of BBB into neurones ¹⁵⁾.

The high toxic 2,3,7,8-Tetra-CDD and 1,2,3,7,8-Penta-CDD are causing pathological SPECT brain findings in this not extremely exposed subject.

These congeners seem to be permeable through the blood-brain barrier in vivo. They may induce the CYP1A1 existing in some brain compartments.

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