RELATIVE POTENCY ESTIMATION OF DIOXIN-LIKE ACTIVITY BY DIOXINS, FURANS AND CO-PLANAR PCBS IN HUMAN ADULTS USING THYROID VOLUME AND FT4 AS OUTCOMES

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Introduction

The re-evaluation of the Toxicity Equivalency Factors (TEFs) for dioxins, dibenzofurans and co-planar PCBs is a continuous process[1]. The current TEFs were derived mainly from *in-vitro* and animal studies and the contribution of human data to this issue is rather limited. The objective of this study was an attempt to use the data on background serum concentrations of dioxins, dibenzofurans and co-planar PCBs for estimation of their relative potencies by relating them to two thyroid outcomes, the thyroid volume and FT4 serum concentration.

Materials and methods

The PCBRISK (EU 5thFP project Evaluating Human Health Risk from Low-dose and Long-term PCB Exposure QLK4-CT-2000-00488) database, collected within 2002-2003, containing data on concentration of PCDDs, PCDFs and coplanar PCBs, determined by gas chromatography coupled to high-resolution mass spectrometry, in 322 adult human sera, has been cleaned and verified. Only concentration data >LOD were used. Cross-tabulation has shown that 71 serum concentration data on 2,3,7,8-TCDD were available. Thyroid volume, determined by ultrasound, and FT4 serum concentration were chosen as health outcomes and were related to the PCDDs, PCDFs and coplanar PCBs serum concentrations. Bivariate regressions between the outcome and concentration of individual congeners indicated direction of change of each outcome. Multiple regressions with backwards elimination were used for identification of signal congeners or their subsets.
The benchmark concentrations (BMCs) were calculated for the thyroid volume and FT4 serum concentration, for each individual PCDD, PCDF and coplanar PCB congener. Sex and age were always taken into consideration as confounders. Individual congeners were included as confounders on the basis of the percentage of detection and concentration level. BMC(1)/BMC(*i*) is a relative potency factor (RPF(*i*)) indicating relative toxicity of the *i*-th chemical compared to the 1th chemical. The resulting RPFs were compared with tabulated I-TEFs and WHO-TEFs[1,2].

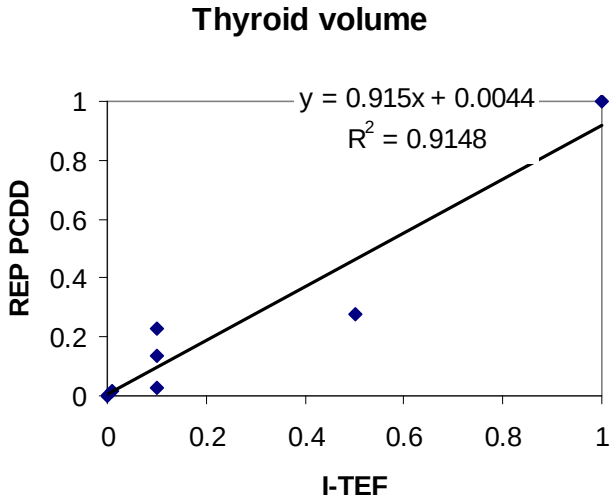
Results and discussion

The bivariate regressions have shown that PCDDs are associated with a decrease of the thyroid volume and FT4 level, PCDFs, depending on congener, with both decrease and increase of the thyroid volume and FT4 level, while co-planar PCBs increase the thyroid volume and decrease FT4 level. For both the thyroid volume and FT4 serum level the ratios of the slopes for individual congeners to the 2,3,7,8-TCDD slope were approximately related to published TEFs. Such a relation did not appear for PCDFs and co-planar PCBs. Multiple regressions with backwards elimination confirmed as a signal congener only 2,3,7,8-TCDD for thyroid volume. The BMCs for thyroid volume and FT4 associated with 2,3,7,8-TCDD concentration were compared with the BMCs of individual PCDD, PCDF and coplanar PCB congeners and were considered to be the RPFs. The relations between these two variables were approximated by linear ($y= bx+a$) or power ($y=ax^b$) function as considered meaningful. The parameter values and coefficients of determination R^2 for PCDDs are shown in Table. The strongest relation was found between the RFPs and I-TEFs for PCDDs and thyroid volume shown in Figure. For PCDFs and co-planar PCBs the R^2 values did not indicate any correlation.

	Parameter	Thyroid volume		FT4		FT4 when 1,2,3,4,7,8-HxCDD was excluded	
		I-TEF	WHO-TEF	I-TEF	WHO-TEF	I-TEF	WHO-TEF
Linear function	a	0.0044	0.0427	0.6017	0.59	0.279	0.2422
	b	0.915***	0.601*	0.5864	0.495	0.9126	0.8063^{+}
	R^2	0.915	0.6169	0.0851	0.0948	0.4817	0.5798
Power function	a		0.4712	1.996	1.533	1.415	1.0978
	b		0.6827	0.7058	0.5931	0.681	0.5729
	R^2		0.8652	0.7226	0.738	0.8287	0.8488

*** p≤0.001, * p≤0.05, + p≤0.1

By comparing the R^2 values in Table it can be concluded that: The RPFs for PCDDs correlate better with I-TEFs when linear function was used as compared with WHO-TEFs. When compared with WHO-TEFs power function described the relationship better. With FT4 as an outcome power function proved a relationship between RPFs and TEFs. When the data for the outlying 1,2,3,4,7,8-HxCDD was excluded the R^2 value increased.



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References:

1. Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. (2006); *Toxicol Sci*. 93(2):223-41
2. Kutz FW, Donald G, Barnes DG, Erich W, Bretthauer EW, David P, Bottimore DP, Greim H. (1990); *Environ Toxicol Chem.* 26(1&4): 99-109