EXPLORING POSSIBLE DOSE-RESPONSE RELATIONSHIPS BETWEEN EXPOSURE TO PCDDs/Fs AND ACQUIRED DYSCHROMATOPSIA IN HUMANS

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Introduction

There is evidence that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) causes toxic neuropathy in rats[1] whereas a causal relationship with human peripheral neuropathy and effects on the peripheral nervous system are still discussed[2,3]. The aim of our present investigation is the exploration of possible neurotoxical effects of TCDD and its congeners. Color vision tests are a sensitive method to test for the presence of neurotoxicity[4]. In humans, the existence of color vision impairment after exposure to polychlorinated dibenzo-*p*-dioxins and -furans (PCDDs/Fs) has not been investigated, yet. Farnsworth Panel D-15 test[5] and Lanthony Desaturated Panel D-15 test[6] were used to test for acquired dyschromatopsia. Whereas the Farnsworth test enables the detection of median to serious dyschromatopsia, the Lanthony test is more directed to screen for moderate syndromes (luminescence and saturation of the color is reduced). Due to more pale and less pronounced colors this test is better suited to determine small effects.

We have focussed in the present investigation on the question whether there is a potential ability of TCDD exposure to elicit neurotoxical effects which express themselves as alterations of color vision in humans, and if so, whether a dose-response relationship between the degree of acquired dyschromatopsia and the internal body burden of TCDD can be established. We used data of a German cohort of workers occupationally exposed to PCDDs/Fs reported previously[7].

Materials and Methods

The cohort consisted of a sub-population of former regular employees of chemical plants in Ingelheim and Hamburg, Germany, where exposure to PCDDs/Fs had occurred in the production of lindane and 2,4,5-trichlorophenol, and for whom bio-monitoring data had been obtained between 1986 and 1994[8,9]. From the comprehensive medical examination of the workers we report here parameters which have been associated with visual problems e.g. age, smoking, overweight and blood pressure. Workers with diagnosed eye disease, and other diseases which cause dyschromatopsia were excluded from this investigation. During the medical examinations color vision tests were performed under standard lightening conditions[10,11]. Vision acuity was tested using Oculus (Wetzlar) system. Congenital dyschromatopsia was diagnosed with the Ishihara plates and with the Heidelberg Anomaloscope. Left and right eyes were examined separately in *individually randomized* sequence. The examination distance between eye and the D-15 panel was 50 cm. Farnsworth Panel D-15 test consists of a 15 numbered movable color caps C1 to C15 and one reference cap P. The colors C1-C15 have to be ordered according to similarity by the subject after being mixed in a random fashion by the medical examiner. There exists a normal sequence

C1-C15 of the colors starting with P and resulting in a standard color tone circle. Each subjects's color vision ability was determined by his individual sequence D1-D15 and the color confusion index (CCI)[12] calculated as the ratio of the total color difference score (TCDS) of the subjects' sequence D1-D15 and the TCDS of the correct sequence C1-C15. The TCDS is a matrix of "distances" in the virtual color space between the 16 colors of the respective panel. For a detailed explanation and the complete numerical distance matrix see Muttray et al.[11]. The Lanthony test is identical to the Farnsworth test in its application and evaluation except that the color distances are smaller. Acquired dyschromatopsia of each subject was quantified by the Farnsworth CCI and the Lanthony CCI. Vision without color confusion results in a CCI value of 1. A value larger than 1 indicates deviations from this status. CCI values were determined both for the right and for the left eye in a randomized order. Since an effect of learning is plausible the primary endpoint chosen for this analysis is the CCI value obtained with the first eye examined.

This analysis was based on data of 73 workers, for whom both PCDD/F bio-monitoring data and color vision data were available and who fulfilled the inclusion criteria. Color vision tests were performed during a thorough medical examination in the Inst. of Occup., Social and Environ. Medicine in Mainz (A. M.). PCDD/F levels, determined on various occasions during 1986-1994, were extrapolated to the day of medical examination by using a simple first-order elimination kinetic with half-lives reported previously[13]. TEQ-values were calculated by using the WHO concept[14]. Population characteristics and CCIs were described by median, minimum and maximum values. Group differences were tested with Wilcoxon rank sum test. Spearman rank correlation coefficient was used to assess associations between TCDD/TEQ concentration, basic health variables and confounders and the Farnsworth and Lanthony outcome variables. For regression analyses some numerical variables were logarithmically transformed (base 10), whereas smoking and alcohol drinking habit were categorized into ordinal scales, using approximate percentiles of the respective frequency distributions. The color vision was regressed on log (TCDD+1) or $\log_{10}$(TEQ+1),respectively, age, smoking, alcohol-score, body mass, and blood pressure. A significance level of 0.05 was chosen. Due to the exploratory nature of this study all p-values were two-sided and no adjustment for multiple testing was made; instead, the findings were interpreted in light of biological and clinical consistency. The SAS software system was used for statistical computations (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

The characteristics of 73 workers are described in Table 1. More than 75% were without color confusion in the Farnsworth test (CCI value=1) excluding such a median to serious dyschromatopsia in this cohort. In contrast, only 20/69 (27.4%) of the workers showed no color confusion in the Lanthony test (CCI value = 1); 28 (38.4%) had CCI values larger than 1 and smaller than 1.25 and 25(34.3%) had CCI values larger than 1.25. TCDD concentration in body lipid and TEQ values were highest in the group of workers with a CCI > 1.25 and lowest in the group of worker with normal CCI. The other parameters examined showed no such differences between the three CCI groups, except current smoking which was less prevalent for workers with CCI > 1.25 (p=0.04). Spearman rank correlation coefficients are presented in Table 2. A statistically significant correlation was observed both between concentrations (p=0.02) and TEQ values (p = 0.01) and the first-eye Lanthony CCI. The significance of this finding could be confirmed in a multivariable linear regression of first-eye CCI on log10 (TCDD+1) with p=0.02 and on log10 (TEQ+1) with p=0.01 in the presence of body mass index and smoking as possible

Table 1: Characteristics of all study participants and subdivided by the level of acquired dyschromatoposia assessed by Lanthony color confusion index (CCI-FIRST) determined for the first eye examined; n= 73. #Median (minimum, maximum), §percentage, LD lower than detection limit. Statistically significant differences ($p<0.05$) are marked bold.

	Total Population#		CCI=1 20(27.4%)	1<CCI ≤ 1.25 28(38.4%)	1.25<CCI 25(34.3%)
2,3,7,8 TCDD (ppt)	28.56	(LD, 315.40)	**13.80**	**28.67**	**42.46**
TEQ value (ppt)	112.44	(2.23, 936.96)	**55.70**	**125.91**	**162.93**
body mass index	26.8	(16.4, 38.1)	26.19	26.5	26.8
blood pressure (systol.)	130	(110, 185)	130	130	140
blood pressure (diastol.)	85	(70, 120)	87.5	85	90
age (years)	51.2	(26.9, 72.6)	54.0	49.0	53.5
alcohol (per week) §					
none	20.8		25.0	18.5	20.0
< 50 g	26.4		20.0	29.6	28.0
50 - 130 g	26.4		30.0	18.5	32.0
> 130 g	26.6		25.0	33.3	20.0
current smoker (yes) §	44.4		**55.0**	**53.6**	**25.0**

confounders. Similar significant results were obtained with categorical regression applied to the CCI categories defined in Table 1 on the right. Our results show for the first time an association of higher PCDD/F body burden and moderate dyschromatopsia syndromes in heavily exposed workers in chemical industry. In contrast to previous results[11] age was not correlated with CCI and a current smoking was negatively correlated with CCI. Therefore, the results have to be interpreted cautiously for the existence of a causal relationship because of possible selection effects leading to this sub-population of a much larger cohort[8,9],

Table 2: Spearman Rank Correlation (p-values) between the Lanthony color confusion index (CCI) and the TCDD/TEQ levels and basic population characteristics. Statistically significant correlations ($p<0.05$) are marked bold.

	Lanthony CCI FIST EYE		SECOND EYE	
2,3,7,8 -TCDD	**0.29**	(0.017)	0.20	(0.10)
TEQ value[14]	**0.30**	(0.013)	0.15	(0.2)
body mass index	0.03	(0.8)	-0.03	(0.8)
blood pressure (systol.)	0.18	(0.13)	0.13	(0.3)
blood pressure (diastol.)	0.07	(0.5)	0.09	(0.5)
age	0.04	(0.7)	0.12	(0.3)
alcohol consumption	0.07	(0.6)	0.16	(0.17)
currently smoking	**-0.24**	(0.04)	-0.18	(0.13)

because of sensitivity on model choice and distribution assumptions of explanatory variables, and, because of missing information on co-exposure to other agents impairing color vision. Chronic solvent exposure has been related to acquired dyschromatopsia (mainly blue-yellow deficiency)[11]. Unfortunately, reliable data on solvent exposure were not obtainable for a sufficient number of the workers in our sub-cohort such that this confounder could not be assessed. However, we had excluded workers with polyneuropathy in this set and it has to be remarked that the effects of solvents with a half life in the range of hours and days are much less persistent than those of 2,3,7,8 TCDD with a half life of at least 7 years.

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