INFLUENCE OF PRENATAL EXPOSURE TO PCDDS/PCDFS AND PCBS ON THYROID HORMONES IN NEWBORNS AND NEURODEVELOPMENT OF INFANTS: RESULTS FROM THE BIRTH COHORT STUDY IN DUISBURG (2000-ONGOING) COMPARED TO THE DÜSSELDORF PCB COHORT STUDY (1993-2000)

Wilhelm M[1], Ranft U[2], Krämer U[2], Wittsiepe J[1], Lemm F[1], Fürst P[3], Greshake M[1], Eberwein G[4] and Winneke G[5]

[1] Department of Hygiene, Social and Environmental Medicine, Ruhr-University Bochum, Bochum, Germany

[2] Institut für umweltmedizinische Forschung (IUF) an der Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

[3] Chemical and Veterinary State Control Laboratory, Münster, Germany

[4] North Rhine-Westphalia State Environment Agency, Essen, Germany

[5] Medical Institute of Environmental Hygiene at the Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

Introduction

Several cohort studies have shown that developmental neurotoxicity may be associated with prenatal and perinatal exposure to polychlorinated biphenyls (PCBs). This was underlined also by the Düsseldorf cohort study which was initiated in 1993. PCB (#138, #153, #180) levels in milk were negatively associated with mental/motor development as assessed by the Bayley Scales of Infant Development (BSID) in infants at the age of 7, 18, and 30 months [1]. The follow-up of the Düsseldorf cohort demonstrated that by using the Kaufmann Assessment Battery for Children the PCB-related cognitive impairment was also observable at the age of 42 months but no longer at the age of 72 months [2]. These results indicate that early PCB exposure at background levels found in 1993/94 may induce only transient delay in cognitive development rather than irreversible deficits. In 2000 we had the chance to initiate a new birth cohort study in the industrial city of Duisburg which is located only about 30 km down the Rhine River from Düsseldorf in West Germany. From own studies in West Germany [3] we could assume that the exposure to PCBs and other persistent organic pollutants (POPs) had decreased meanwhile and therefore we wanted to find out if there are still POP-related effects observable. Thyroid hormones were included since PCB exposures, especially in animal studies, were found to decrease levels of circulating thyroxine (T4) and it is discussed that developmental toxicity of PCBs might be mediated through disruption of thyroid hormone homeostasis.

Materials and Methods

The Duisburg birth cohort comprised initially of 232 healthy mother-infant pairs living in Duisburg. Recruitment phase was 2000-2002. Criteria of inclusion of healthy mother-infant pairs were: Babies from German speaking or Turkish families born at term (weeks 38 - 42 of pregnancy) with an APGAR score of at least 8 and of parity 1-3, without serious complications or illness during pregnancy or at parturition and without congenital anomalies. Based on these criteria, 37 mother-infant pairs were excluded from further statistical evaluations resulting in a cohort size of 196.

Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) and dioxin-like PCBs were measured in blood and milk samples of the mothers. Details of methods are given elsewhere [4]. The levels of TSH, T3, T4, FT3, and FT4 were measured in serum samples of the pregnant women and in the cord serum by immunometric assay. Neurological examinations were performed at 14 days and 18 months of age at the infants´ homes using the neurological optimality score (NOS) for full-term newborn infant and for toddler-age [5, 6]. Mental and motor development were assessed using the BSID at the ages of 12 and 24 months [1]. Associations between PCDD/F and PCB exposure and thyroid hormone status, neurological, mental and motor development were studied by multiple linear regression analysis. A comprehensive list of potential confounders was collected to provide relevant covariates in the statistical regression modelling for adjustment of association measures, e. g.: parental education and occupation, alcohol and smoking during pregnancy, duration of pregnancy, number of pregnancies, mother's body mass index before delivery, mother's age at delivery, birth weight, nationality, lead and cadmium in blood,

selenium in serum and mercury in urine of the pregnant women, medication during pregnancy (especially iodide and thyroid hormones), disease of the thyroid gland, Apgar score, neonatal jaundice, duration of breastfeeding, assessment of the child's home environment.

Results and Discussion

Mothers (n=169; both blood and milk samples available) from the Duisburg cohort had PCDD/F and PCB levels in the range of 4.34 to 97.3 pg WHO-TEq/g $_{\text{lipid base}}$ (median: 26.37, arithmetic mean: 28.36) in blood and 3.01 to 78.7 pg WHO-TEq/g $_{\text{lipid base}}$ (median: 26.40, arithmetic mean: 27.27) in milk, respectively. Details of the results are given elsewhere [4].

Median values for thyroid hormones in serum of pregnant women (n=117-119) were: FT3 4.0 pmol/l, FT4 8.7 ng/l, T3 2.0 µg/l, T4 100.6 µg/l, TSH 1.3 mIU/l and for cord serum (n=90-96): FT3 2.3 pmol/l, FT4 11.0 ng/l, T3 0.7 µg/l, T4 114.1 µg/l, TSH 7.7 mIU/l. Multiple regression analysis showed no obvious influence of the WHO-TEq (PCDD/F and PCB) in blood on thyroid hormones of mothers and their newborns. However, WHO-TEq (PCDD/F and PCB) in milk was positively associated ($p < 0.1$) with T4, FT4, and T3 in serum of the mothers and negatively ($p < 0.1$) with TSH in serum of newborns. Although minor associations between POPs and thyroid hormone parameters – but in a different direction as reported in some studies – were found, these results do not support the view that exposure to POPs at levels as observed in this study decreases thyroid function.

The NOS at the ages 14 days (n=158) and 18 months (n=151) was not associated with WHO-TEq (PCDD/F and PCB) in blood and milk. There are only few studies on the influence of the prenatal POP exposure on the neonatal and toddler NOS available. For comparison, Huisman et al. [7, 8] found that higher levels of POPs in mother's milk were related to reduced NOS at the age of 14 days and that at the age of 18 months also a small negative effect of prenatal PCB exposure on NOS could be observed among toddlers whose father did not smoke.
Furthermore, no association could be detected between WHO-TEq (PCDD/F and PCB) in maternal blood and milk and the child's mental and motor development as assessed by BSID at the age of 12 (n=106) and 24 months (n=105) (Table 2).

The prenatal PCB exposure of the newborns from the Duisburg cohort was about 2-3 times lower compared with that of the Düsseldorf cohort (Table 1).

Table 1: Comparison of PCB levels in mother's milk collected about the 2nd week after birth from the Düsseldorf (sampling period 1993-94) and the Duisburg (sampling period 2000-2002) cohort.

	PCB 138 [ng/g $_{\text{lipid base}}$]			**PCB 153 [ng/g $_{\text{lipid base}}$]**			**PCB 180 [ng/g $_{\text{lipid base}}$]**			**PCB ∑ [ng/g $_{\text{lipid base}}$]**		
	P50	*P95*	*AM*	*P50*	*P95*	*AM*	*P50*	*P95*	*AM*	*P50*	*P95*	*AM*
Düsseldorf N = 126	141	235	147	181	292	181	85	145	84	405	679	413
Duisburg N = 176	50	109	55	81	184	90	42	100	49	172	377	194

P50, P95 = 50., 95. percentiles; AM = arithmetic mean

Only the BSID was assessed in both cohort studies. For comparison, the associations between prenatal POP exposure and the neuropsychological development are shown for both studies in Table 2.

The development was assessed by BSID and the exposure by WHO-TEq of PCDD/F and PCB (Duisburg study) or by the sum of PCB #138, #153 and #180 (Düsseldorf study), both the concentrations in mother's milk fat around 2 weeks post partum. Results of multiple regression analyses are presented where the scores of BSID are the dependent variables and the log2-transformed exposure concentrations and relevant potential confounders the independent variables.

Table 2: Association of prenatal exposure to PCDD/F and dioxin-like PCBs with the development in early childhood.

Age [month]	*N*	**Mental development**				**Motor development**			
		Mean score BSID	***Change* of score [%] by exposure doubling (95% CI)***		***p-value***	***Mean score BSID***	***Change* of score [%] by exposure doubling (95% CI)***		***p-value***
Düsseldorf§ (1993 - 1994)									
18	112	106	-3.9	(-8.7 ; 1.0)	0.122	66	-7.2	(-10.9 ; 0.8)	0.090
30	104	150	-3.3	(-6.9 ; 0.3)	0.074	95	-5.1	(-10.7 ; 0.8)	0.096
Duisburg (2000 - 2002)									
12	106	86	0.5	(-1.4 ; 2.5)	0.585	60	-0.2	(-2.4 ; 2.0)	0.862
24	105	134	0.8	(-1.1 ; 2.7)	0.402	85	-0.2	(-1.7 ; 1.3)	0.816

* Adjusted for potential confounders
§ Data are adapted from Walkowiak et al. 2001 [1]

We conclude that exposure to PCDD/Fs and dioxin-like PCBs at lower levels does not decrease the levels of thyroid hormones in serum of newborns and mothers. Furthermore, in contrast to the earlier Düsseldorf cohort study in the same region with a significant negative impact of PCB exposure on neurodevelopment, no such effect was observed with the same test in the ongoing Duisburg birth cohort study until the age of 24 months.

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