Exposure to Polychlorinated Organic Compounds and Thyroid Hormone Plasma Levels of Human Newborns

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Abstract

Thyroid hormones are essential for the normal neurological development of humans. Polychlorinated organic compounds (POCs) like organochlorine pesticides (OCPs), polychlorinated biphenyl's (PCBs), dibenzodioxins and dibenzofurans (PCDDs and PCDFs) are suspected to interfere with the thyroid hormone system because of their structural similarity to thyroid hormones.
In the present study, the association of prenatal exposure to POC-compounds and thyroid hormone levels in a group of 93 Dutch human newborns was investigated. Exposure was estimated by means of OCP-, PCB-, and PCDD/F-levels in mother's milk, an indirect measure of prenatal exposure. Plasma thyroxin (T4) levels of the infants were determined 5-7 days after birth. Univariate analyses demonstrated significant negative associations between plasma T4 levels of newborns and exposure to different POC-compounds. In the multivariate analyses these associations changed substantially. It appeared that Body Mass Index of the mother and smoking during pregnancy by the mother should be considered as potential confounding factors studying the association between POC-exposure and thyroid hormone levels.

Introduction

In the last few years polychlorinated organic compounds (POCs) like organochlorine pesticides (OCPs), polychlorinated biphenyl's (PCBs), dibenzodioxins and dibenzofurans (PCDDs and PCDFs), have been suspected to interfere with the endocrine system of both humans and wildlife. Unborn or newborn children are expected to be in particular at risk, because exposure to relatively high levels is occurring in a crucial period of the child's development[1,2]. One of the hormone systems which could be affected is the thyroid hormone system[1-3]. Because of the structural similarity of PCBs and dioxins to thyroid hormones, they are suspected to either decrease or mimic their biological action. This might result in irreversible neurological damage, as thyroid hormones are essential for normal neurological development in humans[3]. The main route of human exposure to POCs is food (approximately 95%). POCs are stable, lipophilic pollutants and therefore accumulate in the human body. Newborns can already be contaminated at birth with these substances, as transplacental transport takes place[4].
Altered thyroid hormone levels following (prenatal) exposure to POCs have been found in several experimental animal studies[5-9]. Effects of (prenatal) exposure to POCs on the thyroid hormone

system in humans have been examined only in a few studies. Most of these studies indicate that alterations in plasma thyroid hormone levels might also occur in humans and human neonates[10-14]. In the Netherlands, human milk surveys are performed at five years intervals to study trends in human exposure to POC-compounds. The most recent sampling campaign took place in June 1993. Current levels and determinants of POC levels in human milk have been reported earlier[15]. Parallel to the 1993-campaign, data on thyroid hormone plasma levels of newborns were collected. The aim of the present report is to study associations between prenatal exposure to POCs and thyroid hormone levels of human newborns.

Methods

The sampling strategy in 1993 was similar to the approach used in the former human milk surveys[16] with the exception that at this time the population was restricted to primiparae. In co-operation with 20 maternity centres scattered all over the country, finally 157 mothers were approached for participation. Each respondent was asked to collect a milk sample between day 6 and day 10 after delivery as breast milk POC-levels were used as an indirect measure of prenatal exposure. In addition, they were asked to fill out a questionnaire by which information was obtained on maternal characteristics (age, weight, height, education), personal habits (smoking and alcohol use) and on pregnancy characteristics (length of pregnancy, birthweight).
The analytical programme consisted of compound-specific determinations in the milk sample of ten OCPs, fifteen PCBs, and seventeen 2,3,7,8-substituted PCDDs and PCDFs. Details on analytical methods have been described previously[17]. Thyroid hormone plasma levels were obtained from the national PKU/CHT-screening programme. In this program each newborn child in the Netherlands is screened for phenylketonuria (PKU) and congenital hypothyroidism (CHT). Serum thyroxin (T4) and serum thyroid stimulating hormone (TSH) concentrations are determined 5-7 days after birth by using radioimmunochemical methods.
Data-analysis is performed using SAS V611©. In this study levels and distributions of 42 different congeners were determined. To reduce the number of analyses, the associations of thyroid hormone levels with combined parameters, instead of individual congeners have been studied. For each mother ten sumparameters were calculated adding up the levels of the OCPs, dioxins and furans, indicator PCBs, other dioxin-like PCBs, non-ortho PCBs, total POCs (OCPs, dioxin/furans and PCBs) and on a TEQ-basis[a] : TEQdioxin/furan, TEQnon-ortho, TEQother and TEQtotal (PCBs and dioxins/furans). Part of the samples were below the level of detection for some congeners. To reduce information loss in the present analyses the nondetects were assumed to equal half of the level of detection. Distributions of both exposure parameters and thyroid hormone plasma levels were examined and when parameters where not normally distributed, natural logarithm transformation took place.
To study the association between POC-exposure and plasma T4 levels, first Pearson correlation coefficients were calculated. Furthermore, the differences in mean plasma levels of low and high to POCs exposed groups of newborns were tested. Multivariate linear regression analysis was used to examine possible confounders like maternal and child characteristics. Variables which appeared to be statistically significant associated with thyroid hormone levels at the 0.10 level and of special interest from the literature (smoking of mother during pregnancy [18]) were considered in multivariate regression models.

[a] TEQ values by adding up breast milk levels multiplied by the international toxic equivalency factors (TEFs) for the dioxins and furans[19,20] and the Interim WHO TEFs for the non-ortho PCBs[21]

Results

Of the 157 approached mothers, 121 were willing to participate. After combining questionnaire data, breast milk data and thyroid hormone plasma levels a complete set of data was available of 93 mother-child pairs. Tables 1 and 2 show population characteristics and distribution characteristics of both thyroid hormone parameters and exposure of the study population.

Table 1: Distribution of population characteristics of both mothers and infants (N=93)

		min.	median	max.
CHILD	Plasma T4 (nmol/l)	123	201	313
	Birthweight (grams)	2375	3460	4730
	Duration of pregnancy (weeks)	37	40	42
MOTHER	Age (years)	18	29	38
	Prenatal BMI [b]	18	22	30

[a] below level of detection, [b] Body Mass Index or Quetelet-Index: by definition calculated as weight/(length)^2, min=lowest, max=highest

Table 2: Distribution of the exposure parameters among the study population (N=93)

Parameters	N	min.	25-perc.	50-perc.	75 perc.	max.
sumOCP[a]	76	0.22	0.39	0.50	0.69	2.21
sumDioxin/Furan[b]	90	131.5	293.5	385.0	546.6	1125.2
sumPCBindicator[c]	72	102.5	203.6	263.4	331.8	606.7
sumPCBother[c]	70	53.3	99.6	121.2	157.1	295.9
sumPCBnon-ortho[b]	90	49.8	110.2	142.5	187.4	312.7
sumPOCtotal[a]	64	0.39	0.70	0.91	1.08	3.08
TEQdioxin/furan[d]	90	8.4	17.8	21.6	28.1	47.5
TEQnon-ortho[d]	90	2.8	6.3	7.9	11.3	21.1
TEQother[d]	70	4.7	9.8	11.5	14.7	27.9
TEQtotal[d]	66	19.9	34.9	42.8	54.4	87.2

[a] mg/kg fat, [b] pg/g fat, [c] ng/g fat, [d] pg TEQ/g fat; min = lowest, max = highest, perc.=percentile

Univariate analyses pointed out that all the exposure parameters were negatively associated with plasma T4 levels of the infants. Correlation coefficients ranged from -0.06 to -0.20. A borderline significant correlation was observed between TEQdioxin/furan and T4 (p=0.055, N=90). Dividing the mother-child pairs into low and high to POCs exposed groups (by means of the median of the exposuregroup of interest, table 2) confirmed these negative associations. Mean plasma T4 levels in high-exposed infants were lower than in low-exposed infants. These differences ranged from 0.9 to 7.4% for the different exposure groups (figure 1). Dividing the mother child-pairs in tertiles or quartiles demonstrated similar trends.

Body Mass Index of the mother (BMI) was associated with both plasma T4 and exposure. Smoking of the mother during pregnancy was associated with exposure and combined with BMI also with plasma T4 levels. When these factors were considered in multivariate analyses, the significant negative univariate association between TEQdioxin/furan and plasma T4 disappeared (table 3) and both a significant negative association between OCPs and plasma T4 and significant interactions between BMI, smoking and OCPs appeared (table 4). Similar effect patterns were demonstrated for the other pollutant groups.

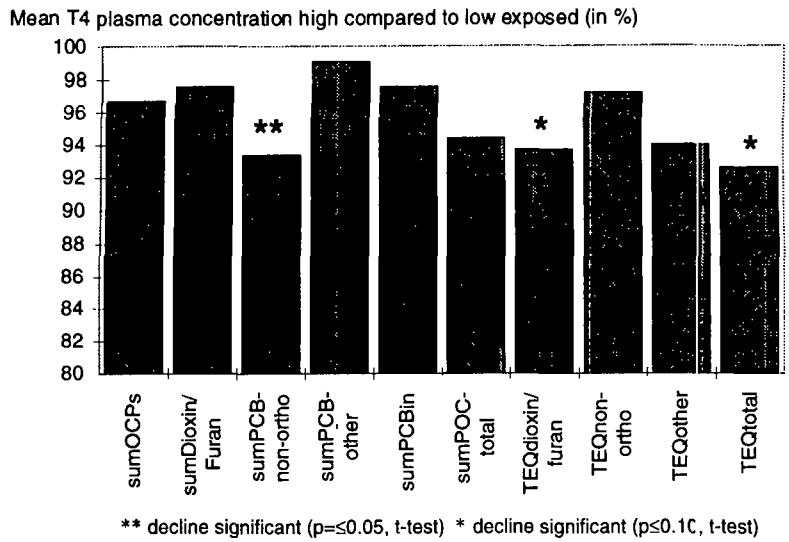

Figure 1 Mean plasma T4 levels in high to POC-compounds exposed groups of newborns as a percentage of the means of low exposed groups (median of exposure is cut-off point). Axis scale starts at 80%

Table 3 Association (regression coefficients and p-values) between prenatal exposure to dioxin/furan-TEQ[1] and plasma T4 levels of newborns (N=89)

	Univariate		Multivariate	
	rc	p-value	rc	p-value
TEQdioxin/furan	-19.1	0.07	-11.6	NS
BMI	3.9	0.008	3.5	0.03
Smoking	3.7	NS	2.4	NS

[1] log-transformed values

Table 4 Association (regression coefficients and p-values) between prenatal exposure to organochlorine pesticides (OCPs)[1] and plasma T4 levels of newborns (N=75)

	Univariate		Multivariate	
	rc	p-value	rc	p-value
OCPs	-4.4	NS	-126.8	0.06
BMI	4.0	0.02	6.5	0.02
OCPs*BMI	-	-	6.1	0.05
Smoking	8.5	NS	-98.2	NS
OCPs*Smoking	-	-	-65.5	0.002
BMI*Smoking	-	-	3.1	NS

[1] log-transformed values

Discussion

Measured POC levels in the present study are reasonably well comparable to other reported Dutch values[13,14], differences might be due to analytical variance. Plasma T4 levels of the study population appeared to be in the normal range, none of the children had an abnormal PKU-CHT test. A significant reduction of plasma T4 in high to dioxin-TEQ, PCB-dioxin-TEQ and non-ortho PCBs exposed groups of newborns was found, as well as a significant negative univariate correlation between dioxin-TEQ and plasma T4 levels. Multivariate analyses in this study showed that these univariate associations were modified by BMI of the mother and smoking during pregnancy. Furthermore, in some models complex interactions between these variables and exposure existed.

So far, other studies which have been performed on the association between POC-exposure and the thyroid hormone status of human(newborn)s reported contradictory results. In accidentally or occupationally to PCBs and PCDFs exposed persons, both increased and decreased serum T3 and T4 concentrations have been reported, compared to non-exposed persons[11,12]. Pluim et al.[13] reported elevated T4 plasma levels in a group of Dutch newborns exposed to high dioxin-TEQ concentrations (29.0-62.7 pg TEQ/g fat, N=19), compared to a group infants exposed to low dioxin-TEQ concentrations (8.7-28.0 pg TEQ/g fat, N=19). A comparable study by Koopman-Esseboom[14] demonstrated dioxin-TEQ, total PCB-dioxin-TEQ, planar and non-planar PCB-TEQ in human milk to correlate negative (Spearman correlation) with maternal plasma T3 and T4 levels and positive with plasma TSH levels in a group of newborns (N=79). A significant correlation of TEQ-levels with plasma T4 levels of the infants has not been demonstrated. In contrast to the Pluim data, infants of mothers in high to dioxin-TEQ (>30.75 pg TEQ/g fat) and PCB-dioxin-TEQ (>72.43 pg TEQ/g fat) exposed groups had significantly lower plasma T4 levels than infants in low dioxin-TEQ (≤30.75 pg TEQ/g fat) and PCB-dioxin-TEQ (≤72.43 pg TEQ/g fat) exposed groups.

Likewise, experimental animal studies demonstrated inconsistent findings as species-dependent associations between POC-exposure and plasma thyroid hormone levels were found. Elevated plasma T3, T4 and TSH levels were found in hamsters and guinea pigs after exposure to 2,3,7,8-TCDD[5,6]. Decreased plasma T3 and T4 levels and increased plasma TSH levels were observed after exposure to PCBs and dioxin/furans in rats and monkeys[7-9].

Unlike most of the epidemiological studies, in the present study findings were adjusted for potential confounders. The results of the multivariate linear regression analyses show that performing only univariate analysis appeared to be insufficient. Little is known about factors which influence plasma T4 levels of newborns. Infants of mothers who smoked during pregnancy are reported to have higher cord serum T4 levels[18]. Smoking is already known to correlate with lower POC breast milk levels probably through an effect of smoking on the fat metabolism[22]. Body Mass Index of the mother was in this study associated with higher plasma T4 levels of the infants. The mechanism underlying this association is, yet, not fully understood but might in part be explained by the important role of thyroid hormones on the fat metabolism.

It can be concluded that when studying the association between prenatal exposure and the thyroid hormone status of newborns, adjusting for confounders is necessary. Future studies will be needed to gain more insight in potential confounders and their interactions to clarify the inconsistencies reported so far on this issue.

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Literature Cited

(1) Birnbaum, L.S. *Environ. Health. Perspect.* **1994**, 102(8), 676-679.
(2) Feeley, M.M. *Environ. Health. Perpsect.* **1995**, 103(Suppl 2), 147-150.
(3) Porterfield, S.P. *Environ. Health. Perspect.* **1994**, 102(Suppl 2), 125-130.
(4) Jensen, A.A. *Transfer of chemical contaminants into human milk* **1991**. In: Jensen, A.A; Slorach, S.A. (Eds.) Chemical contaminants in human milk. Boca Raton, 9-19.
(5) Mc. Kinney, J.D.; Fawkes, J.; Jordan, S. Chae, K.; Oatley, S.; Coleman, R.E; Briner, W. *Environ. Health Perspect.* **1985**, 61, 41-53.
(6) Henry, E.C.; Gasiewicz, T.A. *Toxicol. Appl. Pharmacol.* **1987**, 89, 165-174.
(7) Brewster, D.W; Elwell, M.R.; Birnbaum, L.S. *Toxicol. Appl. Pharmacol.* **1988**, 93, 231-246.
(8) Morse, D.; Brouwer, A. *Organohalogen Compounds* **1994**, 21, 439-443.
(9) Goldey, E.S.; Kehn, L.S.; Lau, C.; Rehnberg, G.L.; Crofton, K.M *Toxicol. Appl. Pharmacol.* **1995**, 135, 77-88.
(10) Dewailly, E.; Bruneau, S.; Ayotte, P.; Laliberté, C.; Gingras, S.; Belanger, D.; Ferron, L.; *Chemosphere* **1993**, 27(1-3), 359-366.
(11) Emmett, E.A.; Maroni, M.; Jefferys, J.; Schmith, J.; Levin, B.K.; Alvares, A. *Am J Ind Med* **1988**, 14, 47-62.
(12) Murai, K.; Okamura, K.; Tsuji, H.; Kajiwara, E.; Watanbe, E.; Kimihiro, A.; Fujishima, M. *Environ. Res.* **1987**, 44, 179-187.
(13) Pluim, H.J.; Vijlder, J.J.; Olie, K.; Kok, J.H.; Vulsma, T.; van Tijn, D.A.; van der Slikke, J.W.; Janna, G. *Environ. Health. Perspect.* **1993**, 101(6), 504-508.
(14) Koopman-Esseboom, C. *Effects of prenatal exposure to PCBs and dioxins on early human development* **1995**, Thesis, Erasmus University Rotterdam, The Netherlands, ISBN: 90-75340-03-6.
(15) Cuijpers, C.E.J.; Liem, A.K.D.; Albers, M. *Organohalogen Compounds* **1996**, 30, 43-47.
(16) Albers, J.M.C.; Kreis, I.; Liem, A.K.D.; Van Zoonen, P. *Arch. Environ.Contam.Toxicol.* **1996**, 30, 285-291.
(17) Liem, A.K.D.; Albers, J.M.C.; Baumann, R.A.; Van Beuzekom, A.C.; Den Hartog, R.S.; Hoogerbrugge, R.; De Jong, A.P.J.M.; Marsman, J.A. *Organohalogen Compounds* **1995**, 26, 69-74.
(18) Meberg, M.; Marstein, S. *Acta Paediatr. Scand.* **1986**, 75, 762-766.
(19) NATO/CCMS (North Atlantic Treaty Organisation, Committee on the Challenges of Modern Society) *International toxicity equivalency factors (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds* **1988**, North Atlantic Treaty Organisation, Brussels, report no. 176.
(20) Van Zorge, J.A.; Van Wijnen, J.H.; Theelen, R.M.C.; Olie, K.; Van den Berg, M. *Chemosphere* **1989**, 19, 1881-1895.
(21) Ahlborg, U.G.; Becking, G.C.; Birnbaum, L.S.; Brouwer, A.; Derks, H.J.G.M.; Feeley, M.; Golor, G.; Hanberg, A.; Larsen, J.C.; Liem, A.K.D.; Safe, S.H.; Schlatter, C.; Waern, F.; Younes, M.; Yrjänheikki, E. *Chemosphere* **1994**, 28, 1049-1067.

(22) Cuijpers, C.E.J.; Liem, A.K.D.; Albers, J.M.C.; Kreis, I.A.; Lebret, E. *Contamination of human milk with polychlorinated compounds in the Netherlands, 1993; the role of determinants* **1997**, RIVM report, no.529102004 (in Dutch).