Effects of PCBs, p,p′-DDT, p,p′-DDE, HCB and β-HCH on thyroid function in preschool children

M Álvarez-Pedrerol,[1] N Ribas-Fitó,[1] M Torrent,[2] D Carrizo,[3] J O Grimalt,[3] J Sunyer[1,4]

See Editorial, p 452

[1] Centre for Research in Environmental Epidemiology-IMIM, Barcelona, Spain; [2] Primary Health Care Center of Maó, Menorca, Spain; [3] Department of Environmental Chemistry, Institute of Chemical and Environmental Research (IIQAB-CSIC), Barcelona, Spain; [4] Pompeu Fabra University, Barcelona, Spain

Correspondence to: Mar Alvarez-Pedrerol, Centre for Research in Environmental Epidemiology- IMIM, C. Doctor Aiguader 88, 08003 Barcelona, Spain; malvarez1@imim.es

Accepted 28 September 2007
Published Online First 12 October 2007

ABSTRACT

Objective: Several studies have shown that some organochlorine compounds (OCs) can interfere with the thyroid system. As thyroid hormones (THs) are essential for normal brain development, it is important to study the association between THs and OCs during pregnancy and childhood. We have evaluated the relationship between thyroid function and OCs in preschool children.

Methods: Children from a general population birth cohort in Menorca (n = 259), Spain were assessed at the age of 4 years. Concentrations of THs (free T4 and total T3), thyrotropin (TSH) and a range of OCs were measured in peripheral blood.

Results: Blood levels of dichlorodiphenyl trichloroethane (p,p′-DDT), β-hexachlorocylcohexane (β-HCH), polychlorinated biphenyls (congeners PCB-138, PCB-153 and PCB-118) were related to lower total T3 levels ($p<0.05$). In addition, free T4 was inversely associated with PCB-118, while no relationship was found between TSH and any of the measured OCs.

Conclusions: This study suggests that even at background levels of exposure, OCs may affect the thyroid system, particularly total T3 levels.

Organochlorine compounds (OCs) such as polychlorinated biphenyls (PCBs), dioxins, chlorobenzenes, dichlorodiphenyl trichloroethane (p,p′-DDT) and hexachlorocyclohexanes are widespread environmental pollutants. They are highly lipophilic and chemically stable compounds that persist in the environment and accumulate in the food chain and in human tissues. In recent years, OCs have been detected in human milk, blood and adipose tissue in the general population.[1 2]

OCs have several well known toxic effects. Thyroid effects, generally hypothyroidism, have been found in both animals[3 4] and humans,[5] although results are controversial. The association between thyroid hormones (THs), thyrotropin (TSH) and OCs in humans has been studied mainly in newborns,[6–15] toddlers[16–18] and adults.[5] Nevertheless, young children are also vulnerable to environmental insults, since neurodevelopmental processes such as myelination, which is dependent on THs, are not completed until adolescence.[19 20] Osius *et al* studied the relationship between THs (free T3 and free T4), TSH and PCBs in 7–10-year-old children,[21] Schell *et al* studied the effects of PCBs, p,p′-dichlorodiphenyl dichloroethylene (p,p′-DDE) and hexachlorobenzene (HCB) on T4 and TSH in a group of adolescents,[22] and Ilsen *et al* studied the effects of dioxins in a small group of preschool children.[23] To our knowledge, no other studies have been done in children. Most reports have focused on the effects of PCBs and dioxins on TH levels[6 7 9–11 13 15–18 21 23] and some studies have suggested that other OCs such as p,p′-DDT, p,p′-DDE, β-hexachlorocylcohexane (β-HCH) or HCB may also disrupt the thyroid system.[8 12 14 22] However, further research is required to assess the effects of a full range of OCs in preschool children, particularly since their neurological systems are still developing.

The objective of this study was to evaluate the effects of background exposure to OCs (PCBs, p,p′-DDT, p,p′-DDE, β-HCH and HCB) on levels of THs (free T4 and T3) and TSH in preschool children from the general population.

METHODS

Study population

A population-based birth cohort was set up on the island of Menorca, a popular tourist destination in the northwest Mediterranean, and included all children born between July 1997 and December 1998. A total of 482 children were enrolled (written consent was obtained from parents) and 468 (97.1%) provided data up to their 4th-year visit. OC and TH measurements in serum at age 4 years were obtained from 259 (55%) of these children and were included in the analysis. The most common reasons for non-inclusion in the study were parental refusal for blood extraction from their child (24% of the enrolled children) or an insufficient quantity of serum for OC and/or TH measurement.

Organochlorine compounds

HCB (formerly used as a fungicide), β-HCH, p,p′-DDT and its metabolite dichlorodiphenyl dichloroethylene (p,p′-DDE), used as pesticides, were analysed in serum at birth and at 4 years of age. Polychlorinated biphenyls (summation of congeners PCB-28, PCB-52, PCB-101, PCB-118, PCB-138, PCB-153 and PCB-180) were also assessed because of their potential effects on the thyroid. The most common PCBs (PCB-118, PCB-138, PCB-153 and PCB-180) were also analysed separately. All analyses were carried out in the Department of Environmental Chemistry of the Institute of Chemical and Environmental Research (IIQAB-CSIC) in Barcelona, Spain using gas chromatography (GC) with electron capture detection (Hewlett-Packard 6890N GC-ECD; Hewlett-Packard, Avondale, PA, USA) and GC coupled to chemical ionisation negative-ion mass spectrometry (Hewlett-Packard 5973 MSD), which has been previously described.[24] Limits of detection (LOD) and quantification (LOQ) ranged from 0.02 to 0.09 and from 0.03 to 0.13 ng/ml, respectively. OC values were substituted with one-half of the

Table 1 Characteristics of the study population at age 4

	Children included (n = 259)	Children not included† (n = 209)
Child variables		
Gestational age (weeks)	39.3	39.4
Gender (% males)	47.9	55.4
Birth height (cm)	48.9	49.1
Birth weight (g)	3197	3183
Height at age 4 (cm)	107	107
Weight at age 4 (kg)	18.6	18.6
Geographical location (% of children living in this area)		
Ciutadella	51	40
Maó	24	19
Other	25	41*
Duration of breastfeeding (%)		
<3 weeks	22	21
3–19 weeks	32	32
>19 weeks	46	47
Fish consumption (at least twice/week, %)	55	54
OCs at birth (cord blood), geometric mean (ng/ml)		
Sum of PCBs	0.72	0.59
HCB	0.33	0.30
p,p′-DDE	1.13	0.98
p,p′-DDT	0.07	0.06
β-HCH	0.23	0.25
Maternal variables		
Mean age at delivery (years)	33	32
Social class (%)		
Professional, manager, technician	13	11
Skilled manual and non-manual	51	53
Partially skilled and unskilled	14	16
Unemployed	22	20
Education (%)		
High	15	9
Secondary	29	29
Primary	49	55
Less than primary	7	7
Smoking at delivery (%)	24	17*
Smoking at 4 years after delivery (%)	34	28
Paternal variables		
Social class (%)		
Professional, manager, technician	17	15
Skilled manual and non-manual	70	73
Partially skilled and unskilled	13	11
Unemployed	0	1
Smoking at 4 years after delivery (%)	38	32

*p<0.05 (differences between included and not included children).
†Children with data up to the 4th-year visit but not included in the analysis because of lack of data on THs, TSH or organochlorine levels at 4 years of age.
β-HCH, β-hexachlorocylcohexane; HCB, hexachlorobenzene; OCs, organochlorine compounds; PCBs, polychlorinated biphenyls; p,p′-DDE, p,p′-dichlorodiphenyl dichloroethylene; p,p′-DDT, dichlorodiphenyl trichloroethane; THs, thyroid hormones; TSH, thyrotropin.

detection limit when they were below the detection limit. OCs measured at birth and at 4 years were correlated (correlations between 0.14 and 0.46, $p<0.05$) except for p,p′-DDT which was not statistically significantly correlated (correlation 0.12, $p<0.06$).

Thyroid hormone assessment

Thyroid function was assessed at age 4 years by measuring the concentrations of TSH, T3 and free T4 in serum samples by chemiluminescence assay (ARCHITECT system; Abbott Laboratories, Abbott Park, Illinois, USA) in the Reference Laboratory of Catalonia in 2004. Inter-assay coefficients of variation (CV) for the TSH, free T4 and total T3 measurements were under 5.2%, 7.8% and 5.3%, respectively, and intra-assay coefficients were 3.3%, 4.2% and 3.0%, respectively. The reference ranges proposed by the laboratory were 0.35–5 mU/l for TSH, 80–200 ng/dl for total T3 and 0.7–1.7 ng/dl for free T4. As all samples were collected in the morning, there should be no circadian variation effects. Samples were stored at –20°C prior to analysis.

Other variables

Information on parental education, socioeconomic background (using the UK Registrar General's 1990 classification according to parental occupation by ISCO88 code), marital status, maternal disease and obstetric history, parity, duration of breastfeeding, gender, alcohol consumption during pregnancy, children's cigarette exposures (during the mother's pregnancy and when the child was 4 years old) and dietary fish intake was obtained through questionnaire. Information on gestational age and anthropometric measurements at birth was available from clinical records. Anthropometric measurements were also taken at age 4 years.

Statistical analysis

We conducted a cross-sectional analysis among participants at age 4 years to assess the relationships between THs and TSH levels (outcome variables) and OCs (exposure variables). OCs and TSH showed a non-normal distribution and were log transformed before being included in the models. Unadjusted and adjusted linear regression models were performed using THs and TSH as continuous variables. OC levels were first treated as categorical variables (categorised into quartiles) and given the linearity observed in most of the associations between quartiles of OCs and THs; models were repeated using the OCs as continuous variables. Models were adjusted for those variables that appeared to be statistically significantly associated with TH levels at the 0.20 level of significance in the bivariate analysis (child's weight at age 4 years, gestational age, mother's age at delivery, geographical location and mother's smoking habits when the child was aged 4 years) in addition to those variables identified from the literature, including sex and duration of breastfeeding. All statistical analyses were conducted with the STATA 8.2 statistical software package.

Table 3 presents the crude association between total T3, free T4 and TSH, and quartiles of the different OCs. Total T3 was associated with HCB, p,p′-DDT, β-HCH, PCB-118 and the sum of PCBs, and a linear trend (p trend) was observed in the relationship with β-HCH, PCB-153 and PCB-118, and the sum of PCBs. For instance, children with higher PCB-118 levels (last quartile) had 11.5 ng/dl of T3 less than children from the reference group (first quartile). Free T4 concentration was only associated with PCB-118 (p trend = 0.003), and TSH with the sum of PCBs (p trend = 0.046).

RESULTS

The characteristics of the study population are described in table 1. Participating children were more likely than non-participating children to have mothers who smoked 4 years after delivery (34% vs 28%, respectively) and to live in the two main cities of Menorca. However, there were no other

Table 2 Thyroid hormone (T4 and T3) and thyrotropin concentrations and levels of organochlorine compounds at 4 years of age (n = 259)

	Geometric mean	SD	% Detected	Min	PC25	PC50	PC75	Max
THs and TSH								
Free T4 (ng/dl)	1.04	0.14		0.4	0.97	1.05	1.15	1.44
Total T3 (ng/dl)	1.48	22		25	137	150	164	226
TSH (mU/l)	1.63	0.78		0.45	1.23	1.67	2.2	5.01
OCs (ng/ml)								
HCB	0.32	0.45	99.5	<dl	0.19	0.31	0.51	4.52
p,p′-DDE	0.88	3.38	99.5	<dl	0.44	0.81	1.76	43.88
p,p′-DDT	0.06	0.11	91.5	<dl	0.03	0.05	0.10	0.66
β-HCH	0.22	0.45	90.0	<dl	0.11	0.19	0.30	5.65
PCB-138	0.18	0.56	99.0	<dl	0.11	0.17	0.28	8.71
PCB-180	0.12	0.48	100	0.01	0.06	0.12	0.21	7.20
PCB-153	0.25	0.70	100	0.01	0.14	0.25	0.41	10.88
PCB-118	0.09	0.12	99.5	<dl	0.07	0.10	0.13	1.82
PCB-52	0.04	0.31	73.0	<dl	<dl	0.03	0.05	4.95
PCB-101	0.08	0.14	99.5	<dl	0.05	0.08	0.11	2.09
PCB-28	0.02	0.34	49.0	<dl	<dl	0.01	0.02	5.5
Sum of PCBs	0.82	2.6	100	0.15	0.55	0.78	0.18	41.17

β-HCH, β-hexachlorocylcohexane; <dl, below detection limit; HCB, hexachlorobenzene; OCs, organochlorine compounds; PC25, 25th percentile; PC50, 50th percentile; PC75, 75th percentile; PCBs, polychlorinated biphenyls; p,p′-DDE, p,p′-dichlorodiphenyl dichloroethylene; p,p′-DDT, dichlorodiphenyl trichloroethane; SD, standard deviation; THs, thyroid hormones; TSH, thyrotropin.

significant differences between participants and non-participants.

The concentrations of THs, TSH and the different OCs are given in table 2. The PCB congeners with the highest concentrations were PCB-153, PCB-138, PCB-180 and PCB-118. PCB-153 contributed approximately 30% to the sum of all seven congeners analysed. One of the children had very high levels of all PCBs and β-HCH, having levels approximately 10-fold greater than the other children. THs (free T4 and T3) were positively correlated (correlation 0.19, $p<0.001$), but TSH was not correlated with any of the THs (data not shown).

The magnitude of the association between the potential confounders and T3 is shown in table 4. Weight at 4 years and gestational age showed the strongest association with the outcome (β (standard error, SE) = 2.58 (0.51) and β (SE) = −1.50 (0.75), respectively).

The coefficients from the adjusted models using the OC levels categorised into quartiles confirmed the association with total T3 (table 5). Also for T4 the adjusted association was similar to that shown in table 3, while the association between sum of PCBs and TSH disappeared (data not shown). When multivariate models were conducted using the OCs (log transformed) as continuous variables, most compounds were negatively associated with total T3 (table 4). The toxicants with the strongest association were p,p′-DDT (β (SE) = −2.51 (1.14)), PC-153 (β (SE) = −5.21 (2.39)) and PCB-118 (β (SE) = −4.19 (1.73)). Free T4 was associated with continuous PCB-118 (β (SE) = −0.025 (0.011)) and continuous β-HCH (β (SE) = −0.015 (0.008)), although the latter was not statistically significant ($p = 0.070$). When models were repeated excluding the child with the highest levels of PCBs and β-HCH, the coefficients for the OCs were slightly higher (data not shown). TSH was not related to any of the OCs when analysed as continuous variables (data not shown). Adjustment for the other OCs diminished the effect of p,p′-DDT, β-HCH and HCB; however, it is difficult to distinguish the proper effect of each OC on THs because of their high collinearity (correlations between 0.32 and 0.91). Further stratification by gender showed that the effects were greater among boys, although associations were not statistically heterogeneous ($p>0.5$), except for PCB-118 ($p = 0.17$).

DISCUSSION

In a group of 259 preschool children from the general population, we found a statistically significant negative relationship between levels of total T3 and p,p′-DDT, β-HCH, PCB-138, PCB-153 and PCB-118. In addition, free T4 was negatively related to PCB-118.

Inverse relationships between PCBs and T4[6 10 17 18 22] and positive associations with TSH[6 17 22] have been observed in several studies. In agreement with the results reported here, the selective effect of PCBs on T3 levels has been reported in newborns from Quebec[12] and in school children from Hessen, Germany.[21] In the latter study, Osius *et al* found that PCB-118, PCB-138, PCB-153, and PCB-180 levels were negatively related to free T3 concentrations without any significant association with TSH or T4[21] (with the exception of a positive relationship between PCB-118 and TSH). The levels of exposure observed in both reports were slightly lower than those seen in the present study. Few studies have assessed the effects of other OCs such as p,p′-DDT, p,p′-DDE, β-HCH and HCB.[8 12 14 22] Ribas-Fitó *et al* found that prenatal exposure to β-HCH, but not p,p′-DDE or HCB, was positively associated with TSH levels in newborns (THs were not measured).[8] Schell *et al* showed a positive relationship between TSH and p,p′-DDE, while no relationship was observed with HCB in adolescents.[22] Moreover, Tasker *et al* observed a negative association between HCB and p,p′-DDE and total T3 but no association with p,p′-DDT,[12] and Asawasinsopon *et al* found a negative relationship between p,p′-DDE, p,p′-DDT and total T4 in newborns (T3 was not measured).[14] This heterogeneity in the results could be due to a variety of factors that are difficult to control in an epidemiological study, such as differences in environmental levels of OCs, diet, selection of the subjects, age range and sample size. Moreover, the high collinearity between the different OCs makes it difficult to discern the specific effect of each OC on THs. Nevertheless, we found an association between THs and a number of OCs (even after adjusting for the other OCs), suggesting that the OCs examined in the current study play a specific role in disrupting thyroid activity.

Altered TH levels following exposure to OCs have also been found in experimental animal studies.[25–28] The mechanisms involved in the alteration of TH homeostasis are still not fully

Table 3 Unadjusted association (coefficient and standard error) between thyroid hormones and thyrotropin concentrations and quartiles of organochlorine compounds (n = 259)

	lnTSH		Free T4		Total T3	
	Coefficient	p Trend	Coefficient	p Trend	Coefficient	p Trend
HCB quartiles (ng/ml)						
Reference†	0.46 mU/l		1.06 ng/dl		155 ng/dl	
0.194–0.304	−0.02 (0.08)		0.00 (0.02)		−6.1 (3.8)	
0.305–0.506	0.02 (0.08)		0.00 (0.02)		−8.8 (3.8)*	
0.507–4.52	0.13 (0.08)	0.079	−0.02 (0.02)	0.602	−5.3 (3.8)	0.120
p,p′-DDE quartiles (ng/ml)						
Reference†	0.50 mU/l		1.05 ng/dl		151 ng/dl	
0.436–0.807	−0.05 (0.08)		0.00 (0.02)		0.1 (3.8)	
0.808–1.75	−0.06 (0.08)		0.01 (0.02)		−1.4 (3.8)	
1.76–43.9	0.09 (0.08)	0.280	−0.02 (0.02)	0.379	−5.0 (3.8)	0.166
p,p′-DDT quartiles (ng/ml)						
Reference†	0.42 mU/l		1.06 ng/dl		156 ng/dl	
0.026–0.049	0.04 (0.08)		0.00 (0.02)		−7.5 (3.8)*	
0.050–0.103	0.11 (0.08)		0.00 (0.02)		−9.0 (3.8)*	
0.104–0.657	0.12 (0.08)	0.101	−0.03 (0.03)	0.360	−7.9 (3.8)*	0.40
β-HCH quartiles (ng/ml)						
Reference†	0.57 mU/l		1.08 ng/dl		155 ng/dl	
0.108–0.190	−0.15 (0.08)		−0.03 (0.02)		−5.0 (3.8)	
0.191–0.304	−0.16 (0.08)*		−0.04 (0.02)		−7.1 (3.8)	
0.305–5.65	−0.01 (0.08)	0.833	−0.05 (0.02)	0.070	−9.0 (3.8)*	0.015
PCB-138 quartiles (ng/ml)						
Reference†	0.50 mU/l		1.06 ng/dl		153 ng/dl	
0.105–0.174	−0.09 (0.08)		0.00 (0.02)		−0.8 (3.8)	
0.175–0.276	0.05 (0.08)		0.00 (0.02)		−4.8 (3.8)	
0.277–8.71	0.02 (0.08)	0.382	−0.01 (0.02)	0.674	−6.2 (3.8)	0.061
PCB-180 quartiles (ng/ml)						
Reference†	0.44 mU/l		1.07 ng/dl		151 ng/dl	
0.064–0.115	−0.01 (0.08)		−0.04 (0.02)		2.6 (3.8)	
0.116–0.211	0.14 (0.08)		−0.01 (0.02)		−4.4 (3.8)	
0.212–7.20	0.09 (0.08)	0.097	−0.02 (0.02)	0.694	−4.3 (3.8)	0.097
PCB-153 quartiles (ng/ml)						
Reference†	0.49 mU/l		1.06 ng/dl		152 ng/dl	
0.141–0.250	−0.07 (0.08)		0.00 (0.02)		2.0 (3.8)	
0.251–0.410	0.03 (0.08)		0.01 (0.02)		−4.9 (3.8)	
0.411–10.88	0.07 (0.08)	0.208	−0.02 (0.02)	0.482	−6.3 (3.8)	0.032
PCB-118 quartiles (ng/ml)						
Reference†	0.39 mU/l		1.09 ng/dl		155 ng/dl	
0.069–0.098	0.17 (0.08)*		−0.03 (0.02)		−3.2 (3.8)	
0.099–0.128	0.09 (0.08)		−0.06 (0.02)*		−4.8 (3.8)	
0.129–1.824	0.12 (0.08)	0.247	−0.07 (0.02)**	0.003	−11.5 (3.8)**	0.003
Sum of PCBs quartiles (ng/ml)						
Reference†	0.41 mU/l		−0.04 ng/dl		155 ng/dl	
0.547–0.775	0.08 (0.08)		−0.01 (0.02)		−4.7 (3.8)	
0.776–1.171	0.09 (0.08)		−0.05 (0.02)		−7.4 (3.8)	
1.172–41.17	0.16 (0.08)	0.046	1.08 (0.02)	0.193	−8.3 (3.8)*	0.021

*p<0.05, **p<0.01 (in comparison with the reference category).
†Children in the lowest quartile of exposure.
β-HCH, β-hexachlorocylcohexane; HCB, hexachlorobenzene; PCBs, polychlorinated biphenyls; p,p′-DDE, p,p′-dichlorodiphenyl dichloroethylene; p,p′-DDT, dichlorodiphenyl trichloroethane; TSH, thyrotropin.

understood. Because of the structural similarity between some OCs and THs, OCs are suspected to either decrease or mimic the biological action of THs. The possible explanatory mechanisms which have been proposed include (i) interference with the hypothalamic-pituitary-thyroid axis,[29 30] (ii) increased biliary clearance of T4 through the induction of thyroid metabolising enzymes[31 32] and (iii) competitive binding to TH transport proteins such as transthyretin (TTR)[33 34] resulting in decreased plasma TH levels. The negative association observed between OCs and total T3 could be explained by inhibition of type I monodeiodinase, which converts T4 in peripheral sites to biologically active T3, or by activation of type III monodeiodinase, which catalyses the deiodination of T4 to reverse T3 and of T3 to 3,3′-T2 (3,3′-diiodothyronine). Unfortunately, no analytical data on free T3, sulfate T3 and reverse T3 are available to test this hypothesis. It has been observed in several animal studies that some OCs have marked effects on deiodinase activity,[25 26 35] but it is unclear if this is a direct effect or a compensatory mechanism secondary to changes in TH levels. Overall, further research is needed to explain why these effects appear to be specific to total T3. In addition, we observed that PCB-118 showed a negative association with free T4, which could be explained by interaction

Table 4 Bivariate coefficients between T3 concentrations and all covariables included in the multivariate models (n = 259)

	Bivariate association with T3	
	Coefficient (SE)	p Value
Weight at 4 years of age (kg)	2.58 (0.51)	<0.000
Mother's age (years)	−0.33 (0.25)	0.191
Gestational age (weeks)	−1.50 (0.75)	0.048
Duration of breastfeeding		
<3 weeks	Reference	
3–19 weeks	−0.37 (3.60)	0.917
>19 weeks	−0.96 (3.31)	0.771
Mother's smoking habits		
No	Reference	
Yes	4.20 (2.68)	0.118
Geographical location (village)		
Ciutadella	Reference	
Maó	0.63 (3.20)	0.844
Castell	−9.67 (4.98)	0.053
Alaior	2.24 (4.71)	0.635
Ferreries	18.70 (5.19)	0.000
Sant Lluis	10.76 (5.31)	0.044
Other	7.78 (6.81)	0.254
Sex		
Female	Reference	
Male	1.26 (2.54)	0.622

SE, standard error.

with the aryl hydrocarbon receptor (AhR), since this is the only congener analysed with coplanar structure which has dioxin-like properties.[36]

OCs are also known to be neurotoxic.[37 38] Brain damage caused by exposure to these compounds could be mediated, at least in part, by their ability to alter TH levels. These hormones play an essential role in brain development.[39 40] Deficiency in THs during the perinatal period results in severe mental and physical retardation.[39 40] Furthermore, since OCs can reach the fetus as they can pass through the placental barrier,[41] it is important to elucidate the effects of OCs on TH homeostasis and development. Previous analyses carried out in this cohort showed that THs and TSH, despite being within the normal range, were related to cognitive function and attention behaviour,[42] suggesting that even small changes in TH levels may have significant effects on brain function. Additionally, exposure to background levels of p,p′-DDT during pregnancy was also associated with a decrease in cognitive skills in this study population at age 4 years.[43] Nevertheless, further evaluation of the inter-relationships between OCs, THs and neurodevelopment in these preschool children will be important in order to elucidate the role of THs in the relationship between OCs and cognitive function.

The cross-sectional design of the present study is a major limitation since the single measures preclude determination of the order in which the OCs had an effect. Most other previous population studies have evaluated this association using a cross-sectional approach. However, effects on TH concentrations following the administration of OCs have been observed in animal studies.[25–28] OCs were also measured at birth (cord blood); however, the correlations between OCs at birth and at 4 years were moderate although statistically significant. This poor correlation is probably explained by duration of breastfeeding, since maternal milk is the most important source of OCs during childhood. Moreover, the mechanisms underlying the effects of OCs on thyroid function are expected to follow a short (acute/subacute) rather than a long term pattern.[29–35] Thus we decided to focus on the relationship between THs, TSH and OCs measured cross-sectionally at the age of 4 years.

A second limitation relates to the low proportion of children in whom both THs and OCs were measured (54%). However, few differences were observed between participating and non-participating children, and so any resulting effects from selection bias are likely to be minimal. Conversely, strengths of this study are the large sample size when compared with most other studies that have evaluated the effects of OCs on TH levels in newborns and children, and the fact that we were able to adjust for a number of potential confounders. Moreover, the results can be extrapolated to other preschool populations since this is a population of healthy children exposed to background levels of OCs.

In summary, this research supports evidence that OCs can alter the thyroid system. However, more experimental studies are necessary to better understand the mechanisms involved. Although TH levels were within the normal range, small changes in these levels could have significant effects on cognitive function. Additional studies are therefore required to more fully understand the effects of OCs on THs in children of different ages, as well as the possible causal relationships between OCs, THs and neurodevelopment.

Table 5 Adjusted† coefficients (standard error) between total T3 concentrations and organochlorines categorised into quartiles and as continuous variables (log transformed) (n = 259)

	Quartiles of OCs‡				
	Reference (ng/dl total T3)	2nd	3rd	4th	Continuous OCs
HCB (ng/ml)	108.57 (10.76)	−3.37 (3.94)	−7.44 (4.13)	−3.14 (4.63)	−1.68 (1.83)
p,p′-DDE (ng/ml)	104.94 (10.85)	0.85 (4.08)	0.69 (4.34)	−3.27 (4.70)	−1.90 (1.62)
p,p′-DDT (ng/ml)	112.36 (10.62)	−9.25 (3.80)*	−10.75 (3.98)**	−8.11 (4.18)	−2.51 (1.14)*
β-HCH (ng/ml)	109.37 (10.61)	−4.42 (3.69)	−8.13 (4.00)*	−8.54 (4.12)*	−2.44 (1.23)*
PCB-138 (ng/ml)	106.44 (10.91)	1.05 (3.88)	−5.10 (4.30)	−5.18 (4.80)	−4.69 (2.31)*
PCB-180 (ng/ml)	108.79 (10.82)	3.30 (4.03)	−4.38 (4.47)	−5.06 (4.94)	−2.77 (1.88)
PCB-153 (ng/ml)	108.79 (10.82)	3.30 (4.03)	−4.38 (4.47)	−5.06 (4.94)	−5.21 (2.39)*
PCB-118 (ng/ml)	110.66 (10.84)	−1.75 (3.87)	−3.99 (3.91)	−9.49 (−3.90)*	−4.19 (1.73)*
PCBs (ng/ml)	109.54 (10.86)	−3.59 (3.92)	−7.74 (4.23)	−7.94 (4.71)	−4.00 (2.64)

*p<0.05, **p<0.01.
†Models have been adjusted for child's weight at age 4 years, gender, geographical location, gestational age, mother's age at delivery, mother's smoking habits when child was aged 4 years and duration of breastfeeding.
‡Quartiles defined in table 3.
β-HCH, β-hexachlorocylcohexane; HCB, hexachlorobenzene; OCs, organochlorine compounds; PCBs, polychlorinated biphenyls; p,p′-DDE, p,p′-dichlorodiphenyl dichloroethylene; p,p′-DDT, dichlorodiphenyl trichloroethane.

Main messages

- Background levels of OCs affect thyroid function in children.
- Children with higher levels of p,p′-DDT, β-HCH and PCBs (congeners PCB-138, PCB-153 and PCB-118) had lower concentrations of T3, while free T4 was only negatively associated with PCB-118.

Policy implications

- As thyroid hormones are essential for normal brain development, the lower levels of T3 or free T4 observed in children with higher exposure to OCs may affect cognitive function.
- Further studies in newborns and children are required to more fully understand the effect of OCs on the thyroid system and neurodevelopment.

Acknowledgements: We are indebted to Mrs Maria Victoria Iturriaga for her assistance in contacting the families and administering the questionnaires. We are also grateful to all teachers and parents of the children from Menorca for patiently filling out our questionnaires.

Funding: This study was funded by grants from the Spanish Ministry of Health (FIS-97/1102 and FIS-PI041436), Instituto de Salud Carlos III (Red RCESP C03/09, INMA G03/176 and CB06/02/0041), "Fundació La Caixa" (97/009-00 and 00/077-00) and the Generalitat de Catalunya (CIRIT 1999SGR 00241).

Competing interests: None.

REFERENCES

1. **Suzuki G,** Nakano M, Nakano S. Distribution of PCDDs/PCDFs and Co-PCBs in human maternal blood, cord blood, placenta, milk, and adipose tissue: dioxins showing high toxic equivalency factor accumulate in the placenta. *Biosci Biotechnol Biochem* 2005;**69**:1836–47.
2. **Koopman-Esseboom C,** Huisman M, Weisglas-Kuperus N, *et al*. Dioxin and PCB levels in blood and human milk in relation to living areas in The Netherlands. *Chemosphere* 1994;**29**:2327–38.
3. **Hallergen S,** Darnerud PO. Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats--testing interactions and mechanisms for thyroid hormone effects. *Toxicology* 2002;**177**:227–43.
4. **Braathen M,** Derocher AE, Wiig O, *et al*. Relationships between PCBs and thyroid hormones and retinol in female and male polar bears. *Environ Health Perspect* 2004;**112**:826–33.
5. **Hagmar L.** Polychlorinated biphenyls and thyroid status in humans: a review. *Thyroid* 2003;**13**:1021–8.
6. **Koopman-Esseboom C,** Morse DC, Weisglas-Kuperus N, *et al*. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res* 1994;**36**:468–73.
7. **Longnecker MP,** Gladen BC, Patterson DG Jr, *et al*. Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. *Epidemiology* 2000;**11**:249–54.
8. **Ribas-Fito N,** Sala M, Cardo E, *et al*. Organochlorine compounds and concentrations of thyroid stimulating hormone in newborns. *Occup Environ Med* 2003;**60**:301–3.
9. **Sandau CD,** Ayotte P, Dewailly E, *et al*. Pentachlorophenol and hydroxylated polychlorinated biphenyl metabolites in umbilical cord plasma of neonates from coastal populations in Quebec. *Environ Health Perspect* 2002;**110**:411–17.
10. **Fiolet DCM,** Cuijpers CEJ, Lebret E. Exposure to polychlorinated organic compounds and thyroid hormone plasma levels of human newborns. *Organohalogen Compounds* 1997;**34**:459–65.
11. **Steuerwald U,** Weihe P, Jorgensen PJ, *et al*. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *J Pediatr* 2000;**136**:599–605.
12. **Takser L,** Mergler D, Baldwin M, *et al*. Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. *Environ Health Perspect* 2005;**113**:1039–45.
13. **Wang SL,** Su PH, Jong SB, *et al*. In utero exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. *Environ Health Perspect* 2005;**113**:1645–50.
14. **Asawasinsopon R,** Prapamontol T, Prakobvitayakit O, *et al*. The association between organochlorine and thyroid hormone levels in cord serum: a study from northern Thailand. *Environ Int* 2006;**32**:554–9.
15. **Pluim HJ,** de Vijlder JJ, Olie K, *et al*. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. *Environ Health Perspect* 1993;**10**:504–8.
16. **Matsuura N,** Uchiyama T, Tada H, *et al*. Effects of dioxins and polychlorinated biphenyls (PCBs) on thyroid function in infants born in Japan--the second report from research on environmental health. *Chemosphere* 2001;**45**:1167–71.
17. **Nagayama J,** Lida T, Hirakawa H, *et al*. Effects of lactational exposure to chlorinated dioxins and related chemicals on thyroid functions in Japanese babies. *Organohalogen Compounds* 1997;**33**:446–50.
18. **Nagayama J,** Okamura K, Iida T, *et al*. Postnatal exposure to chlorinated dioxins and related chemicals on thyroid hormone status in Japanese breast-fed infants. *Chemosphere* 1998;**37**:1789–93.
19. **Rice D,** Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000;**108**:511–33.
20. **Oppenheimer JH,** Schwartz HL. Molecular basis of thyroid hormone-dependent brain development. *Endocr Rev* 1997;**18**:462–75.
21. **Osius N,** Karmaus W, Kruse H, *et al*. Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. *Environ Health Perspect* 1999;**107**:843–9.
22. **Schell LM,** Gallo MV, DeCaprio AP, *et al*. Thyroid function in relation to burden of PCBs, p,p′-DDE, HCB, mirex and lead among Akwesasne Mohawk youth: a preliminary study. *Environ Toxicol Pharmacol* 2004;**18**:91–9.
23. **Ilsen A,** Briet JM, Koppe JG, *et al*. Signs of enhanced neuromotor maturation in children due to perinatal load with background levels of dioxins. Follow-up until age 2 years and 7 months. *Chemosphere* 1996;**33**:1317–26.
24. **Carrizo D,** Grimalt JO, Ribas-Fito N, *et at*. Physical-chemical and maternal determinants of the accumulation of organochlorine compounds in four-year-old children. *Environ Sci Technol* 2006;**40**:1420–6.
25. **Gould JC,** Cooper KR, Scanes CG. Effects of polychlorinated biphenyls on thyroid hormones and liver type I monodeiodinase in the chick embryo. *Ecotoxicol Environ Saf* 1999;**43**:195–203.
26. **Morse DC,** Groen D, Veerman M, *et al*. Interference of polychlorinated biphenyls in hepatic and brain thyroid hormone metabolism in fetal and neonatal rats. *Toxicol Appl Pharmacol* 1993;**122**:27–33.
27. **van den Berg KJ,** Zurcher C, Brouwer A. Effects of 3,4,3′,4′-tetrachlorobiphenyl on thyroid function and histology in marmoset monkeys. *Toxicol Lett* 1988;**41**:77–86.
28. **Goldey ES,** Kehn LS, Lau C, *et al*. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicol Appl Pharmacol* 1995;**135**:77–88.
29. **Khan MA,** Hansen LG. Ortho-substituted polychlorinated biphenyl (PCB) congeners (95 or 101) decrease pituitary response to thyrotropin releasing hormone. *Toxicol Lett* 2003;**144**:173–82.
30. **Santini F,** Vitti P, Ceccarini G, *et al*. In vitro assay of thyroid disruptors affecting TSH-stimulated adenylate cyclase activity. *J Endocrinol Invest* 2003;**26**:950–5.
31. **Schuur AG,** Brouwer A, Bergman A, *et al*. Inhibition of thyroid hormone sulfation by hydroxylated metabolites of polychlorinated biphenyls. *Chem Biol Interact* 1998;**109**:293–7.
32. **Hood A,** Allen ML, Liu Y, *et al*. Induction of T(4) UDP-GT activity, serum thyroid stimulating hormone, and thyroid follicular cell proliferation in mice treated with microsomal enzyme inducers. *Toxicol Appl Pharmacol* 2003;**188**:6–13.
33. **Cheek AO,** Kow K, Chen J, *et al*. Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environ Health Perspect* 1999;**107**:273–8.
34. **Purkey HE,** Palaninathan SK, Kent KC, *et al*. Hydroxylated polychlorinated biphenyls selectively bind transthyretin in blood and inhibit amyloidogenesis: rationalizing rodent PCB toxicity. *Chem Biol* 2004;**11**:1719–28.
35. **Hood A,** Klaassen CD. Effects of microsomal enzyme inducers on outer-ring deiodinase activity toward thyroid hormones in various rat tissues. *Toxicol Appl Pharmacol* 2000;**163**:240–8.
36. **Birnbaum LS,** DeVito MJ. Use of toxic equivalency factors for risk assessment for dioxins and related compounds. *Toxicology* 1995;**105**:391–401.
37. **Ribas-Fito N,** Sala M, Kogevinas M, *et al*. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *J Epidemiol Community Health* 2001;**55**:537–46.
38. **Faroon O,** Jones D, de Rosa C. Effects of polychlorinated biphenyls on the nervous system. *Toxicol Ind Health* 2001;**16**:305–33.
39. **de Escobar GM,** Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab* 2004;**18**:225–48.
40. **Anderson GW.** Thyroid hormones and the brain. *Front Neuroendocrinol* 2001;**22**:1–17.
41. **Jacobson JL,** Fein GG, Jacobson SW, *et al*. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. *Am J Public Health* 1984;**74**:378–9.
42. **Alvarez-Pedrerol M,** Ribas-Fitó N, Torrent M, *et al*. TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. *Clin Endocrinol* 2007;**66**:890–8.
43. **Ribas-Fito N,** Torrent M, Carrizo D, *et al*. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. *Am J Epidemiol* 2006;**164**:955–62.

Effects of PCBs, p,p′-DDT, p,p′-DDE, HCB and β-HCH on thyroid function in preschool children

M Álvarez-Pedrerol, N Ribas-Fitó, M Torrent, D Carrizo, J O Grimalt and J Sunyer

Occup Environ Med 2008 65: 452-457 originally published online October 12, 2007
doi: 10.1136/oem.2007.032763

Notes