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POPs and THs in placenta

# Association of *In Utero* Persistent Organic Pollutant Exposure with Placental Thyroid Hormones

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*In utero* exposure to persistent organic pollutants (POPs) can result in thyroid function disorder, leading to concerns about their impact on fetal and neonatal development. The present study was performed to investigate the associations between placental levels of various POPs and thyroid hormones (THs). In a prospective Danish study initially established for assessing congenital cryptorchidism, 58 placenta samples were collected from mothers of boys born with (28) and without (30) cryptorchidism. The concentrations of polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins/furans (PCDD/Fs), organotin chemicals (OTCs), organochlorine pesticides (OCPs), thyroxine ($T_4$), 3,3',5-triiodothyronine ($T_3$), and 3,3',5'-triiodothyronine ($rT_3$) were measured. The associations between placental THs and various POPs were analyzed using multiple linear regression. Five PBDEs, 35 PCBs, 14 PCDD/Fs, 3 OTCs, 25 OCPs, $T_4$, $T_3$, and $rT_3$ were measured. No correlation between THs and the odds of cryptorchidism was found. Several POPs were

significantly associated with THs: a) $T_4$ was inversely associated with BDEs 99, 100, ΣPBDE, and 2378-TeCDD, and positively associated with 1234678-HpCDF; b) $T_3$ was positively associated with 2378-TeCDF and 12378-PeCDF; c) $rT_3$ was positively associated with PCB 81, 12378-PeCDF and 234678-HxCDF, and inversely associated with tributyltin (TBT), ΣOTC, and methoxychlor (MOC). These results revealed that POP exposures were associated with TH levels in placenta, a possible mechanism for the impacts of POP exposures on children's growth and development. This study provides new insight into the complexity of thyroid-disrupting properties of POPs. More research is needed to elucidate the biological consequences of POP exposures.

We measured placental thyroid hormones (THs) and 82 persistent organic pollutants (POPs). The results showed that *in utero* exposure to certain POPs may be associated with placental THs.

## Introduction

Thyroid hormones (THs) are a group of tyrosine based hormones that act on cells of almost all tissues and therefore are involved in important physiological processes during a life span (1,2). The human thyroid system is susceptible to disruption by endogenous (e.g., autoantibodies) or exogenous (e.g., iodine) factors, by interfering with the sodium-iodide symporter, TH metabolism, receptors, and TH transport (3). Consequently, there are concerns regarding the chronic background exposure to persistent organic pollutants (POPs), which have been shown or are suspected to have thyroid-disrupting properties.

POPs have been used in a wide variety of commercial and industrial applications over the past few decades. They are also released from traffic and incineration. Common POPs include polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs), organotin chemicals (OTCs), and organochlorine pesticides (OCPs), among others. Diet, inhalation, and inadvertent dust ingestion are possible exposure pathways to these chemicals for humans (4,5). Although the international agreements intended to reduce or cease their production, POPs are still widely detectable in the biotic and abiotic environment due to their high lipophilicity and resistance to degradation (6). POPs have been detected in human samples such as blood and breast milk from all over the world (7).

POPs are transferred to the fetus across the placenta during pregnancy (8-10). Passive diffusion and/or active uptake are involved in this process. The placenta can also act as a repository for these lipophilic chemicals. Thus, there is a risk for disruption of the fetal development because POPs in placenta may affect the amount of THs delivered to the fetus. This is particularly important during early pregnancy when the fetus depends solely on maternally-derived THs (11). Even subtle changes in maternal TH transfer can lead to various detrimental outcomes such as miscarriage, intra-uterine growth retardation, hypertensive disorders, preterm delivery, and a decreased child IQ (12).

Disruption of TH levels following POP exposure has been observed *in vitro* and in animal studies (13,14). Human epidemiological studies have also found associations between POP

exposures and TH disruption in the general population (15,16), i.e. in e-waste recycling workers (17,18), pregnant women (19-22) and infants (22). Recent studies suggested that prenatal exposure to POPs may interfere with the neurological development of the children (23), as well as their motor, cognitive and behavioral performance (24,25). However, all these studies were conducted with serum, plasma, or breast milk samples. Only one study was performed in placenta on the associations of THs with PBDEs (26), while no research is available for PCBs, PCDD/Fs, OTCs, and OCPs. It is therefore worthwhile to conduct a comprehensive analysis by including as many POPs as possible to have a complete overview of the association between *in utero* POP exposures and THs.

The potential thyroid-disrupting effects of POPs in background exposed populations are of interest because THs act at extremely low serum concentrations (free concentration: 8-30 pg $mL^{-1}$), while POPs can mimic or inhibit the response of the hormones at low doses (e.g., the low dose cut-off of BDE 99 is 0.3 mg $kg^{-1}$ $d^{-1}$) (27,28). The purpose of this study was to investigate the possible association of background exposures of POPs (PBDEs, PCBs, PCDD/Fs, OTCs, and OCPs) with placental levels of THs (thyroxine ($T_4$), 3,3',5-triiodothyronine ($T_3$), and 3,3',5'-triiodothyronine ($rT_3$)) in a Danish population that gave birth to boys with and without cryptorchidism.

## Materials and Methods

### Study Population

The placenta samples were obtained from a joint prospective, longitudinal birth cohort study performed from 1997 to 2001 at the National University Hospital (Rigshospitalet, Hvidovre Hospital), Copenhagen, Denmark. The standardized recruitment strategy, inclusion criteria, participation rate and clinical examination techniques have been reported earlier with details (29,30). Placentas were collected at birth by the midwives and kept frozen in polyethylene bags at -20 °C. Upon analysis, placentas were defrosted, mechanically homogenized and aliquoted into 20-mL glass tubes. Fifty-eight placenta samples were derived from mothers of healthy boys (n = 30) and mothers of boys with cryptorchidism (n = 28) at birth in a nested case-control design. The number of included placenta samples was determined by funding. The demographical variables of both groups are shown in **Supplemental Table 1** (31).

This study followed the Helsinki II declaration (World Medical Association 2004). The Danish ethics committee (KF01-030/97) and the Danish Data Protection Agency (1997-1200-074) approved the study. Informed written consent was obtained from the parents of each boy.

### Data Collection

We determined the total concentrations of $T_4$, $T_3$ and $rT_3$ in placenta samples. Detailed information about the hormones, sample preparation, extraction procedure, analytical method, reagents, and instrumentation have been described earlier (32). Briefly, a 100-mg placenta sample was extracted using solid/liquid extraction, liquid/liquid extraction, and weak cation-exchangers (Bond Elut Plexa PCX) SPE cleanup. Finally, the compounds were quantified by

liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS). An antioxidant solution consisting of 10 mg $mL^{-1}$ citric acid monohydrate, L-(+)-ascorbic acid and R,R-dithiothreitol was added to reduce the deiodination of THs. Isotope labeled analogues of THs (i.e., $^{13}C_6$-$T_3$, $^{13}C_6$-$rT_3$, and $^{13}C_6$-$T_2$) were spiked before extraction to assess the potential deiodination. The results confirmed that no conversion of THs happened during the analytical process. The method quantification limits (MQL) of $T_4$, $T_3$, and $rT_3$ were 0.7, 0.3 and 0.2 ng $g^{-1}$, respectively. The procedural recoveries for the hormones were 81.0 – 105%, with a coefficient of variation (CV) of 0.5 – 6.2%. The intra-day CVs and inter-day CVs were 0.5 – 4.19% and 1.19 – 6.38%, respectively (32).

PBDEs, PCBs, PCDD/Fs, OTCs and OCPs were targeted for analysis in this study. The methods for the sample cleanup and quantification of the compounds have been described in detail previously (30,33-35). The method for lipid measurement has been shown previously (30). A brief description of the methods is given in the **Supplemental method** (31). In addition, we included the World Health Organization toxic equivalent (WHO-TEQ) values of PCDD/Fs and PCBs. This parameter was developed to measure the combined toxicity of dioxin and dioxin-like compounds through the toxic equivalency factors (TEFs), which assesses the toxicity of each congener relative to 2378-TeCDD (36).

**Statistics**

We determined the potential effects of POPs on thyroid status for congeners with a detection frequency > 50%, except for dibutyltin (DBT), tributyltin (TBT), and triphenyltin (TPhT), which were detected in 38%, 41% and 34% of the samples, respectively. We included OTCs regardless of detection frequency because of the growing concerns about environmental effects as well as a lack of studies on the TH effects of these chemicals. Concentrations below LOQs were replaced by the LOQ divided by the square root of 2. The distributions of POP values were much closer to log-normal than normal and were thus $log_{10}$-transformed. $T_4$, $T_3$ and $rT_3$ were normally distributed and not transformed. Normality was confirmed using Kolmogorov-Smirnov test. We used Spearman's rank correlations to evaluate the interrelationship of POP congeners and analysis of variance (ANOVA) to examine associations between demographic characteristics and POP concentrations. Adjusted and unadjusted logistic regressions were used to compare placental TH concentrations in cases with cryptorchidism and controls. As no differences were observed, cases and controls were pooled for analysis of the association between POPs and THs by multiple linear regression for individual POP congeners and the sums.

Potential confounders considered for inclusion in the models were parameters known to influence THs, i.e., maternal age, gestational age, parity (nulliparous vs. one or more live birth), maternal pre-pregnant body mass index (BMI), smoking during pregnancy (yes vs. no), mode of delivery (three categories: vaginal delivery, vacuum extraction, and cesarean section), birth weight, and birth length. Final models included variables that were loosely associated with the THs ($p < 0.20$) in bivariate analyses.

All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC) and R (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria). A $p$-value < 0.05 was considered significant, and $p < 0.10$ was considered as a tendency of association.

## Results

**Table 1** summarizes the characteristics of all the participating women and newborns. The mean (±SD) age of women was 30.4 ± 3.5 years. Among them, 19 (32.8%) were > 30 years of age; forty-seven (81%) had a BMI value of < 25; thirty-nine (67.2%) did not smoke; forty-nine (84.5%) had a normal delivery; thirty-five (60.3%) were nullipara; fifty-four (93.1%) babies were delivered at over 37 weeks of gestation (full term). The demographical parameters did not differ significantly between the cryptorchid and control groups except for gestational age, which was lower in boys with cryptorchidism ($p < 0.06$) (**Supplemental Table 1** (31)).

As shown in **Table 1**, the mean concentration of $T_4$ was 37.6 ng $g^{-1}$ fresh weight (fw) (range: 16.3 – 68.3 ng $g^{-1}$ fw). The mean concentration of $rT_3$ was 4.57 ng $g^{-1}$ fw (range: 1.82 – 9.03 ng $g^{-1}$ fw). The mean level of $T_3$ was 0.85 ng $g^{-1}$ fw (range: 0 – 2.34 ng $g^{-1}$ fw). TH levels were similar across age, BMI, parity, mode of delivery, and birth length of the infants. However, $T_4$ placental level was lower in mothers that smoke ($p < 0.029$). $T_4$ concentration increased with increasing gestational age ($p < 0.004$) and birth weight ($p < 0.004$). However, $T_3$ and $rT_3$ were not correlated with any of the studied characteristics. Placental concentrations of THs did not significantly differ between cryptorchid and control boys (**Table 2).**

The concentrations of a total of 82 POPs and their sums, as well as the WHO-TEQ values of PCDD/Fs and PCBs in placenta are shown in **Supplemental Table 2** (31)**.** The limit of quantification (LOQ) values were 0.004 – 0.14 ng $g^{-1}$ lipid for PBDEs (33), 0.17 pg $g^{-1}$ lipid for non-*ortho*-PCBs, 0.01 ng $g^{-1}$ lipid for mono- and di-*ortho*-PCBs, 0.12 – 0.25 pg $g^{-1}$ lipid for tetra to hepta chlorinated PCDD/Fs, 1.2 pg $g^{-1}$ lipid for octa chlorinated PCDD/Fs (37), 0.1 ng $g^{-1}$ fw for DBT, 0.02 ng $g^{-1}$ fw for TBT and TPhT (34). The limit of detection (LOD) values of the OCPs ranged from 0.01 ng $g^{-1}$ lipid to 1.24 ng $g^{-1}$ lipid (30).

As shown in **Table 3** and **Supplemental Table 3** (31)**.** $T_4$ was inversely significantly associated with the sum of 5 PBDEs (β = -19.0; 95% CI: -35.7, -2.37; $p < 0.026$) as well as with BDE 99 (β = -20.2; 95% CI: -35.2, -5.29; $p < 0.009$), BDE 100 (β = -13.5; 95% CI: -26.8, -0.22; $p < 0.047$) with a tendency for BDE 47 (β = -14.1; 95% CI: -28.5, 0.24; $p < 0.054$). $T_3$ and $rT_3$ were not significantly associated with any of the PBDE congeners.

$T_4$ showed negative tendencies with PCB 99 (β = -15.9; 95% CI: -33.4, 1.65; $p < 0.075$), PCB 118 (β = -13.4; 95% CI: -29.0, 2.27; $p < 0.092$) and PCB 167 (β = -11.7; 95% CI: -25.7, 2.29; $p < 0.099$). No statistically significant associations between $T_3$ and PCB congeners was observed. $rT_3$ was positively significantly associated with PCB 81 (β = 2.55; 95% CI: 0.37, 4.72; $p < 0.023$) with a positive tendency for PCB 101 (β = 0.80; 95% CI: -0.06, 1.65; $p < 0.067$) and PCB 183 (β = 2.08; 95% CI: -0.35, 4.51; $p < 0.091$).

$T_4$ was inversely significantly associated with 2378-TeCDD (β = -18.4; 95% CI: -34.6, -2.25; $p < 0.026$) with a tendency for 12378-PeCDD (β = -13.4; 95% CI: -28.8, 2.01; $p < 0.087$), while positively and significantly associated with 1234678-HpCDF (β = 14.1; 95% CI: 4.37, 22.8; $p < 0.005$) with a positive tendency for OCDD (β = 10.8; 95% CI: -1.94, 23.5; $p < 0.095$). $T_3$ was positively significantly associated with 2378-TeCDF (β = 1.08; 95% CI: 0.33, 1.83; $p < 0.006$) and 12378-PeCDF (β = 0.73; 95% CI: 0.07, 1.40; $p < 0.032$). $rT_3$ was positively significantly associated with 12378-PeCDF (β = 2.53; 95% CI: 0.41, 4.64; $p < 0.020$) and 234678-HxCDF (β = 3.11; 95% CI: 0.94, 5.27; $p < 0.006$), and although not statistically significant, showed a positive tendency with 123478-HxCDF (β = 2.68; 95% CI: -0.47, 5.82; $p < 0.093$), 123678-HxCDF (β = 2.66; 95% CI: -0.41, 5.73; $p < 0.088$) and 1234678-HpCDF (β = 1.43; 95% CI: -0.24, 3.10; $p < 0.092$).

$rT_3$ was inversely significantly associated with TBT (β = -2.65; 95% CI: -3.79, -1.51; $p < 0.001$) and the sum of OTCs (β = -4.96; 95% CI: -7.78, -2.14; $p < 0.001$), while none of the OTCs showed a significant association with $T_4$ or $T_3$.

β-hexachlorocyclohexane (β-HCH) showed negative tendencies with $T_4$ (β = -13.9; 95% CI: -28.7, 0.90; $p < 0.065$), $T_3$ (β = -0.68; 95% CI: -1.44, 0.09; $p < 0.081$) and $rT_3$ (β = -2.06; 95% CI: -4.50, 0.38; $p < 0.097$), although none of them were statistically significant. Methoxychlor (MOC) was inversely significantly associated with $rT_3$ (β = -2.30; 95% CI: -3.88, -0.72; $p < 0.005$).

## Discussion

We measured placental $T_4$, $T_3$ and $rT_3$ by an UPLC-Q-TOF-MS method, which offers good sensitivity and specificity (32). The TH levels reported here corresponded well with previous findings in human placenta (26,38). Placental levels of some contaminants might be representative of fetal exposures due to the placental transfer of POPs during gestation (39).

We observed correlations between $T_4$ and gestational age, maternal smoking, and birth weight, which were in accordance with previous studies (40-43). These variables were therefore included in the statistical analysis as cofounders. Some other researchers have also found associations of THs with mode of delivery (40), alcohol consumption (44), and maternal BMI (45).

A previous review suggested that THs may play a role in the development and function of the testis (46). However, this study revealed no difference of THs between the two groups. Bruker-Davis *et* al. also reported no difference of THs in cord blood from mothers that gave birth to boys with and without cryptorchidism (10). However, the results may be very different when a different matrix (i.e., maternal serum, cord blood, infant serum or placenta) and different TH measurements (i.e., total concentrations or free concentrations) were used.

In this study, POPs were generally negatively associated with total $T_4$ and positively associated with total $T_3$ and total $rT_3$. Previous studies have reported positive (20-22), negative (20,22), and no associations (47) between certain POP and TH serum concentrations in pregnant

women and newborns. However, our results may not be directly comparable to these studies. Only one study exists on THs and brominated flame retardants in placenta, in which placental BDE 99 and BDE 209 were negatively associated with $rT_3$ in male infants, while BDE 99 and 2,4,6-tribromophenol (2,4,6-TBP) were positively associated with $T_3$ in female infants (26).

Various mechanisms are involved in the thyroid-disrupting process of POPs: (i) POPs may disrupt the activity of the thyroid gland by interference with the proteins on the thyrocyte; (ii) POPs may competitively bind to TH binding proteins, i.e., transthyretin (TTR) and thyroid hormone receptors (TR); (iii) POPs may affect the peripheral TH metabolism and clearance by interference with the enzymes (48). Total $T_4$ in placenta mainly originates from maternal free $T_4$, while total $T_3$ and total $rT_3$ were derived entirely from placental and foetal metabolism of $T_4$ (49). Disrupting the TH-protein binding and metabolism in placenta may be of significance. TTR plays a crucial role in transferring free $T_4$ across the placenta (48). Binding of certain POPs to TTR may facilitate the transport of these compounds, while reducing $T_4$ delivery to the fetus.

**Associations of $T_4$ with POPs**

Our results revealed inverse associations of BDEs 47, 99, 100 and ΣPBDE with $T_4$, which were in accordance with a previous report (26). This could be due to the strong affinities between TTR and BDE 47, 99, and BDE 100 (50). PCBs were expected to show associations with $T_4$ because of their structural resemblance with $T_4$. Boas *et* al. also suggested negative associations between perinatal PCB exposure and THs (48). However, only negative tendencies between $T_4$ and PCB 99, 118 and PCB 167 were found in this study. This might be due to the differences in the applied matrix and biological indicators of exposure. For example, Majidi *et* al. analyzed the TH effect of PCBs using standardized concentrations expressed in total PCB equivalent per kg of lipids in maternal plasma (μg $PCB_{MPEQ}$ $kg^{-1}$ lipids). The results suggested little evidence for the impact of PCBs on thyroid function in pregnant women and newborns (51). PCDD/Fs are able to bind to and activate the aryl hydrocarbon receptor (AhR), inducing UDPGT and cytochrome P450 enzymes, which may stimulate the excretion of $T_4$ (52). This may explain the inverse association of 2378-TeCDD with $T_4$ observed here. However, we also observed positive associations between $T_4$ and 12378-PeCDD, 1234678-HpCDF, and OCDD here, probably due to the inhibitory effect of dioxins on the deiodinase activities. Dichlorodiphenyltrichloroethane (DDT) (and its metabolite DDE) and hexachlorobenzene (HCB) may be associated with THs by interference with the thyroid peroxidase (TPO) and binding proteins (48). We observed negative association of $T_4$ with β-HCH in this study. This might be explained by the similar bioconcentration factor of β-HCH and HCB, which may lead to a similar mechanism of action.

**Associations of $rT_3$ with POPs**

$rT_3$ is an inactive metabolite of $T_4$ formed by deiodination. Inhibition of DIO activities by POPs may lead to reduction in $T_4$ metabolism, causing lower levels of placental $rT_3$ (53). For example, Leonetti *et* al. reported a negative association between $rT_3$ and BDE 99 among males (26), which, however, was not observed here. Our study found that TBT, ΣOTC, β-HCH, and MOC were inversely associated with $rT_3$. We also found positive associations between $rT_3$ and PCB

81, 101, 183, 12378-PeCDF, 123478-HxCDF, 123678-HxCDF, 234678-HxCDF, and 1234678-HpCDF, suggesting an alternative mechanism of action. OTCs are a group of chemicals used as biocides in antifouling paints. We observed the association between $rT_3$ and TBT placental exposure for the first time. This association was also found in samples in which TBT concentration >LOQ ($\beta$ = -1.53; 95% CI: -2.85, -0.20; $p < 0.026$). TBT can cross the placenta, inducing physiological and morphological changes, resulting in abnormal fetal and postnatal development (54). The present study suggested that *in utero* exposure of OTC, especially TBT, is negatively associated with $rT_3$.

**Associations of $T_3$ with POPs**

Among the 82 POPs investigated, $T_3$ only showed positive associations with 2378-TeCDF and 12378-PeCDF, and negative tendency with β-HCH, suggesting a low sensitivity of $T_3$ concentration for POP exposures. Placental $T_3$ is produced by deiodination in the placenta and foetus, whereas $T_4$ is partly derived from the of maternal free $T_4$. Therefore, the feedback regulation, which is induced by $T_3$, may not take place in placenta, and thus maternal pituitary regulation might be out of regulatory function for placental $T_3$.

We also estimated the associations of THs with the WHO-TEQ values of PCDD/Fs (PCDD/F_WHO-TEQ) and PCBs (PCB_WHO-TEQ). As shown in **Supplemental Table 3** (31), no significant associations were observed.

**Strengths and Limitations**

This study has several unique strengths: (a) This is the first study investigating thyroid-disrupting effect of as many as 82 POPs, as well as the WHO-TEQ values of PCDD/Fs and PCBs, which provides an overview of the possible relationships between the POPs and THs in placenta; (b) UPLC-Q-TOF-MS was adopted for TH analysis, which provides better accuracy and reliability than IA methods; (c) A wide variety of demographical characteristics were assessed and considered in the statistical analysis. Taking various characteristics into consideration increases the robustness. However, the study also has certain limitations. For example, the number of samples is limited (n=58), which may reduce the statistical power. Only placenta samples from mothers that gave birth to boys were included in this research, thus we could not reveal any sex-dependent effect. The hydroxylated metabolites of certain POPs (e.g., OH-PCBs and OH-PBDEs), which generally show higher affinities to the TH-binding proteins, were not included. The THs and POPs measured here reflect the situation at delivery instead of gestation. Our previous study suggested that milk analyses might be more reliable toward the lower end of concentrations (33). Free THs may be more important for analyzing the effects of POP exposures, while total concentrations were measured here. Additionally, the enzyme activities in placental samples might help to explain the TH-disrupting effects of the POPs.

Finally, with as many as 82 POP congeners, their sums and 3 THs, some significant associations may occur by chance. However, in particular the associations between PBDEs and $T_4$ appear robust, as all associations showed the same direction and there is a well-known structure resemblance of PBDEs to $T_4$.

## Conclusion

In summary, our results suggest that background exposure to POPs is associated with TH levels in placenta. Our results highlight the challenges of assessing effects on thyroid function, especially during pregnancy, due to the complexity of contaminant mixtures and the sensitivity of the thyroid system of the pregnant woman and the fetus. Finally, the results of this study should be interpreted with caution due to the limited number of subjects included in the analysis. The findings should be confirmed with more placenta samples from both boys and girls, also including the DIO enzyme activities and the hydroxylated metabolites of PBDEs and PCBs.

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Disclosure Summary:
The authors report no conflicts of interest in this work.

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**Table 1.** Correlations between demographic characteristics and TH placental concentrations using t-test and analysis of variance (ANOVA).

| | | | Measures of THs in placenta (mean (SD)) | | |
|---|---|---|---|---|---|
| Characteristics | *n* | % | $T_4$ (ng $g^{-1}$ fw) | $T_3$ (ng $g^{-1}$ fw) | $rT_3$ (ng $g^{-1}$ fw) |
| Mean (SD) | 58 | 100 | 37.6 (10.9) | 0.85 (0.50) | 4.57 (1.63) |
| Median (minimum, maximum) | 58 | 100 | 37.7 (16.3, 68.3) | 0.69 (0, 2.34) | 4.21 (1.82, 9.03) |
| Maternal characteristics | | | | | |
| Age (years) | | | | | |
| <30 | 39 | 67.2 | 35.5 (10.4) | 0.88 (0.51) | 4.65 (1.72) |
| ≥30 | 19 | 32.8 | 42.1 (11.0) | 0.79 (0.49) | 4.41 (1.47) |
| BMI (kg $m^{-2}$) | | | | | |
| <25 | 47 | 81.0 | 37.4 (10.9) | 0.86 (0.52) | 4.72 (1.68) |
| ≥25 | 10 | 17.2 | 38.4 (11.9) | 0.73 (0.38) | 4.05 (1.28) |
| Smoking | | | | | |
| Yes | 19 | 32.8 | 42.1 (11.0)* | 0.79 (0.49) | 4.41 (1.47) |
| No | 39 | 67.2 | 35.5 (10.4) | 0.88 (0.51) | 4.65 (1.72) |
| Mode of delivery | | | | | |
| Vaginal delivery | 49 | 84.5 | 37.4 (11.5) | 0.83 (0.51) | 4.63 (1.61) |
| Vacuum extraction | 3 | 5.17 | 43.6 (1.77) | 1.14 (0.50) | 5.48 (3.03) |
| Cesarean section | 6 | 10.3 | 36.7 (7.89) | 0.82 (0.47) | 3.66 (0.65) |
| Parity | | | | | |
| 1 | 35 | 60.3 | 36.8 (10.6) | 0.87 (0.51) | 4.62 (1.65) |
| 2 | 18 | 31.0 | 37.9 (10.3) | 0.84 (0.55) | 4.45 (1.80) |
| 3 | 5 | 8.62 | 42.4 (16.4) | 0.75 (0.23) | 4.71 (1.00) |
| Gestational age (days) | | | | | |
| <268 | 7 | 12.1 | 31.0 (7.3)* | 0.74 (0.46) | 3.92 (0.48) |
| 268–278 | 12 | 20.7 | 33.1 (10.5) | 0.99 (0.59) | 4.29 (1.82) |
| 278–288 | 25 | 43.1 | 38.7 (9.5) | 0.84 (0.49) | 4.80 (1.82) |
| ≥288 | 14 | 24.1 | 43.0 (12.8) | 0.79 (0.48) | 4.43 (1.50) |
| Infant characteristics | | | | | |
| Birth weight (kg) | | | | | |
| <3 | 5 | 8.62 | 28.6 (5.2)* | 0.90 (0.46) | 3.69 (0.65) |
| 3–4 | 43 | 74.1 | 37.0 (9.8) | 0.83 (0.53) | 4.62 (1.65) |
| ≥4 | 10 | 17.2 | 44.9 (13.8) | 0.90 (0.39) | 4.82 (1.86) |
| Birth length (cm) | | | | | |
| <50 | 5 | 8.62 | 31.8 (7.6) | 0.83 (0.55) | 3.76 (0.63) |
| 50–55 | 43 | 74.1 | 37.1 (10.4) | 0.86 (0.53) | 4.74 (1.71) |
| ≥55 | 10 | 17.2 | 42.9 (13.2) | 0.83 (0.35) | 4.26 (1.57) |

Abbreviations: fw, fresh weight; BMI, body mass index before pregnancy; SD, standard deviation.

*$p$<0.05

**Table 2.** Association between placental TH concentrations and odds of cryptorchidism.

| THs (ng $g^{-1}$) | OR[a] (95% CI[b]) | |
|---|---|---|
| | Unadjusted | Adjusted[c] |
| $T_4$ | 1.05 (1.00 to 1.12) | 1.04 (0.98 to 1.11) |
| $T_3$ | 0.50 (0.14 to 1.60) | 0.53 (0.15 to 1.73) |
| $rT_3$ | 1.31 (0.93 to 1.94) | 1.35 (0.94 to 2.05) |

[a]Odds ratio.

[b]95% confidence intervals.

[c]Models adjusted for maternal smoking, gestational age and infant birth weight.

**Table 3**. Significant or marginal associations between various POPs and TH concentrations in placenta from women participating in the Danish Cohort Study.

| POPs[a] | $T_4$ | | $T_3$ | | $rT_3$ | |
|---|---|---|---|---|---|---|
| | β (95% CI)[b] | $R^2$ | β (95% CI)[b] | $R^2$ | β (95% CI)[b] | $R^2$ |
| PBDEs | | | | | | |
| BDE 47 | -14.1 | 0.27 | 0.02 | 0.01 | 1.36 | 0.08 |
| | (-28.5 to 0.24)# | | (-0.74 to 0.78) | | (-1.04 to 3.77) | |
| BDE 99 | -20.2 | 0.32 | -0.07 | 0.01 | 1.59 | 0.09 |
| | (-35.2 to -5.29)** | | (-0.88 to 0.75) | | (-0.99 to 4.16) | |
| BDE 100 | -13.5 | 0.28 | 0.03 | 0.01 | 1.74 | 0.10 |
| | (-26.8 to -0.22)* | | (-0.68 to 0.74) | | (-0.47 to 3.96) | |
| ΣPBDE | -19.0 | 0.29 | 0.02 | 0.01 | 1.72 | 0.09 |
| | (-35.7 to -2.37)* | | (-0.88 to 0.92) | | (-1.10 to 4.55) | |
| PCBs | | | | | | |
| PCB 81 | 0.92 | 0.22 | 0.56 | 0.06 | 2.55 | 0.15 |
| | (-13.0 to 14.9) | | (-0.14 to 1.26) | | (0.37 to 4.72)* | |
| PCB 99 | -15.9 | 0.27 | 0.08 | 0.01 | 1.16 | 0.07 |
| | (-33.4 to 1.65)# | | (-0.85 to 1.01) | | (-1.78 to 4.10) | |
| PCB 101 | 0.69 | 0.22 | 0.06 | 0.02 | 0.80 | 0.12 |
| | (-4.69 to 6.08) | | (-0.22 to 0.33) | | (-0.06 to 1.65)# | |
| PCB 118 | -13.4 | 0.26 | 0.10 | 0.01 | -0.38 | 0.06 |
| | (-29.0 to 2.27)# | | (-0.73 to 0.92) | | (-3.01 to 2.25) | |
| PCB 167 | -11.7 | 0.26 | 0.05 | 0.01 | -0.14 | 0.06 |
| | (-25.7 to 2.29)# | | (-0.69 to 0.79) | | (-2.50 to 2.21) | |
| PCB 183 | -8.75 | 0.24 | -0.16 | 0.02 | 2.08 | 0.11 |
| | (-23.8 to 6.27) | | (-0.94 to 0.62) | | (-0.35 to 4.51)# | |
| PCDD/Fs | | | | | | |
| 2378-TeCDF | 0.42 (-15.3 to 16.2) | 0.22 | 1.08 (0.33 to 1.83)** | 0.15 | 1.01 (-1.55 to 3.58) | 0.07 |
| 2378-TeCDD | -18.4 (-34.6 to -2.25)* | 0.29 | -0.29 (-1.15 to 0.58) | 0.02 | 0.16 (-2.62 to 2.94) | 0.06 |
| 12378-PeCDF | 7.93 (-5.50 to 21.4) | 0.24 | 0.73 (0.07 to 1.40)* | 0.10 | 2.53 (0.41 to 4.64)* | 0.15 |
| 12378-PeCDD | -13.4 (-28.8 to 2.01)# | 0.26 | -0.23 (-1.04 to 0.58) | 0.02 | 1.39 (-1.18 to 3.96) | 0.08 |
| 123478-HxCDF | -6.23 (-25.9 to 13.4) | 0.23 | -0.34 (-1.35 to 0.67) | 0.02 | 2.68 (-0.47 to 5.82)# | 0.11 |
| 123678-HxCDF | 3.10 (-16.1 to 22.3) | 0.22 | 0.03 (-0.96 to 1.02) | 0.01 | 2.66 (-0.41 to 5.73)# | 0.11 |
| 234678-HxCDF | 9.51 (-4.46 to 23.5) | 0.25 | 0.18 (-0.55 to 0.91) | 0.02 | 3.11 (0.94 to 5.27)** | 0.19 |
| 1234678-HpCDF | 14.1 (4.37 to 22.8)** | 0.33 | 0.26 (-0.28 to 0.79) | 0.03 | 1.43 (-0.24 to 3.10)# | 0.11 |
| OCDD | 10.8 (-1.94 to 23.5)# | 0.26 | -0.02 (-0.69 to 0.64) | 0.01 | 0.59 (-1.54 to 2.72) | 0.07 |

| | | | | | | |
|---|---|---|---|---|---|---|
| OTCs | | | | | | |
| TBT | -0.07 (-8.33 to 8.19) | 0.22 | -0.18 (-0.60 to 0.24) | 0.03 | -2.65 (-3.79 to -1.51)** | 0.33 |
| ΣOTC | -2.20 (-21.3 to 16.9) | 0.22 | -0.43 (-1.41 to 0.54) | 0.03 | -4.96 (-7.78 to -2.14)** | 0.24 |
| OCPs | | | | | | |
| β-HCH | -13.9 | 0.27 | -0.68 | 0.07 | -2.06 | 0.11 |
| | (-28.7 to 0.90)# | | (-1.44 to 0.09)# | | (-4.50 to 0.38)# | |
| MOC | -3.08 (-13.4 to 7.27) | 0.23 | -0.30 (-0.82 to 0.23) | 0.04 | -2.30 (-3.88 to -0.72)** | 0.19 |

Abbreviations: OCDD, octachlorodibenzo-*p*-dioxin; TBT, tributyltin; OCS, octachlorostyrene; β-HCH, β-hexachlorocyclohexane; MOC, methoxychlor.

[a]Placental concentrations of PBDEs, PCBs, PCDD/Fs, OTCs and OCPs were $\log_{10}$-transformed. PBDEs, PCBs, PCDD/Fs and OCPs were expressed on lipid basis, OCTs were expressed on fresh weight basis.

[b]Adjusted for maternal smoking, gestational age, and neonatal birth weight.

$^{*}p<0.05$. $^{**}p<0.01$. $^{\#}p<0.10$.