Environ Sci Pollut Res (2017) 24:16592–16603
DOI 10.1007/s11356-017-8992-7

RESEARCH ARTICLE

Temporal trends of lipophilic persistent organic pollutants in serum from Danish nulliparous pregnant women 2011–2013

Christian Bjerregaard-Olesen[1] · Manhai Long[1] · Mandana Ghisari[1] · Bodil H Bech[2] · Ellen A Nohr[3] · Niels Uldbjerg[4] · Tine B Henriksen[5,6] · Jørn Olsen[2] · Eva C Bonefeld-Jørgensen[1]

Received: 12 December 2016 / Accepted: 4 April 2017 / Published online: 21 April 2017

Abstract The use of the lipophilic persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs) and several organochlorine pesticides (OCPs) has been prohibited for more than 30 years. In this study, we present the temporal trends of the lipophilic POP serum concentrations in Danish nulliparous pregnant women between 2011 and 2013. We randomly selected 197 pregnant women (gestational age 11–13) from the Aarhus Birth Cohort. The concentrations of the lipophilic POPs in the serum samples were analyzed using gas chromatography. The concentrations were corrected for total serum lipids. The statistical analysis was performed by regression analysis with adjustment for age, BMI, gestational age at blood draw, and smoking status. The serum concentrations of PCB 118, 138, 153, 156, 170, 180, 187, and hexachlorobenzen, *trans*-nonachlor, β-hexachlorocyclohexane (β-HCH), and *p,p'*-dichlorodiphenyldichloroethylene were lower in 2013 than in 2011. However, the oxychlordane concentration was lowest in 2011. The serum levels of most lipophilic POPs followed downward trends during the study period, which was expected, as these compounds has been banned for many years. The upward trend of oxychlordane was unexpected and presumably a chance finding.

Keywords Determinants · Time trends · Organochlorine pesticides · Polychlorinated biphenyls · Predictors · Pregnancy

In the second paragraph of the Statistics section, the text was added: However, the PBDE data were not available for 39 samples from 2011 and these samples were excluded from the statistical analyses involving ∑lipPOP

Equation 2 in statistics was corrected.

Responsible editor: Hongwen Sun

Electronic supplementary material The online version of this article (doi:10.1007/s11356-017-8992-7) contains supplementary material, which is available to authorized users.

✉ Eva C Bonefeld-Jørgensen
ebj@ph.au.dk

[1] Centre for Arctic Health & Molecular Epidemiology, Department of Public Health, Aarhus University, Bartholins Allé 2, Build. 1260, DK-8000 Aarhus C, Denmark

[2] Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

[3] Research Unit for Gynaecology and Obstetrics, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

[4] Department of Clinical Medicine-Obstetrics and Gynaecology, Aarhus University Hospital, Skejby, Denmark

[5] Perinatal Epidemiology Research Unit, Aarhus University Hospital, Skejby, Denmark

[6] Department of Pediatrics, Aarhus University Hospital, Skejby, Denmark

Abbreviations

AMAP	Arctic Monitoring and Assessment Programme
BMI	Body mass index
CI	Confidence interval
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
LOQ	Limit of quantification
OCP	Organochlorine pesticide
PFAA	Perfluorinated alkyl acid
PBB	Polybrominated biphenyl
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
POP	Persistent organic pollutant

Introduction

The production of many organochlorine compounds including polychlorinated biphenyls (PCBs) started in the 1930s. PCBs were used as heat transfer fluids, hydraulic fluids, solvent extenders, plasticizers, flame retardants, and dielectric fluids until the use was restricted in 1972 and prohibited since the late 1970s in most industrialized countries including Denmark (Medehouenou et al. 2011; Noren and Meironyte 2000; Takeuchi et al. 2011). As alternatives to PCBs, other compounds such as polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) were then introduced as flame retardants. PBBs and two types of PBDE mixtures (i.e., pentaBDEs and octaBDEs) have been phased out globally, and the use of a third type (i.e., decaBDEs) is being regulated (Sjodin et al. 2004; Wu et al. 2011). Several organochlorine pesticides (OCPs) including dichlorodiphenyltrichloroethane (DDT) and hexachlorobenzene (HCB) have also been banned from use (Andersen et al. 2002; Noren and Meironyte 2000). Many of these polychlorinated and polybrominated compounds are persistent and bioaccumulate in the food chain, causing humans to be exposed through the diet such as fish, meat, and dairy products (Brauner et al. 2011; Brauner et al. 2012; Diamanti-Kandarakis et al. 2009; Halldorsson et al. 2008b; Thomsen et al. 2007). Several OCPs, PBDEs, and PCBs are registered as persistent organic pollutants (POPs) under the Stockholm convention (Stockholm Convention 2009).

Human elimination of the POPs is slow. The median half-life of the DDT metabolite *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) among Brazilian malaria control workers was 28 months, although with large inter-individual variations (Ferreira et al. 2011). Using serum from former capacitor workers, Seegal et al. found that the geometrical mean half-lives over a study period from 1976 to 2004 were 17.8 years for the heavy PCB congeners (i.e., PCBs eluting before DDE using gas chromatography) and 9.6 years for the light congeners (i.e., PCBs eluting after DDE using gas chromatography) (Seegal et al. 2011). In female capacitor workers, the half-lives were between 1.5 and 10 times longer than in males, possibly because the initial PCB concentrations were higher in the males and thus were influenced less by background exposure (Seegal et al. 2011). PBDE levels in serum of Swedish electronic workers decreased during vacations with estimated half-lives of 14 days for BDE-209, 37 days for BDE-203, 110 days for BDE-183, 270 days for BDE-154, and 680 days for BDE-153 (Jakobsson et al. 2003).

Although, the lipophilic POPs have been banned for many years, they may still be of concern to public health, especially for the fetus, which is at a vulnerable stage of life (Bonefeld-Jorgensen 2010). The temporal changes of lipophilic POP concentrations have not been studied much in Europe in recent years, and to our knowledge, no time trend studies have been conducted in Denmark. The lipophilic POP concentrations in human serum may be dependent on factors such as age, body mass index (BMI), parity, and gender (Caspersen et al. 2016; Fernandez-Rodriguez et al. 2015; Long et al. 2015; Medehouenou et al. 2011; Porta et al. 2012; Rylander et al. 2012; Sandau et al. 2000; Wolff et al. 2005). Hence, it is important to control for these covariates when conducting a time trend study by e.g., selecting a homogenous population such as nulliparous pregnant women. To our knowledge, no previous studies of lipophilic POP trends have included only nulliparous pregnant women.

The objectives of the present study was (1) to determine the temporal trends of the most abundant lipophilic POPs in serum of Danish pregnant nulliparous women between 2011 and 2013 and (2) to investigate associations between the lipophilic POP concentrations and the pregnant women's age at delivery, pre-pregnancy BMI, number of miscarriages, and educational level.

Materials and methods

Samples

Blood samples were collected from 197 pregnant women, randomly sampled among Aarhus Birth Cohort participants, who fulfilled the selection criteria of being nulliparous and giving birth to a live born singleton neonate between 2011 and 2013 at the Aarhus University Hospital, Denmark (Mortensen et al. 2013). The blood samples were taken in the first trimester before the end of gestational week 13 and were processed within 2 h after blood drawing and stored as serum at −80° C (Mortensen et al. 2013). The gestational age at the time of blood draw was estimated by ultrasound.

The women filled out a questionnaire including questions about height, pre-pregnancy weight, miscarriages, country of birth, smoking status, alcohol consumption, and educational level (Bjerregaard-Olesen et al. 2016a). The Aarhus Birth Cohort also holds information about the delivery and the newborn reported by the attending midwife.

All participants provided written consent to the storing of their blood samples in the biobank and that the samples and information could be used for research. The study was approved by the Danish National Committee on Health Research Ethics (j.nr: M-20110054) and the Danish Data Protection Agency (j.nr: 2011-41-6014).

Chemical analyses

The chemical analysis of PCBs, PBDEs, and OCPs was conducted at Centre de Toxicologie, Institute National de Santé Publique du Québec, a contract laboratory certified by the Canadian Association for Environmental Analytical Laboratories. The serum samples were analyzed for lipophilic POPs including OCPs (aldrin, alphachlordane, cisnonachlor,

gammachlordane, HCB, mirex, oxychlordane, *p,p'*-DDE, *p,p'*-DDT, β-hexachlorocyclohexan (β-HCH), and *trans*-nonachlor), PCBs (28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187), BB-153, and PBDEs (15, 17, 25, 28, 33, 47, 99, 100, and 153). Briefly, 2 mL serum was spiked with internal standards ($^{13}C_{12}$-PCB 141, $^{13}C_{12}$-PCB 153, $^{13}C_{12}$-PCB 180, $^{13}C_{12}$-PCB 194, $^{13}C_6$-HCB, $^{13}C_6$-α-HCH, $^{13}C_{10}$-*trans*-nonachlor, $^{13}C_{10}$-oxychlordane, $^{13}C_{12}$-*p,p'*-DDE, $^{13}C_{10}$-Parlar 26, $^{13}C_{10}$-Parlar 50, $^{13}C_{12}$-PBDE 77, 3,6-F_2-PBDE 99, and PBDE 101). The serum proteins were denatured using reagent grade alcohol followed by addition of a saturated ammonium sulfate solution and liquid-liquid extraction using *n*-hexane. The extracts were evaporated, reconditioned in 0.5 mL hexane, and purified on activated florisil columns (60–100 mesh; Fisher Scientific, Nepean, Ontario, Canada), which were eluted using 9 mL dichloromethane:hexane (1:3). The purified extracts were concentrated, and 3 μL was analyzed using gas chromatography (Agilent 7890A) equipped with an Agilent 60 m DB-XLB column (0.25 mm i.d., 0.25 μm film thickness) and coupled to a 5975C mass spectrometer (MS; Agilent technologies, Mississauga, ON, Canada). Helium was used as the carrier gas, and the injections were in splitless mode. The MS used selected ion monitoring (SIM) with negative chemical ionization (NCI) and methane as the reagent gas. The limit of quantification (LOQ) was determined as a signal-to-noise ratio of 3:1, corresponding to 0.02 μg/L for HCB, *p,p'*-DDE and *p,p'*-DDT, 0.01 μg/L for the other OCPs and PCBs, and 0.05 μg/L for the PBDEs. The recoveries varied between 68 and 90% for all analytes, the intra-day precision was 1.2–8.3%, and the inter-day precision was 2.8–13%. Further details have been described elsewhere (Chevrier et al. 2013; Fisher et al. 2016).

Serum lipids were analyzed using a standard enzymatic procedure, and the total lipid concentration was obtained by summation of the concentrations of cholesterol esters, free cholesterol, triglycerides, and phospholipids. Further details have been described elsewhere (Phillips et al. 1989).

The serum concentrations of perfluorinated alkyl acids (PFAAs) were analyzed at the Department of Environmental Science, Aarhus University, as described in a recent study (Bjerregaard-Olesen et al. 2016b). Briefly, 100 μL serum samples were spiked with ^{13}C–labeled internal PFAA standards, diluted with 3 mL 0.1 M formic acid, and extracted by solid phase extraction using OASIS HLB cartridges (3 mL, 60 mg; Waters, Milford, MA, USA). The cartridges were washed with 1 mL Millipore water and conditioned with 2 mL methanol and 2 mL 0.1 M formic acid before addition of the diluted serum samples. The PFAAs were eluted using 2 mL methanol. The extracts were dried and reconstituted in 100 μL 2 mM ammonium acetate/methanol (50/50, *v*/*v*). Sixteen PFAAs (C4, C6-C8, and C10 sulfonates; C5-C14 carboxylates; and C8 sulfonamide) were analyzed in the reconstituted extracts using LC-MS/MS on an Agilent 1100 series HPLC (Agilent technologies, Palo Alto, CA, USA) equipped with a C18 Kinetex column (2.1 × 150 mm, Phenomenex, Torrance, CA, USA) and coupled to a triple quadrupole QTrap 5500 (Sciex, Concorde, ON, Canada). The relative inter-day standard deviation was between 1.2 and 16.7% for all the PFAAs.

Statistics

For the samples that contained POPs at concentrations below the LOQ, we assigned the samples with values of LOQ/2 for the statistical analysis. The lipophilic POP concentrations were corrected for total serum lipids (μg/kg lipid). Only POPs that could be detected in at least 50% of the samples were included in the statistical analysis. In addition to the single compounds, we analyzed the data for three groups of lipophilic POPs:

$$\sum\text{PCB} = \text{PCB 28} + \text{PCB 52} + \text{PCB 99} + \text{PCB 101} + \text{PCB 105} + \text{PCB 118} + \text{PCB 128} + \text{PCB 138} + \text{PCB 153} + \text{PCB 156} + \text{PCB 170} + \text{PCB 180} + \text{PCB 183} + \text{PCB 187}$$

$$\sum\text{OCP} = \text{aldrin} + \text{alphachlordane} + \text{cisnonachlor} + \text{gammachlordane} + \text{HCB} + \text{mirex} + p,p'\text{-DDT} + p,p'\text{-DDE} + \text{oxychlordane} + \beta\text{-HCH} + \text{trans-nonachlor}$$

$$\sum\text{lipPOP} = \sum\text{PCB} + \sum\text{OCP} + \text{BB-153} + \text{BDE-100} + \text{BDE-15} + \text{BDE-153} + \text{BDE-17} + \text{BDE-25} + \text{BDE-28} + \text{BDE-33} + \text{BDE-47} + \text{BDE-99}$$

We did not have a group of brominated flame retardants, as the PBDEs were detected in less than 5% of the samples, but they were included in ∑lipPOP. However, the PBDE data were not available for 39 samples from 2011 and these samples were excluded from the

statistical analyses involving ∑lipPOP. The statistical analyses were conducted using STATA/IC 13, and the statistical significance level was set at $p < 0.05$.

The temporal trend analysis was performed by log-linear regression analysis. Several studies have reported that the lipophilic POP concentrations are associated with age (Fernandez-Rodriguez et al. 2015; Long et al. 2015; Medehouenou et al. 2011; Porta et al. 2012; Rylander et al. 2012; Sandau et al. 2000; Wolff et al. 2005), BMI (Fernandez-Rodriguez et al. 2015; Halldorsson et al. 2008b; Medehouenou et al. 2011; Porta et al. 2012; Wolff et al. 2005), smoking status (Deutch et al. 2007, 2003; Fernandez-Rodriguez et al. 2015; Wolff et al. 2005), and gestational age at blood draw (Adetona et al. 2013; Longnecker et al. 1999). Hence, in the present study, the temporal trends were analyzed for the lipid-corrected crude data and upon adjustment for

Table 1 Characteristics of the 197 randomly selected nulliparous women from the Aarhus Birth Cohort and median concentrations of the lipophilic POPs (μg/kg serum lipids), 2011–2013

	n	2011 66	2012 66	2013 65
Age (years)	Median	29	29	28
	IQR[c]	27–32	26–31	26–32
BMI (kg/m^2)[a]	Median	21.8	22.7	22.0
	IQR[c]	20.3–24.4	20.6–24.3	20.0–24.2
GA at blood draw (weeks)[b]	Median	12	12	12
	Range	11–13	11–13	11–13
Educational level (*n*, (%))	High	19 (29%)	25 (38%)	22 (35%)
	Upper middle	29 (44%)	22 (33%)	25 (40%)
	Lower middle	16 (24%)	17 (26%)	15 (24%)
	Low	2 (3%)	2 (3%)	1 (2%)
Country of birth (*n*, (%))	Denmark	60 (91%)	61 (92%)	59 (91%)
	Outside Denmark	6 (9%)	5 (8%)	6 (9%)
Smoking (*n*, (%))	Never smoked	58 (89%)	55 (83%)	54 (86%)
	Only before pregnancy	6 (9%)	7 (11%)	8 (13%)
	During pregnancy	1 (2%)	4 (6%)	1 (2%)
Alcohol intake (*n*, (%))	No alcohol	20 (31%)	28 (42%)	29 (45%)
	Only before pregnancy	38 (58%)	31 (47%)	30 (46%)
	During pregnancy	7 (11%)	7 (11%)	6 (9%)
PCB118 (μg/kg lipid)	Median	3.2	2.7	2.7
	IQR[c]	2.4–4.5	2.2–3.5	2.1–3.4
PCB138 (μg/kg lipid)	Median	11.0	8.8	8.0
	IQR[c]	8.7–14.0	7.1–13.0	6.6–12.0
PCB153 (μg/kg lipid)	Median	22.3	18.0	18.0
	IQR[c]	18.6–28.5	14.0–25.0	14.0–24.0
PCB156 (μg/kg lipid)	Median	2.1	1.5	1.8
	IQR[c]	<LOQ-3.1	<LOQ-2.6	<LOQ-2.4
PCB170 (μg/kg lipid)	Median	5.5	4.7	4.5
	IQR[c]	3.8–7.7	3.1–6.1	3.4–6.3
PCB180 (μg/kg lipid)	Median	13.9	12.0	12.0
	IQR[c]	9.5–19.7	7.9–16.0	8.7–16.0
PCB187 (μg/kg lipid)	Median	3.5	3.2	2.8
	IQR[c]	2.5–4.6	2.2–4.1	2.2–3.8
HCB (μg/kg lipid)	Median	11.8	10.0	10.0
	IQR[c]	10.0–13.4	8.9–12.0	8.9–12.0
Oxychlordane (μg/kg lipid)	Median	0.5	1.0	1.0
	IQR[c]	<LOQ-1.0	<LOQ-2.0	<LOQ-1.0
p,p'-DDE (μg/kg lipid)	Median	41.1	32.5	35.0
	IQR[c]	28.1–46.5	25.0–54.0	23.0–44.0
β-HCH (μg/kg lipid)	Median	2.8	2.0	2.0
	IQR[c]	1.9–3.6	<LOQ-3.0	<LOQ-2.5
Trans-nonachlor (μg/kg lipid)	Median	2.0	<LOQ	<LOQ
	IQR[c]	<LOQ-2.6	<LOQ-2.4	<LOQ-2.1
∑PCB (μg/kg lipid)	Median	103.0	89.2	88.0
	IQR[c]	85.4–122.8	73.7–107.4	73.8–104.1
∑OCP (μg/kg lipid)	Median	65.9	56.5	57.1
	IQR[c]	52.8–74.9	44.3–76.7	43.1–70.4
∑lipPOP (μg/kg lipid)	Median	193.2	183.4	164.4
	IQR[c]	185.8–232.5	143.2–208.3	144.0–207.0

[a] Body mass index

[b] Gestational age at blood draw

[c] Interquartile range

these potential confounders. A secondary temporal trend analysis was conducted with restriction to women born in Denmark. The slope of the temporal trends (β) was used to assess the population half-lives (pT½) or population doubling times (pT2) of the lipophilic POP levels for the included pregnant women by integration and rearrangement of the first order rate expression (Noren and Meironyte 2000):

$$pT^{1}/_{2} = \ln(2) \Big/ (-\beta)$$
$$pT2 = \ln(2) \Big/ (\beta)$$

The women were divided into four categories according to their educational level (*low*: municipal primary or lower secondary school; *lower middle*: upper secondary school or 1–2 years of vocational training; *higher middle*: additional 3–4 years of education; *high*: >4 years of additional education). The linear associations between the lipophilic POP concentrations and the age at delivery, pre-pregnancy BMI, number of miscarriages, and educational level were determined for the crude data and after adjustment for the following potential explanatory factors: age (continuous), BMI (continuous), gestational age at blood draw (continuous), and smoking status (three categories: *non-smoker, smoked until pregnancy, and smoked during pregnancy*) using linear regression analysis.

Spearman correlation analysis was performed to assess the bivariate correlation between the POPs. Only samples with POP concentrations above the LOQ were included in the bivariate correlation.

Results

Study participants

The characteristics of the 197 study participants are presented by year in Table 1. The median age at delivery, pre-pregnancy BMI, and gestational age at blood draw were similar throughout the study years. The distribution of women across the categories of education, smoking status, and alcohol intake were also similar over the study years. Most of the pregnant women were born in Denmark (91%), and all of the women were living in Denmark at the time of delivery. The women with a non-Danish origin had statistically significantly higher ∑OCP concentrations than the women with a Danish origin, but only slightly higher ∑PCB concentrations (Table S1 in the supplementary material).

Detection frequency

Twelve lipophilic POPs were detected in more than 50% of the samples: PCB 118 (93%), PCB 138 (100%), PCB 153 (100%), PCB 156 (58%), PCB 170 (97%), PCB 180 (100%), PCB 187 (91%), HCB (99%), oxychlordane (55%), *p,p'*-DDE (95%), β-HCH (68%), and *trans*-nonachlor (51%) (Table S2 in the supplementary material). The brominated flame retardants including PBDEs and PBB were detected in less than 5% of the samples (Table S3 in the supplementary material).

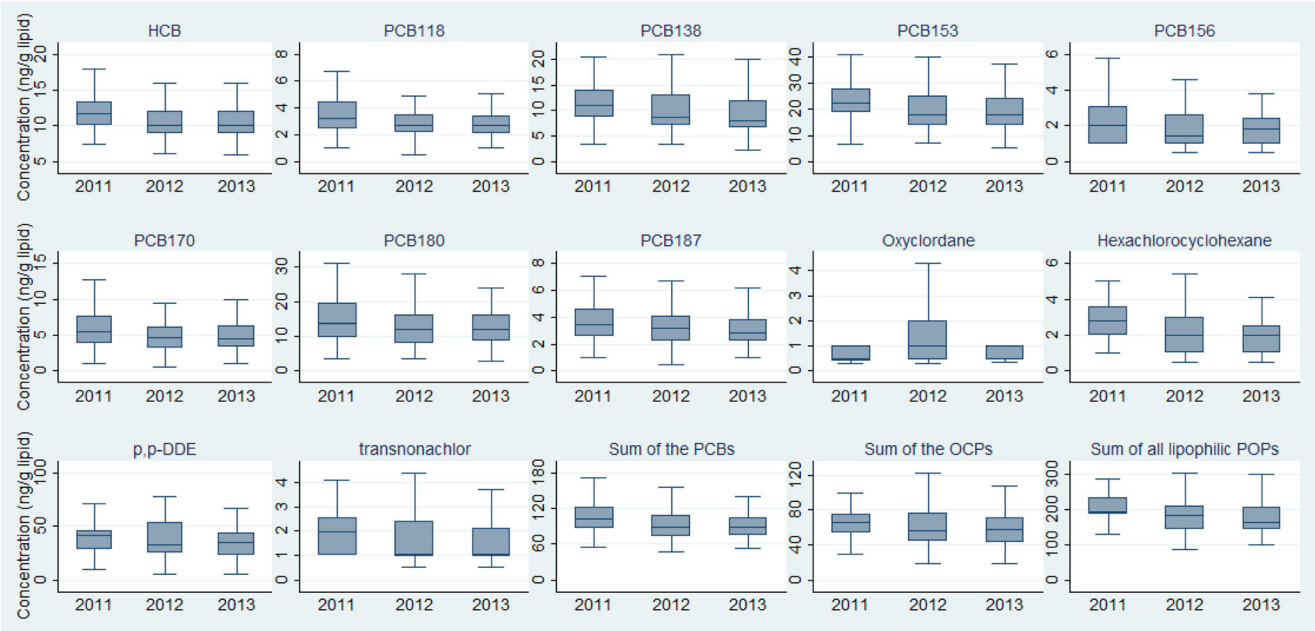

Fig. 1 Temporal trends of the lipophilic POP levels (ng/g serum lipids) in serum from 197 Danish pregnant women in the period from 2011 to 2013. The *boxes* display the 25th and 75th centiles, and the *line inside the boxes* represents the median value. The *whiskers* display the upper and lower values within 1.5 times the interquartile range beyond the box. For the sum of the PCBs, the sum of OCPs, and the sum of lipophilic POPs, see the Methods section

Table 2 Temporal trends of polychlorinated biphenyl levels (μg/kg serum lipids) in serum from 197 Danish pregnant women in the period 2011–2013

		PCB118	PCB138	PCB153	PCB156	PCB170	PCB180	PCB187	∑PCB
Detection	No.	184	197	197	115	192	197	179	
	(%)	93	100	100	58	97	100	91	
Raw trend	Change per year (%)	−7.1	−10.7	−9.2	−10.4	−9.6	−9.2	−6.8	−6.0
	pT½ (years)[c]	9.8	6.3	7.6	6.7	7.2	7.6	10.2	11.6
Adjusted trend[a]	Change per year (%)	−2.5	−7.4	−5.8	−6.0	−6.4	−5.9	−1.9	−4.0
	95% CI	−10.9; 6.0	−15.5; 0.7	−13.6; 1.9	−16.1; 4.1	−15.3; 2.5	−14.3; 2.6	−11.2; 7.4	−9.2; 1.2
	pT½ (years)[c]	28.2	9.4	11.9	11.5	10.9	11.8	36.5	17.3
Restricted trend[b]	Change per year (%)	−6.6	*−10.8*	*−8.5*	−6.9	*−8.9*	*−8.3*	−5.4	*−5.8*
	95% CI	−14.7;1.5	*−18.2; −3.5*	*−15.4; −1.5*	−17.0; 3.2	*−16.9; −0.9*	*−15.9; −0.7*	−13.9; 3.1	*−10.2; −1.4*
	pT½ (years)[c]	10.5	*6.4*	*8.2*	10.0	*7.8*	*8.3*	12.8	*12.0*

Significant results ($p < 0.05$) are marked in italics in the adjusted and restricted analyses

[a] Adjusted for age (continuous), gestational age at blood draw (continuous), pre-pregnancy BMI (continuous), and smoking status (categorical)

[b] Adjusted as 1 and restricted to women who were born in Denmark ($n = 180$)

[c] Population half-lives (years)

Temporal trends

The median concentrations of 11 of the 12 included lipophilic POPs (i.e., PCB118, PCB138, PCB153, PCB156 PCB170, PCB180, PCB187, HCB, *p,p'*-DDE, β-HCH, and *trans*-nonachlor) were lower in 2013 compared to 2011 (Table 1 and Fig. 1). However, the median concentration of oxychlordane was higher in 2013 and 2012 compared to 2011 (Table 1 and Fig. 1). Moreover, the percentage of samples with oxychlordane concentrations above the LOQ increased from 36% in 2011 to 67% in 2012 and 62% in 2013 (Table S2 in the supplementary material).

The temporal trends were statistically significantly different from 0 for HCB ($\beta = -5.4$; 95% confidence interval [95% CI]: −10.6; −0.3), oxychlordane ($\beta = 16.6$; 95% CI: 5.7; 27.4), and β-HCH ($\beta = -14.8$; 95% CI: −25.1; −4.6) when all 197 women were included in the adjusted analysis. In addition to these three compounds, the temporal trends were also statistically significant for PCB138, PCB153, PCB170, PCB180, *trans*-nonachlor, ∑PCB, and ∑lipPOP when the analysis was restricted to women with a Danish origin (Tables 2 and 3 and supplementary Fig. S1). The temporal trends did not change much, when we used data that were not corrected for serum lipids (data not shown).

Table 3 Temporal trends of organochlorine pesticide levels (μg/kg serum lipids) in serum from 197 Danish pregnant women in the period 2011–2013

		HCB	Oxychlordane	*p,p'*-DDE	β-HCH	*Trans*-nonachlor	∑OCP	∑lipPOP
Detection	No.	195	108	187	134	100		
	(%)	99	55	95	68	51		
Raw trend	Change per year (%)	−6.6	11.2	−8.0	−20.4	−12.1	−6.0	−6.6
	pT½ (years)[c]	10.5		8.7	3.4	5.7	11.6	10.6
	pT2 (years)[d]		6.2					
Adjusted trend[a]	Change per year (%)	*−5.4*	*16.6*	−2.1	*−14.8*	−6.9	−1.8	−3.7
	95% CI	*-10.6; −0.3*	*5.7; 27.4*	−13.9; 9.6	*−25.1; −4.6*	−17.5; 3.7	−10.3; 6.6	−11.1; 3.7
	pT½ (years)[c]	*12.8*		32.2	*4.7*	10.0	38.0	18.7
	pT2 (years)[d]		*4.2*					
Restricted trend[b]	Change per year (%)	*−6.2*	*13.5*	−8.4	*−18.8*	*−12.8*	−6.6	*−6.1*
	95% CI	*−11.5; −1.0*	*3.0; 24.0*	−19.2; 2.5	*−28.3; −9.4*	*−22.6; −2.9*	−13.9; 0.6	*−12.2; −0.1*
	pT½ (years)[c]	*11.1*		8.3	*3.7*	*5.4*	10.4	*11.3*
	pT2 (years)[d]		*5.1*					

Significant results ($p < 0.05$) are marked in italics in the adjusted and restricted analyses

[a] Adjusted for age (continuous), gestational age at blood draw (continuous), pre-pregnancy BMI (continuous), and smoking status (categorical)

[b] Adjusted as 1 and restricted to women who were born in Denmark ($n = 180$)

[c] Population half-lives (years)

[d] Population doubling times (years)

Associations between the lipophilic POP concentrations and the women's characteristics

The associations between the lipophilic POP concentrations and the pregnant women's age, BMI, number of miscarriages, and educational level are presented in Table 4. Higher age at delivery was associated with higher concentrations of all the studied lipophilic POPs, being statistically significant for all PCBs, oxychlordane, β-HCH, and *trans*-nonachlor (Table 4).

The lipophilic POP concentrations were mostly inversely associated with the pre-pregnancy BMI, although we found a positive association for β-HCH ($\beta = 0.02$, 95%CI: 0.00; 0.04). The associations were statistically significant for PCB153, PCB156, PCB170, PCB180, PCB187, HCB, *trans*-nonachlor, ∑PCB, and ∑POP (Table 4).

For nine of the 12 analyzed lipophilic POPs, we found that the concentrations were inversely associated with the number of miscarriages, although none of the associations were statistically significant (Table 4).

A higher educational level was associated with higher concentrations of PCB187, *p,p'*-DDE, and ∑OCP but lower concentrations of PCB118, PCB138, PCB153, PCB156, PCB180, HCB, oxychlordane, β-HCH, ∑PCB, and ∑lipPOP, although only statistically significantly for β-HCH (Table 4).

Table 4 Continuous linear regression between the serum concentrations (μg/kg serum lipids) of persistent organic pollutants and study variables in 197 Danish pregnant women, 2011–2013

	Analysis	Age at delivery		Pre-pregnancy BMI		Miscarriages		Educational level	
		β	95% CI	β	95% CI	β	95% CI	β	95% CI
PCB 118	Crude	*0.03*	*0.01; 0.04*	−0.01	−0.03; 0.01	−0.06	−0.16; 0.04	0.05	−0.03; 0.13
	Adjusted[a]	*0.02*	*0.01; 0.04*	−0.01	−0.03; 0.01	−0.09	−0.20; 0.01	−0.02	−0.11; 0.08
PCB 138	Crude	*0.04*	*0.02; 0.05*	−0.01	−0.03; 0.00	−0.01	−0.11; 0.10	0.07	−0.01; 0.15
	Adjusted[a]	*0.03*	*0.02; 0.05*	−0.01	−0.03; 0.00	−0.05	−0.15; 0.05	−0.01	−0.10; 0.08
PCB 153	Crude	*0.04*	*0.03; 0.06*	*−0.03*	*−0.04; −0.01*	0.02	−0.08; 0.12	*0.09*	*0.02; 0.17*
	Adjusted[a]	*0.04*	*0.02; 0.05*	*−0.02*	*−0.04; −0.01*	−0.02	−0.12; 0.07	−0.01	−0.09; 0.08
PCB 156	Crude	*0.05*	*0.03; 0.07*	*−0.04*	*−0.06; −0.02*	0.02	−0.12; 0.15	0.08	−0.02; 0.19
	Adjusted[a]	*0.04*	*0.02; 0.06*	*−0.04*	*−0.06; −0.02*	−0.02	−0.15; 0.10	−0.09	−0.20; 0.02
PCB 170	Crude	*0.06*	*0.04; 0.08*	*−0.05*	*−0.07; −0.03*	0.07	−0.06; 0.20	*0.15*	*0.05; 0.25*
	Adjusted[a]	*0.06*	*0.04; 0.07*	*−0.05*	*−0.06; −0.03*	0.00	−0.11; 0.11	0.00	−0.10; 0.09
PCB 180	Crude	*0.06*	*0.04; 0.07*	*−0.04*	*−0.06; −0.02*	0.06	−0.06; 0.18	*0.14*	*0.05; 0.23*
	Adjusted[a]	*0.05*	*0.04; 0.07*	*−0.04*	*−0.06; −0.02*	0.00	−0.11; 0.10	−0.01	−0.10; 0.09
PCB 187	Crude	*0.05*	*0.03; 0.07*	*−0.03*	*−0.05; −0.01*	0.04	−0.08; 0.17	*0.16*	*0.06; 0.25*
	Adjusted[a]	*0.05*	*0.03; 0.07*	*−0.03*	*−0.05; −0.01*	−0.01	−0.12; 0.11	0.03	−0.07; 0.13
HCB	Crude	0.01	0.00; 0.02	*−0.02*	*−0.03; −0.01*	−0.02	−0.08; 0.04	0.02	−0.03; 0.07
	Adjusted[a]	0.01	−0.01; 0.02	*−0.02*	*−0.03; −0.01*	−0.03	−0.09; 0.04	−0.01	−0.06; 0.05
Oxychlordane	Crude	*0.05*	*0.03; 0.07*	−0.01	−0.03; 0.01	0.01	−0.13; 0.15	0.06	−0.05; 0.17
	Adjusted[a]	*0.05*	*0.03; 0.07*	0.00	−0.03; 0.02	−0.06	−0.20; 0.08	−0.07	−0.19; 0.05
p,p'-DDE	Crude	0.02	−0.01; 0.04	−0.01	−0.03; 0.01	−0.07	−0.21; 0.08	0.06	−0.06; 0.17
	Adjusted[a]	0.01	−0.01; 0.03	−0.01	−0.03; 0.01	−0.09	−0.24; 0.06	0.05	−0.08; 0.18
β-HCH	Crude	*0.06*	*0.04; 0.08*	0.02	−0.01; 0.04	0.11	−0.03; 0.25	−0.04	−0.15; 0.07
	Adjusted[a]	*0.06*	*0.04; 0.08*	0.02	0.00; 0.04	0.00	−0.13; 0.13	*−0.13*	*−0.24; −0.02*
Trans-nonachlor	Crude	*0.04*	*0.02; 0.06*	*−0.03*	*−0.05; 0.00*	−0.02	−0.16; 0.11	0.10	0.00; 0.21
	Adjusted[a]	*0.03*	*0.01; 0.06*	*−0.02*	*−0.04; 0.00*	−0.06	−0.20; 0.07	−0.01	−0.12; 0.11
∑PCB	Crude	*0.03*	*0.02; 0.04*	*−0.02*	*−0.03; −0.01*	0.01	−0.06; 0.08	*0.06*	*0.00; 0.11*
	Adjusted[a]	*0.02*	*0.01; 0.04*	*−0.02*	*−0.03; −0.01*	−0.02	−0.08; 0.05	−0.02	−0.08; 0.04
∑OCP	Crude	0.01	0.00; 0.03	−0.01	−0.03; 0.01	−0.04	−0.14; 0.07	0.03	−0.05; 0.11
	Adjusted[a]	0.01	−0.01; 0.03	−0.01	−0.03; 0.01	−0.05	−0.16; 0.05	0.01	−0.08; 0.10
∑lipPOP	Crude	*0.02*	*0.00; 0.03*	*−0.02*	*−0.03; 0.00*	−0.01	−0.09; 0.07	0.03	−0.04; 0.09
	Adjusted[a]	0.01	0.00; 0.03	*−0.01*	*−0.03; 0.00*	−0.03	−0.11; 0.05	−0.02	−0.09; 0.06

Statistically significant results ($p < 0.05$) are marked in italics

[a] Adjusted for age (continuous), pre-pregnancy BMI (continuous), gestational age at blood draw (continuous), and smoking status (categorical)

Correlations

The bivariate Spearman correlations were positive and statistically significant between ∑OCP, ∑PCB, and ∑lipPOP (Table 5 and Table S4), but the correlations between the lipophilic POPs and the PFAAs were weak (Table 5 and Table S5).

Discussion

Temporal trends of lipophilic POPs

As shown in Table 1 and Fig. 1, the median serum concentrations of 11 of the 12 analyzed lipophilic POPs were lower in 2013 compared to 2011. The temporal trend analyses were statistically significant only for three compounds, HCB, oxychlordane, and β-HCH, in the analysis where all 197 women were included (Tables 2 and 3). Three women with a non-Danish origin had up to 10 times higher *p,p'*-DDE levels and 3–5 times higher ∑lipPOP levels than the mean of the other 194 women. We conducted a secondary analysis with restriction to women with a Danish origin (n = 180), and in this analysis, the temporal trends were now statistically significant for eight compounds including HCB, oxychlordane, β-HCH, PCB138, PCB153, PCB170, PCB180, *trans*-nonachlor, ∑PCB, and ∑lipPOP (Tables 2 and 3). As the statistical significance was so highly affected by the few outliers, we will in the following focus on the direction of the temporal trend slopes rather than on the statistical significance. The downward trends were expected, since the production and use are regulated for all the lipophilic POPs that were included in the trend analysis (Stockholm Convention 2009).

To our knowledge, there are no studies on recent lipophilic POP time trends in serum from pregnant women in the non-Arctic parts of Europe. However, the Arctic Monitoring and Assessment Programme (AMAP) published a report in 2015 including time trends for pregnant women in the circumpolar region (AMAP 2015). Our results support the data from the AMAP report that showed recent downward trends of PCB and OCP concentrations in pregnant women's whole blood, serum, and plasma in Alaska, Nunavik in Canada, Greenland, Iceland, northern Norway, and coastal Chukotka in Russia (AMAP 2015).

As shown in Table 6, the Danish women in the present study had much lower concentrations of most OCPs compared to the pregnant women from Alaska, Nunavik, Greenland, Murmansk, and Iceland, but the *p,p'*-DDE concentration was similar to northern Norway and Reykjavik (AMAP 2015). For PCBs, the concentrations in the Danish women were lower than for pregnant women from Nunavik, Greenland, and Iceland, but similar to northern Norway, and higher than in Alaska (AMAP 2015) (Table 6).

A study from the US with slightly lower median serum PCB concentrations compared to the present study (Table 6) found downward trends of PCB74, PCB118, PCB138, PCB153, and PCB180 in US pregnant women between 2008–2009 and 2011–2012 (Zota et al. 2013).

Overall, our results agree with the time trends in the other studies, and only differ with regard to the trend for oxychlordane. Oxyclordane was detected in 55% of the samples in the present study, and the concentrations were close to the LOQ for most samples. Hence, we expect that the upward trend for oxychlordane in the present study was a chance finding, since the oxychlordane precursor *chlordane* is under regulation and is included in the Stockholm Conventions annex A (Stockholm_Convention 2009).

Associations between the lipophilic POP concentrations and the women's characteristics

In agreement with most other studies (Caspersen et al. 2016; Fernandez-Rodriguez et al. 2015; Long et al. 2015; Medehouenou et al. 2011; Porta et al. 2012; Rylander et al. 2012; Sandau et al. 2000; Wolff et al. 2005), we found that the PCB and OCP concentrations were higher in older women (Table 4). This association is presumed to be a reflection of the persistency and long human serum half-life of the lipophilic POPs.

There are conflicting results in the literature about the association between lipophilic POP levels in serum and BMI. Our results support studies from Denmark, Norway, and the USA, which reported lower PCB levels for pregnant women with a higher BMI (Caspersen et al. 2016; Halldorsson et al. 2008b; Wolff et al. 2005). We suggest that the lipophilic POPs might be stored in the adipose tissue of women with a high BMI rather than being in circulation. Contrarily, two studies of the adult population in Spain as well as one study of older

Table 5 Spearman correlation coefficients between the summed concentrations of polychlorinated biphenyls (∑PCB), organochlorine pesticides (∑OCP), lipophilic POPs (∑lipPOP), and perfluoroalkyl acids (∑PFAA) in serum of 197 Danish pregnant women, 2011–2013

	∑PCB	∑OCP	∑lipPOP
∑OCP	0.70*		
∑lipPOP	0.87*	0.92*	
∑PFAA	0.07	-0.03	−0.09

For ∑PCB, ∑OCP, and ∑lipPOP, see the Methods section. ∑PFAA is the summed serum level (ng/mL) of perfluorobutane sulfonate, perfluorohexane sulfonate, perfluoroheptane sulfonate, perfluorooctane sulfonate, perfluorodecane sulfonate, perfluorooctane sulfonamide, perfluoropentanoic acid, perfluorohexanoic acid, perfluoroheptanoic acid, perfluorooctanoic acid, perfluorononanoic acid, perfluorodecanoic acid, perfluoroundecanoic acid, perfluorododecanoic acid, perfluorotridecanoic acid, and perfluorotetradecanoic acid

*Significantly different from 0 ($p < 0.05$)

Table 6 Geometric mean plasma and serum concentrations (ng/g lipid) of lipophilic POPs in pregnant women in recent years

Study Years Matrix n	Norway[a] 2003–2008 Plasma 96	Northern Norway[b] 2006–2008 Plasma 515	Reykjavik[b] 2009 Plasma 33	Alaska[b] 2009–2012 Plasma 156	San Fransisco[c] 2011–2012 Serum 36	Greenland[b] 2010–2013 Plasma 194	Aarhus[d] 2011–2013 Serum 197	Nunavik[b] 2013 Plasma 95	Murmansk[b] 2013–2014 Plasma 50
PCB118	8.3	4.1	8.4	3.4	1.5	9.5	2.8	19	26.1
PCB138	21	14.9	15	9.1	2.2	29.4	9.4	n.a.	9.2
PCB153	39	24.8	34	14.8	3.5	60.5	19.4	40	12.2
PCB156	2.9	n.a.	n.a.	n.a.	n.a.	n.a.	1.9	n.a.	n.a.
PCB170	6.3	n.a.	n.a.	n.a.	n.a.	n.a.	4.8	n.a.	n.a.
PCB180	22	16.5	16	5.4	2	29.6	12	17	n.a.
PCB187	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3.3	n.a.	n.a.
HCB	15	9.6	20	15.9	n.a.	25.6	11	20	18.2
Oxychlordane	1.9	n.a.	3.5	7.3	n.a.	18.4	1	22	n.a.
p,p'-DDE	51	38.7	36	82.7	n.a.	131	36.9	130	102
β-HCH	n.a.	n.a.	7.1	3.6	n.a.	3.8	2	2.4	8.5
Trans-nonachlor	n.a.	2.8	6.7	9.9	n.a.	44.2	1	42	n.a.

n.a. not analyzed

[a] Caspersen et al. 2016

[b] AMAP human health report 2015 (AMAP 2015)

[c] Zota et al. 2013

[d] Present study

Canadians found higher serum or plasma levels of most OCPs and PCB congeners with higher BMI (Fernandez-Rodriguez et al. 2015; Medehouenou et al. 2011; Porta et al. 2012). Long et al. (2015) found no statistically significant association between BMI and OCP or PCB levels in 194 Greenlandic pregnant women (Long et al. 2015). The median lipophilic POP concentrations were much lower for the women in the present study compared to the study populations we have used for comparison (Fernandez-Rodriguez et al. 2015; Long et al. 2015; Medehouenou et al. 2011; Porta et al. 2012; Wolff et al. 2005). The association with BMI might be dependent on the lifestyle and diet of the women including their intake of fatty fish (Caspersen et al. 2013), which we do not have sufficient information to adjust for.

The plasma concentrations of PCBs and OCPs have been reported to be lower for pregnant women with a higher parity (Caspersen et al. 2016). This might be due to a placental transfer from the woman to the fetus during pregnancy or a subsequent transfer during the breastfeeding. In the present study, we studied the association between the number of previous miscarriages and the lipophilic POP concentrations in nulliparous women, thus, neglecting the influence from breast feeding. We found a tendency of lower lipophilic POP concentrations with a higher number of miscarriages (Table 4), which might support the hypothesis that some POPs were partly transferred from the pregnant woman to the fetus. This was emphasized by a study in Peruvian pregnant women, where the lipid-corrected lipophilic POP concentrations in maternal serum were found to decrease from the first to the third trimester, and several PCBs and *p,p'*-DDE were detected in cord blood (Adetona et al. 2013). However, lipophilic POPs have also been detected in breast milk (AMAP 2015). Our findings were not statistically significant, which might be because the serum samples were taken in early pregnancy (i.e., gestational week 11–13).

Contrary to our results, Leoni et al. (1989) found statistically significantly higher concentrations of the PCB mixture "Fenclor 54" in pooled serum from 120 Italian women who had miscarried prior to the blood sampling compared to 120 full-term pregnancy controls, whereas the levels of HCB, DDE, and DDT were insignificantly higher for women who experienced miscarriage compared to the controls (Leoni et al. 1989). We suggest that the higher concentration of Fenchlor 54 in the women who miscarried might be explained by a shorter duration of the pregnancy compared to the full-term controls. A case-control study from 2003 reported that 45 women with a history of three or more consecutive miscarriages had similar PCB, HCB, and DDE levels as 30 healthy non-pregnant women (Sugiura-Ogasawara et al. 2003). However, neither of these studies adjusted for other explanatory factors such as age, BMI, and smoking (Leoni et al. 1989; Sugiura-Ogasawara et al. 2003). Overall, the association between the number of miscarriages and the lipophilic POP concentrations may be weak if at all present.

Considering educational level as a proxy for socioeconomic status, our results agreed with those of a previous study, which found no linear associations between PCB levels and

socioeconomic status in Danish pregnant women (Halldorsson et al. 2008b). The overall lack of associations with socioeconomic status might be an indication that the contact with sources of lipophilic POP exposure does not differ much across the social classes of pregnant women in Denmark. Contrarily, studies from the USA, Canada, and Australia found higher lipophilic POP levels with a higher educational level (Medehouenou et al. 2011; Reid et al. 2013; Wolff et al. 2005). Porta et al. (2012) found that Spanish women in the least affluent social classes from the Barcelona Health Survey had the highest levels of *p,p'*-DDT, *p,p'*-DDE, β-HCH, and PCB180, whereas women in the most affluent social classes had the highest levels of HCB, PCB118, PCB138, and PCB153 (Porta et al. 2012).

Bivariate correlations of POP concentrations

As expected, the bivariate Spearman analyses showed positive correlations between the lipid-corrected concentrations of the lipophilic POP groups (Table 5), thus, indicating that the sources of exposure were similar for all the lipophilic POPs. Contrarily, the lipophilic POPs were poorly correlated with the PFAAs (Table 5), which might indicate that the Danish pregnant women's exposure to these compounds comes from different sources. For example, other studies have found that a higher dietary intake of fatty fish was significantly associated with higher PCB and OCP concentrations but not PFAA concentrations in the Danish population (Brauner et al. 2011; Brauner et al. 2012; Eriksen et al. 2011; Halldorsson et al. 2008a, b). In contrast to our results, Long et al. (2015) observed that higher concentrations of the ∑PCB and ∑OCP were associated with higher ∑PFAA concentrations in pregnant Inuit women from Greenland (Long et al. 2015). Due to cultural, dietary, and regional differences, the exposure sources might be very different for the Greenlandic women and the Danish women.

Strengths and limitations of the study

Ideally, all studies on trends should follow the same selection procedure—random sampling from all potential candidates or sampling according to fixed criteria. In the present study, we randomly selected the pregnant women from the Aarhus Birth Cohort. Moreover, the women were not aware of their exposure levels, so the potential selection bias is expected to be non-differential. One of the major strengths of the present study is the design of including only nulliparous women. Lipophilic POPs can be transferred from mother to fetus via the placenta and to the child via breastmilk (Adetona et al. 2013; Covaci et al. 2002; Longnecker et al. 1999), and the serum POP concentrations might therefore be lower for women of higher parity. To avoid confounding from the reproductive history, we included only nulliparous women in early pregnancy.

A limitation to this study is that we included participants over three study years only (i.e., 2011–2013). Thus, it is possible that the observed downward trends were only momentary observations, although we expect them to be long-lasting, as the production and use of PCBs and OCPs have been regulated for more than 30 years in Denmark. We included less than 200 women, which limits the precision of our findings. Our results might not be transferable to other study populations. We found that the lipophilic POP concentrations differed for the women born in Denmark compared to women born elsewhere, and the downward trends for PCB138, PCB153, PCB170, PCB180, *trans*-nonachlor, ∑PCB, and ∑lipPOP were statistically significant only when restricting the analysis to women born in Denmark. Moreover, the associations between lipophilic POP concentrations and BMI and educational level differ much across study populations.

In summary, there are few studies on temporal trends of lipophilic POPs from non-arctic regions, and to our knowledge, this is the first temporal trend study of lipophilic POPs in the Danish population. Except for oxychlordane, we found that the lipophilic POP concentrations followed downward trends in the Danish pregnant women, as also observed for pregnant women in the Arctic regions. The Danish women had much lower OCP concentrations compared to what have been reported for Arctic women in the most recent AMAP report (AMAP 2015). We found associations of higher lipophilic POP concentrations with higher age and lower BMI, whereas the associations with the educational level and number of miscarriages were less clear.

Acknowledgement We thank our fellow researchers of the FETOTOX Project (http://www.fetotox.au.dk) for their contributions to the work. In addition, we want to acknowledge the work of the team at the Centre de Toxicologie, Institute National de Santé Publique du Québec, Québec, Canada, who carried out the quantitative chemical analysis. The study was supported by the Danish Council for Strategic Research (Grant No. 10-092818). The funding sources were not involved in the research activities. The Aarhus Birth Cohort Biobank was funded by a grant from the Danish National Research Foundation with additional support from Tryg Fonden and Aarhus University Research Foundation.

References

Adetona O et al (2013) Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo. Peru Chemosphere. doi:10.1016/j.chemosphere.2013.01.043

AMAP (2015) AMAP Assessment 2015: Human Health in the Arctic

Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-Jorgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicol Appl Pharmacol 179:1–12. doi:10.1006/taap.2001.9347

Bjerregaard-Olesen C et al (2016a) Determinants of serum levels of perfluorinated alkyl acids in Danish pregnant women. Int J Hyg Environ Health 219:867–875. doi:10.1016/j.ijheh.2016.07.008

Bjerregaard-Olesen C et al (2016b) Time trends of perfluorinated alkyl acids in serum from Danish pregnant women 2008–2013. Environ Int 91:14–21. doi:10.1016/j.envint.2016.02.010

Bonefeld-Jorgensen EC (2010) Biomonitoring in Greenland: human biomarkers of exposure and effects—a short review. Rural Remote Health 10:1362

Brauner EV, Raaschou-Nielsen O, Gaudreau E, LeBlanc A, Tjonneland A, Overvad K, Sorensen M (2011) Predictors of polychlorinated biphenyl concentrations in adipose tissue in a general Danish population. Environ Sci Technol 45:679–685. doi:10.1021/es102489c

Brauner EV, Raaschou-Nielsen O, Gaudreau E, Leblanc A, Tjonneland A, Overvad K, Sorensen M (2012) Predictors of adipose tissue concentrations of organochlorine pesticides in a general Danish population. J Expo Sci Environ Epidemiol 22:52–59. doi:10.1038/jes.2011.39

Caspersen IH, Knutsen HK, Brantsaeter AL, Haugen M, Alexander J, Meltzer HM, Kvalem HE (2013) Dietary exposure to dioxins and PCBs in a large cohort of pregnant women: results from the Norwegian Mother and Child Cohort Study (MoBa). Environ Int 59:398–407. doi:10.1016/j.envint.2013.07.001

Caspersen IH et al (2016) Determinants of plasma PCB, brominated flame retardants, and organochlorine pesticides in pregnant women and 3 year old children in The Norwegian Mother and Child Cohort Study. Environ Res 146:136–144. doi:10.1016/j.envres.2015.12.020

Chevrier C, Warembourg C, Gaudreau E, Monfort C, Le Blanc A, Guldner L, Cordier S (2013) Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. Epidemiology 24:251–260. doi:10.1097/EDE.0b013e31827f53ec

Covaci A, Jorens P, Jacquemyn Y, Schepens P (2002) Distribution of PCBs and organochlorine pesticides in umbilical cord and maternal serum. Sci Total Environ 298:45–53

Deutch B, Pedersen HS, Jorgensen EC, Hansen JC (2003) Smoking as a determinant of high organochlorine levels in Greenland. Arch Environ Health 58:30–36. doi:10.3200/AEOH.58.1.30-36

Deutch B, Pedersen HS, Asmund G, Hansen JC (2007) Contaminants, diet, plasma fatty acids and smoking in Greenland 1999–2005. Sci Total Environ 372:486–496. doi:10.1016/j.scitotenv.2006.10.043

Diamanti-Kandarakis E et al (2009) Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 30:293–342. doi:10.1210/er.2009-0002

Eriksen KT, Sorensen M, McLaughlin JK, Tjonneland A, Overvad K, Raaschou-Nielsen O (2011) Determinants of plasma PFOA and PFOS levels among 652 Danish men. Environ Sci Technol 45:8137–8143. doi:10.1021/es100626h

Fernandez-Rodriguez M et al (2015) Levels and predictors of persistent organic pollutants in an adult population from four Spanish regions. Sci Total Environ 538:152–161. doi:10.1016/j.scitotenv.2015.07.162

Ferreira CP, De-Oliveira AC, Paumgartten FJ (2011) Serum concentrations of DDT and DDE among malaria control workers in the Amazon region. J Occup Health 53:115–122

Fisher M et al (2016) Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ Health 15:59. doi:10.1186/s12940-016-0143-y

Halldorsson TI, Fei C, Olsen J, Lipworth L, McLaughlin JK, Olsen SF (2008a) Dietary predictors of perfluorinated chemicals: a study from the Danish National Birth Cohort. Environ Sci Technol 42:8971–8977

Halldorsson TI, Thorsdottir I, Meltzer HM, Nielsen F, Olsen SF (2008b) Linking exposure to polychlorinated biphenyls with fatty fish consumption and reduced fetal growth among Danish pregnant women: a cause for concern? Am J Epidemiol 168:958–965. doi:10.1093/aje/kwn204

Jakobsson K, Thuresson K, Höglund P, Sjodin A, Hagmar L, Bergman A (2003) A summary of exposures to polybrominated diphenyl ethers (PBDEs) in Swedish workers, and determination of half-lives of PBDEs Organohalogen. Compd 61:17–20

Leoni V et al (1989) PCB and other organochlorine compounds in blood of women with or without miscarriage: a hypothesis of correlation. Ecotoxicol Environ Saf 17:1–11

Long M, Knudsen AK, Pedersen HS, Bonefeld-Jorgensen EC (2015) Food intake and serum persistent organic pollutants in the Greenlandic pregnant women: the ACCEPT sub-study. Sci Total Environ 529:198–212. doi:10.1016/j.scitotenv.2015.05.022

Longnecker MP, Klebanoff MA, Gladen BC, Berendes HW (1999) Serial levels of serum organochlorines during pregnancy and postpartum. Arch Environ Health 54:110–114. doi:10.1080/00039899909602244

Medehouenou TC et al (2011) Polychlorinated biphenyls and organochlorine pesticides in plasma of older Canadians. Environ Res 111:1313–1320. doi:10.1016/j.envres.2011.09.017

Mortensen LM et al (2013) Data resource profile: the Aarhus birth cohort biobank (ABC biobank). Int J Epidemiol 42:1697–1701. doi:10.1093/ije/dyt199

Noren K, Meironyte D (2000) Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. Chemosphere 40:1111–1123

Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL (1989) Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 18:495–500

Porta M et al (2012) Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002. Sci Total Environ 423:151–161. doi:10.1016/j.scitotenv.2012.02.001

Reid A, Callan A, Stasinska A, Heyworth J, Phi DT, Odland JO, Hinwood A (2013) Maternal exposure to organochlorine pesticides in Western Australia. Sci Total Environ 449:208–213. doi:10.1016/j.scitotenv.2013.01.067

Rylander C, Lund E, Froyland L, Sandanger TM (2012) Predictors of PCP, OH-PCBs, PCBs and chlorinated pesticides in a general female Norwegian population. Environ Int 43:13–20. doi:10.1016/j.envint.2012.02.008

Sandau CD, Ayotte P, Dewailly E, Duffe J, Norstrom RJ (2000) Analysis of hydroxylated metabolites of PCBs (OH-PCBs) and other chlorinated phenolic compounds in whole blood from Canadian inuit. Environ Health Perspect 108:611–616

Seegal RF et al (2011) Estimating the half-lives of PCB congeners in former capacitor workers measured over a 28-year interval. J Expo Sci Environ Epidemiol 21:234–246. doi:10.1038/jes.2010.3

Sjodin A et al (2004) Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. Environ Health Perspect 112:654–658

Stockholm Convention (2009) Listing of POPs in Stockholm Convention. Stockholm Convention. http://chm.pops.int/Convention/ThePOPs/ListingofPOPs/tabid/2509/Default.aspx. Accessed 24th July 2014

Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K (2003) PCBs, hexachlorobenzene and DDE are not associated with recurrent miscarriage. Am J Reprod Immunol 50:485–489

Takeuchi S, Shiraishi F, Kitamura S, Kuroki H, Jin K, Kojima H (2011) Characterization of steroid hormone receptor activities in 100 hydroxylated polychlorinated biphenyls, including congeners identified in humans. Toxicology 289:112–121. doi:10.1016/j.tox.2011.08.001

Thomsen C, Liane VH, Becher G (2007) Automated solid-phase extraction for the determination of polybrominated diphenyl ethers and polychlorinated biphenyls in serum—application on archived Norwegian samples from 1977 to 2003. J Chromatogr B Analyt Technol Biomed Life Sci 846:252–263. doi:10.1016/j.jchromb.2006.09.011

Wolff MS, Deych E, Ojo F, Berkowitz GS (2005) Predictors of organochlorines in New York City pregnant women, 1998–2001. Environ Res 97:170–177. doi:10.1016/j.envres.2004.07.014

Wu JP, Guan YT, Zhang Y, Luo XJ, Zhi H, Chen SJ, Mai BX (2011) Several current-use, non-PBDE brominated flame retardants are highly bioaccumulative: evidence from field determined bioaccumulation factors. Environ Int 37:210–215. doi:10.1016/j.envint.2010.09.006

Zota AR et al (2013) Temporal comparison of PBDEs, OH-PBDEs, PCBs, and OH-PCBs in the serum of second trimester pregnant women recruited from San Francisco General Hospital, California. Environ Sci Technol 47:11776–11784. doi:10.1021/es402204y