# Drivers of maternal accumulation of organohalogen pollutants in Arctic areas (Chukotka, Russia) and 4,4'-DDT effects on the newborns

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**Keywords:** Arctic; Chukotka; human biomonitoring; POPs; 4,4'-DDT effects on newborns; maternal serum; organochlorine compounds

## Abstract

**Background:** One of the most worrying consequence of the production and use of persistent organohalogen pollutants (POPs) is the high accumulation in Arctic populations because of long-range transport. Study of the effects in these populations may illustrate human impacts that are difficult to assess in other locations with lower exposure to these compounds and more diverse pollutant influences.

**Objective:** We aimed to identify the main maternal characteristics influencing on the accumulation of these compounds and the effects on the newborns in a highly exposed Arctic population (Chukotka, Russia).

**Methods:** Organochlorine and organobromine compounds were analysed in maternal venous serum ($n = 250$). The study included data on residence, educational level, age, parity and body mass index (BMI) from self-reported questionnaires and measured anthropometric characteristics of newborns.

**Results:** Concentrations of β-hexachlorocyclohexanes, hexachlorobenzene, 4,4’-DDT and polychlorobiphenyls were high when compared with those generally found in adult populations later than year 2000. The polybromodiphenyl ethers were negligible. These POP concentrations were higher than in Alaska and Arctic Norway and similar to those in Canada. The Chukotka mothers living in inland areas showed significant lower concentrations than those living in the coast ($p<0.001$) except for 4,4’-DDT. The population from the Chukotsky District, a specific coastal area, showed the highest concentrations. Residence was therefore a main concentration determinant ($p<0.001$) followed by maternal age, and in some cases parity and BMI ($p<0.05$). 4,4’-DDT showed an association with the anthropometric characteristics of the newborns ($p<0.05$). Mothers with higher 4,4’-DDT concentrations had longer gestational ages and gave birth to infants with higher weight and length.

**Conclusions:** The maternal accumulation patterns of POPs were mainly related with residence. Most of these compounds were found in higher concentration in women living at coastal areas except 4,4’-DDE and 4,4’-DDT which were of inland origin. This last pesticide was the pollutant showing positive associations with gestational age and newborn’s weight and length. To the best of our knowledge, this is the first study reporting statistically significant associations between maternal 4,4’-DDT exposure and anthropometric characteristics of the newborns.

## 1. Introduction

Persistent organic pollutants (POPs) include a large variety of toxic substances, such as hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs), mirex, polychlorobiphenyls (PCBs), polybromodiphenyl eters (PBDEs) and dichlorodiphenyltrichloroethane (DDT) and its metabolites.

Many POPs are semi-volatile, stable to environmental degradation and may undergo long-range atmospheric transport, being found in areas where they have not been used or produced, like polar regions and high-mountains (Wania et al., 1993; Arellano et al., 2014). These pollutants are lipophilic and have affinity for the adipose tissue of living organisms where they bioaccumulate (Hites et al., 2004; Corsolini et al., 2014; Mitchell et al., 2012). In parallel to bioaccumulation, they biomagnify through the food chain and are eventually ingested by humans (Johnson-Restrepo et al., 2005).

In 2001 these compounds were banned by the Stockholm Convention (Stockholm Convention, 2001) but human populations are still exposed to them. Diet is the main POP exposure source among general population. Because of their lipophilicity, these compounds are mainly found in animal products including meat, fat, fish, dairy items and eggs (Junqué et al., 2017; Llobet et al. 2003; Martí-Cid et al., 2007). Arctic marine mammals accumulate high POP concentrations by ingestion from the food web (Braune et al., 2005; Hickie et al., 2005; Ikonomou and Addinson, 2008; Kucklick et al., 2002). These animals are the major traditional food source for indigenous people because of the availability and high nutritional values of their meat (Sharma, 2010). Arctic populations therefore undergo significant exposure to these compounds despite their limited production or use in these areas.

Once ingested, POPs are able to cross the placenta leading to prenatal exposure of the foetus (Vizcaíno et al., 2014; Jeong et al., 2018). Exposure to POPs during pregnancy may have adverse impact on child development and health. In utero exposure has been associated with low fetal growth and premature delivery, neurocognitive deficit, obesity, lower respiratory tract infections and wheeze and hormonal disruptions (López-Espinosa et al., 2016; Grandjean and Landrigan, 2014; Gascón et al., 2017; Muscogiuri et al. 2017; Morales et al. 2012). The study of these compounds in venous maternal serum during pregnancy provides significant assessments on the accumulation rates in the newborns (Vizcaino et al., 2014; Vafeiadi et al., 2014). Moreover, birth outcomes may show intermediate effects between prenatal toxic exposures and children's health problems later in life, hence the influence of environmental agents on birth outcomes must be investigated (Vafeiadi et al. 2014).

Previous studies showed extremely high levels of serum organochlorine compounds (OCs) in women from the Chukotka Peninsula (Russia; Figure 1) (Sandanger et al. 2003; Anda et al., 2007). In this context, the present study is aimed to investigate the POP evolution in a Chukotka native population by analysis of serum samples from pregnant women living both in coastal and inland areas, to examine the dependence of maternal POP accumulation from a set of socio-demographic factors and to identify the effects of this accumulation on different birth outcomes such as gestational age, weight, length and head circumference.

## 2. Methods

### *2.1. Population and study design*

Chukotka is an autonomous region (Autonomous Okrug; Figure 1) also called Chukchi Okrug using the generic name of the inhabitants that is located in the far northeast of the Russian Federation (latitude: 64-69°N; longitude 162-173°E) and separated from Alaska by the Bering Strait. About 50% of the territory is located above the Arctic Circle. This region is divided in districts (Figure 1).

Between 2014 and 2015, maternal venous blood was collected from women (n=250) in the last week of pregnancy. The study also included a maternal questionnaire data for family history, life-style, behavioural risk factors, as well as potential nutritional, occupational and household sources of exposure to POPs following the one used for indigenous women residents of Chukotka in AMAP (2004). Maternal height and weight, and length, weight and head circumference of infants at birth were measured. Informed consent was requested from the participating mothers.

Patient recruitment was performed in the sequence in which they were admitted to the regional delivery department in the period from 20th August 2014 to 18th February 2015 on the basis of their voluntary consent to participate in the study. The exclusion criteria were as follows, refusal to give informed consent (2 persons), blood or plasma transfusion within the prior 72 hours (1 person), bleeding disorders during pregnancy (1 person), taking in commonly known medications that have a negative impact on lipid levels such as antipsychotics, anticonvulsants or hormones (3 persons).

The study protocol and informed consent form were approved by the local Committee for Biomedical Ethics at the Northwestern State Medical University named after I. Mechnikov, St. Petersburg, dated 11.02.2014.

### *2.2. Analytical methods*

The procedures for sample preparation and analysis have already been described elsewhere (Grimalt et al., 2010). Briefly, serum samples were placed into centrifuge tubes and the recovery standards 1,2,4,5-tetrabromobenzene (TBB) and PCB-209 were added. POP extraction and isolation were achieved by addition of *n*-hexane and $H_2SO_4$, vortex mixing and centrifugation. The supernatant *n*-hexane layer was aspirated into a second centrifuge tube. The acid layer was re-extracted two more times with *n*-hexane. All the *n*-hexane extracts were combined. This n-hexane solution was further purified by oxidation with concentrated $H_2SO_4$, vortex stirring and centrifugation. The acid was removed and $H_2SO_4$ was added again, followed by mixing and centrifuging once more. The supernatant organic phase was transferred to a conical bottomed, graduated tube and reduced to near dryness under a gentle stream of nitrogen. Then, the sample was transferred to gas chromatographic vials using three rinses of isooctane which were again reduced to dryness under a very gentle stream of nitrogen. Finally, they were dissolved with 100 µL of PCB-142 (internal standard) in isooctane.

Subsequent PBDEs analyses involved isooctane evaporation under a very gentle stream of nitrogen gas and dissolution with 20 µL of [3-$^{13}$C]BDE-209 and 30 µL of BDE-118 as internal standards (Vizcaíno et al., 2009).

Twenty OCs, pentachlorobenzene (PeCB), HCB, α-HCH, β-HCH, γ-HCH, δ-HCH, PCB congeners 28, 52, 101, 118, 138, 153 and 180, 2,4'-DDD, 4,4'-DDD, 2,4'-DDE, 4,4'-DDE, 2,4'-DDT, 4,4'-DDT and mirex were quantified by gas chromatography and electron capture detection (GC-ECD, Agilent Technologies 7890A). The instrument was equipped with a HP-5MS capillary column (60 m length, 0.25 mm internal diameter, 0.25 µm film thickness; JW Scientific) protected with a retention gap. Two µL were injected in splitless mode. Injector and detector temperatures were 250°C and 320°C, respectively. The oven temperature program started at 90°C, held for 2 min, then it increased to 130°C at 15°C/min and to 290°C at 4°C/min with a final holding time of 15 min. Ultrapure helium was used as carrier gas. Nitrogen was the make-up gas. Compound quantification was performed as described elsewhere (Carrizo and Grimalt, 2009). Confirmation of the POP structures and checking for coelutions was performed with a GC (Agilent Technologies 7890N) coupled to a mass spectrometer (MS, Agilent Technologies 5975C) operating in negative chemical ionisation mode (GC-NICI-MS).

GC-NICI-MS was also used for identification and quantification of the PBDE congeners (17, 28, 47, 66, 71, 85, 99, 100, 138, 153, 154, 183, 190 and 209). The instrument was equipped with a DB-5 fused silica capillary column (15 m length, 0.25 mm I.D., 0.10 µm film thickness) protected with a retention gap. One µL was injected.

The oven temperature program started at 90°C which was kept for 1.5 min and continued by heating to 200°C at 40°C/min, a second increase up to 275°C at 5°C/min and a third to 300°C at 40°C/

min. This temperature was held for 10 min and then increased to 310°C at 10°C/min with a final holding time of 2 min. Ammonia was used as reagent gas. Identification and quantification were performed by injection of PBDEs standard solutions (Vizcaíno et al., 2009).

### 2.3. Quality control

One procedural blank was included in each sample batch. Method detection limits were calculated from the average signals of the procedural blank levels plus three times the standard deviation. They ranged between 0.0014 and 0.027 ng/mL for the OCs and 0.0015-0.014 ng/mL for the brominated compounds. The limits of quantification were calculated from the averages of the procedural blanks plus five times the standard deviation ranging between 0.0020 and 0.038 ng/mL for the OCs and 0.0022 and 0.035 ng/mL for the PBDEs.

The methods were validated by analysis of proficiency testing materials obtained from the Artic Monitoring and Assessment Program (AMAP Ring Test, 2014). The IDAEA-CSIC laboratory participates regularly in the AMAP Ring Test Proficiency Program for POPs in human serum and the results were almost always within the acceptable range of ±2SD of the consensus values, the causes of results out of this range were identified and solved, they did not refer to one or a few specific compounds.

### 2.4. Data analysis

Data analysis and graphics were performed using the statistical software R (R Development Core Team, 2018). Statistics was focused on the compounds found above limit of detection in more than 40% of the samples: HCB, α-HCH, β-HCH, 4,4’-DDE, 4,4’-DDT, PCB-118, PCB-138, PCB-153, PCB-180 and mirex. One-half of the limits of detection and limits of quantification were assigned to non-detected and non-quantified values, respectively.

Sample serum lipid content (TL) was calculated from the cholesterol (TC) and the triglyceride (Tg) concentrations (TL (g/L) = 2.27*TC + Tg + 0.623; (Phillips et al., 1989).

Geometric means (GMs) and 95% confidence intervals (CI) were used for the descriptive analyses. Statistical differences between groups were tested for significance using Kruskall-Wallis rank test.

Multivariate curve resolution models using alternating least squares (MCR-ALS) (Tauler, 1995) and principal component analysis (PCA) were performed to assess the POP differences between the different areas of residence of the mothers. Before inclusion in the analysis, data were standardized and log transformed. The probability of the normal contour line from PCA was set at 69%.

Linear multivariate models with standardized variables were used to assess the dependences of maternal serum POP concentrations from age, body mass index (BMI), parity, smoking, education, residence and travel to other regions:

$$\log(OC) = \beta_1(Age) + \beta_2(BMI) + \beta_3(Parity) + \beta_4(Education) + \beta_5(Smoking) + \beta_6(Residence) + \beta_7(Travel) + \epsilon$$

. The obtained standard β coefficients were transformed into relative changes (%) in order to get better representation. For each variable, median serum concentrations by unit change (c), $(\exp(c*\beta)-1)*100$, and the corresponding confidence intervals, $(\exp(c*\beta \pm z_{1-\alpha/2}*SE(\beta))-1)*100$, were calculated using β and standard errors (SE) from the multiregression analysis and *c* set as the difference between the first and third quartile (Barrera-Gómez et al., 2015).

The effects of maternal POPs on fetal growth outcomes, e.g. birth weight, length and head circumference, were assessed by linear multivariate models. The differences between POP concentrations between girls and boys were evaluated using Kruskall-Wallis rank test (Bravo et al., 2017). A sensitivity analysis was also performed for women with parity 1.

## 3. Results and discussion

### *3.1. Socio-demographic characteristics*

The socio-demographic characteristics of the women included in the study and the anthropometric features of their newborns are shown in Table 1. Of the participating women, 146 were from inland cities (58%) and 104 (42%) were from coastal areas, 59 of these from Chukotsky District. Their average age was 27.8 years, with an overall age range between 15 and 44 years. According to pre-pregnancy BMI, 25% of the women were overweight or obese, while 68% had normal weight and only 7% were underweight. In 39% of the participant women, the actual newborn was the only child, in 32% it was the second child and in 29% they had 3 or more children. There was only one case of stillbirth. During pregnancy, 30 and 33% of the women smoked tobacco and consumed alcohol, respectively.

Of the infants, 51% were boys and 49% girls, the average weight and length were 3,368 g and 52.5 cm, respectively. More detailed information about boys and girls can be found in Table 1. Gestational age average was 275 days (39.2 weeks), ranging from 165 to 348 days (23.6-49.7 weeks). Eighty-eight percent of the infants were born in the expected gestational age range (37-42 weeks), while 8% were preterm and 4% postmature. Almost all of them had values for head circumference in the normal range, (33.2-35.7 and 32.7-35.1 cm, for boys and girls respectively) (WHO, 2018).

### *3.2. Distributions of organohalogenated compounds*

4,4’-DDT and the PCB-138 and PCB-153 were found above limit of detection in all cases (Table 2). HCB, 4,4’-DDE, PCB118 and the α and β isomers of HCH were detected in more than 90% of the mothers (94-99%). PCB180 was above limit of detection in 78% of the samples and mirex in 43%. The remaining pollutants were detected in less than 40% of the mothers.

The most abundant POP was 4,4’-DDE, with a median of 121 ng/g lipid (Table 2), followed by β-HCH, HCB and PCB-153 (37.8, 29.3 and 24.6 ng/g lipid, respectively). Average 4,4’-DDE represented 92% of total DDTs, β-HCH was the most abundant isomer contributing 86% of total HCHs, and PCB-153 was the most abundant PCB congener representing 45% of the sum of PCBs, followed by PCB-138 (25%), PCB-118 (17%) and PCB-180 (10%).

None of the PBDEs congeners were found in more than 40% of the samples. Only 2 of the 14 PBDEs, BDE153 and BDE190, were above limit of detection in 15% of the samples. The low detection of these compounds is not related to differences in LOD or LOQ of the method used in the present study (Vizcaino et al., 2009) with other studies, e.g. Forde et al (2014), Kalantzi et al (2011). The lack of detectable concentrations of these compounds in a large number of samples probably reflects the use of PBDEs in comparison to the OCs which has involved delays in the long-range transport and distribution of the organobrominated pollutants. A similar contrast in the distribution of both types of POPs was observed in the environmental distribution of the High Tatra mountains where the OCs were showing a distribution dominated by long-range transport and temperature effects but the PBDEs were still not reflecting these trends because of the latter use (Gallego et al., 2007). In view of these low concentrations further analyses were only devoted to the OCs.

### *3.3. Differences between coastal and inland dwellers*

All POP levels were higher in mothers from coastal than in inland sites (Figure 2). The differences were statistically significant for HCB, β-HCH, PCB-118, PCB-138, PCB-153, PCB-180, mirex ($p<0.001$) and 4,4’-DDE ($p<0.01$).

The use of a multivariate curve resolution model using alternating least squares (MCR-ALS) method indicated that POPs data from the coastal group was composed of two subgroups, one showing more variability than the other. According to this information, further examination of the data showed one area of low POP variability, Chukotsky District, which was treated as a separate zone from the other coastal zones (Figure 1).

Further insight on the significance of these areas was obtained from principal component analysis (PCA) of these POP concentrations (Figure 3). The biplot of scores and loading of PC1 and PC2, which accounted for 69% of the total variance showed that PC1 was mainly influenced by all the studied compounds except 4,4'-DDE and 4,4'-DDT, which influenced PC2. The Chukotsky District samples (Figure 3, in red) could be distinguished from the other two groups by higher concentrations of PCBs, HCB, mirex and HCHs.

As shown in Figure 4, POP concentrations in mothers from the Chukotsky District (Figure 1) were higher than those in mothers from the other districts. The differences were highest for the PCB congeners. Thus, the geometric average concentrations of PCB-138, PCB-153 and PCB-180 from the Chukotsky district were about 3.3-4.2 higher than the geometric averages of the whole maternal cohort of the present study (Table 3). The ratio between the GMs of the Chukotsky District and the other districts for PCB118 was 2.4. Similar results were obtained from comparison of the medians (Table 3). Two other compounds showing a strong contrast between the Chukotsky District and the whole Chukotka cohort were HCB and mirex, with geometric average ratios of 3.1 and 3.7, respectively (Table 3). In the case of β-HCH, the Chukotsky District/Chukotka cohort ratio was 2.6, significantly higher than 1. On the contrary, 4,4'-DDE and 4,4'-DDT showed negligible differences in these ratios, 1.2 and 1.1, respectively.

These results are consistent with those of a previous study (AMAP, 2004) in which the concentrations of some of these OCs were determined in mothers from the Chukotsky (n = 47), Anadyrsky (n = 39) and Lul'tinsky Districts (n = 5) and Anadyr Town (n = 12) (Figure 1). The GMs of HCB, β-HCH, mirex and ΣPCBs in the former District, 1.6, 2.0, 0.1 and 3.8 ng/mL, respectively, were higher than those in the other two districts and Anadyr town, 0.5-0.6, 0.6-1.0, 0.01-0.03 and 0.8-1.5 ng/mL, respectively. Conversely, as found in the present study, the GM concentrations of 4,4'-DDE and 4,4'-DDT in Chukotsky District, 2.4 and 0.2 ng/mL, respectively, were not significantly different from those of the other districts, 1.2-2.2 and 0.2-0.4 ng/mL, respectively.

Linear multivariate models considering residence, either Chukotsky district, coastal, or inland, and maternal characteristics, e.g. age, parity, education, smoking, travel to other regions, afforded a better comparison of the main variables determining POP accumulation. In these models, the different residence categories were evaluated in pairs, Chukotsky District, coastal and inland, after taking into account the effect of the maternal variables (Figure 5). The results showed that residence was one of the main determinants of POP accumulation, namely for PCBs, β-HCH and mirex.

These differences in POP concentrations may be explained by the diverse diets of coastal and inland populations. The former has a rich diet in marine mammals (whale, walrus, seal) as a food staple. These mammals are in the top of the food web being the highest bioaccumulators of long-range transported POPs to marine Arctic areas. The latter mainly consume reindeer meat and fish (Dudarev, 2012), involving a lower intake of marine sourced POPs. These diet differences between inland and coastal populations are even stronger when considering the Chukotsky District (Figure 1) that is mainly populated by Chukchi or Yupik indigenous people whose economy is much more focused on traditional marine mammal hunting and reindeer herding (Pelyasov, et al. 2017, ANSIPRA, 2018). The uniform distribution of DDT and its metabolites in coastal and inland populations is consistent with the past extensive use of this insecticide to protect reindeer skin against mosquito bites (AMAP, 2004) which overcomes possible influences related with long-range transport, including atmospheric inputs from China.

### *3.4. Comparison with other studies*

In general, concentrations of β-HCH, HCB, 4,4'-DDT and PCBs in mothers of Chukotka are high when compared with other adult populations after year 2000 (Table 3). The concentrations from the mothers from Chukotsky District are even more prominent. Other pollutants such as PBDEs are found below limit of detection in 85% of the cases.

#### *3.4.1. Comparison with other sites than Arctic populations*

The concentrations of β-HCH in the present Chukotka study (median; 38 ng/g lipid) are higher than all cases previously reported except in a China study (median; 74 ng/g lipid; Table 3). The concentrations of HCB in Chukotka (median; 29 ng/g lipid) are higher than all these other cases compared except in China and Tunisia (75 and 39 ng/g lipid, respectively). However, the medians of the Chukotsky District for β-HCH and HCB (93 and 99 ng/g lipid, respectively) are higher than all previous cases (Table 3).

The distributions of PCBs in the blood serum of the Chukotka mothers are dominated by PCB-153 and PCB-138 and PCB-118 are the second and third most abundant congeners, respectively. This distribution is different from that reported in some constituents of the Russian dietary composition, e.g. butter, in which PCB-118 was the second most abundant congener (Polder et al., 2010). The difference is consistent with the predominant origin of the PCBs from marine food as consequence of the global long-range transport of these compounds. In fact, the PCB congener distributions of the mothers from Chukotsky District (Figure 1) show even higher relative proportion of PCB-138 with respect PCB-118 and nearby the same proportion of PCB-118 and PCB-180, which reinforces the distinct composition of the marine sourced PCB mixtures in the mothers with higher marine mammal components in the diet. This group of mothers have the highest PCB composition when compared with previously reported literature data (Table 3). Comparison of the individual PCB congeners also show that blood serum of these mothers contained the highest concentrations of PCB-118, PCB-138 and PCB-153 than in these previous studies (Table 3).

Comparison of the medians of the whole Chukotka mothers included in this study with previous maternal population studies from Canada (AMAP, 2015), Liege (Belgium), Sabadell (Catalonia) or Tunisia exhibit higher concentrations (Table 3). In these cases, comparison of the concentrations of some specific congeners such as PCB-118 is difficult because they were not often reported (Table 3).

Regarding DDT and its metabolites, 4,4'-DDT in the present study (median; 8.5 ng/g lipid) is higher than in all these previously mentioned studies except for those in Bizerte (Tunisia) and China (median; 24 and 17 ng/g lipid, respectively). 4,4'-DDE in Chukotka (median; 120 ng/g lipid) is higher than previous studies in populations from Argentina, South Africa, the Caribbean, Canada, Belgium or South Korea, similar to those found in Texas and Tunisia and lower than in China, Attika (Greece) and Sabadell (Spain) (median; 230, 270 and 110 ng/g lipid, respectively). The concentrations of the Chukotsky District (median; 160 ng/g lipid) are higher than in these previous cases except Attika (Greece) and China (Table 3).

### *3.4.2. Comparison with other Arctic populations*

The Chukotka population, and more specifically that from Chukotsky District, are characterised for having higher levels when compared with other Arctic inhabitants (Table 3). Thus, all POPs are found in higher concentrations in Chukotsky District than in Alaska and Norway. The population of this District has also higher levels than in the Arctic Canada with the exception of 4,4'-DDE (median; 150 ng/g lipid).

The whole Chukotka population of the present study has higher POP concentrations than in Alaska and Norway, with the only exception of PCB180 (GM; 16 and 5.4 ng/g lipid, respectively). However, the concentrations in the Arctic Canada are close to those of the global Chukotka region. Thus, levels of PCB-138, PCB-153 and PCB-180 (GM; 20, 47 and 22 ng/g lipid, respectively) are found higher in the former than in the population of Chukotka (GM; 17, 31 and 5.4 ng/g lipid, respectively). The same is the case of 4,4'-DDE, with GM of 150 and 120 ng/g lipid in the Arctic Canada and Chukotka, respectively. The concentrations of all other POPs are higher in Chukotka than in Arctic Canada (Table 3).

In comparison with other Arctic sites, the mothers from Chukotka and Canada show similar concentrations which are higher than in other locations while Alaska has the populations with lowest concentrations.

### 3.4.3. *Comparison with previous studies in Chukotka*

For a better comparison of the data from the present study with previous results three different entries have been calculated, the whole Chukotka cohort (n=250), Chukotsky District (n=63) and Uelen city (n=11) (see Figure 1). Comparison of the present study with the results found in the same area during 2001 and 2002 (Anda et al., 2007) shows a significant decrease, between 3 and 5 times (Table 3). This decrease is not observed for PCBs when these previous results are compared with those from the population of the Chukotsky District.

A decreasing trend is also observed in Chukotsky District when comparing the present and previous results from AMAP (2004) maternal concentration. The GMs of HCB, β-HCH, ΣHCHs, 4,4'-DDE and ΣPCBs in plasma were 1.6, 2.0, 2.1, 2.4 and 3.8 ng/mL, respectively, whereas the present observations are 0.28, 0.29, 0.30, 0.96 and 0.50 ng/mL, respectively. 4,4'-DDT is the only compound not showing a decreasing trend between these two studies, 0.20 and 0.25 ng/mL (AMAP (2004) and the present study, respectively.

One previous study (Sandanger et al., 2003) was specifically performed in 2001-2002 in Uelen (Figure 1). Comparison of the results from this study (n = 50) with the concentrations observed in the same area in our study (n = 11) show a clear decrease for all compounds, between 13% and 90% depending on the POP (Table 3).

These observed changes are consistent with the dietary changes in Chukotka. At the end of the 1980 years a “European” type of diet was adopted by most of the indigenous population under the age of 30 years (Kozlov, 2004). However, in 2002 still 76% of the Chukotka population declared preference for native food over European diet. Progressive introduction of this European diet may have led to a drop of OCs.

### 3.5. *Associations between POPs in blood serum and maternal characteristics*

Linear multivariate models of the maternal socio-demographic characteristics and POP concentrations provide a comprehensive description of the main maternal factors related with the concentrations of these pollutants (Table 4, Figure 6). As mentioned above, area of residence is the main determinant for most POPs, e.g. HCB, β-HCH, mirex and PCB-118, PCB-138, PCB-153 and PCB-180 ($p < 0.001$ in all cases). These compounds show the highest β coefficients for residence among the determinant variables considered. 4,4'-DDE also displays a significant age dependence ($p<0.001$) being residence the second highest β coefficient (Table 4).

Aside from residence, age is the main determinant for 4,4’-DDE ($p<0.001$), 4,4’-DDT ($p< 0.01$) and the second highest for β-HCH, PCB-118, PCB-138 and PCB-180 ($p<0.05$) showing a positive significant correlation (Table 4). This trend is consistent with increases in the concentrations of PCBs and organochlorine pesticides with age observed in other studies (Coakley, et al. 2018, Bravo, et al. 2017).

The third variable influencing the most on the POP concentrations is travel to other regions (Table 4). Women who never left Chukotka have significant higher concentrations of HCB ($p<0.01$), PCB-153 ($p < 0.05$), PCB-180 ($p < 0.01$) and mirex ($p < 0.0001$) than those who spent time periods away from this area. This correlation is consistent with residence. Travelling to other regions likely involved dietary changes and lower exposure to POPs.

Parity is also a main determinant for HCB ($p<0.05$), 4,4’-DDE ($p<0.01$), 4,4’-DDT ($p < 0.05$) and mirex ($p<0.05$). Higher values are associated with significantly lower concentrations of 4,4’-DDE and 4,4’-DDT. This trend is expected and found in other similar studies (Veyhe et al., 2015 Vizcaino et al., 2014 and Manaca et al., 2013). The positive correlation between parity and HCB concentrations is unexpected.

Higher body mass index involves higher statistically significant increases of 4,4’-DDT ($p<0.01$), 4,4’-DDE ($p<0.05$) and β-HCH ($p<0.001$; Table 4; Figure 6). Overweight does not lead to pollutant dilution when the main food sources ingested have these lipophilic pollutants in high concentrations. In these conditions consistent associations between higher BMI and higher pollutant concentrations are observed (Bravo et al., 2017), as it is the case of the present study. Regarding smoking, this activity is only significant for mirex, representing higher accumulation of these compounds at higher tobacco consumption (Figure 6).

Maternal residence is therefore the main determinant of the concentrations of HCB, β-HCH, mirex and PCBs, and the second main determinant of 4,4’-DDE. Maternal age is the main determinant of 4,4’-DDE and 4,4’-DDT and the second highest of the other POPs. Travel to other regions is also determinant. Women who never left Chukotka have significantly higher concentrations of HCB and PCBs than those who spent time periods elsewhere. Parity is also a main determinant for HCB, 4,4’-DDE and 4,4’-DDT, involving lower concentrations at higher values. Higher BMI involve higher statistically significant increases of 4,4’-DDT, 4.4’-DDE and β-HCH, which is consistent with intake of food sources that have these lipophilic pollutants in high concentrations.

### *3.6. Newborn anthropometric characteristics and maternal OC concentrations*

The possible associations between exposure to these POPs and gestational age or infant birth weight, length and head circumference have been examined by multivariate regression analysis adjusting for mother's age, parity, smoking and drinking alcohol habits (Table 5). Smoking was a strong determinant for birth weight and length, hence two additional separated models were performed with the group of smoker and non-smoker mothers. As the results were the same to those obtained with the entire dataset, the final models include all the original variables (age, tobacco and alcohol consumption).

The main feature arising from these multivariate analyses is the significant association of 4,4'-DDT exposure with birth weight, length and gestational age ($p<0.05$ in all cases; Table 5). These associations show a consistent trend by which mothers with higher 4,4'-DDT concentrations had longer gestational age and gave birth to children with higher weight and length. No associations were observed for HCHs, mirex and most PCB congeners, except for HCB and PCB-153 which were associated with circumference head ($p<0.05$).

As mentioned before, parity is an important determinant of the concentrations of OCs in blood serum. Accordingly, a sensitivity analysis restricted to women with parity 1 was performed. The calculations involved the same regression models of Table 5 for this group of mothers (n = 84). The results showed that birth length and weight were again positively associated with higher 4,4'-DDT concentrations with statistical significance ($p < 0.05$ and 0.01, respectively). The association between gestational age and 4,4'-DDT was no longer statistically significant. These results give further ground to the association between birth outcomes and 4,4'-DDT exposure.

We also studied separately male (n = 118) and female (n = 125) infants vs. 4,4'-DDT maternal exposure for identification of specific anthropogenic gender effects (Tatsuta et al., 2017). Significant associations were found between higher 4,4'-DDT concentrations and higher birth weight in the first case ($p<0.05$) and higher birth length in the second ($p<0.05$). The association with gestational age lost significance. On the other hand, no significant differences in gender offspring were observed in association to maternal concentrations of these studied POPs. Since no specific gender association was observed for this insecticide we continued the study with the entire dataset for higher statistical power.

Often, the newborn anthropometry changes associated with maternal exposure to environmental pollutants involve birth weight decreases, e.g. Ha et al (2001), Gouveia et al (2004), which is related with diverse toxicity effects of these compounds. In the present case, the observed 4,4'-DDT effects are related with the endocrine disrupting properties. Cell culture experiments have shown that exposure to 4,4'-DDT promote adipogenesis (Kim et al., 2016). Laboratory studies with rats have also shown that 4,4'-DDT intake may generate transgenerational inheritance of obsesity (Skinner et al., 2013). Studies of the Child and Health Cohort Study of San Francisco Bay showed a weak positive association between maternal 4,4'-DDT venous concentrations and gestational age (Jusko et al., 2006). The relations between birth weight and length and maternal 4,4'-DDT concentrations were not significant. Studies of children fat increases at 6.5 years of age showed statistically significant overweight in boys (Valvi et al., 2012). To the best of our knowledge, this is the first study showing an association between newborn anthropometric parameters and 4,4’-DDT exposure.

Studies on 4,4’-DDE, the major 4,4’-DDT metabolite, and anthropometric outcomes at birth reported discrepant results; either no effect (Casas et al., 2015; Govarts et al., 2018) or smaller birth weight and preterm delivery (Longnecker et al., 2001). However, this last study was performed on children born between 1959 and 1966 with a much higher 4,4’-DDE maternal serum concentration, median 25 ng/ml, than the studies which did not find any effect, 0.45-0.60 ng/ml (Casas et al., 2015; Govarts et al., 2018). These last 4,4’-DDE concentrations are similar to those of the present Chukotka cohort, 0.92 ng/ml, in which no effects were observed.

On the other hand, studies in a INMA cohort with similar 4,4’-DDE maternal concentrations, medians 125-135 ng/g lipids, as in the Chukotka case, median 120 ng/g lipids (Table 2), showed that higher exposure to this metabolite involved rapid newborn weight gain (6 months) and infant overweight (14 months; Mendez et al., 2011). The observed increase in weight and length at higher maternal concentrations is consistent with the observed metabolic effects for 4,4’-DDE.

However, these two compounds have different routes of interaction with human metabolism. Thus, in utero exposure to 4,4’-DDT has been described to decrease cognitive skills among pre-schoolers depending on genetic variability (Morales et al., 2008). These neurotoxic effects are specific of 4,4’-DDT (Ribas-Fito et al., 2006). In Chukotka, the observed influence of maternal 4,4’-DDT concentrations evidences a metabolic interaction of 4,4’-DDT already in the early life period which suggests that the deleterious effects identified in other cohorts will also occur at most advanced growth ages.

The other significant associations between higher maternal concentration of PCB-138 and lower gestational age and PCB-153 and size of the head circumference (Table 5) are consistent with other studies indicating effects of low-level environmental pollutants and fetal growth (Vafeiadi et al., 2014; Tatsuta et al., 2017). However, only these two congeners showed significant associations in the present cohort and these were related with different anthropometric characteristics which did not ground defined causal-effect relationships.

## 4. Conclusions

Women’s residence was one of the main determinants for the PCBs, HCB, mirex and β-HCH, blood serum concentrations in pregnant women, involving higher concentrations in those living at the coast and particularly those from the Chukotsky District (Table 1). These differences can be explained by the different diets as people from the coastal areas have a more traditional diet, based on marine mammal hunting and reindeer herding than inland people. In this context, women from coastal areas who did not travel to other regions had highest concentrations of HCB, mirex, PCB-153 and PCB-180.

Other characteristics of the mothers such as age, are also main determinants of the concentrations of β-HCH, 4,4’-DDE, 4,4’-DDT and some PCB congeners.

The positive associations of maternal concentrations of 4,4’-DDT with higher birth weight, length and gestational age evidences that exposure to this compound has effectively an interaction with newborn metabolism. This pesticide is the POP showing a better defined influence on children’s growth. The present study provides evidence of the influence of 4,4’-DDT on the anthropometric characteristics of the newborns for the first time. It is clear from the results of the present study that exposure to POPs, and particularly 4,4’-DDT, needs to be reduced for the benefit of the local inhabitants’ health.

## Conflicts of interests

The authors declare they have no actual or potential competing financial interests.

## Acknowledgements

The authors are grateful to all women who participated in the study and the health staff who collected the samples. This study was partially funded by the Norwegian Ministry of Foreign Affairs through the Arctic Monitoring and Assessment Programme (AMAP). Also EU projects NEUROSOME (H2020-MSCA-ITN-2017-766251), HEALS (FP7-ENV-2013- 603946) and EDCMET (H2020-SC1-BHC-2018-SEP-210505108) are also acknowledged.

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**Table 1.** Socio-demographic characteristics of studied population in Chukotka (n=247)

| | **Participants n (%)** |
|---|---|
| **All women** | 250 (100) |
| **Age (n=247)** | 27.8±7.1 |
| **BMI (n=244)** | |
| Underweight (<18.5 kg/m$^2$) | 17 (7) |
| Normal weight (18.5-25 kg/m$^2$) | 165 (68) |
| Overweight (25-30 kg/m$^2$) | 40 (16) |
| Obese (≥25 kg/m$^2$) | 22 (9) |
| **Parity (n=247)** | |
| 1 | 97 (39) |
| 2 | 79 (32) |
| ≥3 | 71 (29) |
| **Educational Level (n=247)** | |
| Elemental or lower secondary | 39 (16) |
| Secondary | 72 (29) |
| Secondary Special | 76 (31) |
| High Education | 60 (24) |
| **Area of residence (n=250)** | |
| Inland | 146 (58) |
| Coastal | 45 (18) |
| Chukotsky District (Coastal) | 59 (24) |
| **Travel to other region (n=241)** | |
| Never | 53 (22) |
| Once a year | 123 (51) |
| 1-3 times a year | 65 (27) |
| **Smoking (n=247)** | |
| Yes | 75 (30) |
| No | 172 (70) |
| **Alcohol consumption (n=246)** | |
| Yes | 83 (34) |
| No | 163 (66) |
| **Children** | 245 (100) |
| **Gender (n=243)** | |
| Boys | 125 (51) |
| Girls | 118 (49) |
| **Weight (g)** | |
| Boys (n=125) | 3,374±652 |
| Girls (n=116) | 3,352±549 |
| **Length (cm)** | |
| Boys (n=125) | 52.6±3.7 |
| Girls (n=116) | 52.4±3.6 |
| **Gestational age (n=232)** | |
| Preterm (<37 weeks) | 19 (8) |
| Normal (37-42 weeks) | 204 (88) |
| Postmature (>42 weeks) | 9 (4) |
| **Head circumference (cm)** | |
| Boys (n=125) | 34.4±2.1 |
| Girls (n=116) | 34.4±2.4 |

**Table 2.** Serum POP concentrations (ng/ g lipid and ng/mL) in the population of study

| | LD[1] (ng/mL) | LQ[1] (ng/mL) | DF[2] (%) | Lipid Adjusted (ng/g lipid) (n=246) | | | | Non-adjusted (ng/mL) (n=250) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | GM | (95% CI)[3] | Median | Range | GM | (95% CI)[3] | Median | Range |
| **PeCB** | 0.006 | 0.010 | 1 | <LD | | <LD | nd-2.1 | <LD | | <LD | nd-0.017 |
| **HCB** | 0.027 | 0.038 | 99 | 35 | (31-40) | 29 | nd-850 | 0.28 | (0.25-0.32) | 0.29 | nd-6.0 |
| **α-HCH** | 0.007 | 0.011 | 94 | 3.2 | (2.9-3.5) | 3.3 | nd-100 | 0.025 | (0.023-0.028) | 0.027 | nd-0.88 |
| **β-HCH** | 0.010 | 0.017 | 98 | 35 | (30-41) | 38 | nd-660 | 0.28 | (0.24-0.33) | 0.29 | nd-5.0 |
| **γ-HCH** | 0.013 | 0.020 | 38 | <LQ | | <LD | nd-13 | <LQ | | <LD | nd-0.091 |
| **δ-HCH** | 0.020 | 0.031 | 21 | <LD | | <LD | nd-93 | <LD | | <LD | nd-0.85 |
| **2,4'-DDD** | 0.007 | 0.012 | 14 | <LD | | <LD | nd-9.2 | <LD | | <LD | nd-0.077 |
| **4,4'-DDD** | 0.002 | 0.004 | 27 | <LQ | | <LD | nd-53 | <LQ | | <LD | nd-0.50 |
| **2,4'-DDE** | 0.013 | 0.020 | 7 | <LD | | <LD | nd-9.7 | <LD | | <LD | nd-0.067 |
| **4,4'-DDE** | 0.013 | 0.021 | 99 | 120 | (110-130) | 120 | nd-1100 | 0.96 | (0.86-1.1) | 0.92 | nd-5.4 |
| **2,4'-DDT** | 0.005 | 0.008 | 36 | <LQ | | <LD | nd-74 | <LQ | | <LD | nd-0.69 |
| **4,4'-DDT** | 0.005 | 0.008 | 100 | 9.0 | (8.4-9.7) | 8.5 | 2.0-67 | 0.25 | (0.22-0.29) | 0.065 | 0.014-0.51 |
| **Mirex** | 0.005 | 0.008 | 43 | <LQ | | <LD | nd-46 | <LQ | | <LD | nd-0.26 |
| **PCB-28** | 0.010 | 0.016 | 27 | <LD | | <LD | nd-36 | <LD | | <LD | nd-0.24 |
| **PCB-52** | 0.005 | 0.008 | 18 | <LD | | <LD | nd-750 | <LD | | <LD | nd-7.0 |
| **PCB-101** | 0.001 | 0.002 | 9 | <LD | | <LD | nd-8.0 | <LD | | <LD | nd-0.058 |
| **PCB-118** | 0.011 | 0.017 | 98 | 10 | (9.0-11) | 9.2 | nd-1100 | 0.081 | (0.071-0.091) | 0.073 | nd-9.7 |
| **PCB-138** | 0.002 | 0.003 | 100 | 17 | (15-19) | 14 | 1.3-440 | 0.13 | (0.12-0.15) | 0.12 | 0.013-4.1 |
| **PCB-153** | 0.007 | 0.012 | 100 | 31 | (27-35) | 25 | 3.9-880 | 0.25 | (0.22-0.29) | 0.20 | 0.032-8.2 |
| **PCB-180** | 0.011 | 0.018 | 78 | 5.4 | (4.6-6.4) | 5.4 | nd-230 | 0.044 | (0.037-0.052) | 0.049 | nd-2.2 |

[1] LD, LQ: Limit of Detection and Limit of Quantification; [2] DF: Detection Frequency, % of samples above the limit of detection; [3] GM(95%CI): Geometric mean with 95% confidence intervals.

**Table 3.** Comparison of median concentrations of POPs in human serum from Chukotka with other populations (in ng/g lipid).

| | Location | Year | N | PCB- | PCB- | PCB- | PCB- | β- | 4,4'- | 4,4'- | HCB | Mire | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arctic | Chukotka | 2014-2015 | 250 | 9.2<br>[10] | 14<br>[17] | 25<br>[31] | 5.4<br>[5.4] | 38<br>[35] | 120<br>[120] | 8.5<br>[9.0] | 29<br>[35] | <LD<br>[0.83 | *Present studv* |
| | Chukotsky District | 2014-2015 | 63 | 22<br>[25] | 47<br>[55] | 120<br>[130] | 20<br>[22] | 93<br>[92] | 160<br>[140] | 8.6<br>[9.5] | 99<br>[110] | 2.0<br>[3.1] | *Present study* |
| | Uelen city (Chukotsky | 2014-2015 | 11 | 30<br>[24] | 18<br>[53] | 130<br>[130] | 19<br>[22] | 180<br>[150] | 200<br>[190] | 11<br>[11] | 170<br>[150] | 5.5<br>[2.8] | *Present study* |
| | Chukotka | 2001-2002 | 48 | [49] | [38] | [97] | [25] | [210] | [310] | [31] | [160] | - | *Anda et al., 2007* |
| | Uelen city (Chukotsky D.) | 2001-2002 | 50 | 140<br>[110] | 250<br>[210] | 640<br>[540] | 160<br>[150] | 520<br>[410] | 560<br>[520] | 36<br>[34] | 200<br>[170] | 29<br>[27] | *Sandanger et al., 2003* |
| | Alaska[b] | 2009-2012 | 156 | [3.4] | [9.1] | [15] | [5.4] | [3.6] | [83] | [2.5] | [16] | [2.3] | *AMAP, 2015* |
| | Canada[b] | 2007-2008 | 485 | [7.5] | [20] | [47] | [22] | [5.5] | [150] | [6.8] | [32] | - | *AMAP, 2015* |
| | Norway | 2007-2009 | 508 | [4.1] | [15] | [25] | [16] | - | [39] | - | [9.6] | - | *Veyhe et al., 2015* |
| Southern hemispher | Ushuaia (Argentina) | 2011-2012 | 199 | 3.3<br>[2.8] | 5.8<br>[5.3] | 8.1<br>[7.7] | 1.0<br>[1. 6] | 6.8<br>[5.1] | 27<br>[33] | 3.0<br>[2.7] | 8.3<br>[8.7] | -<br>- | *Bravo et al., 2017* |
| | Salta (Argentina) | 2011-2012 | 471 | 6.1<br>[4.8] | 5.9<br>[5.3] | 7.3<br>[6.8] | 1.0<br>[1.6] | 11<br>[7.8] | 58<br>[67] | 5.2<br>[5.7] | 5.8<br>[5.2] | -<br>- | *Bravo et al., 2017* |
| | Bolivia | 2013 | 200 | - | - | - | - | - | 200 | - | - | - | *Arrebola et al., 2016* |
| | South Africa | 2008 | 117 | [1.5] | [3.6] | [3.2] | - | - | [29] | [7] | - | - | *Channa et al., 2012* |
| North America | Texas (USA) | 2005-2009 | 461 | 2.5 | 5.3 | 8.2 | 6.5 | 1.7 | 110 | 2.1 | 8.0 | 1.6 | *Mumford et al., 2015* |
| | Caribbean[c] | 2008-2011 | 438 | [1.8] | [3.8] | [7.0] | [4.1] | - | [70] | <LD | [3.6] | - | *Forde et al., 2014* |
| | Canada[b] | 2007-2009 | 525 | 2.8 | 5.4 | 8.8 | 6.2 | 3.0 | 75 | <LD | 7.1 | <LD | *CHMS, 2010* |
| Europe | Liege (Belgium) | 2015 | 251 | - | <LD | 54 | 41 | <LD | <LD | - | - | - | *Pirard et al., 2018* |
| | Attika (Greece) | 2007 | 61 | 4.4 | 20 | 34 | 25 | 18 | 270 | 6.3 | 23 | - | *Kalantzi et al., 2011* |
| | Sabadell (Spain) | 2004-2006 | 631 | - | [16] | [31] | [20] | [30] | [130] | - | [35] | - | *Ibarluzea et al., 2011* |
| North Africa | Bizerte (Tunisia) | 2011-2012 | 113 | <LD | 24 | 49 | 32 | 9.5 | 120 | 24 | 39 | - | *Ben Hassine et al., 2014* |
| | Tunis/Ariana (Tunisia) | 2012 | 54 | - | 26 | 110 | 30 | <LD | 130 | - | 20 | - | *Artacho-Cordon et al.,* |
| Asia | China | 2010 | 81 | - | - | - | - | 74 | 230 | 17 | 75 | 0.23 | *Guo et al., 2014* |
| | Korea | 2011 | 105 | 2.3 | 4.6 | 9.0 | - | 7.6 | 57 | 5.2 | 9.5 | - | *Kim et al., 2013* |

In brackets geometric mean concentration; [a]See Figure 1; [b]Human plasma analysis instead of serum; [c]Results from 10 differents sites.

**Table 4.** Results of the regression models showing effects of various determinants in blood serum (n=226).

| Compound | Variable | Std. β[a] | p | Compound | Variable | Std. β[a] | p |
|---|---|---|---|---|---|---|---|
| **HCB** | Age | 0.083 | 0.21 | **PCB-118** | Age | 0.15 | **0.040** |
| | BMI[1] | 0.017 | 0.75 | | BMI[1] | 0.096 | 0.11 |
| | Parity | 0.14 | **0.031** | | Parity | -0.013 | 0.85 |
| | Education[2] | -0.053 | 0.44 | | Education[2] | -0.011 | 0.89 |
| | Smoking[3] | 0.082 | 0.19 | | Smoking[3] | 0.015 | 0.82 |
| | Residence[4] | 0.38 | **<0.0001** | | Residence[4] | 0.41 | **<0.0001** |
| | Travel other region[5] | -0.20 | **0.0018** | | Travel other region[5] | -0.10 | 0.14 |
| **α-HCH** | Age | 0.026 | 0.75 | **PCB-138** | Age | 0.14 | **0.038** |
| | BMI[1] | 0.11 | 0.093 | | BMI[1] | 0.034 | 0.55 |
| | Parity | 0.030 | 0.70 | | Parity | -0.074 | 0.25 |
| | Education[2] | 0.032 | 0.70 | | Education[2] | 0.0013 | 0.98 |
| | Smoking[3] | 0.034 | 0.66 | | Smoking[3] | 0.076 | 0.23 |
| | Residence[4] | 0.056 | 0.46 | | Residence[4] | 0.50 | **<0.0001** |
| | Travel other region[5] | -0.053 | 0.51 | | Travel other region[5] | -0.12 | 0.057 |
| **β-HCH** | Age | 0.17 | **0.015** | **PCB-153** | Age | 0.067 | 0.30 |
| | BMI[1] | 0.21 | **0.00053** | | BMI[1] | 0.025 | 0.64 |
| | Parity | 0.040 | 0.56 | | Parity | -0.025 | 0.69 |
| | Education[2] | -0.0006 | 0.99 | | Education[2] | 0.00034 | 0.99 |
| | Smoking[3] | 0.084 | 0.21 | | Smoking[3] | 0.042 | 0.49 |
| | Residence[4] | 0.33 | **<0.0001** | | Residence[4] | 0.50 | **<0.0001** |
| | Travel other region[5] | -0.11 | 0.13 | | Travel other region[5] | -0.15 | **0.015** |
| **4,4'-DDE** | Age | 0.28 | **0.00037** | **PCB-180** | Age | 0.16 | **0.019** |
| | BMI[1] | 0.13 | **0.050** | | BMI[1] | 0.020 | 0.72 |
| | Parity | -0.23 | **0.0024** | | Parity | -0.011 | 0.87 |
| | Education[2] | 0.063 | 0.42 | | Education[2] | 0.0024 | 0.97 |
| | Smoking[3] | 0.14 | 0.058 | | Smoking[3] | 0.049 | 0.45 |
| | Residence[4] | 0.22 | **0.0022** | | Residence[4] | 0.44 | **<0.0001** |
| | Travel other region[5] | 0.0072 | 0.92 | | Travel other region[5] | -0.19 | **0.0045** |
| **4,4'-DDT** | Age | 0.25 | **0.0016** | **Mirex** | Age | -0.024 | 0.72 |
| | BMI[1] | 0.18 | **0.0064** | | BMI[1] | 0.055 | 0.33 |
| | Parity | -0.18 | **0.016** | | Parity | 0.14 | **0.030** |
| | Education[2] | -0.068 | 0.39 | | Education[2] | 0.031 | 0.66 |
| | Smoking[3] | 0.12 | 0.11 | | Smoking[3] | 0.15 | **0.023** |
| | Residence[4] | -0.065 | 0.37 | | Residence[4] | 0.25 | **<0.0001** |
| | Travel other region[5] | -0.080 | 0.29 | | Travel other region[5] | -0.28 | **<0.0001** |

[a] $^{\beta}$coefficients of the multivariate regression models after standardizing all the variables. [1]BMI: Body mass index; [2]Elemental education as the reference level; [3]Women who don't smoke as reference; [4]Inland as reference category for residence; [5]Women who never travel to other regions as reference category.

**Table 5.** Results of the regression models showing effects of various POPs in children birth outcomes.

| | **Gestational age[a]** | | **Birth weight[b]** | | **Birth length[b]** | | **Head circumference[b]** | |
|---|---|---|---|---|---|---|---|---|
| | **Std. β[c]** | ***p*-value** | **Std. β[c]** | ***p*-value** | **Std. β[c]** | ***p*-value** | **Std. β[c]** | ***p*-value** |
| **Total (n=243)** | | | | | | | | |
| **HCB** | -0.082 | 0.40 | -0.19 | 0.065 | -0.17 | 0.11 | -0.22 | **0.048** |
| **α-HCH** | 0.083 | 0.17 | 0.095 | 0.13 | 0.029 | 0.67 | 0.097 | 0.15 |
| **β-HCH** | -0.016 | 0.84 | 0.080 | 0.35 | -0.038 | 0.67 | 0.076 | 0.40 |
| **4,4'-DDE** | -0.049 | 0.59 | -0.017 | 0.86 | 0.036 | 0.72 | 0.067 | 0.52 |
| **4,4'-DDT** | 0.16 | **0.048** | 0.21 | **0.013** | 0.21 | **0.020** | 0.10 | 0.27 |
| **PCB-118** | 0.15 | 0.28 | 0.057 | 0.69 | 0.088 | 0.56 | 0.071 | 0.65 |
| **PCB-138** | -0.70 | **0.021** | -0.49 | 0.13 | -0.55 | 0.11 | -0.56 | 0.10 |
| **PCB-153** | 0.43 | 0.077 | 0.22 | 0.40 | 0.45 | 0.092 | 0.57 | **0.039** |
| **PCB-180** | 0.11 | 0.30 | 0.15 | 0.21 | 0.020 | 0.87 | -0.10 | 0.43 |
| **Mirex** | 0.054 | 0.53 | 0.036 | 0.69 | 0.018 | 0.85 | -0.0088 | 0.93 |

[1] Gestational age model adjusted for mother's age, parity, tobacco and alcohol consumption and children's birth weight and length; [2]Birth weight, length and head circumference models adjusted for gestational age (categorized in preterm, normal and postmature), mother's age, parity and tobacco and alcohol consumption. [c]β coefficients of the multivariate regression models after standardizing all the variables.

## FIGURE CAPTIONS

**Figure 1**. Map of Chukotka showing the locations of the population participating in this study. Green dots inland areas. Purple and red dots coastal zones. Shadowed zone: Chukotsky District. Cities: 1: Lavrentiya, 2: Enurmino, 3: Lorino, 4: Uelen, 5: Neshkan, 6: Inchoun, 7: Beringovsky, 8: Anadyr, 9: Ceperveem, 10: Ugolnye Copi, 11: Providèniya, 12: Novoye Chaplino, 13: Ritkuchi, 14: Lamutskoye, 15: Meynypilgyno, 16: Egvekinot, 17: Vajegy, 18: Hatirka, 19: Konergino, 20: Alkatvaam, 21: Nunligran, 22: Snezhnoye, 23: Sireniki, 24: Ust-Belaya, 25: Markovo, 26: Kanchalan, 27: Bilibino, 28: Pevek. Districts: A: Chukotsky District, B: Providensky District, C: Lul'tinksy District, D: Anadyrsky District, E: Chaunsky District, F: Bilbinsky District.

**Figure 2.** Geometric means of the organochlorine compounds concentrations (ng/g lipid) in mothers from Chukotka living in inland or coastal areas. The vertical bars plot the 95% confidence intervals.

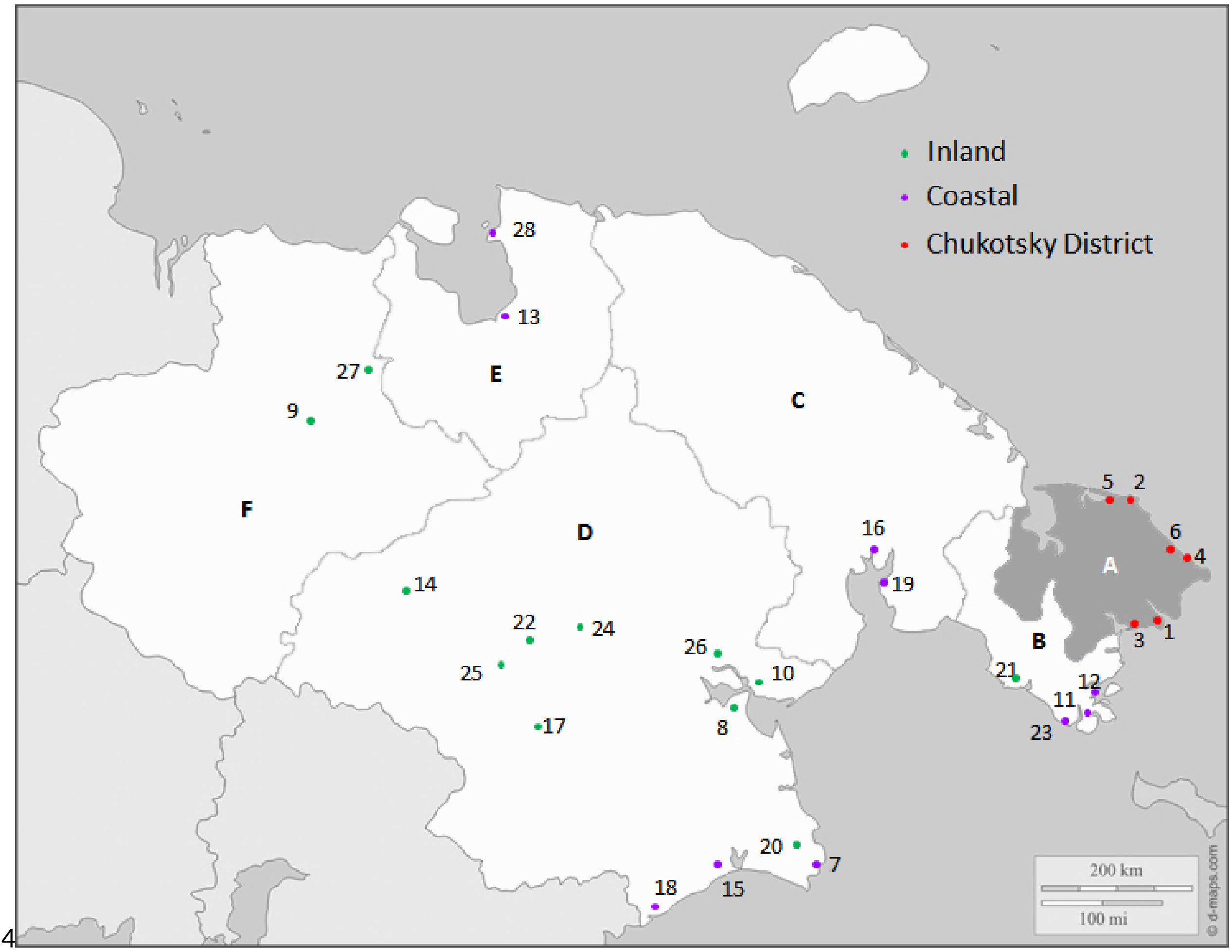
**Figure 3.** Biplot of scores and loadings onto the first and second principal components for major organochlorine compounds by location.

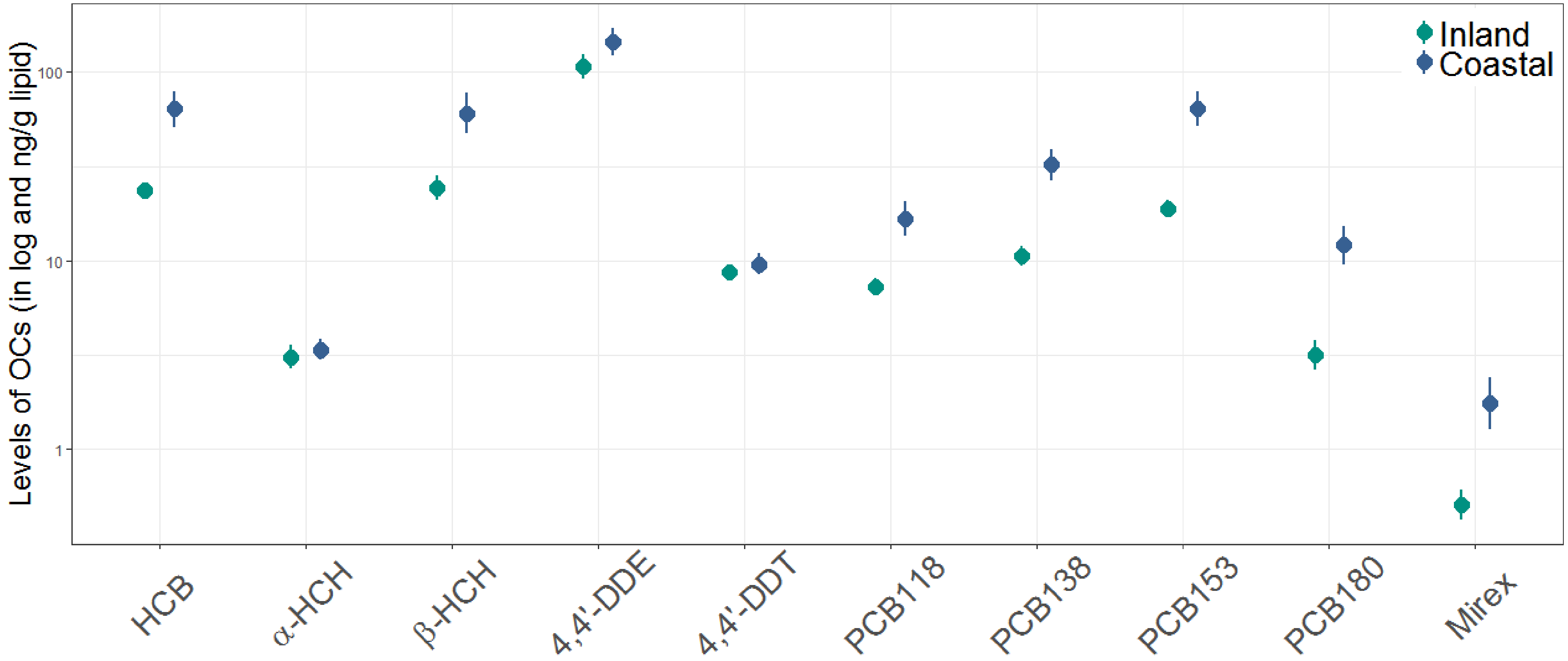
**Figure 4.** Geometric means of the organochlorine compounds concentrations (ng/g lipid) in mothers from Chukotka living in inland and coastal areas and Chukotsky district. The vertical bars plot the 95% confidence intervals.

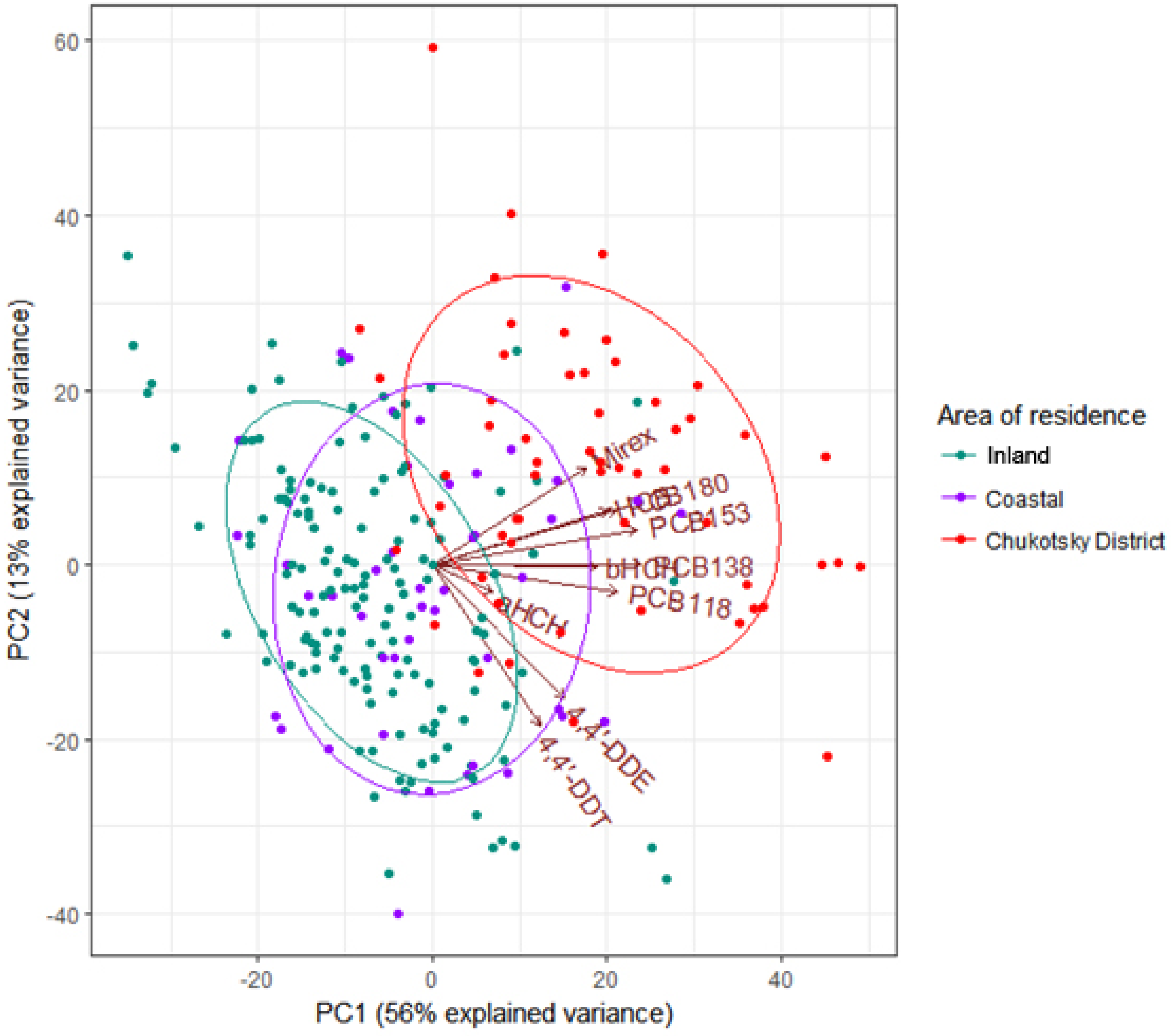
**Figure 5.** Relative change (%) in median serum organohalogen concentrations by unit change calculated from the β coefficients and standard errors of the multiregression analyisis. The units of changes for each variable were set as the difference between the first and third quartile.

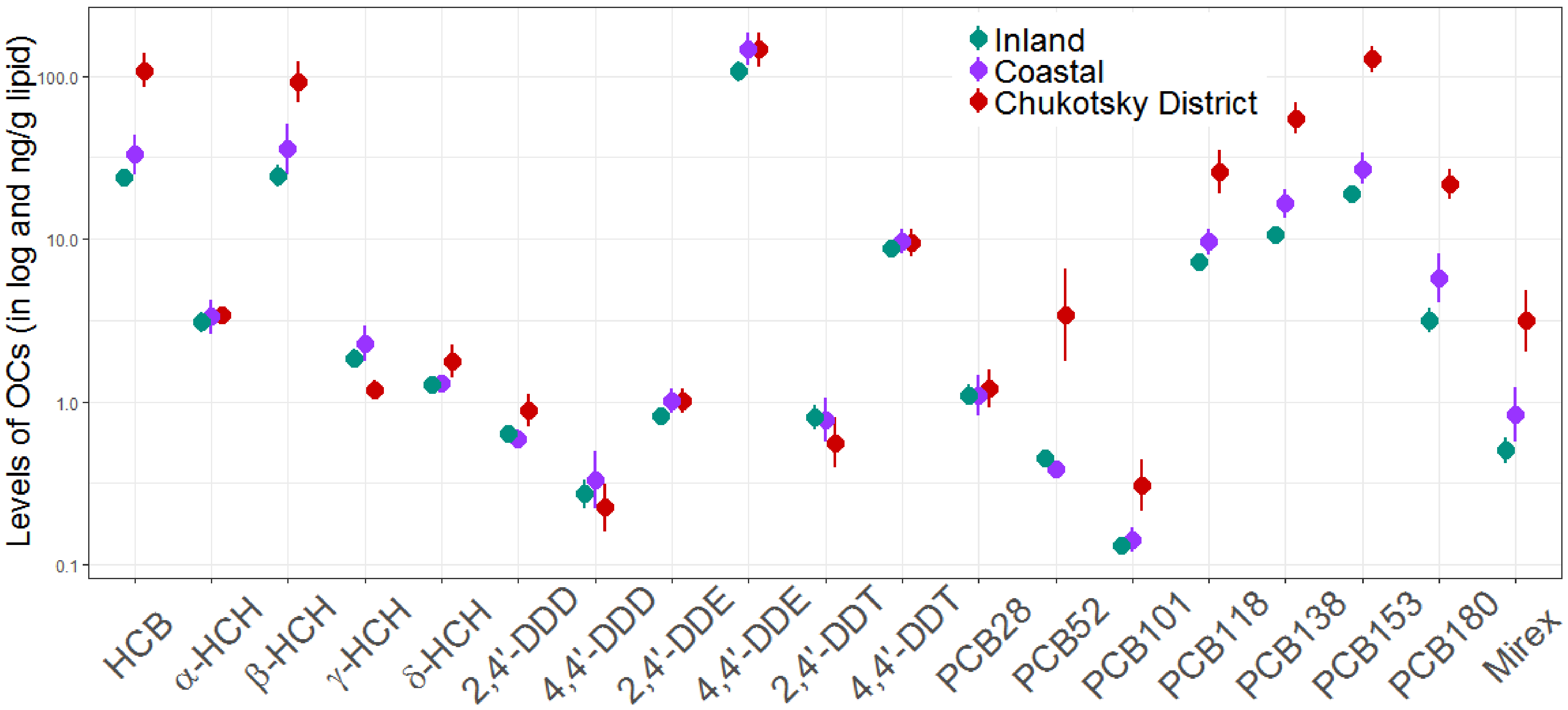
**Figure 6.** Relative change (%) in median serum organohalogen concentrations by unit change calculated from the β coefficients and standard errors of the multiregression analysis described in Table 3. The units of changes for each variable were set as the difference between the first and third quartile.

**Figure 7.** Educational level plot of the geometric means and the 95% confidence intervals (ng/g lipid) of the organochlorine compounds concentrations in pregnant women.


● Inland
● Coastal
● Chukotsky District
A
B
C
D
E
F
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
200 km
100 mi
© d-maps.com

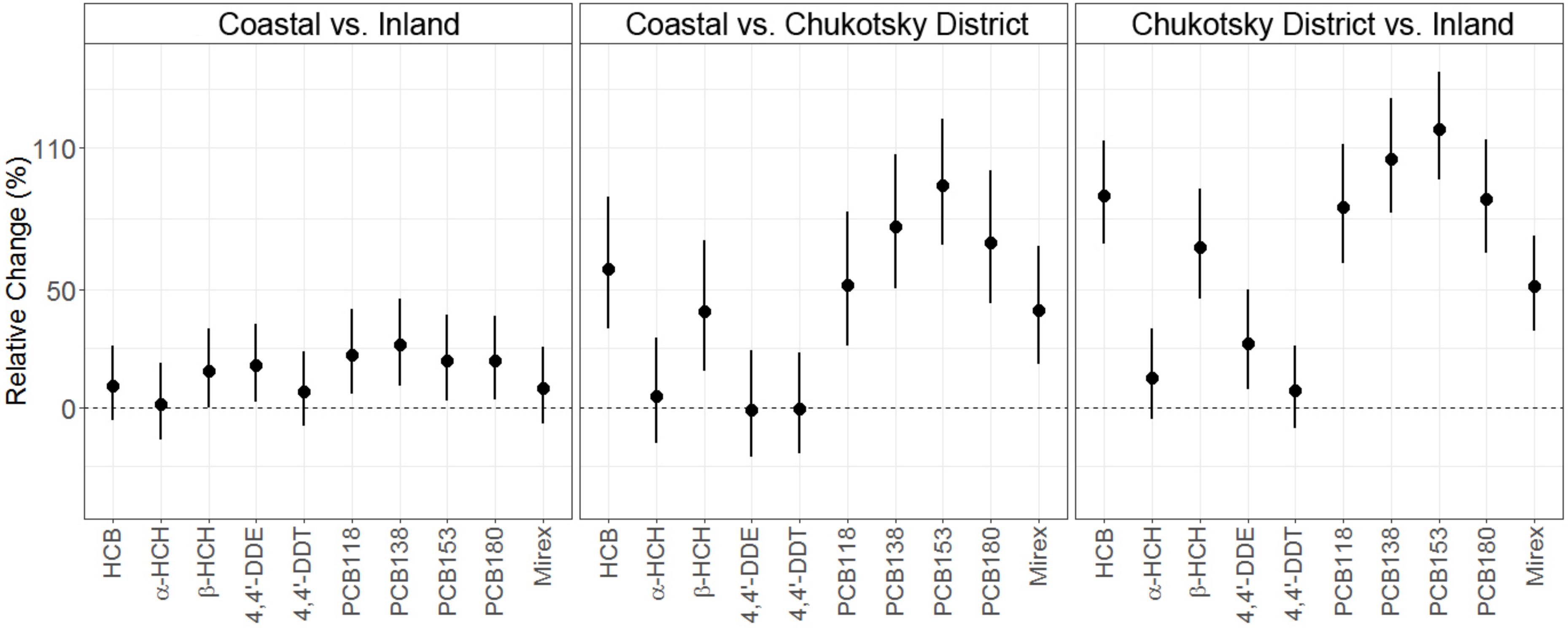

Levels of OCs (in log and ng/g lipid)
100
10
1
Inland
Coastal
HCB
α-HCH
β-HCH
4,4'-DDE
4,4'-DDT
PCB118
PCB138
PCB153
PCB180
Mirex


60
40
20
0
-20
-40
-20
0
20
40
PC2 (13% explained variance)
PC1 (56% explained variance)
Mirex
HCB
PCB180
PCB153
bHCH
PCB138
PCB118
HCH
4,4'-DDE
4,4'-DDT
Area of residence
Inland
Coastal
Chukotsky District

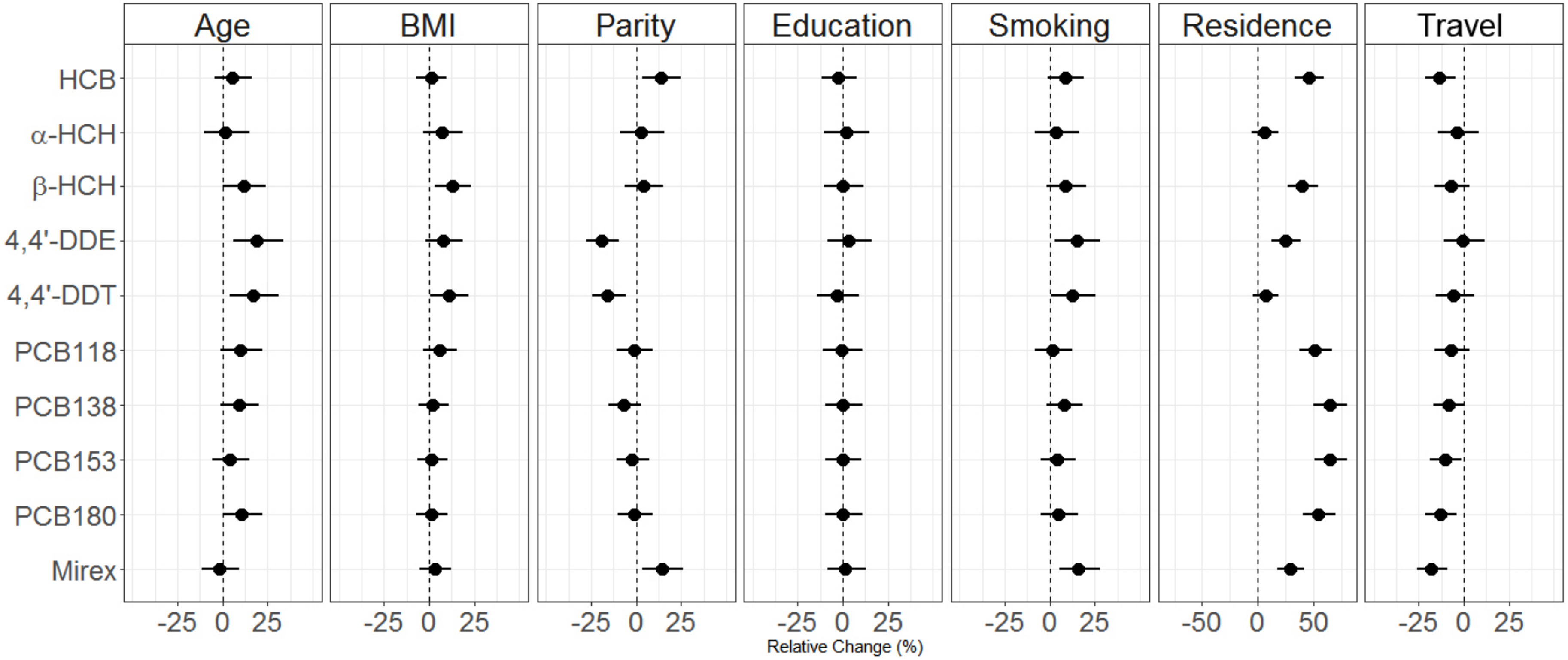

Levels of OCs (in log and ng/g lipid)
100.0
10.0
1.0
0.1
Inland
Coastal
Chukotsky District
HCB
α-HCH
β-HCH
γ-HCH
δ-HCH
2,4'-DDD
4,4'-DDD
2,4'-DDE
4,4'-DDE
2,4'-DDT
4,4'-DDT
PCB28
PCB52
PCB101
PCB118
PCB138
PCB153
PCB180
Mirex

846

65
66


Coastal vs. Inland
Coastal vs. Chukotsky District
Chukotsky District vs. Inland
Relative Change (%)
110
50
0
HCB
α-HCH
β-HCH
4,4'-DDE
4,4'-DDT
PCB118
PCB138
PCB153
PCB180
Mirex

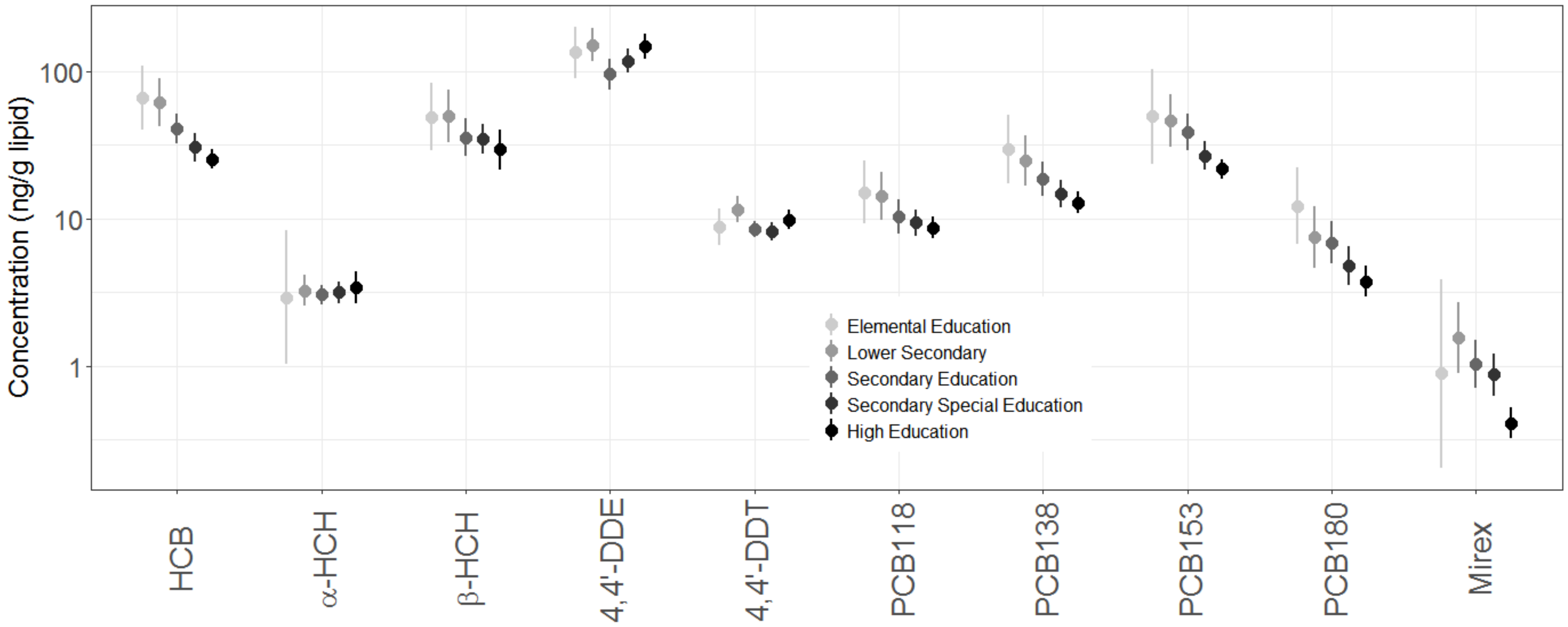
847



Age
BMI
Parity
Education
Smoking
Residence
Travel
HCB
α-HCH
β-HCH
4,4'-DDE
4,4'-DDT
PCB118
PCB138
PCB153
PCB180
Mirex
-25
0
25
-50
50
Relative Change (%)

848

69
70


Concentration (ng/g lipid)
100
10
1
HCB
α-HCH
β-HCH
4,4'-DDE
4,4'-DDT
PCB118
PCB138
PCB153
PCB180
Mirex
Elemental Education
Lower Secondary
Secondary Education
Secondary Special Education
High Education

849