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Effects of biometrics, location and persistent organic pollutants on blood clinical-chemical parameters in polar bears (*Ursus maritimus*) from Svalbard, Norway

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Abstract

In the present study, blood clinical-chemical parameters (BCCPs) were analysed in 20 female and 18 male Svalbard polar bears (*Ursus maritimus*) captured in spring 2007. The aim was to study how age, body condition (BC), biometrics, plasma lipid content and geographical location may confound the relationship between persistent organic pollutants (POPs) including PCBs, HCB, chlordanes, DDTs, HCHs, mirex and OH-PCBs and the concentrations of 12 specific BCCPs (hematocrit [HCT], hemoglobin [HB], aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], γ-glutamyltransferase [GGT], creatine kinase [CK], triglycerides [TG], cholesterol [CHOL], high-density lipoprotein [HDL], creatinine (CREA], urea, potassium (K]), and to investigate if any of these BCCPs may be applied as potential biomarkers for POP exposure in polar bears. Initial PCA and O-PLS modelling showed that age, lipids, BC and geographical location (longitude and latitude) were important parameters explaining BCCPs in females. Following subsequent partial correlation analyses correcting for age and lipids, multiple POPs in females were still significantly correlated with HCT and HDL (all $p < 0.05$). In males, age, BM, BC and longitude were important parameters explaining BCCPs. Following partial correlation analyses correcting for age, biometrics, lipids and longitude in males, multiple POPs were significantly correlated with HCT, ASAT, GGT and CHOL (all $p < 0.05$). In conclusion, several confounding parameters has to be taken into account when studying the relations between BCCPs and POPs in polar bears. When correcting for these, in particular HCT may be used as a simple cost-efficient biomarker of POP exposure in polar bears. Furthermore, decreasing HDL concentrations and increasing CHOL concentration with increasing POP concentrations may indicate responses related to increased risk of cardiovascular disease. We therefore suggest to further study POP exposure and lipidome response to increase knowledge of the risk of cardiometabolic syndrome in polar bears.

Introduction

Persistent organic pollutants (POPs) are a group of organic compounds that primarily originate from anthropogenic sources and include pesticides, industrial chemicals, and by-product from combustion or industrial processes. Examples of POPs include polychlorinated biphenyls (PCBs), polybrominated diphenyl ether (PBDE), hexachlorobenzene (HCB), chlordanes, and DDT (El-Shahawi et al. 2010). Although POPs are structurally a diverse group of chemicals, most of them have low water solubility, they are highly lipophilic, and resistant to physical, chemical and biochemical degradation (AMAP, 2004; Borgå et al. 2004). Their toxic effects, persistence and capacity for long-range transport and bioaccumulation have raised concern about their environmental impact, and have led to restrictions or even complete ban on the use of these chemicals in many countries (Godduhn and Duffy, 2003; El-Shahawi et al. 2010; Letcher et al. 2010). Due to their physical-chemical properties, they can reach high concentration in top predators, such as polar bears (Letcher et al. 2010; Riget et al. 2016). Despite the restrictions and bans, POPs may remain at significant (and potentially toxic) levels in biota for decades due to their persistent nature (Brown et al. 2018, Dietz et al. 2013 a,b). In mammals, POPs may be transferred from mothers to their offspring *in utero* and through lactation (Bytingsvik et al. 2012 a,b; Polischuk et al. 2002). The Arctic is characterized by low temperatures, limited nutrient availability, and pronounced seasonality with short growing seasons (Sobek et al. 2010). Due to the seasonal absence of sea ice polar bears have adapted to the lack of access to marine mammal prey, and go through a seasonal period of fasting, with a preceding period of feeding in which they must obtain sufficient fat reserves for reproduction and/or later fasting. These adaptations do also influence on the accumulation and dynamics of POPs in the Arctic biota. During the fasting period, lipid stores are metabolised. This often leads to mobilization of lipophilic contaminants stored in fat depot, and the blood levels of contaminants will increase. Contaminants in the blood can be distributed throughout the body, exposing various vital organs to the toxic compounds, and hence, increase the animal's susceptibility for adverse effect with potential negative physiological effects (Cherry et al. 2009; Routti et al. 2010; Tartu et al. 2017a). In polar bears, the hormone and vitamin concentrations, organ

morphology, as well as reproductive and immune systems are likely to be influenced by PCB exposure (Dietz et al. 2015; Letcher et al. 2010; Sonne 2010).

In most cases, biotransformation processes lead to detoxification of POPs, which will protect the organisms. However, in some cases biotransformation of parent compounds may result in metabolites being more toxic than the parent compound (Walker et al. 2006). For instance, toxic and endocrine disrupting hydroxylated PCB metabolites (OH-PCBs) are formed by the oxidative metabolism of PCBs by cytochrome P450 (CYP P450) monooxygenase enzyme systems (Grimm et al. 2015). As the ultimate predator in Arctic food chains, polar bears are especially at risk of accumulating lipophilic compounds. Although recent temporal decreases in POP concentrations in polar bears from Svalbard have been reported (Bytingsvik et al. 2012a), a recent study has reported that the concentrations in polar bears are increasing on Greenland (Riget et al. 2016), presumably due to climate change related alterations in Arctic food web structures (Brown et al. 2018, McKinney et al. 2013). Other recent studies have indicated that the concentrations of PCBs in polar bears may be above toxic threshold levels for immune, reproductive and carcinogenic effects (Dietz et al. 2015), and possible effects of PCBs on the population level in polar bears have been discussed (Pavlova et al. 2016; Nuijten et al. 2016).

Analysis of blood clinical-chemical parameters (BCCPs) provides valuable information for evaluating the health and physiological status, as well as identifies target organs for toxicity in organisms (Castellanos et al. 2010; Firat and Kargin 2010). Blood clinical-chemical parameters have previously been applied as biomarkers showing that POP exposure may affect liver, kidney and bone metabolism in free-living wildlife (Sonne et al. 2010, 2012, 2013). Using BCCPs integrate changes in physiological status across organs-systems and tissue reflecting perturbations in biochemical pathways, cellular integrity and overall homeostasis (Klaassen 2013). Specifically, for polar bears the lipidome may be affected by POP exposure, as may the overall metabolome (Tartu et al. 2017a). Therefore, BCCPs related to cholesterol and triglyceride metabolism as well as liver, kidney and bone metabolism may be affected as an indication of changes in the overall metabolism, homeostasis and organ

functioning (Sonne 2010). The aim of this study was therefore to examine 1) how age, body condition, plasma lipid content, geographical location and body mass may confound the relationships between POPs and BCCPs in 20 female and 18 male Svalbard polar bears captured in spring 2007 and 2) based on this evaluate if any of the analysed BCCPs may be applied as potential biomarkers for POP exposure in polar bears.

Material and Methods

Field sampling

Field sampling procedures are described in details in Bytingsvik et al. (2012). Briefly, blood samples were collected from 38 polar bears (20 females and 18 males, all independent bears aged >3 years) captured at Spitsbergen and Edgeøya, Svalbard, Norway (76.7 – 79.8 °N, 11.8 – 21.3 °E) in March/April 2007. Sampling location, capture day (Julian day) and a selection of biometric data were recorded. Age was estimated by either counting annual growth layers in cementum of an extracted vestigial premolar tooth (Calvert and Ramsay 1998) or was known if a bear was first time captured as a cub. Capture and handling procedures followed standard protocols (Stirling et al. 1989; Derocher and Wiig, 2002), and were approved by the National Animal Research Authority (NARA), Norway. Blood was collected from the femoral vein. Within 8 h after sampling, the samples were separated into plasma and blood by centrifugation (3500 rpm, 10 min) and the BCCPs were analysed on the fresh whole blood or plasma samples. Further, plasma samples were stored at − 20 °C in the field and then at − 70 °C in the lab freezer until analysis of POPs.

Analyses of BCCPs

Previously it has been shown that variations in concentrations of several BCCPs, such as ALAT, GGT, alkaline phosphatase (ALKP), urea, cholesterol, lactate dehydrogenase, glucose, creatinine kinase may be linked to exposure of POPSs/OHCs in reptiles, birds, and mammals including humans) (Edqvist et al. 1992; Sonne et al. 2008a, 2010, 2013, Camacho et al. 2013; Singh and Chan 2018). In this study

the plasma samples were analysed for BCCPs, using a “dry” clinical-chemistry analyser with test-strip devices (Reflotron®, Boehringer-Mannheim, Mannheim, Germany). Prior to the analysis, the samples were kept at ca. 5 °C. The BCCPs subjected for analysis were two hematologic parameters (HCT, HB), four enzymes (ASAT, ALAT, GGT and CK), five metabolites (TG, CHOL, HDL, CREA, and UREA), and one mineral (K). Two or three parallels were analysed for each animal and for each parameter.

Hematocrit (HCT) is the volume fraction of erythrocytes in whole blood while hemoglobin (HB) is the iron-containing pigment of the erythrocytes being responsible for oxygen and CO_2 binding and transport so measurements of these may help finding anaemia, blood loss, or dehydration (D´Orazio and Meyerhoff, 2008; Kirk et al. 2010; Nuttal and Klee, 2001). Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) are enzymes widely distributed in animal tissues, and elevated blood levels are a nonspecific indicator of liver and kidney dysfunction with ALAT being the most liver-specific (Evans, 2009; Franson 1982; Marshall and Bangert, 2008; Panteghini and Bais, 2008). Gamma-glutamyl transferase (GGT) is an enzyme found in liver, kidney and pancreas and is used as a sensitive indicator for hepatobiliary diseases (Krefetz and McMillin, 2005; Marshall and Bangert, 2008). Creatine kinase (CK) is an enzyme with highest activity in muscle and brain and elevated levels of CK indicate either growth or high metabolism (muscle) or physical activity. CK may also help in diagnosis of central nervous system and thyroid gland diseases (Krefetz and McMillin, 2005; Panteghini and Bais, 2008). Creatinine (CREA) is synthesized in the muscle, mainly from the turnover of creatine, and is a marker of growth and metabolism (Newman and Price, 2001). Triglycerides (TG) and cholesterol (CHOL) are some of the major lipids in blood and physiological changes in these are related either to recent diet or to mobilization of lipid from fat to blood. However, it may e.g. also be an indicator of liver or intestinal disease (Burnett, 2010; Marshall and Bangert, 2008; Rifai et al. 2001; Van den Steen et al. 2010). High-density lipoprotein (HDL) is a complex mixture of lipoproteins inversely related to major adverse cardiovascular events in humans (Lüscher et al. 2014). The kidney secretes CREA while UREA is synthesized in the liver and these are indicators of glomerular function (Marshall and Bangert, 2008). Potassium (K) is the major intracellular cation in the body, with the

highest concentrations within the cells and is essential for many cellular functions as for instance nerve impulses and contractility of muscles (Heusel et al. 2001; Polancic, 2005).

Analysis of POPs

The POP analyses were performed at the Laboratory of Environmental Toxicology at the Norwegian School of Veterinary Science, Oslo, Norway. The multicomponent method used for extraction, determination of plasma lipid (%), clean-up and analysis of OC pesticides is described in detail in Bernhoft et al. (1997), analysis of PBDEs and HBCDs in Murvoll et al. (2006), and OH-PCBs and OH-BDE in Berg et al. (2010) and Løken (2006). For final detection and quantification a high-resolution gas chromatograph (Agilent 6890 Series, Agilent Technologies, Santa Clara, CA, USA) connected to a quadrupole mass spectrometer (MS) (Agilent 5973 Series) was used. The following compounds were subjected for analysis in the plasma samples: CB-28, -47, -52, -66, -74, 99, -101, -105, -114, -118, -123, -128, -137, -138, -141, -149, -151, -153, -156, -157, -167, 170, -180, -183, -187, -189, -194, -206, 4'-OH-CB106, 4-OH-CB107, 4'-OH-CB108, 3-OHCB118, 4'-OH-CB130, 3´-OH-CB138, 4-OH-CB146, 4´-OH-CB159, 4'-OH-CB172, 3'-OHCB180, 4-OH-CB187, BDE-28, -47, -99, -100, -153, -154, -183, -209, 4-OH-BDE42, 3-OHBDE47, 6-OH-BDE47, 4'-OH-BDE49, 2'-OH-BDE68, HBCD, TBBPA, HCB, oxychlordane, trans-chlordane, trans-nonachlor, cis-nonachlor, *o.p´*-DDT *p.p´*-DDT, *p.p´*-DDE, *o.p´*-DDD, *p.p´*-DDD, α-HCH, β-HCH, γ-HCH, and mirex. The Laboratory of Environmental Toxicology at the Norwegian School of Veterinary Science is accredited for determination of several POPs in biological matrices. The method is not accredited for determination of OH-metabolites, but it is validated the same way. To ensure adequate quality assurance and control, standard validation procedures were used for all the samples and for the quantification of all the POPs. The limit of detection (LOD) was determined threefold to the signal to noise level. To avoid missing values in the statistical analysis, the samples with concentration below the detection limit were replaced by random values between zero and the detection limit for the given compound. Compounds that were detected in less than 60 % of the plasma samples were excluded from the data analysis.

Statistical analysis

The POPs that were detected in the plasma sample of more than 60 % of the individuals, and thus statistically treated were: CB-47, -74, -99, -101, -105, -114, -118, -128, -137, -138, 153, -156, -157, -170, -180, -183, -187, -189, -194, -206, 4-OH-CB107, 3´-OH-CB138, 4OH-CB146, 4´-OH-CB159, 4-OH-CB187, BDE-47, HCB, oxychlordane, trans-nonachlor, *p.p´*-DDT, *p.p´*-DDE, α-HCH, β-HCH, and mirex. We used plasma POP concentrations in wet weight in the statistical analysis. In addition to this, capture location (latitude and longitude), age, biometric variables (body mass [BM], contour body length [CBL], straight body length [SBL], girth, head length, zygomatic width, body condition - body condition index [BCI]) calculated according to Cattet et al. (2002) and plasma lipid content were included.

Multivariate data analysis (principal component analysis [PCA] and orthogonal partial least squares [O-PLS] regression) were performed using the software Simca 14 (Umetrics, Umeå, Sweden). Correlation analysis and other tests were performed using the software STATISTICA version 13 (Statsoft Inc., Tulsa, OK, USA). First, we used PCA to explore interrelationships between individual POP, BCCPs and sex. Since there was a clear sex separation in the PC analysis, all statistical analyses were conducted separately for females and males. Shapiro-Wilk test was used to test if the data were normally distributed. Due to the fact that some of the variables were not normally distributed, a non-parametric Mann-Whitney U test was conducted to compare biological factors, capture variables and BCCPs and POPs between males and females. Orthogonal partial least squares (O-PLS) regression was then applied separately in the two sexes to find linear relationships between the single-Y (response variable, i.e. individual BCCPs) and the X-matrix (predictor variables, i.e. biological factors, capture variables and POPs). For each O-PLS model, a R^2X, R^2Y and a Q^2 value were calculated, where the R^2 – values show the goodness of fit (explained variation) for X- and Y-variables, respectively, and Q^2 shows the goodness of prediction (predicted variation). Further, the models were examined by regression coefficients (CoeffCS) and variable influence on projection (VIP) to investigate which X-

variables were most important in explaining the variation in Y. The original models were optimized by removing variables with VIP<0.5, which are considered of low importance, and further the variables were deleted one-by-one until the best significant model was achieved. If this was not achieved ($p>0.05$), the model was defined as non-significant. The significances of the models were tested by ANOVA based on comparison of cross-validated predictive residuals (CV-ANOVA, Eriksson et al. 2008). All variables were mean-centered and scaled to unit variance and in cased of skewed data, variables were $\log_{10}$-transformed. To assess the relationships (positive or negative) between the response variable and the predictor variables, the CoeffCS were ploted with jack-knife confidence intervals indicating the reliability of the estimated relationships in models. To additionally test the relationships found in the O-PLS model, Pearson product-moment correlation (Pearson correlation) was applied on $\log_{10}$-transformed variables to examine the correlations between the clinical-chemical parameter, contaminants, and the biometric variables separately for females and males. Finally, the possible use of the BCCPs as potential biomarkers of effects of POPs was tested by partial correlation, correcting for the appropriate confounding biological and/or geographical variable identified by the O-PLS. The level of significance was set to $p < 0.05$ for all tests. Bonferroni correction was not applied when comparing associations between multiple variables because of the increased probability of producing false negatives (Morgan, 2003) which is not desirable in ecotoxicological research due to the precautionary principle.

Results

BCCPs

Capture date (Julian day), capture location and biometrics in the female and male polar bears are shown in Table 1, whereas the results from the analyses of BCCPs in the two sexes are shown in Table 2. The average age of the males and females did not differ significantly, but not surprisingly, males were larger than females whereas the lipid blood content was higher in females (Table 1). Of the twelve analysed BCCPs, males had significantly higher HCT and significantly higher concentrations of ASAT, ALAT,

GGT and CREA than females, whereas females had significantly higher concentrations of CHOL than males (Table 2, all $p < 0.02$). No difference among male and females was found for the remaining six BCCPs (Table 2, all $p > 0.05$).

POP concentrations

The plasma concentrations of contaminants are listed in Table 3. Thirty-four compounds were detected in > 60% of the individuals (Table 3). In general, female polar bears had a higher plasma concentration of 10 PCB-congeners and 2 OH-PCBs, oxychlordane and mirex (Table 3, all $p < 0.05$). Despite that 10 out of 20 PCBs were higher in females than in males, the levels of ∑POPs did not differ significantly between females (176 ng/g ww) and males (131 ng/g ww). The contaminant profiles were in both sexes dominated by Σ_5OH-PCBs, followed by Σ_{20}PCBs and Σ_7OC pesticides. The dominating PCB-congeners in the plasma were CB-153, CB-180, CB-170, CB-194, CB-138 and CB-99. The dominating OH-PCBs were 4-OH-CB187, 4-OH-CB146, and 4-OH-CB107. Among the BFRs, only the PBDE congener BDE-47 was found in detectable levels in > 60% of the individuals. Of the OC pesticides and HCB, oxychlordane dominated the contaminant profile, while mirex and α-HCH was found in the lowest concentrations. The concentrations of POPs beside the PCBs decreased in the following order: chlordane > HCB > trans-nonachlor > *p,p′*-DDE > β-HCH > *p,p′*-DDT > mirex and α-HCH.

Biometrics, location, POPs and BCCPs in females

The PCA for polar bear females, including age, biometric variables, POPs and the BCCPs resulted in three significant principal components (eigenvalues > 1) as shown in Figure 1 and Table S1. These three PCs accounted for 61.2 % of the variation. In the PC1-PC2 loading plot (Figure 1A), most of the biometric variables and GGT, ASAT, ALAT, CK, HCT, HB, HDL, CREA and K are placed to the left along PC1 while latitude, capture date, lipid, age, TG, CHOL, UREA and most POPs (all except for CB-74, α-HCH, *p,p′*-DDE, trans-nonachlor and 4-OH-CB107) are placed to the right along PC1. Most biometric variables appear to have low PC2 values, whereas lipid content, CHOL, HDL and HCT have

high values for PC2. OH-PCB metabolites (4-OH-CB146, 4-OH-CB187 and 3'-OH-CB13) cluster opposite of latitudinal capture location along PC3 (Figure 1B). The dioxin-like mono-ortho PCBs (mo-CBs) appear to be clustered opposite of the size-related biometric variables and HCT.

With respect to O-PLS in females, significant models were achieved for HCT, CK, TG, CHOL and HDL (Table S1). The most significant relationships based on VIPs > 1 are visualised in grey in Figure 2. Several POPs were identified as significant predictors for these BCPPs. In general, high concentrations of certain chlorinated compounds predicted low HCT and low plasma concentrations of CK and TG (Figure 2A, B, D). In contrast, high levels of some chlorinated compounds (and BDE-47) were predictors for high concentrations of CHOL (Figure 2C). For HDL, the O-PLS model showed that 9 compounds were positively and 5 negatively associated to plasma HDL concentrations in the female polar bears. The relationships between the contaminants and the BCCPs indicated in the O-PLS models (Figure 2) were verified using Pearson correlation tests (Table S2). However, also the non-contaminant variables age, BCI, plasma lipid content, capture latitude and capture longitude were included as predictor variables in O-PLS models of the BCCPs. Age was included as a negative predictor in all five significant O-PLS models, i.e. for HCT, CK, CHOL, TG and HDL (Figure 2). Plasma lipid content was included as a positive predictor for CHOL and HDL, whereas BCI was a negative predictor for CK. Latitude was a positive predictor and longitude was a negative predictor for TG, indicating that the TG concentrations increased as the sampling position moved in a north-western direction.

Due to the possible confounding effects of age, plasma lipid content, BCI, latitude and longitude on the BCCPs, partial correlation tests correcting for the appropriate confounding factor(s) were performed using the data on the contaminant predictor variables identified for each of the significant BCCP O-PLS models. Following correction for age, the following compounds with VIP>1 in the O-PLS model were still negatively correlated with HCT: 4'-OH-CB-159, CB-206, CB-194, CB-180 and CB-170 (Table S4, $p<0.024$). When correcting for age and lipids, the following compounds with VIP>1 were still positively correlated with HDL: CB-74, trans-nonachlor, α-HCH, 4-OH-CB-107 and

p,p'-DDE (Table S4, $p<0.03$) and HDL were still negatively correlated with CB-170, CB-153, CB-194 and CB-206 (Table S4, $p<0.001$). In contrast, when correcting CK for age and BCI, none of the contaminants in the O-PLS model correlated with CK, indicating that CK was mainly affected by age and BCI and not the contaminants. Similarly, when correcting for age, latitude and longitude, none of the contaminants in the respective O-PLS model correlated with TG indicating that TG were not affected by the contaminants. Thus, following correction for confounding biological or geographical variables, in the female polar bears only HCT and HDL appeared to be affected by contaminants.

Biometrics, location, POPs and BCCPs in males

The PCA for polar bear males, including age, biometric variables, POPs and the BCCPs resulted in three significant principal components (eigenvalue > 1) as shown in Figure 3 and Table S3. These three PCs accounted for 61.4 % of the variation. In the PC1-PC2 loading plot (Figure 3A), all POPs are characterized by high PC1 loading values. The metabolites (e.g. 4-OH-CB-187, 4-OH-CB-107 and 4-OH-CB-146) and POPs (e.g. CB-74 and CB-105) that are easily biotransformed and excreted are characterized by high PC2 loading values and cluster together (e.g. 4-OH-CB-187, 4-OH-CB-107 and 4-OH-CB-146). The biometric variables have low PC1 and high PC2 values, and all BCCPs except cholesterol, HDL, TG and UREA, have low values along PC1 and PC2, whereas latitude, capture date and lipid content are placed to the right along PC1. It should also be noted that the biometric variables have low PC3 values (Figure 3B). Some of the dioxin-like mo-CBs were positioned opposite of the biomarkers on the PCA plot, indicating negative relationships. With respect to O-PLS, in males significant models were obtained for HCT, HB, GGT, ASAT, TG, CHOL and CREA (Figure 4, Table S3). The most significant relationships based on VIPs > 1 are visualised in grey in Figure 4. Various compounds were generally modelled to have a negative impact on HCT, HB, ASAT and CREA (Figure 4 A,B,C,G), and a positive effect on CHOL (Figure 4F). Moreover, age was included in O-PLS models as a positive predictor for HCT, HB, GGT, CREA and a negative predictor for CHOL. BM and BCI were positively associated with HB and negatively with TG and CHOL (Figure 4). Plasma lipid content

was included as a positive predictor for CHOL and HDL. Finally, longitude was a positive predictor for ASAT, GGT and CREA, indicating that these BCCP concentrations increased as the sampling position moved in a north-western direction (Figure 4).

The correlations between the contaminants included in the O-PLS models and the BCCPs are shown in Table S3. Nevertheless, as in the females, also non-contaminant variables were included as predictor variables in the model. Age was included as a predictor for the variation in HCT, HB, GGT, CHOL and CREA. BM was included as a predictor for HB, TG and CHOL, BCI for HB, TG and CHOL, longitude for ASAT, GGT and CREA, and plasma lipid content for TG and CHOL. Following correction for age, the following compounds with VIP>1 were still negatively correlated with HCT (ordered according to decreasing p-values): mono-ortho CB-156, -153, β-HCH, CB-99, -183, -180, -138, -187, -137, oxychlordane and CB-47 (Table S5, $p<0.042$), indicating that these contaminants were predictors for low HCT values in the male polar bears. When correcting for longitude (for ASAT), only mono-ortho CB-114 remained negatively correlated with this BCCP (Table S5, $p=0.001$). For GGT, correction for age and longitude resulted in remaining negative correlations between GGT and 4-OH-CB-146, HCB and CB-47 (Table S5, $p<0.048$). For CHOL four non-contaminant variables were included as predictors in the O-PLS model (lipid content, age, BM and BCI), and following correction by partial correlation for these, 4'-OH-CB-159 and CB-194 were the only contaminants that correlated (positively) with CHOL (Table S5, $p=0.023$). In contrast, following correction for the appropriate non-contaminant variables in the models, there were no relationships between HB, TG and CREA and any of the contaminants included in their respective models. Thus, following correction for confounding biological or geographical variables, in the male polar bears only HCT, ASAT, GGT and CHOL appeared to be affected by contaminants.

Overall relationships between POPs and BCCPs in males and females

Since one of the aims of the study was to investigate if any of the BCCPs can be used as biomarkers of effects or responses to POPs exposure, the BCCPs identified to correlate with contaminants in the two

sexes following correction for the appropriate confounding biological and/or geographical variables were investigated further using sums of contaminants. Following correction for age in females, there were significant inverse relationships between HCT and ∑pesticides (r=-0.500, p=0.029), ∑PCBs (r=-0.479, p=0.038) and ∑POPs (r=-0.619, p=0.005). Following correction for age and lipids in females, there were significant inverse relationships between HDL and ∑pesticides, (r=-688, p=0.002), ∑PCBs (r=-0.781, p<0.001) and ∑POPs (r=-0.643, p=0.004). In males, there were also significant inverse relationships between HCT and ∑pesticides (r=-0.627, p=0.007), ∑PCBs (r=-0.628, p=0.007) and ∑POPs (r=-0.597, p=0.011) after correction for the identified confounding effect of age. Following correction for plasma lipid content, age, BM and BCI, there was a positive significant relationship between CHOL and ∑PCBs (r=0.568, p=0.034). Following correction for longitude, there were no correlations between ASAT and any of the three main contaminant groups. Furthermore, following correction for age and longitude, there were no significant relationships between GGT and any of the main contaminant groups in males. Altogether, this indicates that following correction for the identified confounding factors, HCT may be an appropriate biomarker for effects of ∑pesticides. Similar for HDL, it may be an appropriate biomarker for exposure to ∑pesticides, ∑PCB and ∑POP in both female and male polar bears while CHOL in males may be a suitable biomarker for ∑PCB exposure.

Discussion

In general, the BCCP levels in the present study were comparable to those reported for free-ranging polar bears by Tryland et al. (2002) and Knott et al. (2011). Moreover, the results clearly show that sex, age, biometrics and geographical location are important when evaluating BCCPs in Svalbard polar bears. This is not surprising, as BCCPs are known to be influenced by sex, age, condition, sampling time, diet, hydration, stress, parasite, disease and other biometric variables in mammals, including humans (Neale et al. 2005; Dawson and Bortolotti 1997; Sonne et al. 2010). It has previously been shown that sex, age, foraging a.o. ecological and biological factors confound the interpretation of the relationship between POP exposure, behaviour and physiological endpoints (Olsen et al. 2003, Tartu

et al. 2017b; van Beest et al. 2016). Age related differences in BCCPs have been documented in previous studies on polar bears from Svalbard (Tryland et al. 2002) and from Manitoba (Canada) by Lee et al. (1977). Tryland et al. (2006) also reported age differences in BCCPs for ringed seals in Svalbard.

In addition to BCCPs, oxychlordane, several PCB congeners and some of their metabolites, mirex and sums of the contaminant groups were higher in the female bears than in the males (Table 3). Higher oxychlordane concentration in females than in males (approx. three times, Mann-Whitney U Test, $p<0.001$) are in agreement with results of Norstrom et al. (1998) who also reported higher concentration of ∑chlordanes in fat of female polar bears (both solitary and with cubs) in comparison to males. This was explained either by sex differences in contaminants metabolism or high concentration of ∑PCBs in males which in consequence induces hepatic CYP2B enzymes and thereby increasing clearance of chlordanes. In our study, the hypothesis of metabolic differences is more plausible to explain the higher concentrations of POPs in females, since PCBs were also higher in females than in males (Table 3). This is in agreement with Polischuk et al. (2002), who found that ∑chlordanes declined by 67% during fasting in sub-adult and adult polar bear males (but remained constant for all females), indicating male-specific metabolism of ∑chlordanes. Further, Polischuk et al. (1995) reported elevated concentrations of ∑PCBs, ∑chlordanes and ∑chlorobenzens in adipose tissue of female polar bears from Hudson Bay during fasting progression. Solitary/pregnant females that gave birth in early fall, showed a twofold rise in organochlorine concentrations in adipose tissue the following winter during pregnancy and lactation, even though they transferred some of their burden to the cubs through milk (Polischuk et al. 1995). Bernhoft et al. 1997 found that adipose tissue of polar bears from Svalbard (Bernhoft et al. 1997) had significantly higher concentrations of ∑chlordanes in adult females than adult (app. 2.5 folds) and old males (app. 5 times). However, in contrast to our study ∑PCBs were also higher in adult males than in females (Bernhoft et al. 1997). Higher ∑chlordanes concentrations in female polar bears adipose tissue than in males were also reported in bears from Wrangle Island in the East Siberian Sea, North America, East-Greenland and Svalbard (Norstrom et

al. 1998). However, in the same report ∑PCBs concentrations were lower in females than in males. Thus, the higher blood ∑chlordanes concentrations in females than in males in our study may confirm sex specific metabolism of this class of compounds as previously suggested (Norstrom et al. 1998).

While findings on differences in ∑chlordanes concentrations in blood and adipose tissue between females and males seem to corroborate well between studies, higher concentration of ∑PCBs in females than in males, as found in our study, have been rarely reported. To date, only two studies reported slightly elevated concentrations of ΣPCB in females compared to males in blood of polar bears (Braathen et al. 2004, Knott et al. 2011). The reasons for this is unknown, but could be because these groups of POPs are released from adipose tissue into the blood to a larger degree in females compared to males due to the differences in time of fasting and mobilization of lipophilic contaminants from adipose to blood, and/or recent feeding in females. The other possible explanation of higher concentration of contaminants in females as compared to males could be explained by differing foraging behavior and sexual dimorphism, with males being significantly larger than females and known to prey on bearded seals while females predominantly prey on ringed seals (Galicia et al. 2016, McKinney et al. 2009). Bearded seals typically feed on benthos and are thus generally a less contaminated food source for polar bears than ringed seals in Svalbard (Bang et al. 2001).

HCT

HCT may be an indicative biomarker of POP exposure and related health effects in both sexes, also ASAT, GGT and CHOL may serve as biomarkers in males. These four BCCPs are all related to kidney and liver functions, anaemia and dehydration. The liver is responsible for the synthesis of hem-proteins that are required by haemoglobin and it therefore plays a major role in regulation of HCT values (Evans 2009; Marshall and Bangert 2008). The inverse relationships between these BCCPs and POPs may reflect that the haematological homeostasis is imbalanced due to biochemical changes in hepatocytes' metabolism. The results are consistent with findings by Neale et al. (2005) in harbour seals (*Phoca vitulina*) showing decreasing levels of HCT with increasing concentrations of PCBs, PBDEs, and DDE.

Similar results were also found in Sprague-Dawley rats exposed to mixtures of PCBs (Mayes et al. 1998) and in female rhesus monkeys (*Macaca mulatta*) exposed to Aroclor 1254 (Arnold et al. 1993). In addition, in epidemiological studies in humans, haematocrit values were lowest in the group with the highest serum PCB concentrations (Serdar et al. 2014). Exactly how such perturbations may influence the physiology of polar bears is unknown. However, it is likely to be co-factors for several subclinical effects that in the end may influence e.g. growth and reproductive performance when combined with other stressing factors (Sonne 2010; Jenssen et al. 2015). However, we cannot conclude that the observed inverse relationship between the POPs and HCT is a causal relationships. The relationship might be due the HCT affects the partitioning of POPs between the blood cells compartment and plasma. HCT measures the volume of red blood cells (RBC) compared to the total blood volume (red blood cells and plasma). Lipophilic organic compounds, such as POPs, penetrate the red blood cells by dissolving in the lipid bilayer membrane (Hinderling, 1997). Therefore, increase in HCT could potentially destabilize POPs equilibrium between plasma and RBC, leading to lower POPs concentrations in plasma.

CHOL and HDL

Since the liver plays an important role in lipid metabolism, the significant positive relationships between CHOL and two of the POPs following correction for lipid content, age, BM and BCI may indicate an effect of these compounds on the liver functions in male polar bears. Nevertheless, the possible effects of ∑PCBs on CHOL became non-significant after correcting for these confounding factors in the males. Furthermore, although a significant O-PLS model was identified for CHOL in females, lipid content and age were clearly confounding the effects of the POPs on CHOL. In males, 4'-OH-CB-159 and CB-194 were positively correlated with CHOL. Elevated plasma/blood concentrations of CHOL have been reported in rats (*Rattus norvegicus*), infant rhesus monkeys (*Macaca mulatta*) and cynomolgus monkeys (*Macaca fascicularis*) experimentally exposed to PCBs

(Arnold et al. 1999; Wade et al. 2002; Marshall and Bangert 2008) and in Norwegian raptor nestlings exposed to organohalogen contaminants (Sonne et al. 2012).

Few studies have focused on the relationship between HDL and POPs. In the present study, we found a negative effect from ∑POPs on HDL levels in female polar bears. Following correction for the confounding factors plasma lipid content and age, it was generally found that the insecticide compounds trans-nonachlor and α-HCH contributed to high concentrations of HDL, whereas higher-chlorinated PCBs contributed to low concentrations of HDL in the females. Previously, increased levels of HDL have been documented in blood of male Sprague Dawley rats feed diets containing OC pesticides similar to those found in the Svalbard polar bears (Ikegami et al. 1991). Lee et al. (2007) found a positive correlation between HDL and OC pesticides among the US human population similar to those found in the Svalbard polar bears. Also Aminov et al. (2013) reported a positive correlation between lipids and ∑PCBs and ∑pesticides in humans. These studies are in accordance with the present studies of polar bears where selected OCs seems to increase HDL. It is, however, also possible that the differing positive versus inverse correlations between the POPs and HDL simply reflect the ability of the compounds to associate with HDL. The high K_{ow}-values of the highly chlorinated PCBs may hinder them from being associated with HDL, whereas the lower K_{ow}-values of CB-74, the pesticides, 4-OH-CB-107 and p,p'-DDE may cause them to be more readily associated with HDL. If that is the case, the associations between the POPs and HDL is not caused by any toxic effects but by physico-chemical interactions.

ASAT and GGT

Exposure to contaminants may also lead to elevated or decreased levels of blood liver and kidney enzymes (ASAT, ALAT) which are sensitive indicators of liver injury (Klaassen 2013). However, in the present study, ASAT was not affected by the POPs in females and in the males, only CB-114 remained significantly negatively associated with ASAT after correcting for the confounding effect of longitudinal catching position. The general finding that ASAT in polar bears was not influenced by the

contaminants is, however, in contrast with previous studies on Greenland sledge dogs (*Canis familiaris*) and Wistar rats exposed to a POP cocktail and PCBs, respectively (Rao and Banerji 1990; Sonne et al. 2008a, 2008b). In the present study, longitude was identified as a confounding factor, and it is possible that differences in diet among bears in the western and eastern part of Svalbard will have affected this. Increased levels of GGT are linked to diseases of both kidney and liver as well as congestive heart failure, diabetes and pancreatitis (Thrall et al. 2004). Although no significant models or associations were identified in the females for GGT, in the present polar bear males, there were inverse associations among some OHCs and GGT. This is in accordance with the results reported by Arnold et al. (1999) who found negative correlations between GGT and PCB congeners in infant rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) monkeys.

Considerations

Polar bear physiological parameters can differ markedly on an annual and seasonal basis due to differences in reproduction status, sex and feeding (Cherry et al. 2009). For example, during breeding season in spring, most male bears are fasting as are some independendt adult females. On the other hand females with yearlings and short 2-years-old are feeding regularly, and females with new born cubs are just emerging form dens (Stirling, 2009). However, and despite these confounding factors, applying biomarkers as a cost-efficient tool to assess either exposure to chemicals or resultant effects has been the focus within ecotoxicological studies and risk assessment since the late 1980s (Hugget et al. 1992; Peakall 1992). Although reliable biomarkers of exposure such as hepatic CYP-P450 enzyme activity or gene expression have been applied, there are still relatively few cost-efficient predictive non-destructive/non-invasive biomarkers used in wildlife mammalian species. Since wildlife species such as polar bears are often protected, there is a need to identify cost-efficient predictive non-destructive biomarkers for assessing health related effects of exposure to anthropogenic pollutants.

The present study indicates that HCT may be a suitable non-destructive biomarker for effects of POP exposures in polar bears. In females, concentrations of HDL may also be a useful biomarker

related to effects of POPs with decreasing HDL levels increasing risk of metabolic syndrome (cardiovascular disease and diabetes) (Aminov et al. 2013; Lee et al. 2007; Rosenbaum et al. 2017). In males, it is possible that CHOL may be a suitable biomarker of health effects of ∑PCBs, although the confounding effects of plasma lipid content, age, BM and BCI should be corrected for. The identification of the multiple confounding factors may complicate the use of CHOL as a biomarker. Nevertheless, several studies have indicated positive associations between PCBs and HDL, and in humans, this has been linked to long-term metabolic syndrome (Aminov et al. 2013; Lee et al. 2007; Rosenbaum et al. 2017).

It should, however, be noted that some BCCPs may have been affected by the capturing of the animals. It has previously been shown that the drugs used to tranquilize the bears (zolazepam and tiletamin) increased levels of liver enzymes such as ASAT and GGT in dogs, although not to levels above reference values (de Mattos et al. 2009). Furthermore, the effects of one single intramuscular dose were low. The potential effects of the capture and immobilization procedure (stress, helicopter pursuit and anaesthetics) in brown bears (*Ursus arctos*) are discussed in Graesil et al. (2014), who pointed out that the variations caused by capture variation are an inherent challenge in studies involving free ranging animals. Furthermore, it is possible that HCT and HB values may be affected by splenic contractions caused by stress, as previously indicated in sheep (Borjesson et al. 2000). Nevertheless, in the present study, all bears were treated similarly in the field, and we assume that the reported values are comparable to those previously reported in the literature for bears captured with the same methodology (Graesil et al. 2014, Tryland et al. 2002). In addition to this, the present study includes a relatively low sample size and thus the outcome of the statistical modelling should be interpreted with caution. Future studies should aim at increasing the sample sizes. It would also be interesting to gain more insight into the BCCP and POP relationship of polar bears sampled in the autumn as their state of physiology differ from that of spring bears. This could add further to our understanding of bear health, metabolism and physiology (Tartu et al. 2017a).

Conclusions

Our analyses suggest that age, BCI, plasma lipid content, geographical location and BM were important predictors for many of the examined BCCPs (CK, TG, HB, CREA) in polar bears. However, following corrections for these confounding factors multiple POPs were still significantly correlated with blood HCT and HDL values in females, and with HCT, GGT, ASAT and CHOL in males. Neither the biometric nor the contaminant variables predicted the concentrations of examined predictor variables ALAT, UREA and K. We can therefore conclude that sex, age, biometric factors, plasma lipid content and geographical location are important variables to consider when studying BCCPs in polar bears. However, when correcting for these, there could also be POP related biological effects on liver and kidney BCCP values. This should be studied further to increase our understanding of the physiology of polar bears and to better understand the biological variation, POP exposure and health status of polar bears. The study also indicates that in particular HCT may be used as a simple and cost-efficient biomarker for exposure or effects of POPs in polar bears. Furthermore, the decreasing HDL concentrations with increasing POP concentrations in females and the increasing CHOL concentrations with increasing PCB concentrations in males may indicate responses to POP exposure and increased risk of vascular and metabolic syndrome.

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TABLES

Table 1. Mean ± standard deviation, median and range (min-max) of capture day, location as latitude and longitude, age, straight length, contour body length, axillary girth, head length, zygomatic width, weight, total body mass (BM), body condition index (BCI), and lipid content of polar bear captured in Svalbard, Norway, 2007.

	Females (n = 20)			**Males (n = 18)**		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
Capture day (1 - 365)	90.0 ± 4.41	99.0	85.0 – 99.0	90.0 ± 4.00	89.0	85.0 - 100
Latitude	78.1 ± 1.11	79.7	76.7 - 79.7	78.3 ± 1.09	78.3	76.9 - 79.8
Longitude	16.2 ± 2.52	21.1	12.0 - 21.1	16.7 ± 2.96	16.6	11.8 - 21.3
Age	10.2 ± 5.57	9.5	3 – 24	10.8 ± 3.75	10.5	4 – 16
Straight length (cm)***	195 ± 5.97	206	183 - 206	226 ± 12.8	226	203 - 252
Contour body length (cm)***	208 ± 7.47	209	196 - 223	242 ± 13.7	244	215 - 265
Axillary girth (cm)***	112 ± 8.92	113	99 - 129	152 ± 17.5	157	106 - 174
Head length (mm)***	336 ± 13.8	334	313 - 364	393 ± 20.1	396	350 - 424
Zygomatic width (mm)***	196 ± 10.2	197	173 - 211	248 ± 26.3	257	195 - 278
BM (kg)***	165 ± 30.7	158	123 - 223	378 ± 87.7	409	171 - 476
BCI[a], ***	-1.53 ± 0.73	-1.61	-2.72 – -0.11	0.10 ± 0.83	0.095	-1.89 – 1.46
Lipid (%) ***	1.54 ± 0.33	1.59	0.83 - 2.07	1.02 ± 0.35	0.99	0.62 - 1.98

[a]Body condition index (BCI) was estimated from the following equation:
BCI = (ln BM – 3.07 × ln straight length + 10.76) ÷ (0.17 + 0.009 × ln straight length) (Cattet et al. 2002).

***: Significant differences among males and females (Mann-Whitney U Test, $p < 0.001$).

Table 2. Mean ± standard deviation (SD), median, and range (min-max) of blood concentrations of hematocrit (HCT), hemoglobin (HB), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyltransferase (GGT), creatine kinase (CK), triglycerides (TG), cholesterol (CHOL), high-density lipoproteins (HDL), creatinine (CREA), urea, and potassium (K) in blood samples of polar bear sampled in Svalbard, Norway, 2007.

	Females (n = 20)			**Males (n = 18)**		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
HCT (%)*	43.1 ± 4.26	43.00	36.0 - 52.0	46.9 ± 5.24	47.3	34.0 - 56.0
HB (mmol/L)	8.59 ± 1.10	8.24	6.97 - 10.5	9.09 ± 1.26	8.82	6.37 - 11.4
ASAT (U/L)**	54.8 ± 15.7	53.3	34.2 - 101	93.5 ± 31.7	83.3	53.4 - 163
ALAT (U/L)**	19.8 ± 9.31	17.3	10.3 - 44.0	42.8 ± 17.3	37.1	16.2 - 88.4
GGT (U/L)**	55.0 ± 53.5	35.2	17.5 - 254	134 ± 128	76.1	13.1 - 509
CK (U/L)	126 ± 80.9	89.3	39.9 - 255	129 ± 70.0	114	62.0 - 377
TG (mmol/L)	1.09 ± 0.53	1.18	0.03 - 2.22	0.97 ± 0.39	0.94	0.07 - 1.64
CHOL (mmol/L)**	8.58 ± 1.31	8.89	5.96 - 10.8	6.61 ± 2.06	6.50	3.90 - 13.1
HDL (mmol/L)	1.05 ± 0.19	1.10	0.62 - 1.40	0.96 ± 0.21	1.01	0.55 - 1.30
CREA (µmol/L)**	105 ± 15.6	103	82.1 - 136	128 ± 27.0	132	86.8 - 183
UREA (mmol/L)	4.71 ± 2.82	4.17	0.42 - 11.5	4.57 ± 3.88	3.68	0.09 - 15.1
K (mmol/L)	4.01 ± 0.36	4.00	3.15 - 4.78	4.24 ± 0.30	4.21	3.68 - 4.83

*: Significant differences among males and females (Mann-Whitney U Test, $p < 0.05$).

**: Significant differences among males and females (Mann-Whitney U Test, $p < 0.01$).

Table 3. Mean ± standard deviation (SD), median, and range (min-max) of persistent organic pollutants in ng/g wet weight (ww) measured in blood samples of polar bears sampled in Svalbard, Norway, 2007.

	Female (n = 20)			Male (n = 18		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
PCB-47	0.20 ± 0.12	0.18	0.068 - 0.46	0.16 ± 0.13	0.13	0.032 - 0.55
PCB-74	0.073 ± 0.029	0.079	0.0030 - 0.12	0.078 ± 0.025	0.071	0.041 - 0.13
PCB-99*	3.5 ± 2.1	3.0	1.3 - 9.7	2.4 ± 2.4	1.7	0.59 - 12
PCB-101**	0.11 ± 0.10	0.081	0.059 - 0.52	0.071 ± 0.026	0.061	0.040 - 0.14
PCB-105mo	0.13 ± 0.052	0.13	0.054 - 0.25	0.11 ± 0.038	0.10	0.056 - 0.18
PCB-114mo*	0.019 ± 0.0076	0.018	0.0043 - 0.033	0.013 ± 0.0051	0.014	0.0032 - 0.020
PCB-118mo	0.38 ± 0.15	0.36	0.17 - 0.80	0.36 ± 0.15	0.32	0.17 - 0.74
PCB-128*	0.050 ± 0.023	0.049	0.0062 - 0.10	0.037 ± 0.034	0.031	0.00056 - 0.16
PCB-137**	0.37 ± 0.23	0.30	0.17 - 1.1	0.22 ± 0.20	0.16	0.050 - 0.96
PCB-138	3.4 ± 1.6	2.7	1.5 - 6.6	2.7 ± 1.9	2.2	0.60 - 8.8
PCB-153**	27 ± 27	16	7.7 - 104	15 ± 18	11	3.4 - 84
PCB-156mo*	0.91 ± 0.52	0.8	0.36 - 2.1	0.63 ± 0.47	0.49	0.25 - 2.3
PCB-157mo	0.81 ± 0.57	0.63	0.23 - 2.2	0.61 ± 0.42	0.52	0.27 - 2.1
PCB-170	6.6 ± 6.8	4.0	1.5 - 28	4.3 ± 3.6	2.9	1.5 - 18
PCB-180	16 ± 21	7.9	3.6 - 83	8.5 ± 8.4	5.5	2.1 - 40
PCB-183**	0.43 ± 0.30	0.32	0.16 - 1.5	0.26 ± 0.26	0.18	0.065 - 1.3
PCB-187	0.073 ± 0.031	0.066	0.024 - 0.14	0.059 ± 0.037	0.047	0.024 - 0.16
PCB-189mo	0.24 ± 0.17	0.18	0.060 - 0.64	0.18 ± 0.13	0.15	0.051 - 0.65
PCB-194*	5.9 ± 7.7	2.9	1.3 - 29	2.9 ± 2.8	2.3	0.93 - 14
PCB-206**	1.3 ± 1.8	0.59	0.30 - 6.3	0.52 ± 0.45	0.40	0.21 - 2.2
4-OH-CB107	9.5 ± 6.6	8.3	1.8 - 33	7.4 ± 3.0	6.8	2.2 - 13
3'-OH-CB138	1.3 ± 0.65	1.2	0.50 - 2.6	1.4 ± 0.68	1.3	0.61 - 3.2
4-OH-CB146**	34 ± 14	29	15 - 65	19 ± 9.1	20	7.0 - 40
4'-OH-CB159*	0.28 ± 0.16	0.28	0.052 - 0.72	0.16 ± 0.10	0.14	0.0048 - 0.33
4-OH-CB187	53 ± 19	56	16.9 - 89	59 ± 32	52	11 - 117
BDE-47	0.14 ± 0.068	0.13	0.037 - 0.31	0.12 ± 0.10	0.072	0.036 - 0.38
HCB	1.5 ± 0.89	1.3	0.40 - 3.8	1.4 ± 0.86	1.4	0.21 - 3.0
Oxychlordane***	7.3 ± 4.2	6.4	3.2 - 20	2.4 ± 2.3	1.6	0.51 - 10
trans-nonachlor	0.52 ± 0.25	0.58	0.037 - 1.0	0.49 ± 0.38	0.37	0.083 - 1.9
p.p'-DDT	0.11 ± 0.090	0.085	0.032 - 0.36	0.077 ± 0.060	0.05	0.0042 - 0.22
p.p'-DDE	0.41 ± 0.25	0.37	0.065 - 1.1	0.32 ± 0.21	0.25	0.12 - 1.0
α-HCH	0.035 ± 0.017	0.037	0.0010 - 0.072	0.036 ± 0.016	0.032	0.014 - 0.075
β-HCH	0.34 ± 0.20	0.33	0.12 - 0.90	0.32 ± 0.24	0.25	0.12 - 1.3
Mirex*	0.045 ± 0.029	0.04	0.0045 - 0.12	0.027 ± 0.015	0.029	0.0017 - 0.062
∑pesticides***	10.3 ± 4.92	9.5	5.01 – 25.4	5.07 ± 3.4	4.03	1.39 – 15.4
∑HCHs	0.377 ± 0.203	0.365	0.138 – 0.961	0.357 ± 0.253	0.286	0.147 – 1.29
∑CHLs***	7.84 ± 4.12	7.06	3.45 – 20.3	2.87 ± 2.42	1.99	0.64 – 10.7
∑DDTs*	0.522 ± 0.234	0.465	0.269 – 1.23	0.392 ± 0.229	0.346	0.163 – 1.12
∑poCBs*	64.3 ± 67	38.5	18.9 – 261	36.8 ± 38.4	27	10.5 – 181
∑moCBs	2.5 ± 1.29	2.08	0.987 – 5.29	1.9 ± 1.04	1.66	1 – 5.49
∑PCBs*	66.8 ± 67.9	40.4	19.9 – 266	38.7 ± 39.4	28.7	11.5 – 187
∑OH-CBs	98.5 ± 35.8	103	35.2 – 189	86.9 ± 43.4	82.8	22.9 – 161
∑POPs	176 ± 75.7	164	95.5 – 398	131 ± 64	134	35.9 – 285

∑OH-CBs/∑PCB	2.38 ± 1.43	2.08	0.145 – 5.14	3.02 ± 1.77	2.72	0.446 – 6.99

*: Significant differences among males and females (Mann-Whitney U Test, $p < 0.05$).
**: Significant differences among males and females (Mann-Whitney U Test, $p < 0.01$).
***: Significant differences among males and females (Mann-Whitney U Test, $p < 0.001$).

FIGURE LEGENDS

Figure 1. Principal component analysis (PCA; PC1 vs. PC2 and PC1 vs. PC3) loading plots including biometric variables, BCCPs and persistent organic pollutants (POPs) in blood samples from polar bear females (n = 20) sampled in Svalbard, Norway, 2007.

Figure 2. Orthogonal partial least squares (O-PLS) regression coefficient plot showing the relationship between hematocrit (HCT), hemoglobin (HB), γ-glutamyltransferase (GGT), creatine kinase (CK) triglycerides (TG), cholesterol (CHOL), high-density lipoproteins (HDL) (Y-variables) and persistent organic pollutants (POPs) and biometric variables (X-variables) in polar bear females (n = 20) sampled in Svalbard, Norway, 2007. All variables are depictured with default jack-knife confidence interval. Closed columns represent variables with VIP (variable influence in projection) values >1.

Figure 3. Principal component analysis (PCA; PC1 vs. PC2 and PC1 vs. PC3) loading plots including biometric variables, BCCPs and persistent organic pollutants (POPs) in blood samples from polar bear males (n = 18) sampled in Svalbard, Norway, 2007.

Figure 4. Orthogonal partial least squares (O-PLS) regression coefficient plot showing the relationship between hematocrit (HCT), hemoglobin (HB), aspartate aminotransferase (ASAT), γ-glutamyltransferase (GGT), triglycerides (TG), cholesterol (CHOL), high-density lipoproteins (HDL), creatinine (CREA) (Y-variables) and persistent organic pollutants (POPs) and biometric variables (X-variables) in polar bear males (n = 18) sampled in Svalbard, Norway, 2007. All variables are depictured with default jack-knife confidence interval. Closed columns represent variables with VIP (variable influence in projection) values >1.

FIGURES

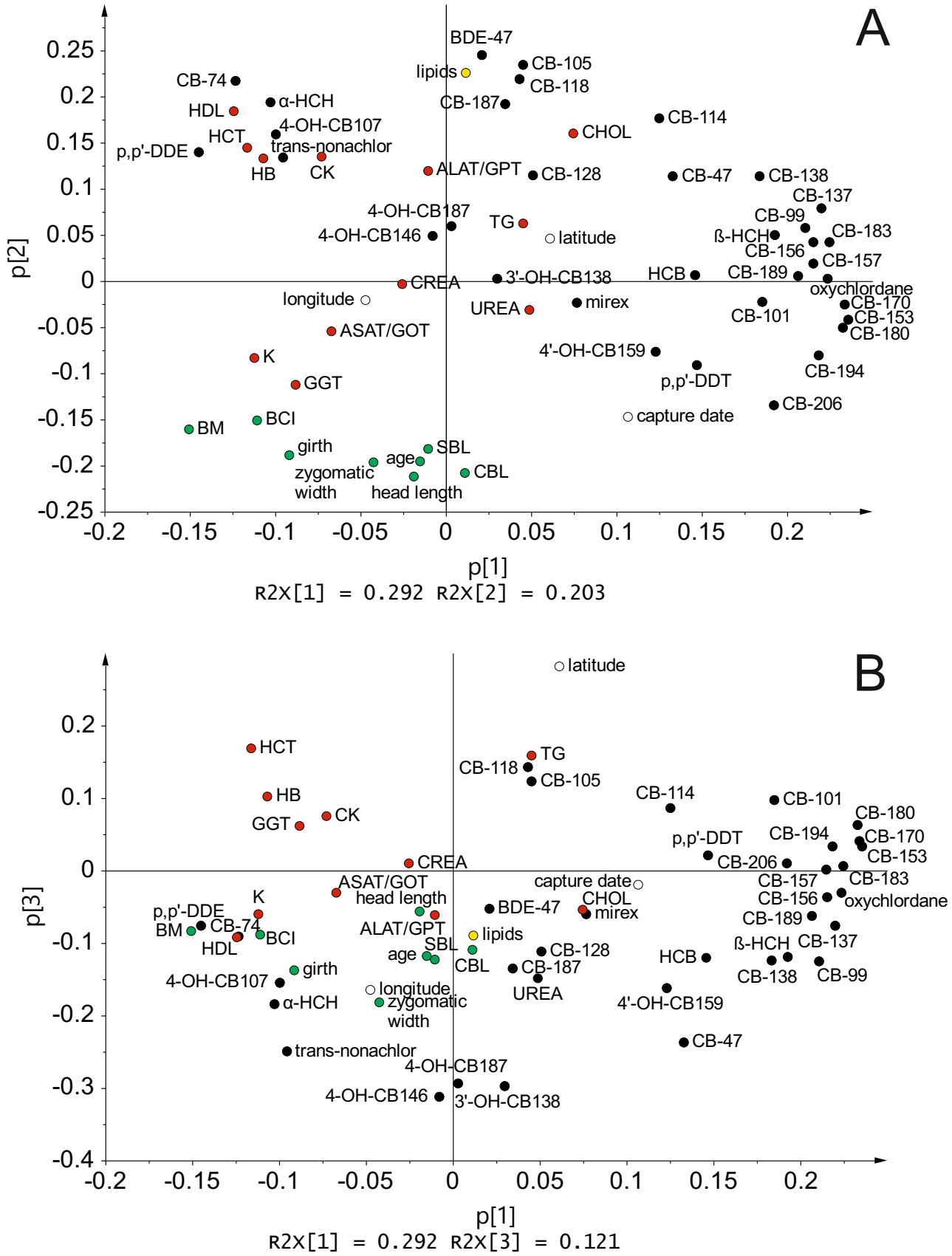
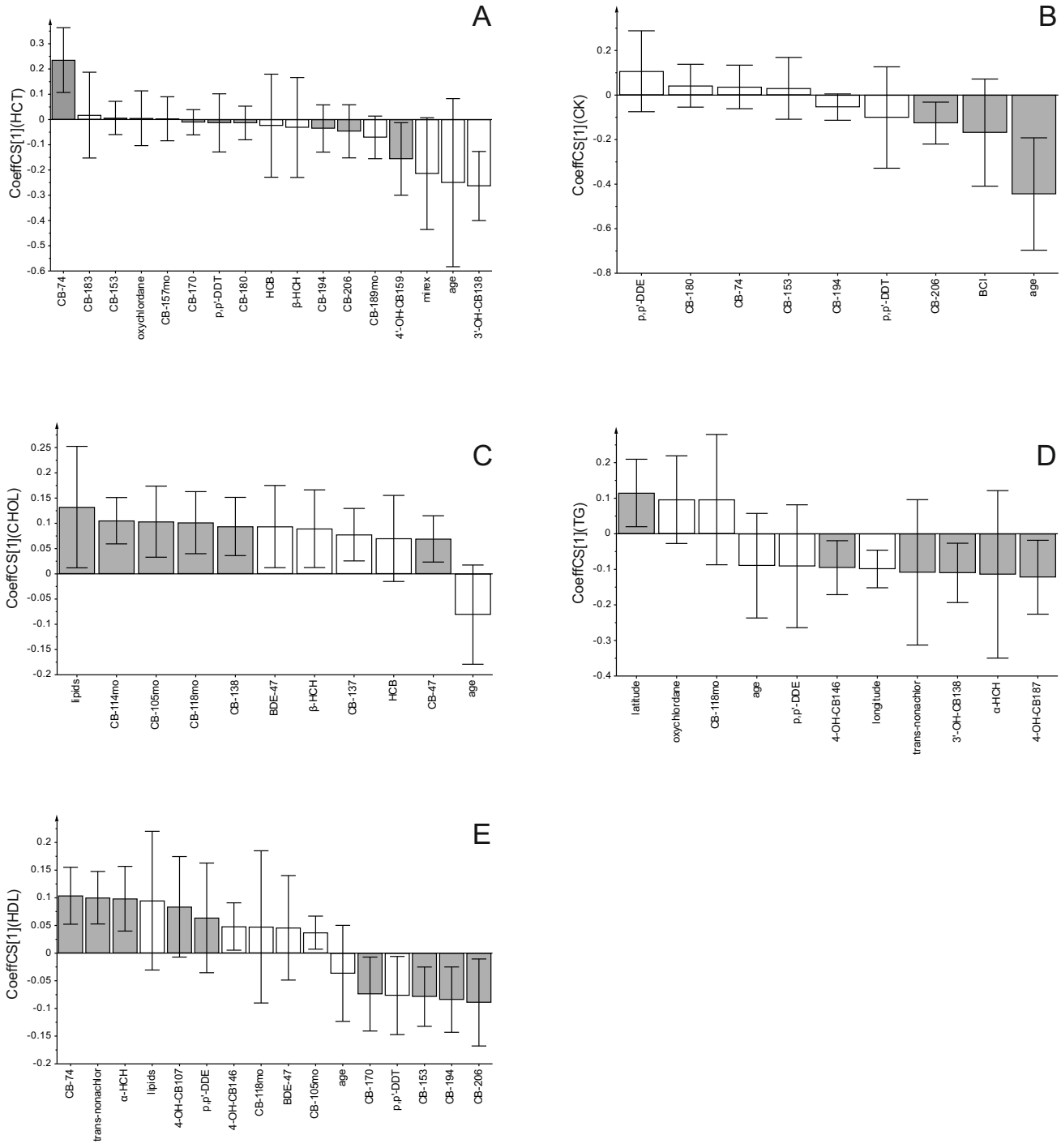


FIGURE 1


A
CoeffCS[1](HCT)
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CB-183
CB-153
oxychlordane
CB-157mo
CB-170
p,p'-DDT
CB-180
HCB
β-HCH
CB-194
CB-206
CB-189mo
4'-OH-CB159
mirex
age
3'-OH-CB138
B
CoeffCS[1](CK)
p,p'-DDE
CB-180
CB-74
CB-153
CB-194
p,p'-DDT
CB-206
BCI
age
C
CoeffCS[1](CHOL)
lipids
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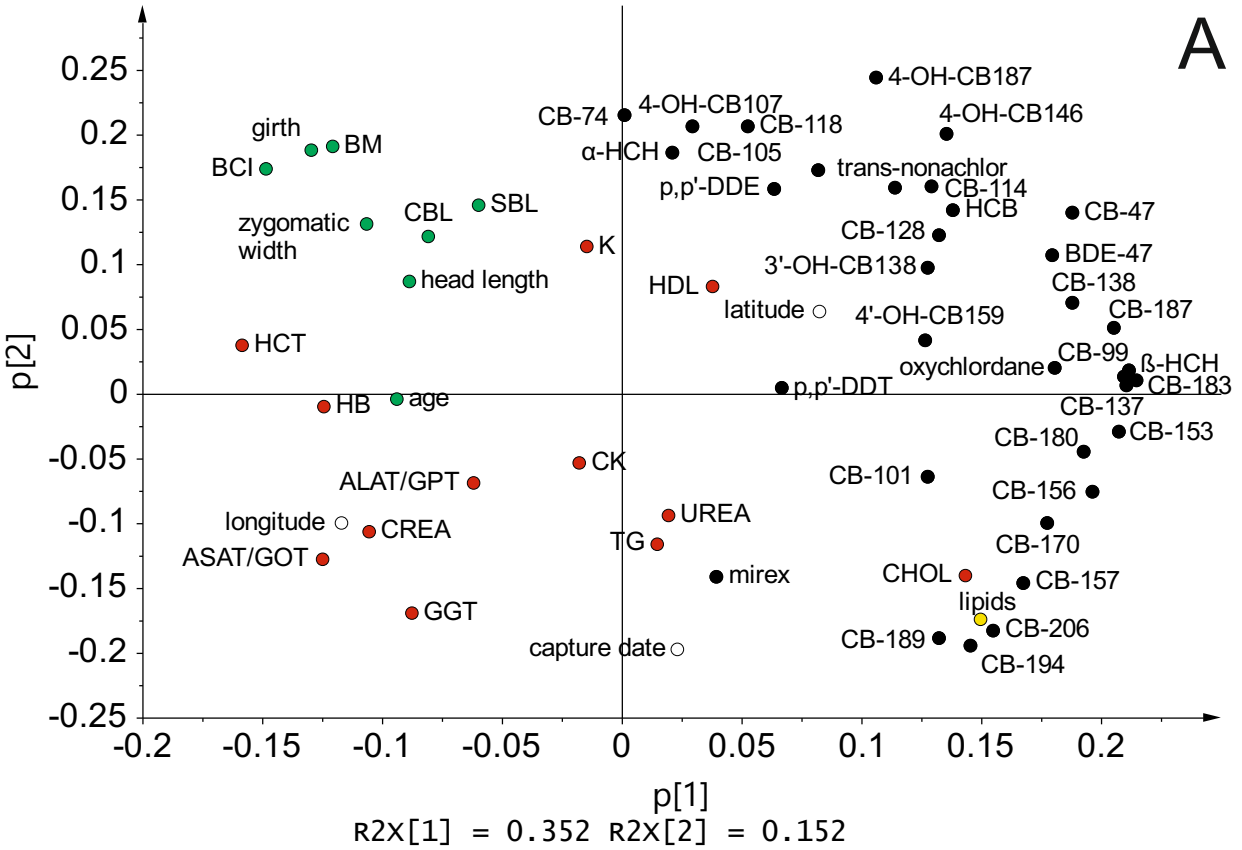
CB-105mo
CB-118mo
CB-138
BDE-47
β-HCH
CB-137
HCB
CB-47
age
D
CoeffCS[1](TG)
latitude
oxychlordane
CB-118mo
age
p,p'-DDE
4-OH-CB146
longitude
trans-nonachlor
3'-OH-CB138
α-HCH
4-OH-CB187
E
CoeffCS[1](HDL)
CB-74
trans-nonachlor
α-HCH
lipids
4-OH-CB107
p,p'-DDE
4-OH-CB146
CB-118mo
BDE-47
CB-105mo
age
CB-170
p,p'-DDT
CB-153
CB-194
CB-206

FIGURE 2


A
p[2]
p[1]
R2X[1] = 0.352 R2X[2] = 0.152
girth
BM
BCI
zygomatic width
CBL
SBL
head length
HCT
HB
age
ALAT/GPT
longitude
CREA
ASAT/GOT
GGT
CK
K
HDL
latitude
TG
UREA
mirex
capture date
CB-74
4-OH-CB107
CB-118
α-HCH
CB-105
p,p'-DDE
4-OH-CB187
4-OH-CB146
trans-nonachlor
CB-114
HCB
CB-47
CB-128
BDE-47
3'-OH-CB138
CB-138
4'-OH-CB159
CB-187
CB-99
oxychlordane
ß-HCH
p,p'-DDT
CB-183
CB-137
CB-180
CB-153
CB-101
CB-156
CB-170
CHOL
CB-157
lipids
CB-189
CB-206
CB-194

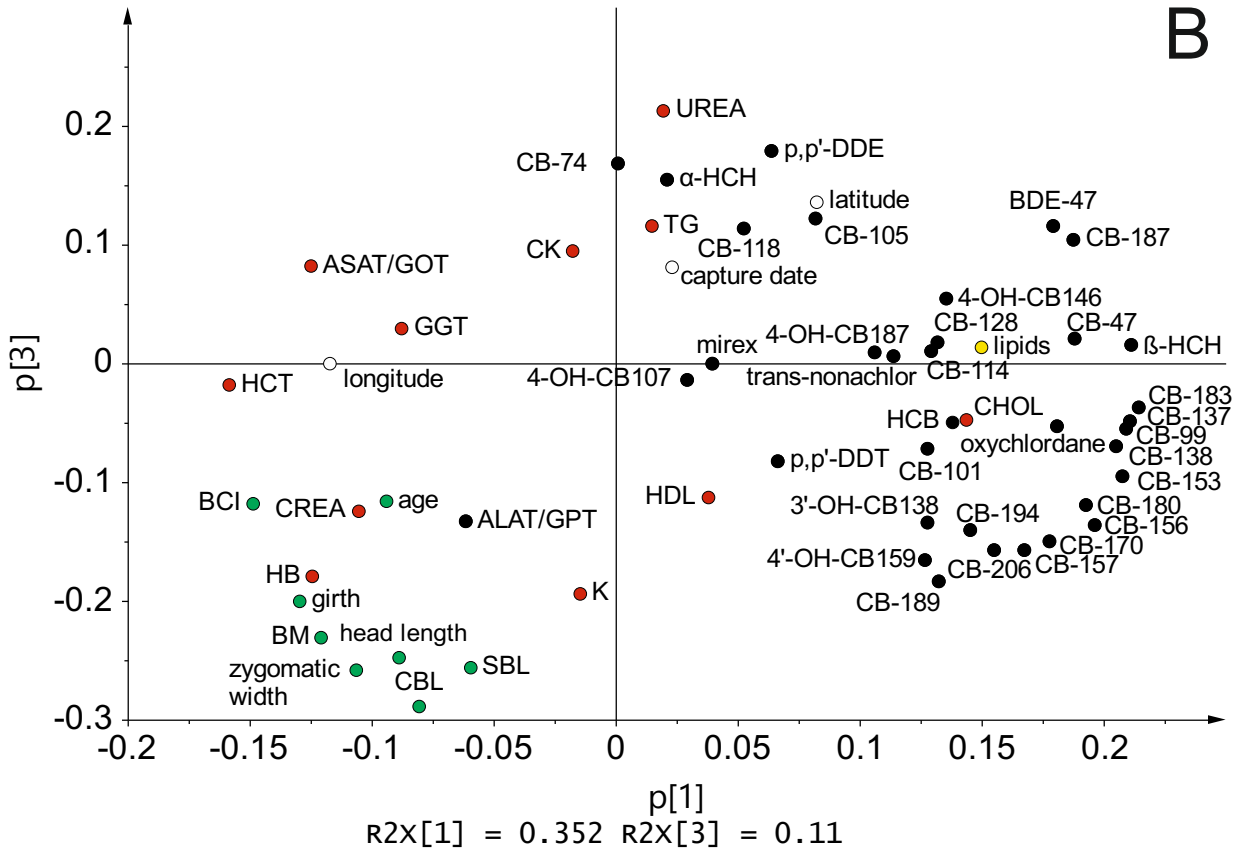

B
p[3]
p[1]
R2X[1] = 0.352 R2X[3] = 0.11
UREA
p,p'-DDE
CB-74
α-HCH
latitude
BDE-47
TG
CB-105
CB-187
CK
CB-118
ASAT/GOT
capture date
4-OH-CB146
GGT
CB-128
CB-47
mirex
4-OH-CB187
lipids
ß-HCH
HCT
longitude
4-OH-CB107
trans-nonachlor
CB-114
CB-183
HCB
CHOL
CB-137
oxychlordane
CB-99
p,p'-DDT
CB-101
CB-138
CB-153
BCI
CREA
age
HDL
3'-OH-CB138
CB-194
CB-180
ALAT/GPT
CB-156
CB-170
4'-OH-CB159
CB-206
CB-157
HB
girth
K
CB-189
BM
head length
zygomatic width
CBL
SBL

FIGURE 3

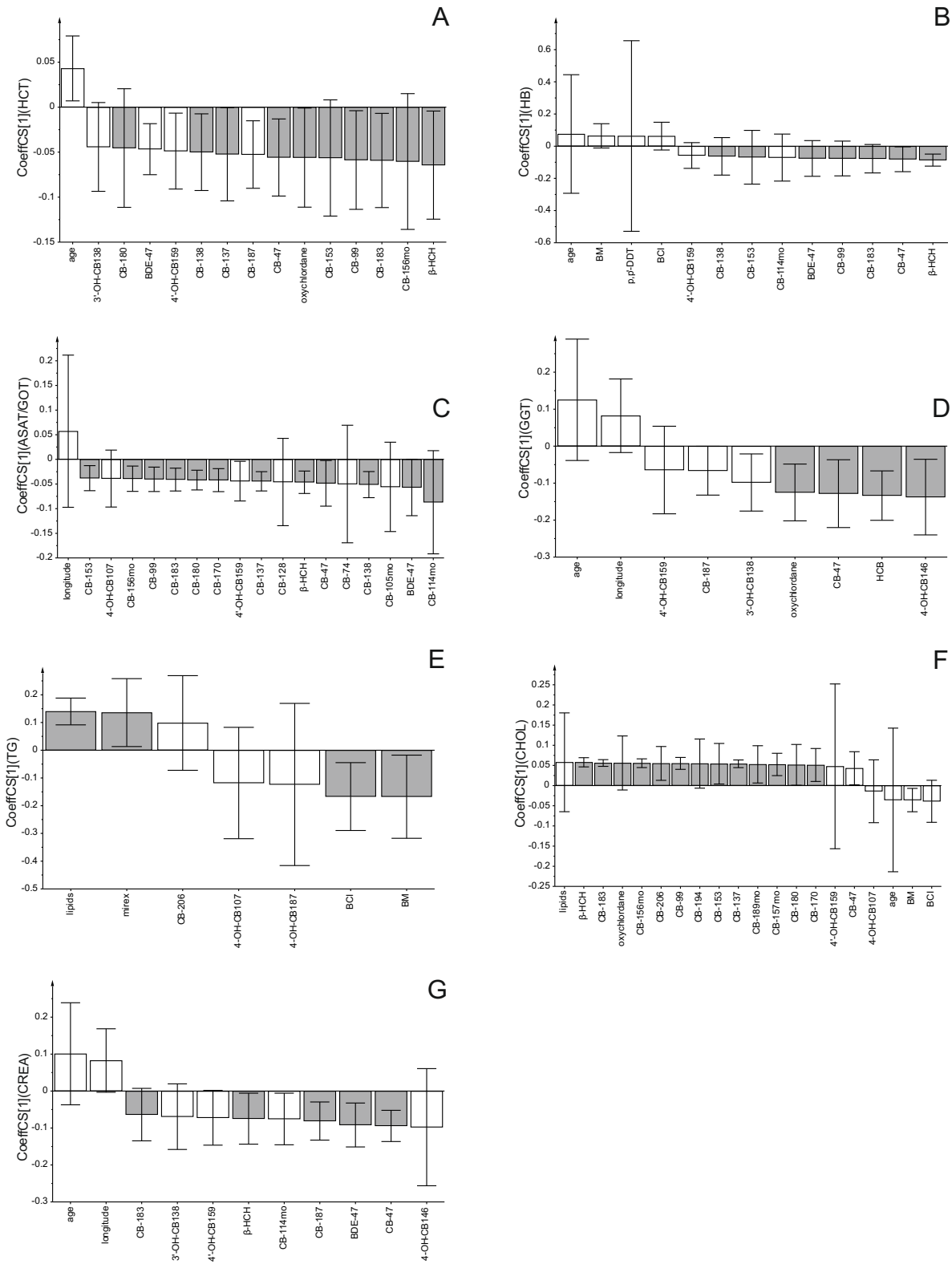

A
CoeffCS[1](HCT)
age
3'-OH-CB138
CB-180
BDE-47
4'-OH-CB159
CB-138
CB-137
CB-187
CB-47
oxychlordane
CB-153
CB-99
CB-183
CB-156mo
β-HCH
B
CoeffCS[1](HB)
age
BM
p,p'-DDT
BCI
4'-OH-CB159
CB-138
CB-153
CB-114mo
BDE-47
CB-99
CB-183
CB-47
β-HCH
C
CoeffCS[1](ASAT/GOT)
longitude
CB-153
4-OH-CB107
CB-156mo
CB-99
CB-183
CB-180
CB-170
4'-OH-CB159
CB-137
CB-128
β-HCH
CB-47
CB-74
CB-138
CB-105mo
BDE-47
CB-114mo
D
CoeffCS[1](GGT)
age
longitude
4'-OH-CB159
CB-187
3'-OH-CB138
oxychlordane
CB-47
HCB
4-OH-CB146
E
CoeffCS[1](TG)
lipids
mirex
CB-206
4-OH-CB107
4-OH-CB187
BCI
BM
F
CoeffCS[1](CHOL)
lipids
β-HCH
CB-183
oxychlordane
CB-156mo
CB-206
CB-99
CB-194
CB-153
CB-137
CB-189mo
CB-157mo
CB-180
CB-170
4'-OH-CB159
CB-47
4-OH-CB107
age
BM
BCI
G
CoeffCS[1](CREA)
age
longitude
CB-183
3'-OH-CB138
4'-OH-CB159
β-HCH
CB-114mo
CB-187
BDE-47
CB-47
4-OH-CB146

FIGURE 4

SUPPLEMENTARY INFORMATION

Table S1. Parameters for PCA and O-PLS models; number of significant components, cumulative (cum) goodness of fit (R^2X and R^2Y), goodness of prediction (Q^2), and cross-validation procedure (CV-ANOVA) p-value in the orthogonal-partial least-square (O-PLS) models with the BCCPs as Y-variables and POPs, biometric variables, age, capture location and lipid content as X-variables in plasma samples of polar bear sampled in Svalbard, Norway, 2007. P1 and O1 represent predictive and orthogonal component in 1+1+0 models.

	Component		**R^2X(cum)**	**R^2(cum)**	**Q^2(cum)**	**p-value (CV-ANOVA)**
Females (n=20)						
	PCA	3	0.617		0.287	
HCT	OPLS	1+1+0	0.706 P1=0.316 O1=0.396	0.694	0.523	0.019
CK	OPLS	1+1+0	0.804 P1=0.333 O1=0.47	0.538	0.462	0.043
CHOL	OPLS	1+0+0	0.52	0.54	0.473	0.004
TG	OPLS	1+0+0	0.378	0.473	0.313	0.041
HDL	OPLS	1+0+0	0.476	0.684	0.612	0.0003
Males (n=18)						
	PCA	3	0.614		0.216	
HCT	OPLS	1+0+0	0.732	0.461	0.331	0.049
HB	OPLS	1+0+0	0.6	0.475	0.391	0.024
ASAT	OPLS	1+0+0	0.572	0.398	0.37	0.031
GGT	OPLS	1+0+0	0.597	0.569	0.441	0.013
TG	OPLS	1+0+0	0.551	0.496	0.412	0.019
CHOL	OPLS	1+0+0	0.731	0.725	0.721	0.00007
CREA	OPLS	1+0+0	0.567	0.454	0.387	0.025

Table S2. Statistically significant ($p<0.05$) Pearson correlations coefficients (p value given in parenthesis) of BCCPs and contaminants, biometrics and geographical parameters (log_{10} transformed) in female polar bears (n = 20).

Variable	ALAT/GPT	ASAT/GOT	CHOL	CK	GGT	HB	HCT	HDL	K	UREA
Capture date						-0.57 (0.009)	-0.517 (0.02)	-0.724 (0.0003)		
Age				-0.72 (0.0003)	0.513 (0.021)	-0.479 (0.033)	-0.522 (0.018)			
CBL				-0.465 (0.039)		-0.522 (0.018)	-0.464 (0.039)			
SBL							-0.487 (0.029)			
Head length							-0.468 (0.038)	-0.545 (0.013)		
Zygomatic width				-0.517 (0.02)		-0.515 (0.02)	-0.568 (0.009)			
BM					0.475 (0.035)				0.511 (0.021)	
Lipid			0.741 (0.0002)					0.72 (0.001)		
a-HCH								0.728 (0.0003)		
ß-HCH			0.452 (0.045)							
Trans-nonachlor								0.741 (0.0002)		
Mirex										0.494 (0.027)
p,p'-DDE	0.496 (0.026)			0.471 (0.036)				0.472 (0.036)		
p,p'-DDT								-0.567 (0.009)		
CB-74							0.495 (0.027)	0.768 (0.00008)		
CB-99		-0.469 (0.037)			-0.452 (0.046)					
CB-101								-0.672 (0.001)		
CB-105mo			0.511 (0.021)						-0.525 (0.018)	
CB-114mo			0.514 (0.02)						-0.698 (0.001)	
CB-118mo			0.521 (0.018)						-0.548 (0.012)	
CB-128								0.54 (0.023)		
CB-137			0.459 (0.042)		-0.541 (0.014)					
CB-138		-0.469 (0.037)	0.517 (0.02)		-0.489 (0.029)					
CB-153						-0.468 (0.037)	-0.458 (0.042)	-0.583 (0.007)		
CB-170							-0.461 (0.041)	-0.548 (0.012)		
CB-180						-0.452 (0.045)	-0.475 (0.034)	-0.626 (0.003)		
CB-183					-0.496 (0.026)	-0.468 (0.038)		-0.477 (0.033)	-0.558 (0.011)	
CB-187										
CB-189mo							-0.489 (0.029)			
CB-194				-0.445 (0.049)		-0.50 (0.025)	-0.548 (0.012)	-0.623 (0.003)		
CB-206				-0.554 (0.011)		-0.558 (0.01)	-0.64 (0.005)	-0.66 (0.002)		
4-OH-CB107								0.62 (0.004)		
3'-OH-CB138							-0.465 (0.039)			
4'-OH-CB159						-0.46 (0.041)	-0.581 (0.007)			
BDE-47			0.477 (0.034)		-0.621 (0.004)					

Table S3. Statistically significant ($p<0.05$) Pearson correlations coefficients (p value given in parenthesis) of BCCPs and contaminants, biometrics and geographical parameters (log_{10} transformed) in male polar bears (n = 18).

Variable	ALAT/GPT	ASAT/GOT	CHOL	CREA	GGT	HB	HCT	HDL	K	TG	UREA
Capture date								-0.70 (0.007)			
Longitude		0.53 (0.023)		0.50 (0.035)							
Age	0.52 (0.027		-0.50 (0.035)	0.68 (0.002)	0.65 (0.004)	0.55 (0.018)					
SBL											
Axial girth			-0.50 (0.029)			0.53 (0.025)			0.47 (0.048)	-0.53 (0.024)	
Head length						0.52 (0.027)					-0.56 (0.015)
Zygomatic width						0.49 (0.038)					
BM			-0.47 (0.048)			0.50 (0.035)			0.50 (0.039)		
TBM			-0.47 (0.048)			0.50 (0.035)			0.50 (0.039)		
BCI			-0.48 (0.043)			0.49 (0.038)			0.52 (0.034)		
Lipid			0.82 (0.00003)								
HCB					-0.69 (0.001)						
ß-HCH		-0.59 (0.01)	0.69 (0.001)	-0.56 (0.018)	-0.48 (0.042)	-0.66 (0.003)	-0.72 (0.001)				
Oxychlordane			0.56 (0.016)		-0.65 (0.004)		-0.63 (0.005)				
CB-47		-0.48 (0.043)		-0.58 (0.011)	-0.67 (0.003)	-0.50 (0.035)	-0.70 (0.007)				
CB-74											
CB-99		-0.51 (0.029)	0.60 (0.009)			-0.49 (0.04)	-0.67 (0.003)				
CB-105mo		-0.55 (0.017)									
CB-114 mo		-0.78 (0.0001)									
CB-137		-0.52 (0.027)	0.57 (0.013)				-0.60 (0.009)				
CB-138		-0.53 (0.023)					-0.57 (0.014)				
CB-153		0.022 (-0.54)	0.68 (0.007)				-0.65 (0.003)				
CB-156 mo			0.72 (0.001)				-0.69 (0.001)				
CB-157 mo			0.65 (0.003)				-0.52 (0.026)				
CB-170			0.60 (0.009)				-0.53 (0.034)				
CB-180		-0.52 (0.027)	0.54 (0.02)				-0.54 (0.022				
CB-183		-0.52 (0.029)	0.61 (0.007)			-0.48 (0.044)	-0.67 (0.002)				
CB-187				0.55 (0.033)			-0.58 (0.011)				
CB-189 mo			0.66 (0.003)								
CB-194			0.71 (0.001)				-0.48 (0.045)				
CB-206			0.74 (0.0004)				-0.52 (0.026)				
3'-OH-CB138					-0.59 (0.031)		-0.47 (0.046)				
4-OH-CB146				-0.55 (0.019)	-0.71 (0.001)						
4'-OH-CB159		-0.55 (0.019)	0.64 (0.004)				-0.52 (0.026)				
4-OH-CB187					-0.70 (0.007)						
BDE-47		-0.62 (0.006)		-0.60 (0.009)		-0.57 (0.013)	-0.51 (0.029)				

Table S4. Statistically significant correlations coefficients (r, p) from the partial regression analyses of HCT, HDL and POPs in females when correcting for age (n = 20).

	Controlling	Contaminants
HCT	age	4'-OH-CB159 (-0.59, 0.008), mirex (-0.59, 0.008), CB-170 (-0.56, 0.013), CB-189mo (-0.56, 0.013), 3'-OH-CB138 (-0.54, 0.017), CB-183 (-0.54, 0.017), CB-194 (-0.53, 0.019), CB-180 (-0.53, 0.021), CB-153 (-0.52, 0.022), CB-206 (-0.52, 0.024), oxychlordane (-0.5, 0.029), ß-HCH (-0.49, 0.032), CB-157mo (-0.49, 0.035)
HDL	age, lipids	CB-206 (-0.77, 0.0002), CB-194 (-0.74, 0.0004), CB-153 (-0.74, 0.0005), CB-170 (-0.71, 0.001), trans-nonachlor (0.64, 0.005), p,p'-DDT (-0.63, 0.005), CB-74 (0.58, 0.011), 4-OH-CB107 (0.57, 0.014), a-HCH (0.53, 0.023), p,p'-DDE (0.511, 0.03)

Table S5. Statistically significant correlations coefficients (r, p) in decreasing order from the partial regression analyses of HCT, ASAT, GGT, CHOL and POPs in males when controlling for age, BCI, BM, longitude and lipids (n = 18).

	Controlling	**Contaminants**
HCT	age	CB-156mo (-0.66, 0.004), CB-153 (-0.62, 0.008), ß-HCH (-0.60, 0.011), CB-99 (-0.60, 0.011),CB-183 (-0.60, 0.012), CB-180 (-0.57, 0.016), CB-138 (-0.56, 0.02), CB-187 (-0.54, 0.024), CB-137 (-0.54, 0.025), oxychlordane (-0.50, 0.042), CB-47 (-0.49, 0.045),
ASAT	longitude	CB-114mo (-0.71, 0.001)
GGT	age, longitude	4-OH-CB146 (-0.64, 0.008), HCB (-0.5374, 0.032), CB-47 (-0.5019, 0.048)
CHOL	age, BCI, BM, lipids	4'-OH-CB-159 (0.60, 0.023), CB-194, (0.57, 0.034)