



Full length article



Polychlorinated alkanes in paired blood serum and breast milk in a Swedish cohort study: Matrix dependent partitioning differences compared to legacy POPs

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ARTICLE INFO

Handling Editor: Marti Nadal

Keywords:

Human exposure

POPs

NorthPop

Lactation

Milk/serum partitioning

ABSTRACT

Background: Polychlorinated alkanes (PCAs) constitute a large group of individual congeners originating from commercial chlorinated paraffin (CP) products with carbon chain lengths of PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, and PCAs-C₁₈₋₃₂, occasionally containing PCAs-C₆₋₉ impurities. The extensive use of CPs has led to global environmental pollution of PCAs. This study aimed to quantify PCAs in paired serum and breast milk of lactating Swedish mothers, exploring their concentration relationship.

Methods: Twenty-five paired samples of mothers' blood serum and breast milk were analysed and concentrations were determined for PCAs C₆₋₃₂ and compared to 4,4'-DDE, the PCB congener 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153), and hexachlorobenzene (HCB).

Results: The median concentrations of PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ and ΣPCAs in serum were 14, 790, 520, 16 and 1350 ng/g lipid weight (lw), respectively, and in breast milk 0.84, 36, 63, 6.0 and 107 ng/g lw. Levels of 4,4'-DDE, CB-153 and HCB were comparable in the two matrices, serum and breast milk at 17, 12 and 4.9 ng/g lw. The results show significant differences of PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇ in breast milk with 22- and 6.2-times lower lw-based concentrations than those measured in serum. On wet weight the differences serum/breast milk ratios of PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ and ΣPCAs were 1.7, 3.2, 1.0, 0.4 and 1.6, respectively, while the ratio for 4,4'-DDE, CB-153 and HCB were each close to 0.1.

Conclusion: Swedish lactating mothers had high serum concentrations of PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇, with the ΣPCAs median serum concentration of 1350 ng/g lw. The breast milk concentration, although considerably lower at 107 ng/g lw, still surpassed those of 4,4'-DDE, CB-153 and HCB, suggesting an exposure risk of infants to PCAs. The variation in blood and breast milk accumulation between PCAs and studied legacy POPs, is rarely discussed but warrants further studies on partitioning properties as well as associated toxicological implications.

1. Introduction

Persistent Organic Pollutants (POPs) are long-lived toxic chemicals. Lipophilic POPs accumulate in the fatty tissues and fluids and adversely affect human health around the world for generations (USEPA, 2023; Wania & MacKay, 1996). Twelve POPs were the initial focus of the

United Nations Environment Programme (UNEP), and their usage started to be restricted in the 1970 s and '80 s. Until then, peak concentrations in humans once exceeded 10 000 ng/g lipid weight (lw) for dichlorodiphenyl-trichloroethane (DDT) and DDT metabolites (Smith, 1999), 5 000 ng/g lw, for β-hexachlorocyclohexane (Solomon & Weiss, 2002), and 1000 ng/g lw for the six indicator non-dioxin-like

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<https://doi.org/10.1016/j.envint.2024.108440>

Received 7 November 2023; Received in revised form 9 January 2024; Accepted 10 January 2024

Available online 12 January 2024

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polychlorinated biphenyls (PCBs) (Malisch et al., 2023), which cause elevated public cancer and other non-communicable disease health risks to the public (Beard, 2006; Ross, 2004).

International restrictions on those legacy POPs have decreased their levels in humans (Abass et al., 2018; Fång et al., 2015). Parallel to this, increasing human concentrations of substitution chemicals with POP properties were observed, which became new challenges to human health (Hooper & McDonald, 2000). A substitution chemical for PCBs is known as chlorinated paraffins (CPs) of carbon chain lengths of polychlorinated alkanes PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C_{≥18}. The former two groups were recently found to be most abundant in breast milk and accounted for 18–46 % of the total summed POPs in the samples from 53 countries (Krätschmer et al., 2021).

The commercial CP products are extremely complex mixtures of polychlorinated alkanes (chemical formula C_nH_{2n+2-x}Cl_x, x ≥ 1) theoretically consisting of millions of PCA congeners (Zhou et al., 2020). The global production of CPs amounts to over 2 million metric tons annually (Devashree P, 2022). The CPs are used as flame retardants, plasticizers, and metal-working fluids (C. Chen et al., 2022). The CP products are commonly categorized into short-chain (SCCPs, PCAs-C₁₀₋₁₃), medium-chain (MCCPs, PCAs-C₁₄₋₁₇), and long-chain classes (LCCPs, PCAs-C_{≥18}), some of which may contain very-short-chain impurities (PCA-C₆₋₉) which were referred to as vSCCPs (Zhou et al., 2019). Despite the fact that CPs are toxic (EI-Sayed Ali & Legler, 2010), difficult to degrade (Zhang et al., 2019), and can accumulate in humans (Li et al., 2017) and animals (L. Chen et al., 2022; Yuan, McLachlan, et al., 2021), the use of these substances continues on a large scale (C. Chen et al., 2022). Hitherto only SCCPs have been regulated in the Stockholm Convention as POPs (Wang et al., 2022), while work is in progress to potentially include MCCPs as a POP.

Unfortunately, a mix up of the commercial CP products and their actual chemical content of PCAs has dominated the scientific literature for decades. This is now to be changed by adopting the recommended terms and abbreviations by Fernandes et al. (2023). The present article adheres to the proposed nomenclature. When CPs are discharged to the environment, they are weathered which leads to changes in the PCA congener composition. Exposure to biota, including wildlife and humans, results in alterations through processes of absorption, distribution, metabolism and excretion (ADME) (Darnerud & Bergman, 2022). Furthermore, their congener specific physicochemical properties may lead to variation in partitioning and overall, their occurrence does not mirror the patterns of commercial CP products.

Human exposure to PCAs occurs via multiple routes including dietary, inhalation, dust ingestion, and dermal absorption (Yuan et al., 2022), and lactational exposure for newborns (Xia et al., 2017). Recent reported median concentrations of PCAs in human serum exceeded 18000 ng/g lw in regional studies in China (Qiao et al., 2018; Zhao et al., 2021). Unlike most legacy POPs which showed similar concentrations in different body compartments, such as human serum and in breast milk, on a lipid weight base (Mannetje et al., 2012), highly different concentrations of PCAs in breast milk and blood (serum or plasma) has been indicated. In the case of China, the high median concentrations of PCAs in breast milk were c.a. 800 – 1000 ng/g lw in urban areas (Darnerud & Bergman, 2022) while the reported pooled breast milk concentrations of PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇, from around the globe were in the ranges of 27–310 and 19–540 ng/g lw, respectively (Krätschmer et al., 2021).

Human biomonitoring of POPs requires the partitioning ratios between different body compartments to extrapolate and compare data of different matrices. There has been systematic documentation and evaluation of their partitioning between human serum and milk for legacy POPs (Darnerud et al., 2015; Mannetje et al., 2012). However, knowledge gaps persist for most POPs including the PCAs.

In this study, we hypothesized that the partitioning behaviour of PCAs in humans differs from legacy organochlorinated POPs, with a stronger accumulation tendency in human blood than in breast milk. To exam the hypothesis, we undertook a comprehensive analysis of PCAs,

PCBs, and organochlorine pesticides in the prospective population-based NorthPop Birth Cohort Study (NorthPop, 2023).

The toxicity and potential health effects of PCAs is not in the scope of this work but we still want to refer the readers to two recent reviews on this important area (Chen et al., 2023; EFSA, 2020) and references cited therein.

2. Materials and methods

2.1. Cohort and sampling

The project has been approved by the Swedish Ethical Review Authority in Umeå (2014–22431 and 2020–01254). Collection of maternal serum and breast milk was performed in a sub-cohort (n = 25) of the NorthPop Birth Cohort Study in Northern Sweden. NorthPop (2023) is a prospective, population-based study where pregnant women in Västerbotten County, Sweden, who are undergoing the routine ultrasound examination at gestational age 17–18 weeks are invited to participate. The inclusion criteria are: pregnant woman ≥18 years of age, understanding the Swedish language, viable pregnancy at gestational age 14–24 weeks, intent to give birth and residing in the catchment area over the next couple of years. NorthPop participants who gave birth during the period from May 11 to May 29th, 2020, and who were breastfeeding their infant, were invited to participate in the current study, which involved a breast milk sample and a blood sample 4 weeks after delivery.

The breast milk sample was obtained after cleaning the woman's hands and nipples with warm water. The milk (20 ml) was hand pumped to a sterile glass container. Aluminium foil was placed between the container and the plastic lid, to avoid contamination.

The blood sample (15 ml) was obtained by venepuncture in a serum tube. After 60 min in room temperature, samples were centrifuged for 10 min at 3000 rpm. Serum was placed in sterile glass tubes and stored. Samples were kept frozen during transport to the laboratory.

2.2. Chemicals

1,5,5,6,6,10-Hexachloro-¹³C-decane was applied as internal standard for analyses of PCAs. 2,2',5,6'-Tetrachlorobiphenyl (CB-53) was used for the other POPs and 2,2',3,3',4,5,5',6-octachlorobiphenyl (CB-198) and 1,1,1,3,10,12,12,12-octachloro-¹³C-dodecane (Cambridge Isotope Laboratories, Andover, MA, U.S.A.) were used as injection standards for CB-153/4,4'-DDE and PCA analysis, respectively. The CAS numbers of the analysed chemicals are detailed in Text S1, and the reference mixtures of PCAs are listed in Table S1.

2.3. Chemical analysis

Samples of about 15 g of breast milk or 5 g of human serum were spiked with the internal standards and then extracted with a mixture of 2-propanol, *n*-hexane and diethyl ether (milk samples) or methyl *tert*-butyl ether (MTBE) (serum samples) according to the modified Jensen II extraction method (Jensen et al., 2003; Sahlström et al., 2015).

The milk extract, i.e., the organic phase, was gently partitioned with a solution of 0.1 M phosphoric acid 0.9 % sodium chloride and the serum extract with a solution of potassium chloride (1.0 %). The aqueous phase was re-extracted with *n*-hexane and the combined organic phases was evaporated to dryness. The extracted weight of lipids was determined gravimetrically. The lipids were dissolved in isoctane and treated with concentrated sulfuric acid. The organic phase was removed, and the sulfuric acid was washed with isoctane. The solvent volumes of the milk sample extracts were reduced to 0.6 ml, of which 0.1 ml was used for the analysis of PCBs and 4,4'-DDE. The remaining portion (0.5 ml) was further worked up by applying an SPE column, packed from bottom to top with 2 g of 2.5 % w/w H₂O-deactivated silica, 8 g of 44 % w/w sulfuric acid silica, and sodium sulfate (Yuan et al., 2018) prior to

instrumental analysis of the PCAs. The solvent of the combined organic phase from the serum samples was reduced after the sulfuric acid treatment to 0.1 ml to undergo instrumental analysis of 4,4'-DDE, CB-153 and HCB, and CB-28, -118, -138 + 163, and -180, and the three HCHs, 4,4'-DDT, and 4,4'-DDD. The organic phase was then applied to a SPE column as above to be used for the analysis of PCAs.

The non-PCA POPs underwent gas chromatographic analysis on instruments equipped with two condensed capillary columns in parallel, each connected to its respective Electron Capture Detector (ECD). The two GC columns used in this setup were: 60 m x 0.25 mm, film thickness 0.25 μ m TG5MS and DB1701, respectively. Helium was used as carrier gas and argon/methane as supplementary gas (Eriksson, 1997). Analysis of PCAs (designated as C_nCl_m , with $n = 6-36$ and $m \geq 2$) was carried out on a UPLC-APCI-Orbitrap-MS instrument according to previously described methodology (Yuan, Tay, et al., 2021).

2.4. QA/QC

The average method quantification limit (MQL), based on Nyberg et al. (2015), for 4,4'-DDE, CB-153, and HCB was 0.028 ng/g lw in breast milk and 0.015 ng/g lw in serum. Quantification of the PCAs, determined as PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ was based on reconstruction of C_nCl_m homologue profiles (Du et al., 2020). Method detection limits (MDLs) for PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ in human milk were 0.41, 13.1, 30, and 1.05 ng/g lw. The MDLs for PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ in serum were 1.72, 89.7, 86.2, and 1.72 ng/g lw, respectively. The MDLs for PCAs were defined as the mean blank level plus three times the standard deviation. As consensus regarding MQL determination of PCAs as a mixture is lacking, no MQL values are estimated here. The recovery of 4,4'-DDE, CB-153 and HCB (mean \pm SD) was determined to be 78 \pm 7 % and 70 \pm 14 % in serum and breast milk, respectively, while recovery of PCAs in serum and breast milk, respectively, was 63 \pm 12 % and 89 \pm 7 %, respectively.

2.5. Statistical methods

Analysed samples with concentrations below MQL/MDL have been replaced with MDQ/MDL divided by the square root of two (Loftis et al., 1989).

Boxplots showing the median and interquartile range (IQR) have been used to graphically display differences between blood serum and milk within NorthPop and other relevant studies. The boxplots also contain "Tukey's outer fence" (i.e. $\pm 3.0 \times$ IQR) (Foreman, 2013; Tukey, 1977) a few values outside this "fence" can be regarded as extreme values.

Simple linear regression (Ordinary Least Square (OLS)-regression) with logged data has been used to study the correlation between milk and serum and the potential to predict probable concentration in milk through a blood sample.

To explore possible influence through leverage by extreme values on the regression analyses also Mann-Kendal trend test was applied. Hence, regression analyses albeit significant, have not been considered significant unless also the corresponding Mann-Kendal tests were significant. To illustrate potential effects of extremes also Theil-slopes (a non-parametric, robust alternative to regression lines) have been plotted. To detect significant differences between milk and serum, the Wilcoxon Signed Rank test (a paired non-parametric test) was used.

In order to estimate required sample sizes (and budget) for an adequate power to detect relations and differences, a power analysis was carried out using data from a pilot study. The power analyses showed that, with a group size of 25 individuals, differences of 25 % or more between plasma and milk could be detected with a power 80 % for PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇. For PCAs-C₁₈₋₃₂ a larger difference, of almost 90 %, was required to achieve 80 % power. (Figure S1). Accordingly, samples from 25 mothers were applied in the present study.

3. Results

The PCA concentrations are presented as PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂ together with 4,4'-DDE, CB-153 and HCB, in the paired serum and breast milk samples from the 25 lactating women, as shown in Fig. 1. The detection frequencies for all these analytes were 1.0 in breast milk, and in serum the PCAs were also detected in all of the samples while the detection frequency of 4,4'-DDE, CB-153 and HCB were 0.96, 0.80 and 0.28, respectively. In serum, the median concentrations for PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂, and Σ PCAs were 14, 790, 520, 16, and 1350 ng/g lw, respectively. In breast milk, the corresponding concentrations were 0.84, 36, 63, 6.0, and 107 ng/g lw. Meanwhile, 4,4'-DDE, CB-153, and HCB showed comparable concentrations in both matrices, at medians of 17, 12, and 4.9 ng/g lw, respectively. Detailed concentration data are presented in Table S2a. Individual concentrations (ng/g lw) of β -HCH, 4,4'-DDT, 4,4'-DDD, CB-28, CB-118, CB-138/CB-163 and CB-180 are given in Table S2b. Few serum concentrations are listed due to numerous non-detects, in contrast to the extensive concentration data in breast milk.

The subsequent statistical analyses of the analytes include number of samples analysed (n), arithmetic means (AM), standard deviations (SD), coefficient of variation (CV), geometrical means (GM), median values, lowest concentration (Min) and highest (Max) concentration. These results are presented in Tables S3a and c for lipid weight-based results in serum and breast milk, respectively, while Tables S3b and d present analogous insights but on a wet weight basis. Tables S3c and d include the additional POPs analysed, i.e., β -HCH, 4,4'-DDT, CB-28, CB-118, CB-138/CB-163 and CB-180. The data shown in Table S2b for serum shows that CB-180 is only quantified in six out of the 25 samples, CB-138+CB-163 in four and CB-28 in two samples.

A deeper exploration of serum/breast milk concentration ratios on both lipid and wet weight basis are presented in Fig. 2. This visualization highlighted significantly higher concentrations in the serum compared to the breast milk on a lipid weight basis for PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, and PCAs-C₁₄₋₁₇, with ratios calculated on median concentrations of 16.1, 21.6, and 8.3, respectively. The ratio for PCAs-C₁₈₋₃₂ was 2.8 but not significantly different between serum and breast milk. The corresponding median ratios for 4,4'-DDE, CB-153, and HCB are 0.97, 0.79

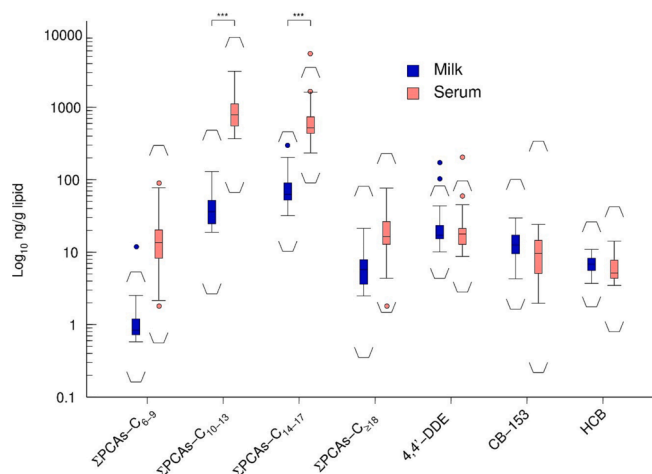


Fig. 1. Logged concentrations (ng/g lw) of the analysed chemicals in milk (blue) and serum (pink) displayed as Box & Whiskers plots with "Tukey's fences". "Whiskers" = $\pm 1.5 \times$ Inter Quartile Range (IQR) (inner fence), outer fence = $\pm 3.0 \times$ IQR. Tukey's outer fence indicates one extreme PCAs-C₁₄₋₁₇ concentration in serum, two extreme 4,4'-DDE concentrations in breast milk and one in serum. The three *** indicate significance concentration differences between serum and breast milk at $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

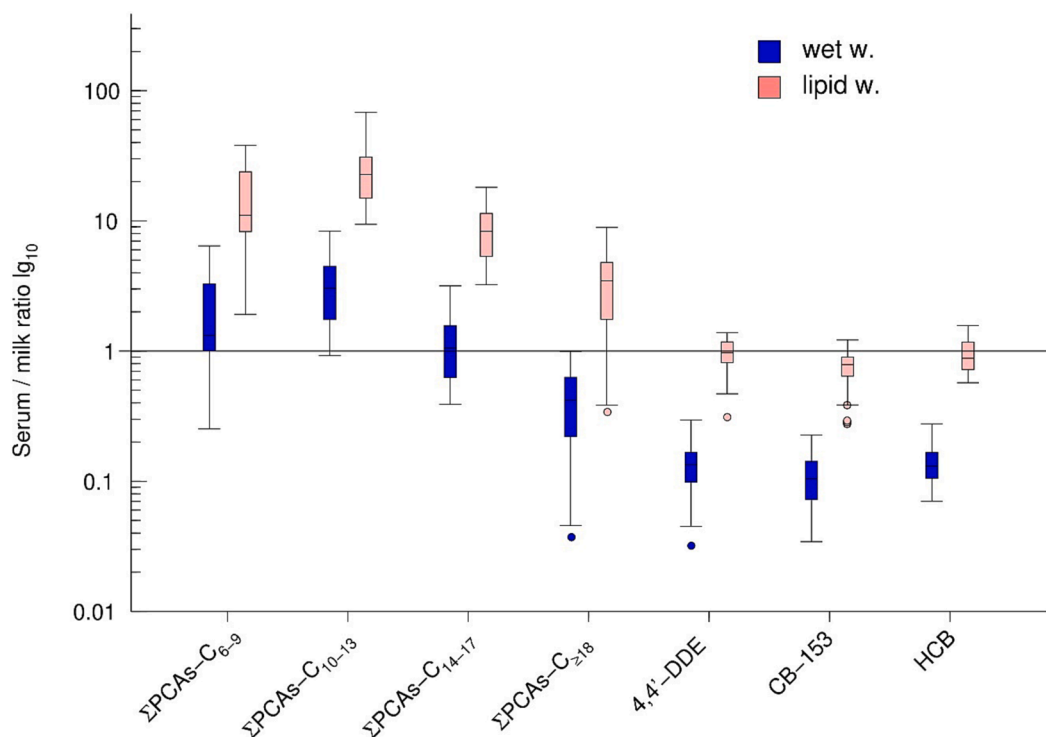


Fig. 2. Ratio serum/breast milk concentration ratios of four PCA groups (PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, PCAs-C₁₈₋₃₂) and of three abundant POPs (4,4'-DDE, CB-153 and HCB) on both wet weight and lipid weight basis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and 0.88, respectively, i.e. close to 1 (cf. Table S5 for Inter Quartile Ranges and percentiles). The wet weight ratios between serum and breast milk underscore a noteworthy trend; PCAs-C₆₋₉ (1.7), PCAs-C₁₀₋₁₃ (3.2), and PCAs-C₁₄₋₁₇ (1) exhibit higher ratios than PCAs-C₁₈₋₃₂ (0.39) and the legacy POPs (around 0.1).

A significance evaluation of the analytes relation between serum and breast milk was performed, based on the lipid weight data, and the results are shown in Fig. 3. PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇ show significant correlations with OLS-regression between levels in serum and breast milk as well as for 4,4'-DDE, CB-153 and HCB. Also, the OLS regression are significant for PCAs-C₆₋₉ and PCAs-C_{≥18} but are affected by the leverage of one or a few single observations and the corresponding non-parametric alternatives give non-significant results.

Differences in the serum and breast milk concentrations of PCAs pertaining to diverse chain length groups, as depicted in Fig. 1, suggest distinct partitioning tendencies for each C_xCl_y homologue group. We observed the distribution patterns of C_xCl_y for PCAs in serum and milk samples from the study cohort as visualised in Fig. 4. PCAs with shorter carbon chain lengths, particularly C₁₀, demonstrated a higher proportion in serum samples than in their milk counterparts. In terms of chlorine substitution, milk samples predominantly ranged between Cl₆ and Cl₈, whereas serum samples were typically between Cl₅ and Cl₆.

Analysis was performed to determine potential correlation between relevant biological factors (milk lipid content, age of the mother, body mass index (BMI), weight gain during pregnancy, number of days between childbirth and milk sampling and number of previous children) versus exposure to PCAs-C₆₋₉, PCAs-C₁₀₋₁₃, PCAs-C₁₄₋₁₇, and PCAs-C₁₈₋₃₂. Only weight gain during pregnancy showed significant and positive correlation for PCAs-C₁₄₋₁₇ and PCAs-C₁₈₋₃₂ (Figure S2).

4. Discussion

4.1. PCA concentrations in serum and breast milk from lactating women

The concentrations of PCAs (Tables S3a and b) were particularly high in the maternal serum with median ΣPCAs values of 1350 ng/g lw (7.8 ng/g ww). The level of ΣPCAs in human serum corresponds to >1 µg/g lw concentrations in 84 % of the samples, which is high (cf. Introduction above for comparison to highest levels reported of e.g. PCBs and DDTs in humans). In contrast the levels of ΣPCAs in breast milk were 107 ng/g lw (4.8 ng/g ww), i.e., approximately an order of magnitude lower than in serum on lipid weight basis (c.f. Tables S3c and d). The scientific reporting has however focused on PCAs in the range of SCCPs (ΣPCAs-C₁₀₋₁₃), with less data on MCCPs (ΣPCAs-C₁₄₋₁₇) and even less on LCCPs (ΣPCAs-C₁₈₋₃₂). The concentrations of ΣPCAs-C₁₀₋₁₃ and ΣPCAs-C₁₄₋₁₇ are far higher than the legacy POPs (4,4'-DDE, CB-153 and HCB (Fig. 1)). While PCA lipid weight concentrations differ between serum and breast milk, other legacy POPs such as DDTs, PCBs and HCB do not differ very much. The levels of POPs compared to the PCA results presented herein can be compared to lipid weight data presented of 18 POPs in breast milk (Fång et al., 2015), a review unable to identify early data on PCAs in breast milk. The present PCA results are compared to a few POPs (DDTs, six PCB congeners, HCB and β-HCH) in the Tables S3a and c. Since only 4,4'-DDE and CB-153 were quantified in most of the 25 serum samples and HCB in seven out of 25 (Tables S2a and b) these are listed in Table S3a and b. Too few observations were made of the additional POPs in serum while quantified in breast milk (Tables S3a and c, respectively). Our data confirm higher ΣPCA lipid weight levels than for the individual POPs in serum while the legacy POPs analysed were in the same range in the two matrices.

The present data on PCAs in serum and breast milk was compared to data presented in the scoping review, Table 2, by Huang et al. (2023) summarising PCAs in human serum and breast milk. The serum levels in the 25 women in the NorthPop cohort is approximately in range with

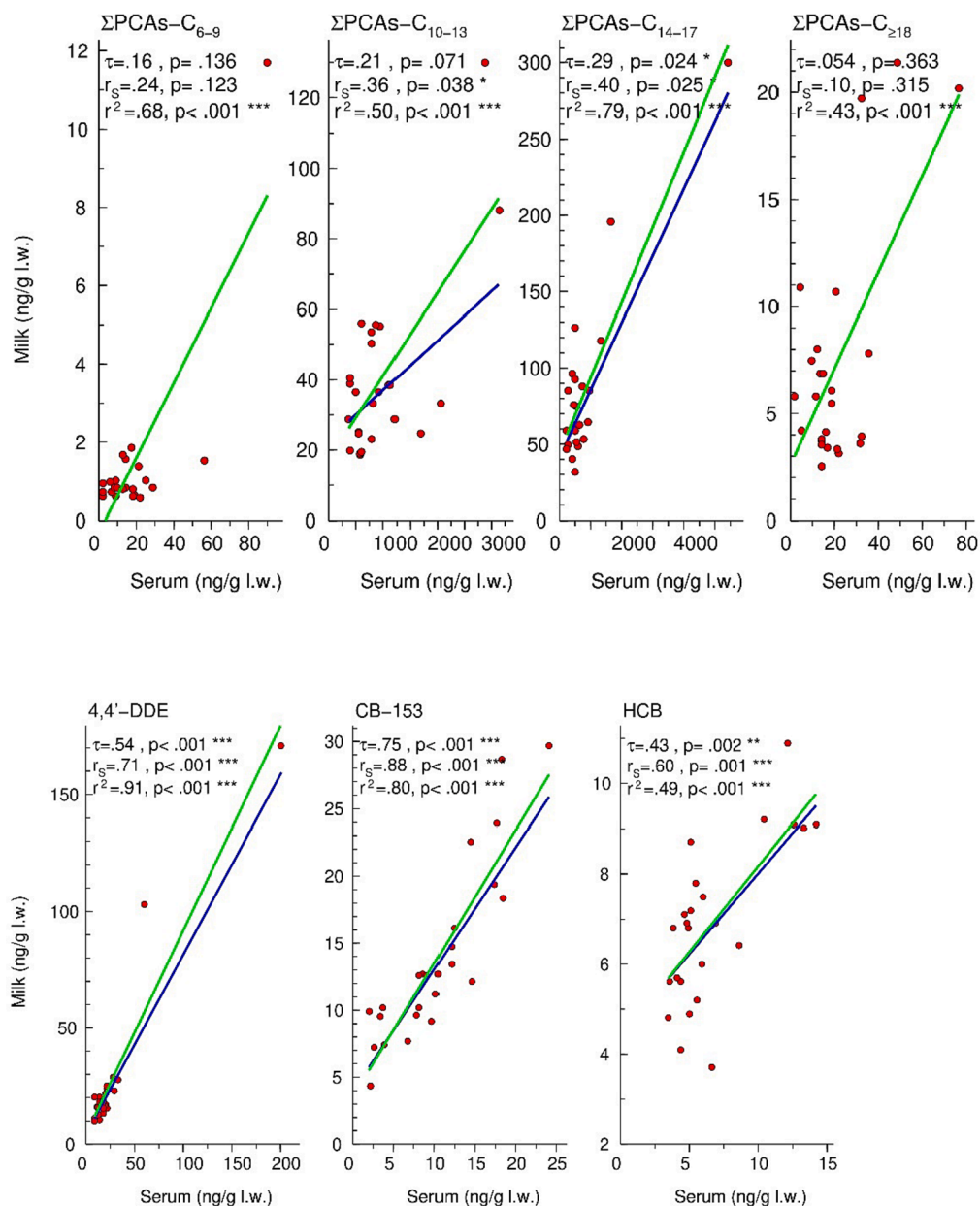


Fig. 3. Significance evaluation of the analytes of lipid weight data. The three asterisks *** indicate $p < 0.001$. The regression lines are Green; Theil-slopes are Blue; τ = Mann-Kendall's tau, r_s = Spearman's rho. The *upper diagrams*: The Ordinary Linear Regression (OLS) regression is significant for PCAs-C₆₋₉ but it is depending on the leverage of one single observation. The corresponding Mann-Kendall and Spearman evaluations do not yield significance. *Lower diagrams*: PCAs-C₁₀₋₁₃ and PCAs-C₁₄₋₁₇ show significant correlations between levels in serum and breast milk also when Spearman's rho is applied. The OLS-regression analysis is questionable for PCAs-C₁₈₋₃₂ since it is strongly related to on single observation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

levels of Σ PCAs₁₀₋₁₃ and Σ PCAs₁₄₋₁₇ in the Czech Republic and Norway, and for Σ PCA_{≥18} in Norwegian women (Huang et al., 2023). The NorthPop concentrations are similar to two early analytical results from Sweden as well (Bergman & Kärrman, 2019). PCAs with carbon chain lengths of 18 and longer are rarely reported in human matrices except for some data from China, Norway and Sweden (Li et al., 2017; Yuan et al., 2022; Zhou et al., 2020). The levels reported from the former two countries have ranges of Σ PCA_{≥18} spanning higher than the present NorthPop cohort (Huang et al., 2023). Exposure levels of Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇ in Chinese serum or plasma are comparable to the European levels but also include some samples with concentrations of around 10 000 ng/g lw and higher.

While PCAs in serum are less frequently reported, more data are available from breast milk, particularly Σ PCA-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇

(cf. Table 2 in (Huang et al., 2023)). It is particularly interesting to compare the PCA levels in pooled samples of breast milk from six regions of the world presented by Krättschmer et al. (2021), with 15 samples from Europe of 9.8–100 and 19–130 ng/g lw for Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇, respectively. These ranges are somewhat higher but still rather similar to the reported levels in Swedish breast milk from 2016 (<12–27.8 and <16–60 ng/g lw) and in the range of levels in women in northern Norway 12–120 and <16–311 ng/g lw (Zhou et al., 2020). Interestingly Krättschmer et al. (2021) reported that breast milk pools from Africa and Asia contained high yet below μ g/g lw levels of Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇, i.e., with concentration ranges of 98–680 ng/g lw and 38–540 ng/g lw, respectively. Only a few studies have so far reported Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇ breast milk levels higher than 1 μ g/g lw (Xia et al., 2017).

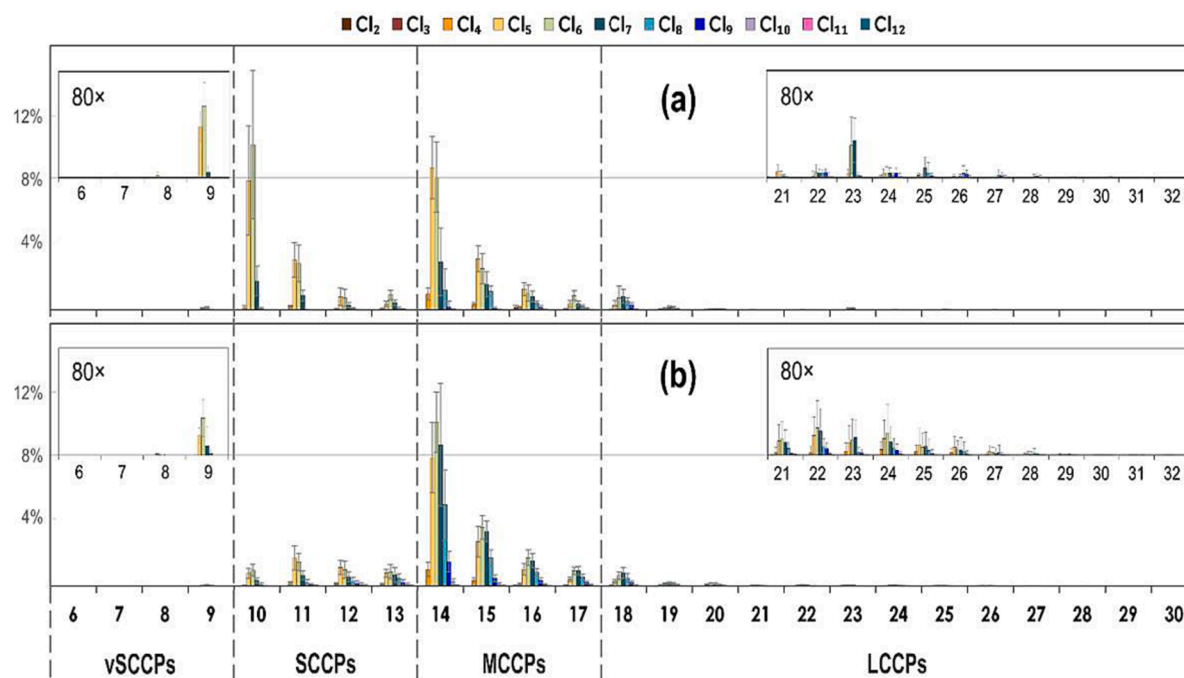


Fig. 4. The average relative abundance of CP carbon-chlorine homologues with standard deviation error bars, for both serum (a) and breast milk samples (b). The figures feature zoomed-in displays of PCAs C_{6-9} and PCAs C_{21-32} CPs. Carbon chain length is represented on the horizontal axes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Literature data confirm higher concentrations of PCAs in the blood (serum or plasma) than in breast milk supporting our hypothesis even though the data are not from paired samples as done in our study. The serum:breast milk quotes are discussed further below.

Since the PCA concentrations are so high in serum it is of interest to compare to other POPs and in particular to PFAS with the highest levels reported for PFOS and PFOA. The PFAS levels are comparably low in breast milk, with e.g., L-PFOS at concentrations of 0.04 ng/mL (Awad et al., 2020) to compare with median concentrations of 1.35, 3.04 and 4.8 ng/g ww of Σ PCAs- C_{10-13} , Σ PCAs- C_{14-17} and Σ PCAs (all analysed), respectively. Similar PFOS concentrations are reported from the paired maternal plasma and breast milk in the New Hampshire Birth Cohort Study with milk median concentration of 0.024 ng/mL (Criswell et al., 2023), and in plasma 2.6 ng/mL. Levels of PFOS in a Swedish reference population group without known particular exposures to PFAS show median levels of 2.9 ng/mL (Xu et al., 2021) as compared with median values in serum (Table S3b) of 4.38, 3.07 and 7.8 ng/g ww of Σ PCAs- C_{10-13} , Σ PCAs- C_{14-17} and Σ PCAs, respectively. Even if the comparison is between just PFOS and two PCA groups, and all analysed PCAs, it is clear that the PCA concentrations are rather similar in serum (or plasma). However, PCA concentrations are far higher than PFOS in breast milk, approximately 33 and 76 times the concentrations for Σ PCAs- C_{10-13} and Σ PCAs- C_{14-17} , respectively. This comparison is considered appropriate given that PFAS levels are dominated by PFOS.

Further, it is relevant to include the occurrence of shorter chain PCAs, PCAs- C_{6-9} and to report PCAs with long chain lengths, i.e., C_{18} and longer. Neither the concentrations of PCAs- C_{6-9} nor PCAs- $C_{\geq 18}$ is negligible (Fig. 1, Tables S3a–d).

The results of the present study stress the very high serum concentrations of PCAs in humans but also relatively high levels in breast milk, which are ingested by the nursing babies. Our study points out the importance of not relying on lipid weight-based data only for comparisons between matrices and/or pollutants.

4.2. Serum-breast milk partitioning of PCAs

Reported data, as summarised by Huang et al. (2023) are showing an apparent difference in breast milk and blood (serum or plasma) concentrations. An initial study of only two persons in Sweden showed low μ g/g lw serum Σ PCAs concentrations (Bergman & Kärrman, 2019) which indicated higher PCA levels than in Swedish breast milk (Zhou et al., 2020). We hypothesised that the partitioning behaviour of PCAs differs in human blood and breast milk from legacy POPs. This is confirmed as shown in Fig. 2 but the results were even more complicated than expected since the lipid weight-based ratios differ depending on the PCA chain lengths. The comparison was performed on what has been known as SCCPs (Σ PCAs- C_{10-13}), MCCPs (Σ PCAs- C_{14-17}) and LCCPs (Σ PCAs- $C_{\geq 18}$) plus inclusion of the shortest Σ PCAs- C_{6-9} , which all showed different partitioning's and that PCAs are more heavily accumulated in human blood than in breast milk. Σ PCAs- C_{6-9} , Σ PCAs- C_{10-13} and Σ PCAs- C_{14-17} are significantly different from the ratios for 4,4'DDE, CB-153 and HCB (legacy lipophilic POPs) while PCAs- C_{18-32} are higher but not statistically significant (Fig. 2). The legacy POP ratios are expected to be 1.0, i.e., the extracted lipid weight-based concentrations shouldn't be different if the partitioning is based on the lipophilicity of the compound studied. This was the case for 4,4'-DDE (0.96) while the median ratios for CB-153 was 0.78 and for HCB 0.87 (based on the paired serum / milk lipid ratios from the individual mothers).

The ratios may be influenced by pollutant protein binding, so called proteinophilic chemicals among which PFOS and other PFAS are well known as well as PCB methyl sulfones binding to uteroglobin, now named PCB binding protein (Härd et al., 1995), and a range of halogenated phenolic chemicals or their metabolites binding to transthyretin (Meerts et al., 2000). In case of PCAs being proteinophilic it is reasonable to think that the serum:breast milk wet weight ratio is influenced similarly. As shown in Fig. 2, PCAs- $C_{\leq 13}$ show higher concentrations in serum than breast milk, PCAs- C_{14-17} are equally partitioned in the two compartments while PCAs- $C_{\geq 18}$ concentrations are lower in serum than breast milk just as for 4,4'-DDE, CB-153 and HCB. It may be hypothesised that PCA congeners are proteinophilic, a hypothesis partly supported by

Sprengel et al. (2021) and by thoughts put forward by Sun et al. (2020). Still, more PCA related work need to be done to understand protein binding properties of this class of environmental pollutants.

The average relative abundance of PCAs-C_{<13} as shown in Fig. 4 are very different between serum (upper diagram) and breast milk (lower diagram). This is a novel observation, potentially indicating an enhanced proportion of higher-chlorinated PCAs in breast milk samples, compared to serum samples, which may be attributed to higher lipid content in breast milk. This observation aligns with the study of Castro et al. (2018), which identified enhanced partitioning between organic carbon and water for PCAs with elevated chlorine content.

In order to semi-quantitatively characterize the partitioning of C_xCl_y, we normalized the instrumental signals of C_xCl_y to the internal standard. Subsequently, we calculated the ratios of individual C_xCl_y between matched serum and breast milk samples, as shown in Fig. 5. PCA chain length C₁₀ displayed the highest ratios, with a range of 8.3 to 97 and a median value of 43, followed by C₁₁ (median: 14) and C₉ (median: 11). As the carbon chain length of CPs increased, the serum-breast milk ratios exhibited a significant exponential decrease ($R^2 = 0.26, p < 0.05$). However, such significant trend was not observed when examining chlorine substitution numbers ($R^2 = 0.07, p < 0.05$). The dependence on chain length on interaction with transthyretin has been discussed by Weiss et al. (2009). They noted a decreased relative competitive binding to transthyretin with increasing chain length for PFAS. This could result in lower partitioning to serum and thus a relative change in accumulation between serum and breast milk.

Serum:breast milk ratios of POPs are rarely reported, possibly due to few studies with paired samples. However, the serum:breast milk ratios of a few PBDE congeners, dioxins and Mirex have been reported (Darnerud et al., 2015; Mannetje et al., 2012) which were compared with PCA lipid weight data from the present study (Table 1). The

Table 1

Comparisons of serum:breast milk ratios as determined on lipid weight (lw) based median concentrations of the reported ratios for the PCA groups reported in the present study with literature data of three PBDE congeners, OCDD, OCDF and Mirex (left part of the table). To the right serum:breast milk ratios as determined on wet weight (ww) based concentrations of the reported ratios for the PCA groups reported in the present study with calculated data from the literature for PFOS and PFOA.

Serum:breast milk ratios (lw based)		Ref.	Serum:breast milk ratios (ww based)		Ref.
PCAs-C ₆₋₉	16.1	1a	PCAs-C ₆₋₉	1.7	1b
PCAs-C ₁₀₋₁₃	21.6	1a	PCAs-C ₁₀₋₁₃	3.2	1b
PCAs-C ₁₄₋₁₇	8.3	1a	PCAs-C ₁₄₋₁₇	1.0	1b
PCAs-C ₁₈₋₃₂	2.8	1a	PCAs-C ₁₈₋₃₂	0.39	1b
BDE-153	1.6	2	PFOS	92	4
BDE-183	3.4	2	PFOA	39	4
BDE-209	17 (Range: 4.8–58)	2			
OCDD	5.5	3			
OCDF	1.9	3			
Mirex	3.2	3			

References. 1a: present study Tables S3a and c; 1b: present study Tables S3b and d; 2: (Darnerud et al., 2015; Mannetje et al., 2012); 3: (Darnerud et al., 2015; Mannetje et al., 2012); 4: (Kim et al., 2011).

perbrominated diphenyl ether (BDE-209) was reported with a ratio of 17 (range 4.8–58) while OCDD and OCDF showed ratios of 5.5 and 1.9, respectively. When ratios are calculated on wet weight basis, to allow comparisons with PFAS (Table 1), PFOA shows a tenfold higher ratio than PCA₁₀₋₁₃ and approximately thirtyfold higher for PFOS (Kim et al., 2011). The latter data underline the importance also of the PCA exposure from breast milk in comparison to PFAS.

The results from the present study, supported by the other studies with paired samples, show the importance of understanding the

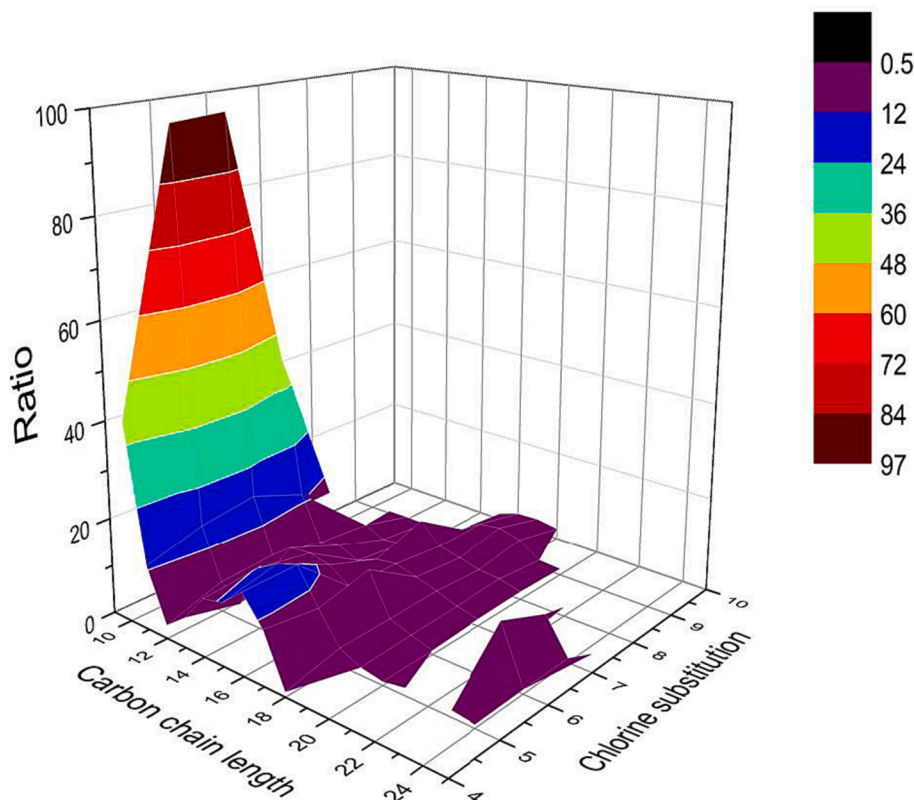


Fig. 5. Ratios of C_xCl_y between serum and breast milk, calculated using normalized instrumental signals. Ratios within specific ranges are color-coded according to the legend on the right of the graphic. Data points with detection frequencies below 80% were excluded from the figure and subsequent correlation statistical analysis. Detailed individual ratio values can be found in Table S4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

retention of different POPs in various body matrices, in this case serum and breast milk. The concentrations cannot easily be modelled for another compartment even though this may be feasible for Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇. It is particularly important to understand the partitioning since breast milk concentrations will not be representative for serum (plasma) levels which are on a Σ PCAs-C₆₋₃₂ approximate an order of magnitude higher in serum than in breast milk which make the PCA concentrations to reach above 1 $\mu\text{g/g lw}$.

Considering the uncertainty, the possible non-linear dependence and the leverage influence from a few measured concentrations in the relation between milk and serum concentrations displayed in Fig. 3 it is at this point not advisable to predict milk concentrations from measured serum sample levels.

4.3. Estimated exposure among infants

To check whether a number of factors that has been shown to affect contaminant concentrations in breast milk (e.g., Lignell et al. (2009)), multiple correlation analyses were carried out. The result of the analyses is presented in Figure S2 where the PCA levels are related to lipid content in milk, age of the mothers, their BMI, weight gain during pregnancy, number of days between delivery and milk sampling and number of previous children. A correlation is only shown between weight gain during pregnancy for Σ PCAs-C₁₄₋₁₇ and Σ PCAs-C₁₈₋₃₂ and the correlation was positive instead of negative.

The same calculation method used for Estimated Daily Intake (EDI) by Zhou et al. (2020) was applied for assessing the EDI of the PCAs, 4,4'-DDE, CB-153 and HCB. The EDI for boys 4 and 12 weeks old, assuming a daily consumption of 125 ml /kg and day and a medium growth according to WHO Child Growth Standards, are shown in Fig. 6. The EDI increases with age of the boys with similar EDI for Σ PCAs-C₁₀₋₁₃ and Σ PCAs-C₁₄₋₁₇ as for 4,4'-DDE and CB-153 while the value is a magnitude higher for Σ PCAs. Accordingly, even though the breast milk concentrations of PCAs are lower than in serum the exposure to the lactating

babies are troublesome high. Measures need to be taken to decrease PCA exposures to humans and in particular to women in fertile ages.

5. Conclusions

The paired sampling performed of serum and breast milk was highly valuable and a basis for several conclusions and confirmations. The results confirm the hypothesis set up but also shed light on other issues as summarised below.

- The Σ PCA concentrations in serum are markedly high, reaching above $>1 \mu\text{g/g lw}$, while in breast milk, they are approximately an order of magnitude lower. To allow proper comparisons with other study results it is necessary to enable conversions between wet weight and lipid weights. Since this require extracted lipid weights also from serum with low relative lipid content, we emphasize the importance of enzymatic lipid determinations of serum samples.
- In order to make comparisons between PCAs and other POPs, independent if they are lipophilic or proteinophilic, it is a prerequisite to standardize reporting to wet weight data but always include relative extractable lipid content in the samples.
- PCAs are reported herein as congeners with specified carbon chain lengths which is of importance for comparisons of PCA congeners between matrices and biological compartments.
- The differences between serum and breast milk partitioning seem to be dependent on PCA chain lengths, though the exact mechanism remains elusive. The behaviour may be influenced by protein binding, metabolism, or due to chemical structure characteristics (e.g., molecular mass, volume, or polarity).
- It is time to report PCAs as their true chemical nature rather than their commercial identification, i.e., chlorinated paraffins.

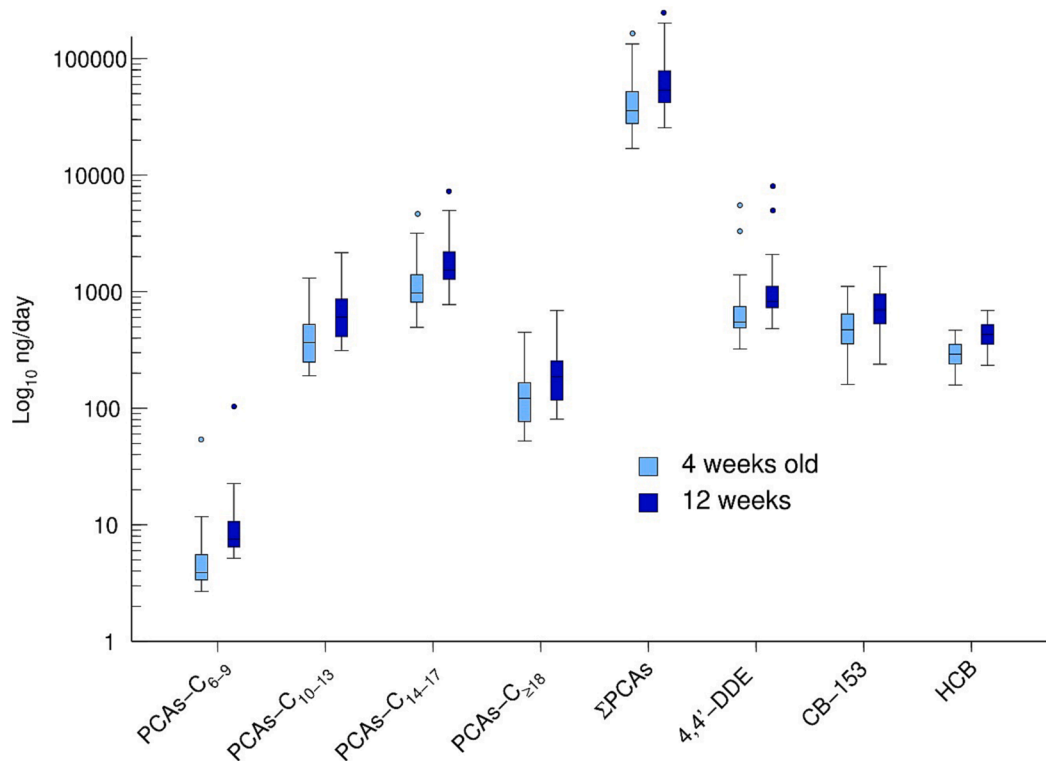


Fig. 6. Estimated Daily Intake for boys 4 and 12 weeks old (assuming a daily consumption of 125 ml /kg and day and a medium growth according to WHO Child Growth Standards). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CRedit authorship contribution statement

Bo Yuan: Writing – original draft, Visualization, Methodology, Investigation. **Anders Bignert:** Writing – original draft, Visualization, Validation, Formal analysis, Conceptualization. **Patrik L. Andersson:** Writing – review & editing, Validation, Investigation. **Christina E. West:** Writing – review & editing, Validation, Investigation. **Magnus Domellöf:** Writing – original draft, Visualization, Validation, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The project was financially supported by the Swedish Environmental Protection Agency, the Health-related environmental monitoring (HÄMI) project #215-20-007, the support from Karin Norström is acknowledged. The contribution from all the 25 mothers was invaluable for performing the study and to whom we extend our sincere gratitude. We also want to thank the NorthPop study staff, Martin Kruså (SU) for sample preparation of milk samples and analysis of POPs, Wanjiao Kong (SU) for sample preparation of serum samples and data processing of PCA results.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108440>.

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