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Longitudinal trends of per- and polyfluoroalkyl substances in children's serum

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ABSTRACT

Studies suggest negative health impacts from early life exposure to per- and polyfluoroalkyl substances (PFASs). However, information on longitudinal exposure to PFASs during childhood is scarce for background-exposed individuals. This study sought to fill this gap by investigating children's longitudinal exposure trends through measurement of PFAS serum concentrations and calculation of body burdens (μg, total in body). Blood of 54 Finnish children was sampled 2005–2015 and analyzed for 20 PFASs at 1, 6 and 10.5 years of age. The body burden was calculated by multiplying the serum concentration by the volume of distribution and the bodyweight for each individual. Associations between serum concentrations or body burdens and parameters, such as sex, breastfeeding duration, body mass index as well as indoor dust and air PFAS concentrations, were evaluated. Serum concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) decreased significantly ($p < 0.001$) with age. In contrast to serum concentrations, body burdens stayed unchanged or even increased significantly ($p < 0.05$), except for PFOA in female children. Breastfeeding duration was positively correlated ($p < 0.001$) with serum concentrations of PFHxS, PFOS, PFOA and PFNA at 1 year of age. Some associations were found at 10.5 years with sex and indoor PFAS concentrations. Observations of longitudinal decreasing trends of serum concentrations can be misleading for understanding exposure levels from external media during childhood, as the serum concentration is influenced by parallel temporal changes and growth dilution. Body burdens account for growth dilution and thus better reflect differences in early-life to adolescence exposure than serum concentrations.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are a structurally diverse group of > 3000 anthropogenic chemicals (KEMI, 2015) that have been classified into various sub-families (Buck et al., 2011), such as the most studied group of perfluoroalkyl acids (PFAAs). PFASs have been commercially produced since the early 1950s (Okazoe, 2009) and are nowadays widely used in many industrial applications, as well as in consumer products (Buck et al., 2011; Kotthoff et al., 2015; Prevedouros et al., 2006). PFAAs are ubiquitous in the environment and present in both environmental and human matrices (Fromme et al., 2009). "Long-chain" PFAAs (i.e. ≥7 perfluorinated carbons for perfluoroalkyl carboxylic acids (PFCAs) and ≥6 perfluorinated carbons for perfluoroalkane sulfonic acids (PFSAs)) bioaccumulate in humans as a result of their slow elimination rates (Barry et al., 2013; Kennedy et al., 2004; Lau et al., 2004; Olsen et al., 2007; Stahl et al., 2011).

PFASs, especially long-chain PFAAs, have displayed an array of toxicological effects in animal studies (Kennedy et al., 2004). Epidemiological studies have shown associations between exposure to elevated concentrations of long-chain PFAAs and adverse health outcomes

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(Barry et al., 2013; Lopez-Espinosa et al., 2016). Several studies have examined associations between prenatal and childhood PFAS exposure and health outcomes. These studies have shown that early life exposure to PFASs affects development during later childhood, e.g. due to lower immune system response (Dalsager et al., 2016; Pennings et al., 2016), lower levels of sex hormones and delayed sexual maturation (Lopez-Espinosa et al., 2011, 2016) and adiposity at later childhood (Braun et al., 2016). In addition, some epidemiological studies have shown a positive association between childhood PFAS exposure and thyroid function in teenage boys (Ballesteros et al., 2017), and association between PFAS exposure and body development of fetuses and children, such as reduced birth weight and increased body mass index (BMI) (Gyllenhammar et al., 2018). These results clearly show that childhood exposure has to be investigated more closely in order to assure that the regulation of PFASs, which is currently predominantly based on data derived from adults, also protects children.

Perfluorooctane sulfonic acid (PFOS) and related substances were added to Annex B of the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2009 (UNEP, 2009), and perfluorooctanoic acid (PFOA) and perfluorohexane sulfonic acid (PFHxS) are currently under consideration for addition to the convention. Recently, several long-chain PFCAs (C8-C14) as well as PFHxS were added to the Candidate List of Substances of Very High Concern (SVHC, ECHA, 2013, 2015, 2017) of the EU chemicals legislation REACH (regulation EU 1907/2006). The uses of PFOS were restricted through EU-legislation almost a decade ago (directive 2006/122/EC, and later moved to regulation EU 757/2010). More recently the EU began to regulate PFOA, its salts and related substances in a wide range of products and applications (regulation EU 2017/1000). The phase-out of perfluorooctanesulfonyl fluoride-based substances by the major manufacturer resulted in a decrease of perfluorooctane sulfonic acid (PFOS) concentrations in human serum samples after the year 2000 in America, Europe and Australia (Calafat et al., 2007; Gebbink et al., 2015; Glynn et al., 2012; Haug et al., 2009; Toms et al., 2014). At the same time, several long-chain PFCAs have increased steadily in the general population (Calafat et al., 2007; Gebbink et al., 2015) despite mitigation actions by the main producers (US EPA, 2006). There is also an increasing concern for human exposure to short-chain PFAAs and various per- and polyfluoroether acids, which are being used as replacements for long-chain PFAAs (Blum et al., 2015; Glynn et al., 2012; Ritter, 2010; Scheringer et al., 2014; Shi et al., 2016; Wang et al., 2013, 2015). Therefore, the quantitation of multiple PFASs (phased-out substances and replacements) in human serum is needed to adequately assess human PFAS exposure and associated health risks.

Measurements in blood serum represent the “gold standard” for monitoring PFASs in humans in epidemiological studies. However, serum concentrations in children cannot easily be related to external exposure due to growth dilution effects resulting from the increasing blood volume and body weight during childhood. Calculation of the body burden of a chemical (defined here as the total amount in μg in the body) is one way to remove the confounding effect of growth dilution. The body burden is a measure of the total accumulated amount of a substance in the body at a given time point, which allows for the detection of changes in external exposure over time.

To date, there are very few published studies that have measured PFASs at several time points during childhood and the reported longitudinal trends in these studies display differences in the range of the PFAS concentrations and time of the peak concentrations (Fromme et al., 2010; Gyllenhammar et al., 2016; Mogensen et al., 2015). Reasons for the reported variable longitudinal trends may include methodological differences (e.g. sampling time points), but may also reflect geographical differences in exposure pathways and sources for infants, toddlers and children. The objectives of this study were to investigate a) longitudinal exposure trends of background-exposed children for PFASs during childhood through measurement of serum concentrations following the same individuals from 1 to 10.5 years of age, b) children's body burden trends of PFASs during childhood, and c) causes for the different exposure trends for PFASs during childhood. To examine causes for or associations with the serum concentrations and body burdens, breastfeeding duration, body mass index as well as PFAS dust concentrations (Winkens et al., 2018) and PFAS air concentrations (Winkens et al., 2017a) of the children's bedrooms were tested for correlation.

2. Materials and methods

2.1. Sampling

The study population consisted of a subset of individuals from a birth cohort study (LUKAS2) in Eastern Finland, for which the mothers of the study subjects were recruited at Kuopio University Hospital (Karvonen et al., 2009). The children were born between May 2004 and May 2005, and the blood samples from 54 children (26 male, 28 female) were collected from the same individuals at the ages of 1 year (range 0.97–1.06) in 2005/2006, 6 years (5.71–6.32) in 2010/2011 and 10.5 years (9.90–10.95) in 2014/2015 (5 mL serum tube, Vacutainer (Becton Dickinson, BD®, Plymouth, UK)). The blood samples were centrifuged for 10 min at 800 $\times g$ to separate the serum fractions, which were stored frozen at −20 °C until analysis. All chemical analyses were performed in 2016 to reduce analytical and methodological variations. Although some of the samples were stored frozen for several years, the chemical stability of PFASs implicates that archiving the samples under such conditions would have negligible effects on the quality of the data (Houde et al., 2006). Written informed consent was obtained from all parents of the participants and the study was approved by the Research Ethics Committee, Hospital District of Northern Savo, Kuopio, Finland (case number 48/2004 and amendments).

2.2. Sample treatment and chemical analysis

At the beginning of the serum analysis, 2.5 ng of mass labelled internal standard for quantitation of PFASs was added to the 0.2 mL serum sample (for a substance list see Table S1). Each sample was extracted with 0.3 mL of 20 mM ammonium acetate in methanol. Prior to instrumental analyses the extracts were diluted with Milli-Q water (1:2 parts, water:extract), and the samples were filtered with 0.2 μm syringe filters (Pall Life Sciences, Ann Arbor, MI). Twenty PFASs (perfluorohexanoic acid, PFHxA; -heptanoic acid, PFHpA; -octanoic acid, PFOA; -nonanoic acid, PFNA; -decanoic acid, PFDA; -undecanoic acid, PFUnDA; -dodecanoic acid, PFDoDA; -tridecanoic acid, PFTrDA; -tetradecanoic acid, PFTeDA; -hexane sulfonic acid, PFHxS; -heptane sulfonic acid, PFHpS; -octane sulfonic acid, PFOS; -decane sulfonic acid, PFDS; *N*-methyl-perfluorooctane sulfonamidoacetic acid, MeFOSAA; *N*-ethyl-perfluorooctane sulfonamidoacetic acid, EtFOSAA; perfluorooctane sulfonamide, FOSA; *N*-methyl-perfluorooctane sulfonamide, MeFOSA; *N*-ethyl-perfluorooctane sulfonamide, EtFOSA; 6:2 polyfluoroalkyl phosphoric acid diesters, 6:2 diPAP; 8:2 polyfluoroalkyl phosphoric acid diesters, 8:2 diPAP) were analyzed using liquid chromatography negative ion electrospray tandem mass spectrometry (LC-ESI-MS/MS). The details of LC-MS/MS parameters have been published earlier (Koponen et al., 2013). A seven point matrix-matched standard curve with concentrations ranging from 0.075 to 50 ng/mL ($r^2 > 0.992$ for each compound) was used for quantitation. The lowest concentration point with acceptable signal to noise ratio and chromatographic peak area was used as the limit of quantitation (LOQ) (details in Koponen et al., 2013), see Table S2 for a LOQ list of the different analytes. Chromatographic peak integration was undertaken with the help of the Xcalibur 2.0.7 software, and the final serum concentrations were calculated in Microsoft Excel.

For quality control, a blank sample and an in-house control serum sample were analyzed in the same way as the real serum samples with each serum sample batch. PFAS levels in the blank samples (n = 3)

were below the LOQ, therefore blank subtraction was not performed. The coefficient of variation for the inter-batch repeatability for PFASs from the in-house control serum sample was 2.6–9.9%. Accuracies determined as concentration relative to the target PFAS concentrations in the in-house control serum sample were 107–134%. These values were considered acceptable with a method uncertainty of 35% obtained from the validation data parameters of accuracy and repeatability.

2.3. Body burden calculations and statistics

The body burdens of the most frequently detected PFASs (PFHxS, PFOS, PFOA and PFNA) were estimated based on serum PFAS concentrations (conc.) and body weights (bw) of the children via the following equation (see Thompson et al., 2010):

$$\text{body burden } (\mu g) = \text{serum conc.} \left(\frac{\mu g}{mL}\right) \times \text{VD} \left(\frac{mL}{kg\ bw}\right) \times \text{bw(kg)} \quad (1)$$

The volumes of distribution (VD) by Thompson et al. (2010) were applied. For PFOA, 170 mL/kg bw was used and also assumed for PFNA and the volume of distribution of 230 mL/kg bw for PFOS was also applied for PFHxS. This extrapolation was justified based on rodent studies that demonstrated volumes of distribution for PFCAs with different chain-lengths to be in the same range (Han et al., 2012).

Statistical analyses were performed with the IBM SPSS Statistics software (version 24, IBM Corp.) or JMP (JMP 12.Ink). All compounds with a detection frequency of < 60% were excluded from statistical analyses, for all other compounds data below the LOQ were replaced by LOQ divided by two. Differences between male and female children were investigated using the Student's *t*-test. To test the differences in PFAS serum concentrations and body burdens between different ages, a repeated-measures ANOVA with a Greenhouse-Geisser correction and Bonferroni post-hoc tests was performed (SPSS 24). Pearson correlation coefficients (r) were calculated to evaluate the association between children's PFAS serum concentrations and breastfeeding duration and children's body mass index (BMI). Correlations between a) floor dust concentrations (n = 50) (Winkens et al., 2018) and serum/body burden levels and b) indoor air concentrations (n = 46) (Winkens et al., 2017a) and serum/body burden levels at the age of 10.5 years were analyzed with Spearman rank tests (ρ).

3. Results

3.1. Longitudinal trends in serum concentrations during childhood

The quantitation frequency of all analyzed PFASs is shown in Table S1. Four PFASs (PFHxS, PFOS, PFOA, PFNA) had a quantitation frequency of > 60% at all studied ages. PFOA and PFOS were quantified in all samples and PFNA in > 98% of the samples, whereas the quantitation frequency of PFHxS declined slightly with age (from 87 to 74%). PFDA was also quantified in 70% of the samples at 1 year of age, but the quantitation frequency decreased with age to slightly below 60%. Among the sulfonamides, MeFOSAA was the most frequently detected compound with 91% at the age of 1 year. After year one, the quantitation frequency of PFHpA, MeFOSAA and EtFOSAA declined to 48–67%, whereas the quantitation frequency increased for PFUnDA with age (5.6, 33 and 31% at 1, 6 and 10.5 years). PFHxA, PFDoDA, PFTrDA, PFTeDA, PFHpS, PFDS, FOSA, EtFOSA and 8:2 diPAP were not detected above the LOQ in any sample and were thus excluded from any further data treatment and discussion.

The median serum concentrations of the most frequently quantified PFASs were in the following order: PFOA > PFOS > PFNA > PFHxS, with concentrations at the age of 1 year, respectively: 6.6, 5.5, 0.80 and 0.47 ng/mL and at the age of 6 years, respectively: 2.7, 2.1, 0.54 and 0.42 ng/mL (Fig. 1). At 10.5 years of age, the median serum concentrations of PFOS and PFOA declined to the same level of 1.5 ng/mL, PFNA was 0.36 and PFHxS 0.21 ng/mL. Serum concentrations of PFOS, PFOA, PFNA and PFHxS decreased significantly between 1, 6 and 10.5 years ($p < 0.001$), but for PFHxS the decrease was not significant between 1 and 6 years ($p = 0.16$). There was no difference in the longitudinal trend between males and females, with the exception of PFNA, which was not significantly decreasing for males between 6 and 10.5 years. The largest absolute range among all compounds' concentrations was observed for PFOS at the age of 1 year (1.7–40 ng/mL; Fig. 1). The absolute and relative variance and the median of the sum of PFAS concentrations among the individuals decreased with increasing child age. The concentration of each PFAS homologue for all individuals grouped by sex is shown in stacked bars per age in Figs. S1, S2 and S3 and Table S3. With the exception of PFOA at 10.5 years ($p < 0.01$, higher for males), there was no significant difference in serum concentrations of PFASs between children's sexes (Table S4).

The PFASs' serum composition for different ages is shown in Fig. S4a and S4b. PFASs that were not quantified in any sample were excluded from the composition calculation. PFOS and PFOA were the predominant compounds, together accounting for 80, 73 and 73% of the median concentrations at the age of 1, 6 and 10.5 years, respectively. They were followed by PFNA (5.6, 8.1 and 9.0%) and PFHxS (3.0, 6.3 and 5.0%, Fig. S4a and S4b). However, it should be noted that the contribution of a single substance differed greatly among the individuals (Fig. S4a). As an example, the contribution of PFOS at the age of 1 year ranged from 24% to 68% (Fig. S4a). The median contribution of PFNA and PFDA increased with age, which is the opposite to what was observed for PFOA. The contribution of other quantified PFASs (PFUnDA, EtFOSAA, 6:2 diPAP and MeFOSA, shown as “other” in Fig. S4a and S4b), appeared to increase with age. The contribution of these less frequently quantified PFASs is likely overestimated due to their very low quantitation frequency and the inclusion of samples < LOQ as LOQ divided by two. The contribution of MeFOSAA seemed to be constant with age. However, due to the very low quantitation frequencies at later ages, this needs to be interpreted with caution.

3.2. Body burden during childhood

In contrast to the decreasing trends of PFOS, PFOA, PFNA and PFHxS in serum concentrations, the body burdens stayed unchanged or were even increasing with age, except for PFOA in females. Significantly higher body burdens were observed in male than in female children at 10.5 years of age for PFNA, PFHxS and PFOA ($p < 0.05$, 0.01 and 0.001, respectively, Table S4). At 6 years of age, PFOA body burdens were lower for females than for males ($p < 0.01$). Due to these differences among the sexes (Table S4), the body burden longitudinal trends were plotted separately for the sexes in Fig. 2. Longitudinal trend analysis of the body burdens revealed that there was a significant increase in PFNA and PFHxS body burden for both sexes between 1 and 6 years ($p < 0.01$) and for PFHxS in males between 1 and 10.5 years ($p < 0.001$). The increase of the PFNA body burden between 1 and 10.5 years was significant for both genders ($p < 0.001$). The PFOA body burden did not change significantly over time for males. However, for female children, the PFOA body burden decreased comparing 1 year of age to later ages ($p < 0.05$). For PFOS the body burdens did not change significantly between 1 and 6 years but increased between 6 and 10.5 years ($p < 0.05$).

3.3. Correlation of PFAS concentrations with other factors

There was a significant positive correlation ($p < 0.001$) between the duration of breastfeeding and the serum concentrations of PFOS, PFOA, PFNA and PFHxS at the age of 1 year ($r = 0.52$, 0.67, 0.60 and 0.60, respectively; Fig. 3). The linear increase between serum concentration and breastfeeding duration was the lowest for PFHxS and PFNA (slopes: PFHxS = 0.06 and PFNA = 0.07 ng/mL/month, compared to 0.61 for PFOA and 0.85 ng/mL/month for PFOS).

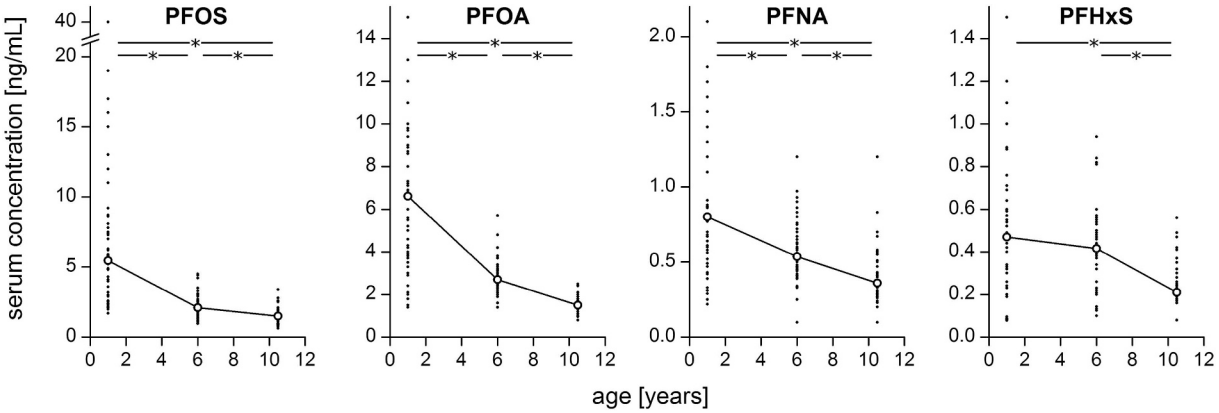

Fig. 1. Serum concentrations of PFOS, PFOA, PFNA and PFHxS (ng/mL) in children aged 1, 6 and 10.5 years (n = 54). Asterisks indicate statistically significant differences between ages. Open circles represent median values.

The serum concentration of PFASs did not correlate with the body mass index (BMI) at any age. Early life serum concentrations were not related to BMIs at later years either (1 vs. 6 and 1 vs. 10.5).

No significant correlation for any PFAS was found between air (Winkens et al., 2017a) and serum concentrations (n = 46, both sampled at the age of 10.5 years). However, a weak correlation was observed between PFNA body burdens and 8:2 FTOH air concentrations ($\rho = 0.35$; $p < 0.05$), as well as for the PFOS body burdens and MeFOSE air concentrations ($\rho = 0.33$; $p < 0.05$). There were also some statistically significant, albeit weak positive correlations (all $\rho \approx 0.3$; $p < 0.05$) between the PFNA and PFOA body burdens and several long-chain PFCAs in air (Table S5). There were some weakly positive and significant ($p < 0.05$) correlations between dust (Winkens et al., 2018) and serum concentrations (PFOA dust and PFHxS serum, as well as linear EtFOSAA and sum branched EtFOSAA dust and PFOA serum, Table S6). The body burden of PFOS was negatively related to 8:2 and 10:2 FTOH concentrations in dust ($\rho = -0.28$ and $\rho = -0.32$, respectively, $p < 0.05$). PFOA dust concentrations were positively related to the body burden of PFHxS and PFNA ($\rho = 0.34$ and $\rho = 0.35$, respectively, $p < 0.05$).

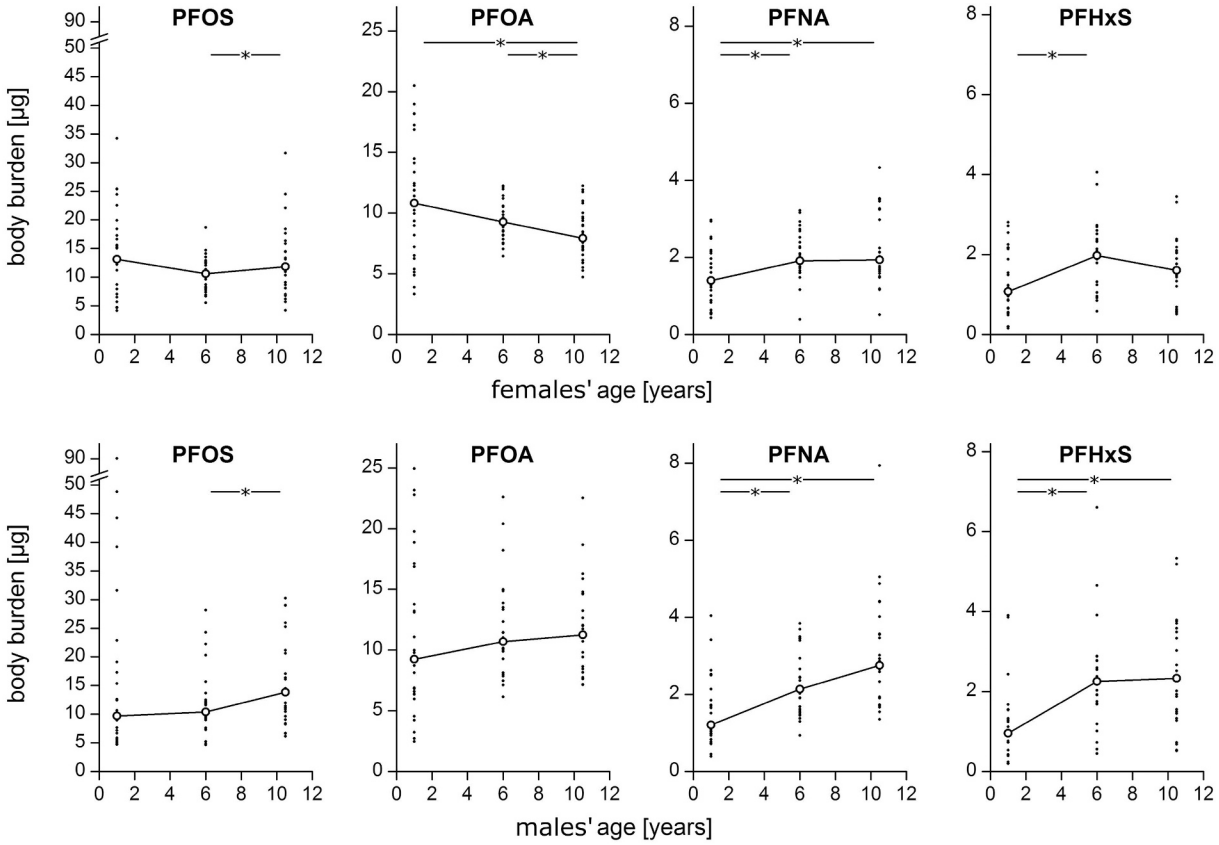

Fig. 2. Body burden of PFOS, PFOA, PFNA and PFHxS (µg) in female (n = 28) and male (n = 26) children aged 1, 6 and 10.5 years. Asterisks indicate statistically significant differences between ages. Open circles represent median values.

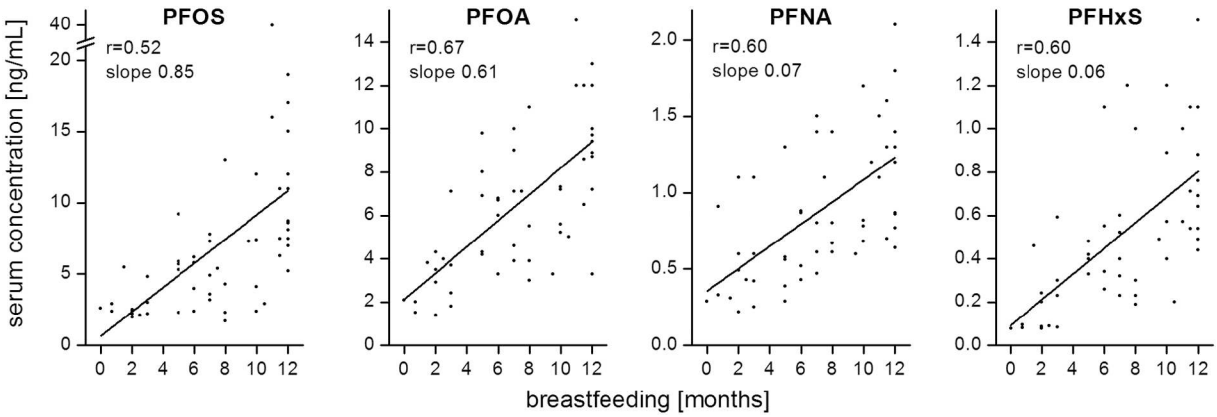

Fig. 3. Children's serum concentration of PFOS, PFOA, PFHxS and PFNA at the age of 1 year plotted against breastfeeding duration in months; children n = 54; note the different scales of y-axes.

4. Discussion

4.1. Longitudinal trends of PFASs in children's serum

To the best of our knowledge, there are only three longitudinal studies of PFASs in children (Fromme et al., 2010; Gyllenhammar et al., 2016; Mogensen et al., 2015), excluding some exposed population studies with mostly two recorded time points. Overall, the peak concentrations of PFOS, PFOA, PFNA and PFHxS at year 1 in this study were in good agreement with previous observations. However, given the different study designs it is difficult to say at what exact age the serum concentrations start to decrease after the maximum. Fromme et al. (2010) investigated infants' serum concentrations at birth with repeated measurements at 6 and 19 months (sampling in 2007–2009). They found a similar composition of PFASs as in our study with concentrations in the order PFOA > PFOS > PFNA > PFHxS. Serum levels increased sharply from birth until 6 months of age and dropped until the next measurement at 19 months (Fromme et al., 2010). Mogensen et al. (2015) reported a downward trend of the serum concentrations for all four PFAAs for children between 11 months and 5 years (sampling in 1997–2000), which is consistent with the trend between 1- and 6-year-olds in the present study. Gyllenhammar et al. (2016) sampled 4-year-old children in Sweden in 2008, which was approximately at the same time we took samples from the 6-year-old Finnish children (2010/2011), and PFOS, PFOA and PFNA serum concentrations were similar at these child ages between the two studies. In contrast to our study, the serum concentrations in the Swedish cohort stayed at the same level and did not decrease at later child ages (4 and 12 years).

To summarize the trend of serum concentrations throughout childhood, there seems to be a sharp increase in PFAS concentrations during the first month(s) of infancy or childhood (Fromme et al., 2010; Verner et al., 2016), followed by a drop (Mogensen et al., 2015; Verner et al., 2016 and our study). The sharp increase is due to the high importance of breastmilk as a PFAS source for infants (Haug et al., 2011; Mogensen et al., 2015; Verner et al., 2016), which is corroborated by the strong correlations between serum concentrations of PFOS, PFOA, PFNA and PFHxS at year 1 and the duration of breastfeeding in the present study and in others' (Mogensen et al., 2015; Verner et al., 2016). The serum concentration drop has its onset after ablactation as the child receives a lower exposure from other sources (Verner et al., 2016). Thereafter, the serum concentrations decrease only slightly (our study, at the age of 6 years) or stay constant until the age of 10.5/12 years (our study; Gyllenhammar et al., 2016). For some individuals, the serum concentration stayed constant (or was even increasing) during childhood. A possible reason for this trend is a lower PFAS exposure in early life, either caused by no or a lower breast milk consumption or a lower PFAS concentration in breastmilk. These children lack the sharp increase in PFAS serum concentrations during the first month(s) of infancy or childhood. The variation in longitudinal trends after ablactation between different studies may be based on sampling year, geographical and exposure source differences. The population in Gyllenhammar et al. (2016) was studied due to concerns based on elevated drinking water concentrations of mainly PFHxS and PFOS (Gyllenhammar et al., 2015). It should also be noted that in the present study, PFHxS did not show a statistically significant decrease between 1 and 6 years of age indicating significant post-lactation exposure.

4.2. Serum concentrations at different child ages

Generally, the serum concentrations observed in the present study were in the same range as in other studies investigating children of similar age. Serum concentrations were comparable to those reported in other studies close to 1 year of age (Fromme et al., 2010; Haug et al., 2009; Toms et al., 2009). The Norwegian study by Haug et al. (2009) was outlying with low PFOA levels (1.6 and 2.6 ng/mL, for 0- to 1-year-olds and 1- to 4-year-olds, respectively) in comparison to the range of 4.6–8.2 ng/mL observed in the present and other studies (Fromme et al., 2010; Toms et al., 2009). Toms et al. (2009) sampled 0.5- to 1-year-olds and 1- to 1.5-year-olds in Australia and presented concentrations that were mostly higher for PFHxS (1.9 and 2.0 ng/mL), PFOS (9.7 and 10.5 ng/mL) and PFOA (7.0 and 7.7 ng/mL) than those in the present study and in the before listed studies. The median serum levels in 6-year-old Finnish children from the present study were at the low end for PFHxS, PFOS, PFOA and PFNA when compared to background exposed children of similar age living in Germany (Hölzer et al., 2008) and in Texas, USA (Schecter et al., 2012). The 9- to < 13-year-old children in Texas (Schecter et al., 2012) had again higher levels for PFOS, PFOA, PFNA and PFHxS (6.3, 3.0, 1.3 and 1.6 ng/mL, respectively) compared to the 10.5-year-old Finnish children (1.5, 1.5, 0.36 and 0.21 ng/mL, respectively). It is noteworthy that the sampling in Texas took place 5 to 6 years before the Finnish sampling in 2014/2015 and we know that production has gone down for PFOA-based chemicals during that period (Wang et al., 2014) and for PFOS-related compounds after the phase-out. Therefore, serum levels likely have declined as well, which has at least been shown for PFOA, PFOS and PFOS precursors for female adults (Gebbink et al., 2015; Glynn et al., 2012). Further, exposure to PFASs in Texas may be different from Finland due to geographical differences in uses of materials and products.

4.3. Body burden during childhood

Even though the serum concentrations of the four main PFASs decreased at some point during childhood (Fig. 1), body burdens were constant or even increased with age, with the exception of PFOA for females, which was decreasing (Fig. 2). This demonstrates that the decrease in serum concentrations is a consequence of growth dilution rather than net-elimination from the body. Longitudinal concentration trends in serum can therefore be misleading for understanding trends of intakes from external exposure during childhood if they are not corrected for an increased body weight and blood volume. For PFOA and PFOS, the body burden does not change significantly during early childhood (age 1 to 6 years). This means that external exposure intake rates are similar to total elimination rates via renal and biliary clearance leading to a steady-state situation. However, for PFNA and PFHxS the external exposure intakes exceeded the total elimination, leading to a continuous accumulation of these compounds right after ablactation (1 to 6, or partly even 1 to 10.5 years). The different trend in body burdens of PFOA/PFOS compared to PFNA/PFHxS in early childhood stages may be due to a combination of several factors. Firstly, PFOA and PFHxS are more readily transferred from the mother to cord blood than PFNA and PFOS and the PFCAs more than PFSAs comparing the same chain length (Beesoon et al., 2011; Fromme et al., 2010; Gützkow et al., 2012; Kim et al., 2011b, 2011a; Liu et al., 2011; Mondal et al., 2014; Pan et al., 2017; Zhang et al., 2013a) and PFOA is more readily transferred via breastmilk than PFNA (Liu et al., 2011; Mondal et al., 2014). These factors combined with the fact that PFOS and PFOA are typically the predominant compounds in mothers' serum with the highest median concentrations (Cariou et al., 2015; Monroy et al., 2008; Papadopoulou et al., 2016) mean that a higher prenatal and likely lactational exposure occurs for these compounds compared to PFNA and PFHxS. This is supported by the flatter increase of PFNA and PFHxS serum concentrations at 1 year of age with increasing breastfeeding length in comparison to the far steeper increase of PFOA and PFOS (Fig. 3). Secondly, although there are currently no data on elimination rates in children, the data from adults consistently demonstrate that PFHxS is more slowly excreted than PFOS whereas PFNA is more slowly excreted than PFOA (Gomis et al., 2017; Olsen et al., 2007; Zhang et al., 2013b). The slower elimination of PFNA/PFHxS would require a longer time of continuous exposure intake before a steady-state is reached. Thirdly, a further explanation for the increasing body burden of PFNA/PFHxS after the age of 1 year could be that the exposure pathways are different from those of PFOA/PFOS, i.e. the PFAS substances occur in different exposure media, which have varying exposure relevance depending on the age (Fig. 2). Mogensen et al. (2015) have hypothesized that the level of PFHxS in early life stages is not solely affected by breastmilk. It could rather be influenced by other exposure sources, such as indoor air and dust. Behavioral and developmental changes during early life stages and childhood affect exposure routes, exposure factors and the body burden (Winkens et al., 2017b). Such changes include for instance diet (from breast milk to baby food and finally to solid food), but also the amount of consumed food or water related to the body weight, and a peak in dust ingestion rates and frequency in hand to mouth contact events between the age of 1 and 3 years (Winkens et al., 2017b). Exposure via dust ingestion and/or direct contact with consumer products for toddlers may, therefore, help to explain the increasing body burdens post lactation (Björklund et al., 2009; Shoeib et al., 2011), or even the delayed increase of PFOS body burdens between 6 and 10.5 years.

4.4. Factors affecting PFAS serum concentrations and body burdens

As discussed above, the duration of breastfeeding was a significant predictor of serum concentrations for PFHxS, PFOS, PFOA and PFNA at the age of 1 year. This is supported by previous studies, which showed a correlation between infants' and mothers' serum concentrations (Mogensen et al., 2015; Mondal et al., 2014; Papadopoulou et al., 2016), mothers' serum and breastmilk concentrations (Fromme et al., 2010; Liu et al., 2011) and that the majority (≥83%) of the estimated daily intake of PFOS and PFOA comes from breastmilk (Haug et al., 2011). PFHxS and PFNA serum concentrations in infants had linear relationships with breastfeeding duration with the lowest slopes in our study. This is supported by the lack of significance in correlations between breastfeeding length and serum concentrations of PFHxS and PFNA for < 3.5-year-olds (Mondal et al., 2014) and for 3-year-olds for PFNA (Papadopoulou et al., 2016).

In addition to the positive associations between breastfeeding length and PFASs in serum, we observed weak positive correlations between the body burden of PFNA/PFOS and indoor air concentrations of 8:2 FTOH/MeFOSE, respectively. Similar observations have previously been interpreted as evidence that intake and metabolism of precursor compounds from indoor air significantly contribute to the serum concentration of PFAAs. Fraser et al. (2012) reported correlations between 6:2, 8:2 and 10:2 FTOH office air and PFOA serum concentrations in adults ($\rho = 0.60$ for 8:2 FTOH) and Makey et al. (2017) between 10:2 FTOH bedroom air and PFOA and PFNA serum concentrations in pregnant women, as well as MeFOSE air and PFOS serum concentrations. The weaker associations between air concentrations and body burdens in the present study suggest that the exposure to PFAS precursors via air is relatively less important for Finnish children compared to the North American adults. The studies' sample sizes were slightly smaller or comparable to the present study (Fraser et al., 2012; Makey et al., 2017). It should further be noted that the body burdens of PFOA and PFNA in the present study were correlated to several long-chain PFCAs in indoor air (Table S5). This association cannot be logically explained by any metabolism pathway (as the C—C bonds in a perfluorinated carbon chain are stable) and thus might be based on co-correlating exposure via different pathways. This is also the case for the dust concentrations of PFOA that correlated weakly positively with the serum concentrations of PFHxS and body burdens of PFHxS and PFNA. Further studies including paired measurements of PFAAs and precursors in several exposure media and human serum would help to clarify the exposure relationship and identify potential confounding factors. It also has to be considered that the air and dust concentrations present a short time window and might vary over time, whereas both the serum concentration and body burden are an integrated measure of several years and are influenced by all possible exposure pathways (transplacental transfer, skin contact, air inhalation, dust, breastmilk, food and drinking water) (Winkens et al., 2017b).

4.5. Sex differences and elimination mechanisms in children

In our study, there were no significant differences in PFAS serum concentrations between sexes, with the exception of lower PFOA concentrations in females at the age of 10.5 years compared to males. Further, females had lower body burdens of PFOA at 6 and 10.5 years of age compared to males, as well as of PFNA and PFHxS at the age of 10.5 years. For other compounds and ages no differences in body burdens were found. Higher PFAS concentrations were found in adult males than in females when several thousand individuals were included (Kärrman et al., 2006; Kato et al., 2011; Toms et al., 2009), whereas studies with smaller sample sizes failed to find any differences among sexes for adults (Kannan et al., 2004; Zhang et al., 2010). For children, lower serum concentrations for females are reported within some studies (Toms et al., 2009; Zhang et al., 2010), whereas others did not find any differences between sexes for children (Frisbee et al., 2010; Olsen et al., 2004; Schecter et al., 2012). In pharmacokinetic modelling studies, menstruation and elimination losses during and after pregnancy (placental transfer and breastfeeding) partly explained lower PFOS and PFOA serum concentrations for adult females compared to males (Gomis et al., 2017; Wong et al., 2014). As the children in our study did

not reach the age of puberty yet (i.e. menstruation among females), dietary habits, hormonal or even behavioral characteristics may have led to the differences between sexes for some PFASs at the age of 10.5 years or partly 6 years. Considering temporal changes, especially the decrease in PFOA body burdens for female children is different from the rather constant body burdens for male children between 1 and 10.5 years (Fig. 2).

PFAS serum concentrations were previously analyzed in Finnish adults aged between 25 and 50 years in 2007 (Koponen and Kiviranta, 2018), which is close to the sampling year of the children at 1 year of age in the present study (sampling in 2005/2006). Adults' serum was dominated by six PFASs (PFHxS, PFOS, PFOA, PFNA, PFDA and PFUnDA). In the present study, PFUnDA was quantifiable in 5.6% of the children's serum samples at 1 year of age, but exceeded 30% at later ages. The higher detection frequency of PFUnDA in adults would support the accumulation with age and suggests a slow elimination. Furthermore, PFUnDA is less well transferred from the mother to the child via transplacental transfer in comparison to PFOA (Zhang et al., 2013a). PFOA had higher median serum concentrations in 1-year-olds than in Finnish adults. PFNA, PFDA and PFOS serum concentrations in the present study were comparable between 1-year-olds and adults, but lower for older children, possibly due to growth dilution. PFCAs are more easily transported through the transplacental barrier than PFSAs and short-chain PFCAs are more easily transported than long-chain PFCAs (up to PFUnDA) (Beesoon et al., 2011; Zhang et al., 2013a). This might explain why there is a difference in the serum level between 1-year-olds and adults for some compounds, but not for others. Adults' PFHxS concentrations were higher than children's at any age. Mogensen et al. (2015) hypothesized a different source for PFHxS during early life exposure than breast milk, which may explain the lower concentrations for PFHxS and would be supported by the steeper regression line between breastfeeding duration and serum concentration for PFOS in comparison to PFHxS (Fig. 3). The range of concentrations for single compounds between individuals is clearly highest among 1-year-olds, which also points toward breastfeeding as the most important exposure pathway for early life stages (Haug et al., 2011), as its duration is highly variable and after ablactation other exposure sources are comparable within a background exposed population.

5. Conclusion

Uptake and elimination of PFASs during childhood is complex and dynamic and we need to consider not only serum concentrations, but also body burdens in order to obtain an unbiased picture of PFAS exposure. The changes over time and disparity between decreasing serum concentrations and partly increasing body burdens are likely caused by other collinear temporal changes. Among those are a) growth dilution due to an increase in blood volume and body mass, b) different transfer efficiencies via transplacental transfer and breast milk, c) discrepancies between elimination and uptake (steady state not reached), d) variations in elimination rates with age, e) production changes that affect single exposure media's concentrations, and f) behavioral and physiological changes that lead to an altered relative importance of specific exposure media, which can have different PFAS patterns (Winkens et al., 2017b). PFHxS and PFNA display increasing temporal trends in body burden during early childhood, whereas PFOS and PFOA display no net-changes between 1 and 6 years, or even a shift toward net-elimination for females and PFOA. The causes for this and for the sex dependent differences for some compounds should be investigated more closely in future studies.

It is worth briefly considering the strengths and weaknesses of this study to support future study designs. The notable strengths of this study are; a) there are few previous longitudinal childhood exposure studies so this study fills an important data gap, b) state of the science analytical methods are used to quantify 20 PFASs, c) complementary data on PFASs in dust and air in the children's bedrooms are available at 10.5 years, and d) there are many other metadata available for performing statistical analyses. Notable weaknesses are; a) the relatively few participants compared to some epidemiological studies, b) the lack of matched serum and breast milk PFAS concentrations for the mothers, c) the lack of dietary samples for the children at the sampling time points, d) the lack of air and dust samples for the 1- and 6-year sampling time points, e) few (three) sampling time points in total, and f) the lack of sampling time points in the early months of life.

Finally, we recommend that longitudinal childhood exposure should be further investigated for PFASs in order to assure that the current regulation, which relies mostly on data from studies on adults, also protects children. There is concern that children, especially in the first few months of life, may have a higher sensitivity and vulnerability to chemicals than adults (Bruckner, 2000; Holsapple et al., 2004; Scheuplein et al., 2002). Future studies should have more sampling time points in the early months and years following birth in order to pinpoint and better understand the peak and decline in serum concentrations as well as the temporal shifts in body burdens. Additionally, an overall assessment of the multiple exposure pathways, which could be coupled to serum concentrations, is needed to understand the causes of trends for different PFASs among sexes, individuals and sub-populations.

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Appendix A. Supplementary data

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