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Multiple pathways of human exposure to poly- and perfluoroalkyl substances (PFASs): From external exposure to human blood

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ABSTRACT

Exposure to PFASs may result in adverse health effects. This study aimed to characterise the exposure to PFASs from diet, house dust, indoor air, and dermal contact and the relative contribution from different external exposure pathways to human serum concentrations. Daily intakes of 18 perfluoroalkyl acids (PFAAs) and 12 PFAA precursors from diet, dust ingestion, inhalation of indoor air and dermal absorption were estimated using a comprehensive dataset comprising 61 adults from the Oslo area, Norway. Concentrations of PFAAs and PFAA precursors in house dust, indoor air, hand wipes, foods and drinks were utilised to estimate the daily intakes. Perfluorooctanesulfonate (PFOS) was the predominant PFAS in serum for this study group. On a median level, perfluorooctanoate (PFOA) contributed most to the total estimated daily intake of PFAAs, with a median intake of 280 (range: 72–1810) pg·kg bw^{-1}·day^{-1}, covering both direct and indirect (precursors) exposure. Out of this, only 3% (range: < 1–48%) of the total PFOA intake came from indirect exposure. Dietary exposure from ingestion of food and drinks was in general the predominant exposure pathway, followed by exposure from ingestion of house dust, inhalation of indoor air, and dermal absorption, but considerable variations were observed among individuals. House dust ingestion and indoor air inhalation contributed most to the total intakes for some participants, for which most of them were among the 20% participants with the highest total estimated intakes. Some statistical significant associations between concentrations of PFASs measured in serum and estimated intakes were observed. Measured serum concentrations and modelled serum concentrations based on external exposure estimates were in the same order of magnitude for PFOS, PFHxS, PFOA, and PFNA, but only PFOA concentrations were comparable, 1.9 and 2.0 ng mL^{-1} for observed and modelled serum concentrations, respectively. The estimated daily intakes of PFASs in this study were lower than the health-based guidance values, e.g. the tolerable weekly intakes derived by EFSA. This study underlines the importance of performing studies considering multiple exposure pathways on an individual basis.

1. Introduction

Poly- and perfluoroalkyl substances (PFASs) are a broad range of synthetic organofluorine compounds. PFASs have been applied to numerous consumer products as surfactants due to their unique physicochemical properties (Prevedouros et al., 2006). The production of PFASs began around the 1950s. During the last two decades, PFASs have received increased attention from both the public and the scientific community because they are widespread and persistent in the environment and several of them bioaccumulate in wildlife and humans. Further, associations between concentrations of PFASs in human blood, in particular, perfluoroalkyl acids (PFAAs) such as perfluoroalkyl sulfonates (PFSAs, $C_nF_{2n+1}SO_3H$) and perfluoroalkyl carboxylates (PFCAs, $C_nF_{2n+1}COOH$) and a range of health outcomes have been observed in epidemiological studies (Bach et al., 2015; Olsen et al., 2009; Steenland et al., 2010). A range of toxicological effects have also been observed in animal studies including carcinogenicity, hormonal disruption, and immunotoxicity (Lau et al., 2007; Rand and Mabury, 2017).

Potential pathways of human exposure to PFASs include dietary and non-dietary ingestion, inhalation, and dermal absorption. Humans can be exposed to PFAAs through both direct and indirect exposure. Direct exposure to PFAAs occur when PFAAs are present in for example the diet or in house dust, and thus human are exposed to the PFAAs through, e.g., ingestion. Among the PFSAs and PFCAs, perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) have

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been restricted and regulated globally or under region legal frameworks (OECD, 2015; REACH, 2014; Stockholm Convention, 2009; U.S. EPA, 2000). Another group of PFAAs, perfluoroalkyl phosphonates (PFPAs) has been recognised as emerging due to their occurrence in the environment such as in wastewater (Llorca et al., 2012), surface water (Jin et al., 2015) as well as indoor dust (De Silva et al., 2012). Indirect exposure to PFAAs may occur through the intake of PFAA precursors, which are biotransformed to PFAAs in our bodies. For example, fluorotelomer alcohols (FTOHs), polyfluoroalkyl phosphate esters (PAPs), perfluoroalkyl sulfonamides (FOSAs) and sulfonamidoethanols (FOSEs) can be transformed to ionic PFAAs (Dagnino et al., 2016; Martin et al., 2010; Xie et al., 2009). Previous studies have indicated that indirect exposure can contribute to human exposure to PFASs (D'eon and Mabury, 2011b; Gebbink et al., 2015; Vestergren et al., 2008). Many previous studies have assessed associations between external exposure to PFASs and serum concentrations including a single source, for example, diet (Haug et al., 2010), dust (Fraser et al., 2012), or air (Makey et al., 2017). However, very limited data exist on the relative contribution of various external exposure pathways based on data from the same individuals. In a previous study from our research group intakes from multiple external pathways were compared to internal doses for 41 individuals, but only data on PFOS and PFOA are available and this study only included women in child bearing age (Haug et al., 2011). Furthermore, dermal exposure was not included.

The aim of this study was to estimate daily intakes of a broad range of PFASs from various external exposure pathways, including diet and house dust ingestion, indoor air inhalation, and dermal absorption through hand wipes, and compare to serum PFAS concentrations. Furthermore, the relative contribution of each exposure pathway was to be explored.

2. Materials and methods

2.1. Study group

This study was conducted within the A-TEAM (Advanced Tools for Exposure Assessment and Biomonitoring) project. The study group consisted of 61 adults (45 women, 16 men) between 20 and 66 years old, who were living in the Oslo area, Norway. The sampling campaign was conducted between November 2013 and April 2014. Details on the sample collections are described elsewhere (Papadopoulou et al., 2016). In brief, the set of samples was obtained from each participant during two consecutive days. The 1-day duplicate diet samples and the hand wipe samples were collected in accordance with instructions by the participants themselves, while researchers collected residential indoor and personal air, house dust (i.e. floor dust, elevated surface dust at higher than 0.5 m above the floor, and vacuum cleaner bag dust), and biological samples (serum, plasma, whole blood). Blood samples were collected at the participants' convenience but within 1–2 weeks from the house visit. Detailed information about dietary habits, a variety of personal characteristics and personal behaviours, and house characteristic of the participant were collected through questionnaires as well as a food diary.

The Regional Committees for Medical and Health Research Ethics in Norway (Reference number 2013/1269) reviewed and approved the study. All participants completed a written consent before participating.

2.2. Sociodemographic characteristics

The following demographic characteristics collected via questionnaires were considered potential determinants of serum PFAS concentrations: gender (woman/man), age (< 41 years/≥ 41 years), parity (nulliparous/primiparous and multiparous), body mass index (BMI, $< 25\ kg/m^2/\geq 25\ kg/m^2$), birth country (Norway/other), and birth country of participants' mothers (Norway/other).

2.3. PFAS intakes from indirect exposure

Estimated total daily individual intakes (described in Section 2.4) included both direct intakes of PFAAs and indirect intakes of PFAAs from the biotransformation of PFAA precursors. However, data on the biotransformation of PFAA precursors to PFAAs are not easily accessible or well understood. Details on biotransformation factors used to calculate indirect exposure are given in Table S3 of SI.

Biotransformation of PFOS precursors (i.e. FOSAs and FOSAs) has previously been observed in animals (Peng et al., 2014; Xie et al., 2009). However, there is lack of biotransformation data for PFOS precursors to PFOS in humans. Similar to Vestergren et al (2008) a biotransformation factor of 0.1 was assumed for the biotransformation of all PFOS precursors to PFOS.

Based on previous studies, there is some evidence that FTOH (e.g., 8:2FTOH) and diPAP (e.g., 8:2diPAP) contribute to body burdens of PFOA (Butt et al., 2014; D'eon and Mabury, 2011a; Dagnino et al., 2016; Fasano et al., 2006). Gomis et al. (2016) used a biotransformation factor of 0.003 for the degradation of 8:2FTOH to PFOA. Further, Butt et al. (2014) has reported lower biotransformation rates of FTOHs to odd carbon number PFCAs compared to even carbon number PFCAs. Thus, one order of magnitude lower biotransformation factors was applied for odd carbon number PFCAs. Biotransformation of 6:2FTOH to PFHxA and PFHpA, 8:2FTOH to PFOA and PFNA, and 10:2FTOH to PFDA and PFUnDA have been considered.

For diPAPs, the initial step of biotransformation is degradation to the respective monoester form (monoPAP), and then further to the respective FTOH (Butt et al., 2014; D'eon and Mabury, 2011a; Dagnino et al., 2016). The biotransformation of PAPs to FTOHs was assumed to be 100% and to further follow the same biotransformation path to PFCAs. The equation below was applied to estimate indirect exposure from PFAA precursors.

$$\text{Indirect EDI} = \text{EDI} \times \text{bf}$$

Indirect EDI is the estimated daily intake of the target PFAA through the biotransformation of PFAA precursors ($pg{\cdot}kg\ bw^{-1}{\cdot}day^{-1}$). bf is the biotransformation factor of the target PFAA precursor to the PFAA (no unit).

2.4. Estimation of daily intakes

As a first step, individual intakes of PFASs from each exposure pathway (ingestion of food and drinks, ingestion of house dust, inhalation of indoor air and dermal absorption) and assessment method (described below) were estimated using individual exposure data and body weight. Data reported in other papers from the A-TEAM study were used for the exposure assessments. (1) Dietary intakes have previously been estimated using three different assessment methods as described in detail in Papadopoulou et al. (2017). In brief, intakes were estimated based on (a) PFAS concentrations measured in duplicate diet samples (separate samples for foods and drinks) (b) multiplying consumption data from food diaries with data on concentrations in food (sixty-eight different kinds of food and drinks) from an extensive database on PFAS concentrations in Norwegian food and drinks (including drinking water) available from previous studies or (c) multiplying consumption data from food frequency questionnaires (FFQs) with concentrations in food from the database (2) Intakes of PFASs from ingestion of house dust were estimated in three ways as described by Papadopoulou et al. (manuscript). Details on collection of house dust samples are given in Papadopoulou et al. (2016), and details on the method used for PFAS determination (e.g. limits of quantification) in house dust is thoroughly described in Padilla-Sánchez and Haug (2016). Intakes were estimated; (a) based on concentrations of PFASs in floor dust from the participants' living rooms (b) based on concentrations in elevated surface dust from the participants' living rooms or (c) based on concentrations in the vacuum cleaner bags from the participants'

houses (3) Exposure to PFASs via inhalation was previously calculated using concentrations of PFAS precursors in indoor air as described by Padilla-Sánchez et al. (2017). However, this present study includes one additional PFASs (i.e., *N*-ethyl perfluorooctanesulfonamide, Et-FOSE, < MDL (50 pg m^3)–13200 pg m^3, median 35 pg m^3) compared to the study by Padilla-Sánchez et al. (2017). Details on the method used for the PFAS determinations are also described in Padilla-Sánchez et al. (2017) (4) PFAS daily intakes from dermal absorption were obtained from the previous study by Poothong et al. (2019). In the previous study, exposure through dermal absorption and hand-to-mouth contact were estimated based on the PFAS concentrations in hand wipe samples. However, only the intake from dermal absorption was used in this study to avoid overestimation, as PFAS intake from dust ingestion was considered to cover also dust on the hands.

This study focused on 18 PFAAs and 12 PFAA precursors in the groups PFSAs, PFCAs, PFPAs, PAPs, FOSAs, FOSEs, and FTOHs. Details on the target PFASs are given in Table S1 of supporting information (SI). Concentrations of PFSAs, PFCAs, PFPAs, PAPs, and FOSAs were available in blood and hand wipes. The same PFASs, as well as FOSEs, had been determined in house dust samples. Only PFAA precursors including FTOHs, FOSAs, and FOSEs had been determined in indoor air samples, while only PFSAs and PFCAs intakes were available from duplicate diet samples (food and drinks), food diaries, and FFQs. Only PFASs detected in more than 45% of the samples were included in the exposure assessments. The serum concentrations and intakes of PFASs in each exposure media can be seen in Table S2 of SI.

Equations applied to estimate individual daily intakes are summarised in Table 1. Uptake fractions from the gastrointestinal tract, lung, and skin were assumed to be 100% (Tian et al., 2016), 100% (Kennedy et al., 2004) and 48% (Franko et al., 2012), respectively. Although a skin uptake fraction was obtained from the total absorbable amount of PFOA in acetone to human epidermis. Thus this estimation might be overestimate for PFOA exposure to human through dermal absorption.

Table 1
Equations applied to estimate daily intakes (EDI) of PFASs from different exposure pathways.

Exposure pathways and equations	Unit	Ref. value
Dietary ingestion:	pg·kg bw^{-1}·day^{-1}	
$EDI_{food} = \frac{C_{food} \times Q_{food} \times F_{uptake-GIT}}{bw}$		
C_{food}: the concentration of the target PFAS in food	pg g^{-1}	
Q_{food}: the amount of food consumed daily	g day^{-1}	
$F_{uptake\text{-}GIT}$: the uptake fraction of PFASs via the gastrointestinal tract	No unit	100%[a]
Dust ingestion:	pg·kg bw^{-1}·day^{-1}	
$EDI_{dust} = \frac{C_{dust} \times Q_{dust} \times F_{uptake-GIT}}{bw}$		
C_{dust}: the concentration of the target PFAS in house dust	pg g^{-1}	
Q_{dust}: the daily dust intake	g day^{-1}	0.05[b]
$F_{uptake\text{-}GIT}$: the uptake fraction of PFASs via the gastrointestinal tract	No unit	100%[a]
Indoor air inhalation:	pg·kg bw^{-1}·day^{-1}	
$EDI_{air} = \frac{C_{air} \times Q_{air} \times F_{uptake-lung}}{bw}$		
C_{air}: the concentration of the target PFAS in indoor air	pg m^{-3}	
Q_{air}: the daily inhalation rate	m^3 day^{-1}	13.3[b]
$F_{uptake\text{-}lung}$: the uptake fraction of PFASs via the lungs	No unit	100%[d]
Dermal absorption:		
$EDI_{dermal} = \frac{Q_{hw} \times t_{exp} \times F_{uptake-dermal}}{bw}$	pg·kg bw^{-1}·day^{-1}	
Q_{hw}: the mass present on hands based on the amount in hand wipes of the target PFAS	pg	
t_{exp}: the exposure duration in one day	day^{-1}	1
F_{dermal}: the uptake fraction of PFASs absorbed through the skin	No unit	48%[e]

bw: individual body weight (kg), uptake fractions:
[a] Tian et al. (2016).
[b,c] U.S. EPA (2011).
[d] Kennedy et al. (2004).
[e] Franko et al. (2012).

As a second step, total daily PFAS intakes were estimated. Direct exposure from PFAAs and indirect exposure from PFAA precursors were taken into account when estimating total daily intakes. Details on which PFAA precursors have been considered for each PFAA can be seen in Table S9 of SI.

For estimation of total daily PFAS intakes one assessment method had to be selected for each exposure pathway. Exposure from inhalation of indoor air and exposure from dermal adsorption were already limited to one assessment method. The total estimated intakes included direct intakes of PFAAs and indirect intakes of PFAAs from the biotransformation of PFAA precursors.

Among the three dietary assessment methods, estimated intakes based on food diaries was selected, as estimates of individual daily intake through food/drinks. There is several reasons for this; only PFOS and PFOA concentrations were detected in the duplicate diet samples; significant correlations for PFOS and PFOA were obtained between all three assessment methods (Papadopoulou et al., 2017); a significant correlation between the estimated PFHxA intakes based on food diaries and the blood concentration was found (Table S5 of SI); the other exposure pathways represent short-term exposure, i.e. intakes from air, dust and dermal absorption, and food diaries also represent short-term exposure.

Estimated intakes based on PFAS concentrations in elevated surface dust was selected as a proxy for intakes from ingestion of dust, as this type of dust are considered more relevant for exposure assessment than floor dust and vacuum cleaner bag dust, as floor dust and vacuum cleaner bag dust may comprise small pieces of food etcetera. Furthermore, similar to dietary intakes based on food diaries, intakes of indoor air, and dermal absorption based on concentrations in hand wipes, intakes based on elevated surface dust represent short-term exposure.

As a third step, the estimated total intakes were compared to measured serum concentrations as described in Section 2.5.

2.5. Modelling serum concentrations based on their estimated daily intakes

A simple one-compartment pharmacokinetic (PK) model with first order clearance was used to model serum concentrations of PFASs (C_P, ng mL^{-1}) as a function of the intake, the elimination rate, and the volume of distribution (Thompson et al., 2010). A steady-state exposure condition and a constant dose from estimated daily intake of PFASs was assumed. Serum PFAS concentrations were modelled using the following equation:

$$CP = DP/(kP * Vd)$$

CP is the modelled serum concentration of the target PFAS (ng mL^{-1}). DP is the estimated total daily intake of the target PFAS (ng·kg bw^{-1}·day^{-1}) including both direct and indirect exposure as described in Sections 2.3 and 2.4. kP is the first order elimination rate of the target PFAS (ln 2 divided by the elimination half-life in days). The biological elimination half-lives of PFHxS, PFOS, and PFOA were based on the results of a recent study reporting serum half-lives of 5.3, 3.4, and 2.7 years for PFHxS, PFOS, and PFOA, respectively (Li et al., 2018). The elimination half-life of PFNA was set to 3.2 years (Zhang et al., 2013). Vd is the volume of distribution of the target PFAS (mL·kg bw^{-1}). Volumes of distribution for PFOS and PFOA were set to 230 and 200 mL kg^{-1}, respectively (Gomis et al., 2017). A previous study on the toxicokinetics of PFCAs in rats reported that the volumes of distributions were not different among PFCAs (Ohmori et al., 2003). Thus, to simplify the estimation, volumes of distribution of 230 and

200 mL kg^{-1} were used for all PFSAs and PFCAs, respectively.

Biomonitoring data of PFASs was obtained from a previous study by Poothong et al. (2017). According to the previous study, whole blood is a more appropriate matrix than serum/plasma for assessing internal exposure to PFHxA and PFOSA (Poothong et al., 2017). Thus, PFOSA and PFHxA concentrations in whole blood were used when exploring association to estimated external intakes, while concentrations in serum were used for the other PFASs.

2.6. Statistical analysis

PFASs with detection frequencies above 45% of the samples were included in statistical analyses, and values below the MDLs were replaced by their MDLs divided by the square root of two. The normality of the PFAS distributions was assessed statistically by Shapiro-Wilks test and visually by histograms. A Mann-Whitney *U* test was used to assess significant differences in serum PFAS concentrations between two groups of population characteristics. Spearman's rank correlation coefficient (*rho*) was used to examine bivariate correlations between PFAS concentrations in serum and estimated PFAS intakes. All statistical tests were performed using the SPSS 24. Statistical significance was defined as p-value < 0.05.

3. Results and discussion

3.1. Population characteristics

The median age of the participants was 41 years (range: 20–66 years). Median body weight of the participants was 69 kg, with a median body mass index (BMI) of 24 kg m^{-2}. Most participants (93%) had an education of more than 12 years. Middle-aged or older participants (≥41 years old) had significantly higher blood concentrations of PFDS, PFNA, PFDA, PFUnDA, and PFTrDA than younger participants (Table S4 of SI). Significant higher concentrations of PFHxS, PFHpS, PFOS, and PFOA were found in men compared to women. Only PFOA concentrations were significantly lower in parous women than in nulliparous women. Significantly, higher concentration of PFUnDA and PFTrDA were observed in participants with BMI < 25 kg m^{-2} compared to participant with BMI ≥ 25 kg m^{-2}. Participants born in Norway had significantly higher levels of PFDS, PFNA, and PFUnDA than the ones born aboard. Participants whose mothers were born in Norway had significantly higher blood concentrations of PFOS, PFDS, PFNA, PFDA, PFUnDA, PFDoDA, and PFTrDA, compared to those with mothers born aboard. Understanding the characteristics of the population, their behaviours and the relationship between these characteristics and the internal dose is crucial knowledge when assessing exposure based on human biomonitoring.

3.2. Associations between biomonitoring data and estimated daily intakes

Bivariate correlations between PFAS serum concentrations and daily intakes (pg·kg bw-1·day − 1) were assessed. Association between serum concentration and dietary intakes using the three different approaches, i.e. duplicate diet, food diaries, and FFQs can be seen in Table S5 of SI. Except a significant negative correlation between PFOA in serum and PFOA intake estimated via the duplicate diet data ($r_s = -0.33$, $p < 0.01$), and an interesting positive correlation between PFHxA in whole blood and PFHxA in food diaries ($r_s = 0.29$, $p < 0.05$), no significant correlations between serum concentrations of PFASs and dietary intakes of the corresponding compound were observed. This finding is in agreement with a previous study of Norwegian women where no significant associations between dietary intakes of PFOS and PFOA and the corresponding compounds in serum were observed (Haug et al., 2011). However, it is in contrast to a study from Norway where the participants had a large variation in consumption of fish and seafood, and significant correlations between dietary intakes of PFOA, PFOS, and PFUnDA and corresponding serum concentrations were found (Haug et al., 2010). Although the estimated dietary intakes did not explain variations in serum concentrations, this does not necessarily mean that ingestion of food is not a significant exposure pathway for PFASs. A likely reason is that the estimated dietary intakes do not sufficiently reflect temporal variations in dietary intakes over several years. Also, this study group was relatively small.

Associations between PFAS serum concentrations and the corresponding estimated intakes from ingestion of dust were assessed (Table S6 of SI). Positive correlations between PFOA concentrations in serum and PFOA intakes based on elevated surface dust ($r_s = 0.28$, $p < 0.05$) and vacuum cleaner bag dust samples ($r_s = 0.33$, $p < 0.01$) were seen. A significant and positive correlation for PFNA was found between PFNA in serum and the corresponding intake via floor dust ($r_s = 0.29$, $p < 0.05$). In addition, several correlations between intakes of PFAA precursors from dust and PFAA concentrations in serum, such as serum PFOS with MeFOSE in floor dust ($r_s = 0.27$, $p < 0.05$), serum PFOA and 8:2diPAP in elevated surface dust ($r_s = 0.3$, $p < 0.05$) were observed. In agreement with a former study from the US (Makey et al., 2017), no significant correlations between PAP intakes based on vacuum cleaner bag dust and serum PFOA concentrations were observed.

Several positive and significant correlations between PFCAs in serum samples and intakes of their precursor compounds from the indoor air were found (Table S7 of SI). Significant positive correlations were observed between air intakes of 10:2FTOH and serum PFUnDA ($r_s = 0.27$, $p < 0.05$). Intakes of 8:2FTOH from the air was significantly correlated with serum PFNA ($r_s = 0.25$, $p < 0.05$). No correlation was found between intakes of 6:2FTOH and serum PFCA concentrations. Also, in previous studies from the US, FTOH concentrations in indoor air were significantly correlated to serum PFOA concentrations (Fraser et al., 2012; Makey et al., 2017), while this was not the case in a former Norwegian study (Haug et al., 2011). Moreover, positive and significant correlations were found between whole blood PFOSA concentrations and MeFOSE and EtFOSE intakes from indoor air ($r_s = 0.4$–0.48, $p < 0.01$), but no correlation between intakes of MeFOSE from air and serum PFOS concentrations were observed.

A significant and positive correlation between serum PFDS and dermal intake of the corresponding compound was found ($r_s = 0.27$, $p < 0.05$) (Table S8 of SI), while no significant correlations between dermal intakes of PFAA precursors and serum concentrations of the corresponding compounds were observed. Presently no other studies have reported correlations between PFAS concentrations in human serum and dermal intakes from hand wipes. The lack of a correlation between PFAS dermal intakes and serum concentrations of the corresponding compound may relate to low contributions of dermal intakes to the total intake.

3.3. Total daily intakes of PFASs

Median relative contributions from direct and indirect exposure are shown in Fig. 1. Direct exposure to PFOA contributed most to intakes from the diet, house dust, and dermal absorption. While indoor air inhalation was dominated by indirect exposure from the PFOA precursor, 8:2FTOH. Previous studies on indoor air have revealed higher levels of PFAA precursors than PFAAs, and thus highlighted the potential importance of PFAA precursors as a source of PFAA exposure (De Silva et al., 2012; Eriksson and Kärrman, 2015; Martin et al., 2010; Shoeib et al., 2011). However, it should be noted that only PFAA precursors were included in the measurement of indoor air in this study. PFOPA was the only PFPA that contributed to the median daily intake of PFASs. This finding is in agreement with the low concentration of PFPAs detected in serum/plasma/whole blood of the same study group (Poothong et al., 2017).

Although indirect exposure pathways contributed minimally to the total exposure, some significant positive correlations between PFAA blood concentrations and indirect intakes from biodegradation of PFAA

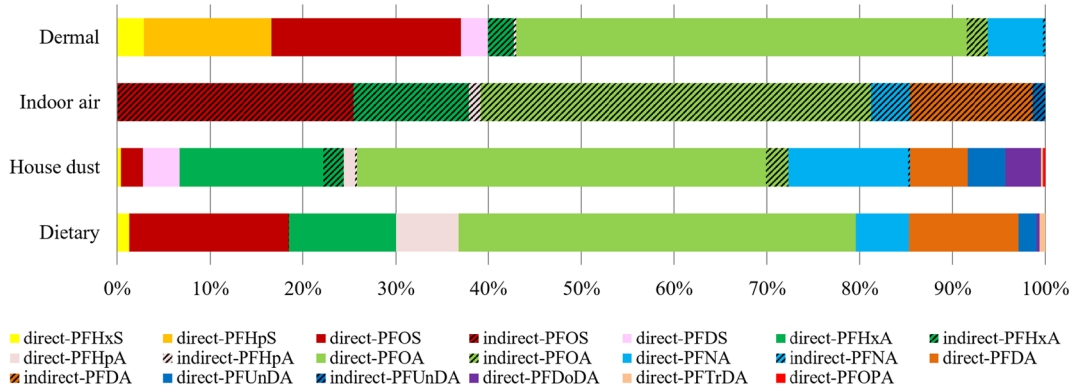

Fig. 1. Median relative contributions (%) of estimated direct and indirect (precursor) intakes to the total PFAS intake via multiple pathways.

precursors were observed (Table S5–S8 of SI). These results suggest that also indirect exposure to certain PFASs may have an impact on the internal dose of these PFASs over time, even though indirect exposure does not represent the major part of the present exposure.

Summary statistics for estimated daily intakes of PFASs (pg·kg bw^{-1}·day^{-1}) from these route-specific intakes are described in Table 2. PFOA dominated the total daily intakes of PFASs, followed by PFOS > PFDA > PFHxA > PFHpA ≈ PFNA > PFUnDA. The median total PFOA and PFOS intakes (i.e., the sum of the route-specific intakes for individuals) were 280 (range: 72–1810) pg·kg bw^{-1}·day^{-1}, and 133 (range: 16–1710) pg·kg bw^{-1}·day^{-1}, respectively. While the total intakes for PFDA, PFHxA, PFHpA, PFNA, and PFUnDA were 88, 77, 42, 42, and 18 pg·kg bw^{-1}·day^{-1}, respectively. Total daily intakes below 10 pg·kg bw^{-1}·day^{-1} were found for PFHxS, PFHpS, PFDS, PFDoDA, PFTrDA, and PFOPA.

Direct exposure to PFOA from diet contributed most to the total intake of PFASs with a median intake of 248 pg·kg bw^{-1}·day^{-1}. Exposure to PFASs from ingestion of food and drinks was also identified as the dominant exposure pathway in general populations in previous studies (Fromme et al., 2009; Trudel et al., 2008; Vestergren and Cousins, 2009). Haug et al. (2011) reported PFOA intakes of 240 pg·kg bw^{-1}·day^{-1} for the Norwegian adults. Also, in a Swedish study based on samples from 1999 to 2010, dietary PFOA intakes between 350 and 690 pg·kg bw^{-1}·day^{-1} were reported (Vestergren et al., 2012).

This finding may indicate that the exposure to PFOA from the diet has decreased in recent years, possibly because of several regulations being issued, even though such comparisons are difficult due to methodological differences.

The European Food Safety Authority (EFSA) has established tolerable weekly intakes (TWIs) of PFOA and PFOS of 6 ng·kg bw^{-1}·$week^{-1}$, and 13 ng·kg bw^{-1}·$week^{-1}$, respectively (EFSA, 2018). Thus, the median estimated total intakes of PFOA and PFOS in this study were lower than TWIs, being 2.0 (0.50–13) and 0.93 (0.11–12) ng·kg bw^{-1}·$week^{-1}$ for PFOA and PFOS, respectively. The US EPA derived

Table 2
Estimated daily intakes of PFASs on an individual body weight basis (pg·kg bw^{-1}·day^{-1}), n = 61.

	PFHxS	PFHpS	PFOS	PFDS	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	PFOPA
Dietary intake													
Mean	11		156		90	47	269	38	72	45	5.4	10	
Median	**7.6**		**100**		**67**	**39**	**248**	**33**	**69**	**11**	**2.0**	**3.4**	
Min	0.90		12		8.8	3.3	41	4.0	11	0.76	0	0	
Max	63		845		464	136	866	137	244	792	79	127	
P95	24		365		284	100	519	77	131	217	24	29	
House dust ingestion													
Mean	3.4		27	2.2	14	3	66	15	22	3.9	12	0.39	1.2
Median	**0.07**		**0.40**	**0.65**	**2.9**	**0.27**	**8.5**	**2.2**	**1.0**	**0.67**	**0.63**	**0.04**	**0.04**
Min	0.005		0.005	0.07	0.31	0.05	0.21	0.04	0.01	0.01	0.01	0.01	0.02
Max	192		1480	50	308	109	1570	182	701	94	486	11	22
P95	1.9		17		42	11	177	65	85	13	23	1.0	3.9
Indoor air inhalation													
Mean			58		4.7	0.47	17	1.7	7.0	0.70			
Median			**3.5**		**1.7**	**0.17**	**5.7**	**0.57**	**1.8**	**0.18**			
Min			1.0		0.38	0.04	0.84	0.08	0.41	0.04			
Max			951		46	4.6	217	22	124	12			
P95			576		19	1.9	63	6.3	30	3.0			
Dermal absorption													
Mean	0.33	3.7	0.32	0.17	0.15	0.02	1.4	0.35					
Median	**0.03**	**0.13**	**0.19**	**0.03**	**0.03**	**0.003**	**0.49**	**0.06**					
Min	0.01	0.02	0	0.01	0	0	0	0					
Max	13	52	4.0	3.6	3.3	0.33	20	2.5					
P95	0.79	19	0.82	0.44	0.46	0.05	3.9	1.5					
Total intakes													
Mean	14	3.7	241	2.4	109	51	353	55	101	50	18	11	1.2
Median	**8.1**	**0.13**	**133**	**0.73**	**77**	**42**	**280**	**42**	**88**	**18**	**4.2**	**3.8**	**0.04**
Min	0.96	0.02	16	0.09	25	8.7	72	11	15	1.4	0.01	0.02	0.02
Max	213	52	1710	51	471	138	1810	251	715	795	486	127	22
P95	29	19	849	8.4	334	103	682	130	181	222	42	31	3.9

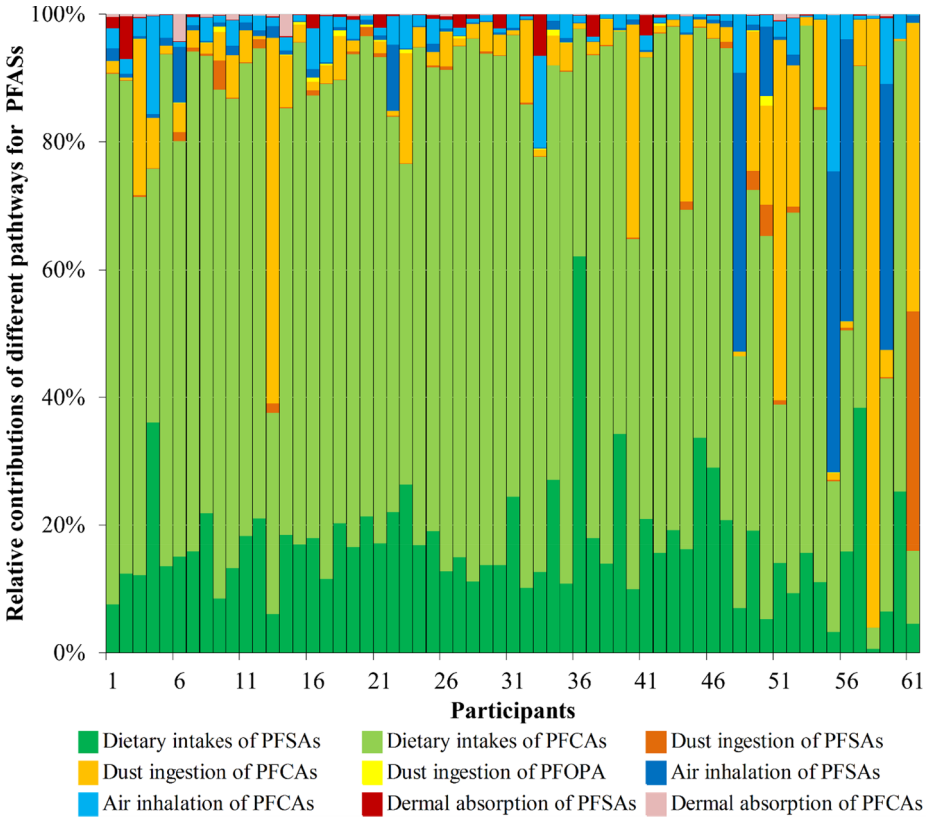

Fig. 2. Relative contribution (%) of multiple exposure pathways for PFAAs in individuals.

oral non-cancer reference doses (RfDs) for both PFOA and PFOS of 20 ng·kg bw^{-1}·day^{-1} (U.S. EPA, 2016a, 2016b), and the maximum estimated individual daily intakes of PFOA and PFOS in this study group are also considerably lower than these RfDs. A recent report from the Agency for Toxic Substances and Disease Registry (ATSDR), U.S. defined the Minimum Risk Levels (MRLs) of PFOA, PFNA, PFOS, and PFHxS based on laboratory animal data at 3, 3, 2, and 20 ng·kg bw^{-1}·day^{-1} (ATSDR, 2018). Interestingly, the maximum PFOS and PFOA intakes in this study were close to the MRLs.

3.4. Relative importance of multiple external exposure pathways

The relative contribution of specific exposure routes for individuals is shown for PFASs in Fig. 2. The participants have been organised with increasing estimated total daily intakes from left to right of the figure (222–4480 pg·kg bw^{-1}·day^{-1}).

The estimated total individual PFAS intakes of each participant can be seen in Fig. S1 of SI. In general, dietary intakes contributed most to the total intake of PFASs, followed by house dust ingestion, indoor air inhalation, and dermal absorption. On a median level, dietary intakes represented 91% of the total intake for PFAAs, but the range was from 4% to 98%. In comparison, ingestion of house dust and inhalation of indoor air contributed 3% (range: < 1%–95%) and 2% (range: < 1%–72%) of the total estimated intake, respectively. Only 0.3% (< 1%–7%) of the total intake originated from dermal absorption.

Previous studies have suggested that human exposure to PFASs occur primarily through the diet (Fromme et al., 2007; Haug et al., 2011; Trudel et al., 2008; Vestergren and Cousins, 2009). However, results presented in this study also showed that other exposure pathways might be of importance. Interestingly, house dust ingestion and indoor air inhalation contributed most to the total intakes for some participants, and most of them were among the 20% participants with the highest total estimated intakes. This result is similar to Haug et al. (2011) where significant positive association between serum and house dust highlighted the importance of indoor environment as an exposure pathway for PFASs. Also on an individual level, ingestion of food, drinks, and dust as well as inhalation of air appear to be more dominant exposure routes than dermal absorption in this study.

When looking at the individual exposure pathways, diet contributed to 92% of the PFOA total intake, while house dust, indoor air, and dermal absorption contributed to 4%, 3%, and less than 1% of the total PFOA intake (Fig. S2 of SI). For PFOS 95% and 3% of the total PFOS intake came from dietary intakes and air inhalation, respectively. Dust ingestion and dermal absorption contributed less than 1% of the PFOS total intake. This finding is in agreement with a previous study from Norway, where ingestion of food was the primary exposure pathway for PFOA and PFOS, and the intakes from food and drinking water represented more than 90% of the total intakes (Haug et al., 2011).

3.5. Comparison between modelled serum concentrations and biomonitoring data

For the four most prevalent compounds in serum (PFHxS, PFOS, PFOA and PFNA), a comparison between the measured serum concentrations and the estimated daily intakes was performed using a one-compartment PK model. Estimated daily intakes were used to model serum concentration using the PK model, and these modelled concentrations were further compared to the corresponding concentrations determined in serum. Despite uncertainties in the parameters included, this model has previously been successfully applied to estimate total intakes of PFOS and PFOA in amongst others the Australian population (Thompson et al., 2010). Bivariate correlations between the observed and modelled serum concentrations were assessed, a significant positive correlation between the observed and modelled serum concentrations was seen only in PFOS ($r_s = 0.29$, $p < 0.05$). Scatter plots illustrating the observed and modelled serum concentrations are presented in Fig. 3. The observed and modelled serum PFOA concentrations were comparable, being 1.9 and 2.0 ng mL^{-1}, respectively. This finding is in

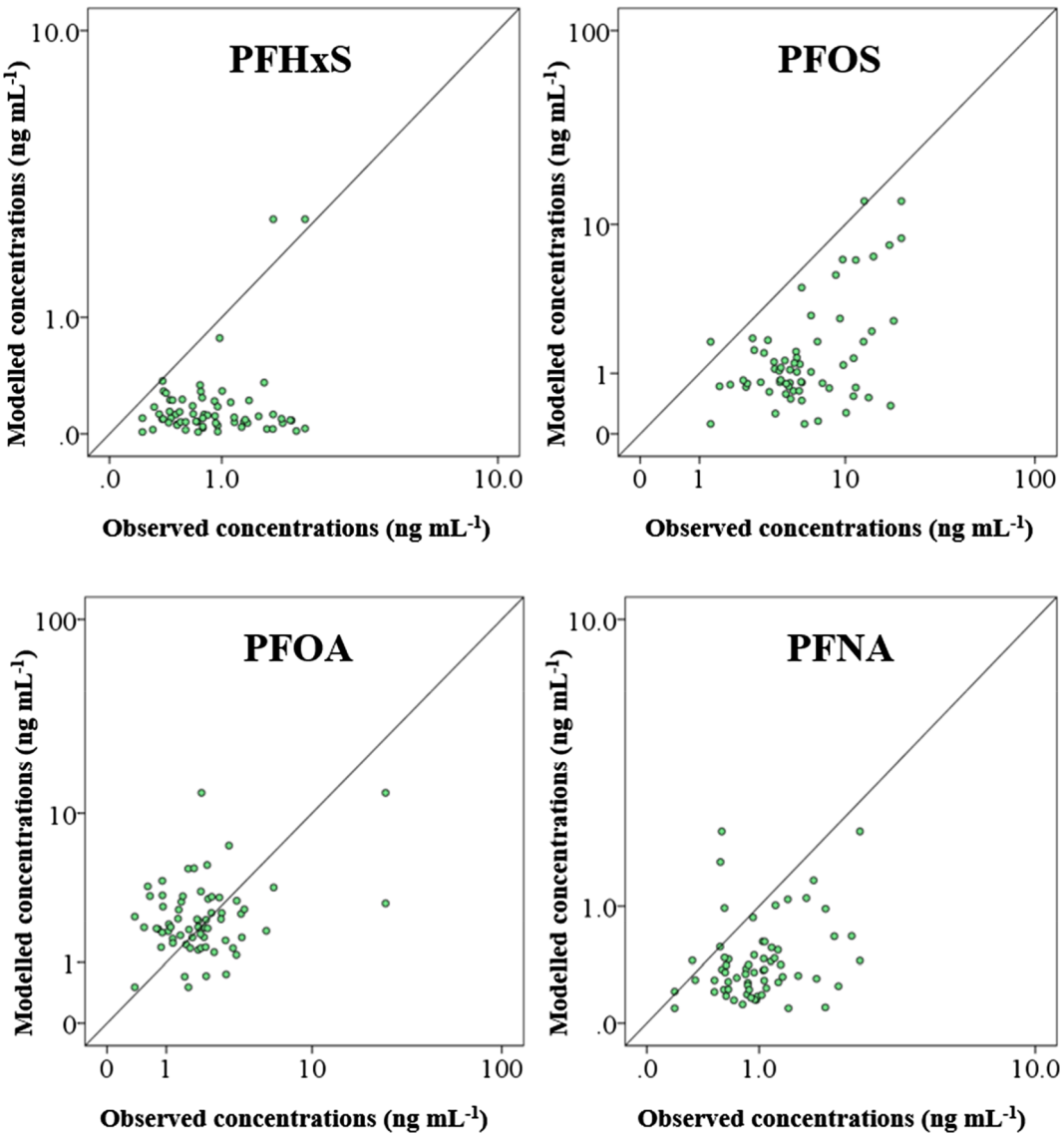

Fig. 3. Scatter plots between observed and modelled serum concentrations (ng mL^{-1}) of PFHxS, PFOS, PFOA, and PFNA. Both axes are presented in a logarithmic scale.

agreement with what was found in the study by Haug et al. (2011). Based on the estimated daily intakes, the model underestimated the serum concentrations of PFHxS, PFOS, and PFNA by a factor of 7, 4, and 3, respectively. Finding higher observed serum concentrations of PFHxS, PFOS, and PFNA than modelled concentrations is reasonable, as the modelled concentrations only consider present intakes, which are thought to be lower than a few years ago, while the observed serum concentrations reflect past exposure due to the long elimination half-life of these compounds in humans. The finding indicates that the exposure to some PFAAs has decreased in recent years.

The difference between the observed and modelled serum concentrations for PFOS found in the present study is in contrast to what was seen in a previous Norwegian study where comparable concentrations were reported (Haug et al., 2011). This contrast could be due to the fact that the estimated intakes in the previous study were based on samples collected closer to the phase-out of PFOS in the year 2000 (U.S. EPA, 2000), which resulted in higher estimated intakes compared to the present study.

4. Study limitations

The sample size of the study group was relatively small (n = 60), which limits the statistical power. Several uncertainties are associated with the estimated intakes due to lack of knowledge on absorption rates, biotransformation rates, etcetera. In this study, only dermal exposure through the hands was considered, but it is likely the most exposed human skin area. However, this study has assessed multiple methods for assessment of each exposure pathway, and compared to biomonitoring data from the same individuals.

5. Conclusions

As PFASs are ubiquitously distributed throughout the environment, general populations are exposed to PFASs through several exposure pathways including dietary and non-dietary ingestion, inhalation, and dermal absorption. In this study, biomonitoring data and estimated intakes including several exposure pathways for adults in Norway are presented. To our knowledge, this is the first study that assesses multiple methods for assessment of exposure from the same exposure

pathway, and both direct and indirect exposure has been considered. On average, ingestion of food and drinks is the most significant exposure pathway for PFASs. However, we observed considerable variation in the contribution of each exposure pathway between individuals, and this was most pronounced for the individuals with the 20% highest estimated PFAS intakes. Modelled serum concentration based on intakes was comparable to measured serum concentration for PFOA. For PFNA, PFHxS, and PFOS the modelled serum concentrations were lower than the measured concentrations in blood, suggesting a higher past than present exposure. The estimated daily intakes of PFASs in this study group were lower than the present health-based guidance values, e.g. the TWIs derived by EFSA (when converted to TWIs) and the Minimum Risk Levels in the recent ATSDR report from the U.S.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105244.

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