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Estimating human exposure to PFOS isomers and PFCA homologues: The relative importance of direct and indirect (precursor) exposure

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ABSTRACT

Contributions of direct and indirect (via precursors) pathways of human exposure to perfluorooctane sulfonic acid (PFOS) isomers and perfluoroalkyl carboxylic acids (PFCAs) are estimated using a Scenario-Based Risk Assessment (SceBRA) modelling approach. Monitoring data published since 2008 (including samples from 2007) are used. The estimated daily exposures (resulting from both direct and precursor intake) for the general adult population are highest for PFOS and perfluorooctanoic acid (PFOA), followed by perfluorohexanoic acid (PFHxA) and perfluorodecanoic acid (PFDA), while lower daily exposures are estimated for perfluorobutanoic acid (PFBA) and perfluorododecanoic acid (PFDoDA). The precursor contributions to the individual perfluoroalkyl acid (PFAA) daily exposures are estimated to be 11–33% for PFOS, 0.1–2.5% for PFBA, 3.7–34% for PFHxA, 13–64% for PFOA, 5.2–66% for PFDA, and 0.7–25% for PFDoDA (ranges represent estimated precursor contributions in a low- and high-exposure scenario). For PFOS, direct intake via diet is the major exposure pathway regardless of exposure scenario. For PFCAs, the dominant exposure pathway is dependent on perfluoroalkyl chain length and exposure scenario. Modelled PFOS and PFOA concentrations in human serum using the estimated intakes from an intermediate-exposure scenario are in agreement with measured concentrations in different populations. The isomer pattern of PFOS resulting from total intakes (direct and via precursors) is estimated to be enriched with linear PFOS (84%) relative to technical PFOS (70% linear). This finding appears to be contradictory to the observed enrichment of branched PFOS isomers in recent human serum monitoring studies and suggests that either external exposure is not fully understood (e.g. there are unknown precursors, missing or poorly quantified exposure pathways) and/or that there is an incomplete understanding of the isomer-specific human pharmacokinetic processes of PFOS, its precursors and intermediates.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are chemicals that have been used for industrial applications and in consumer products since the 1950s (Buck et al., 2011). Perfluorooctane sulfonic acid (PFOS), and related chemicals such as N-methyl and N-ethyl perfluorooctane sulfonamido ethanols (Me- and EtFOSEs) and -sulfonamides (Me- and EtFOSAs) have been manufactured by electrochemical fluorination (ECF) as a mixture of linear (70%) and branched (30%) isomers (Martin et al., 2010). Production of PFOS and related chemicals was phased out in North America and Europe in 2002 by its main producer. Perfluoroalkyl carboxylic acids (PFCAs) have been manufactured by both ECF (producing both linear and branched isomers) and telomerization processes (producing only linear isomers), and major industrial companies have committed to reduce production and eliminate emissions of PFCAs with a chain length $\geq C_8$, and other chemicals that can degrade to these long-chain PFCAs by 2015 (US EPA, 2006).

Human biomonitoring studies have shown that the general population in several countries has been exposed to perfluoroalkyl acids (PFAAs) such as PFOS and PFCAs, as well as to numerous precursors for several decades and that this exposure has changed over time (Glynn et al., 2012; Lee and Mabury, 2011; Loi et al., 2013; Yeung et al., 2013a,b). Ingestion of dust, food, drinking water and inhalation of air have all been identified as human exposure pathways (De Silva et al., 2012; Filipovic and Berger, in press; Gebbink et al., submitted for publication; Shoeib et al., 2011). PFOS and PFOA exposure of the general population has previously been estimated (Trudel et al., 2008), and in a later study the role of precursor exposure was estimated in human exposure to PFOS and PFOA (Vestergren et al., 2008). Human exposure to PFOS and PFCAs via one or multiple exposure pathways is considered as direct exposure, while exposure to their precursors and subsequent biotransformation of these precursors to PFOS and PFCAs is considered as indirect exposure to PFOS and PFCAs. Precursors that can act as an indirect exposure source to PFOS (i.e. they are biotransformed in humans)

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include FOSEs, FOSAs, and intermediates such as perfluorooctane sulfonamidoacetic acids (FOSAAs) (Tomy et al., 2004; Xie et al., 2009; Xu et al., 2004). Chemicals that can be biotransformed to PFCAs in humans include fluorotelomer-based chemicals such as fluorotelomer alcohols (FTOHs) and FTOH-based polyfluoroalkyl phosphate esters (PAPs) (D'Eon and Mabury, 2011; Martin et al., 2005).

For adults, direct exposure to PFOS and PFOA was estimated by Vestergren et al. (2008) to contribute >92% to the total intake of these two chemicals in a low- and intermediate-exposure scenario, whereas in a high-exposure scenario precursors contributed 50–60% to the total PFOS and PFOA exposure. Direct exposure via diet was estimated to be a major exposure pathway; however, the dietary contribution to the estimated intakes was likely overestimated. Using an improved analytical method, Vestergren et al. (2012) later showed that PFOS and PFOA concentrations in food samples had previously been overestimated by an order of magnitude. Since 2008 more literature data have become available on PFAAs and precursors in exposure media. Precursors to $C_{4,\ 6,\ 8,\ 10,\ 12}$ PFCAs, such as 4:2–12:2 FTOHs and PAPs have been reported in exposure media (De Silva et al., 2012; Gebbink et al., submitted for publication; Langer et al., 2010), however, how much these precursors contribute to human PFCA exposure as an indirect exposure pathway has so far not been investigated. Also, temporal trend studies have reported on declining PFAA and precursor concentrations in food (Gebbink et al., submitted for publication; Ullah et al., 2014). Based on mammal studies, exposure to PFAAs could result in hepatotoxic, developmental, immunotoxic, and hormonal effects (Lau et al., 2007).

In human serum samples, the PFOS isomer pattern has been reported to vary widely, containing between 17% and 52% branched isomers of total PFOS. However, serum samples generally contain a higher percentage of branched isomers relative to linear PFOS compared to ECF isomer pattern (30% sum branched isomers of total PFOS) (Beesoon et al., 2011; Glynn et al., 2012; Gützkow et al., 2012; Karrman et al., 2007; Rylander et al., 2009; Zhang et al., 2013b). The mechanisms or processes causing this enrichment of branched isomers in blood are not fully understood. In rats and humans, isomer-specific differences in uptake and elimination rates for linear and branched PFOS isomers have been observed (Benskin et al., 2009a; De Silva et al., 2009; Zhang et al., 2013a). Also, reported differences in biotransformation rates of branched and linear precursor isomers could influence the PFOS isomer pattern (Benskin et al., 2009b; Peng et al., 2014). PFOS and/or precursor isomers have been identified and quantified in several human exposure media; however, the data are still limited. PFOS isomer patterns have been reported in dust, food, and drinking water, while for PFOS precursors only the FOSA isomer pattern was reported in drinking water (Beesoon et al., 2011; Filipovic and Berger, in press; Gebbink et al., submitted for publication). To date, there is no information available regarding the overall PFOS isomer pattern humans are exposed to via multiple direct and indirect exposure pathways. Studies have shown that branched PFOS isomers affect genes in avian species to a greater extent than the linear isomer (O'Brien et al., 2011).

In this study we tested the following hypotheses: i) based on temporal trend monitoring studies the estimated human exposure to PFOS and PFOA is lower, and the indirect intake is relatively more important compared to previous estimations, ii) given that PFOA is the dominant PFCA in human serum, estimated total intakes for other PFCA homologues (perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluorodecanoic acid (PFDA) and perfluorododecanoic acid (PFDoDA)) are lower than PFOA, and contributions of direct versus indirect exposure vary widely by homologue, and iii) the PFOS isomer pattern in total PFOS intake can help to explain the isomer pattern observed in human serum. The direct and indirect intakes of PFAAs and precursors are estimated through four major exposure pathways (ingestion of dust, dietary and drinking water intake, and inhalation of air) using the latest monitoring data that have become available since 2008 (including samples from 2007).

2. Methodology

2.1. Modelling

The approach used here to estimate the indirect (precursor) contribution to PFOS and PFCA exposure has been previously described by Vestergren et al. (2008) and uses Scenario-Based Risk Assessment (SceBRA) modelling (Trudel et al., 2008). The methodology defines typical low-exposure, intermediate-exposure, and high-exposure to chemicals of the general adult population through multiple pathways. The 5th percentile, median, and 95th percentile of each input parameter are used to represent the low-, intermediate-, and high-exposure scenarios, respectively. The low-exposure scenario represents a "best case" scenario with respect to human exposure to PFAAs, whereas the high-exposure scenario represents a "worst case" scenario. Fig. 1 shows the concept of the estimation of precursor contribution to PFOS and PFCA exposure, and the PFAAs and precursors that are included in this study (see Table S1 for PFAA and precursor chemical structures).

In this study, peer-reviewed data are included that were published after the study by Vestergren et al. (2008). This includes samples that were taken during and after 2007. There have been significant advances in analysis of PFAAs and their precursors in exposure media in recent years (e.g. increased instrument sensitivity and improved understanding of contamination issues) (Berger et al., 2011). Therefore, the use of recent data will not only allow for an assessment of the recent exposure situation but will also allow for a more accurate assessment. Certain PFAAs and precursors were phased out in North America and Europe in 2002, however, they are still produced in some continental Asian countries, especially China (Wang et al., 2014). Therefore, only literature data of samples collected in North America, Europe, Korea, and Japan are included in this study, representing exposure to PFAAs and precursors of the general adult population in industrial countries in the northern hemisphere with similar histories of production and use of PFAS products. Blood serum concentrations of PFCAs in industrial countries (e.g. USA, Europe, and Japan) are similar, and profiles and temporal trends are also similar (Vestergren and Cousins, 2009). This suggests similar exposure to PFAAs in these countries.

In order to determine which parameters were most influential in the intake estimations, the sensitivity (S) is calculated as the change in the output ($\Delta O/O$) as a result of changing input values (I) by a small fixed amount (ΔI). Every input parameter is increased by 1%, thus $(\Delta I/I) = 0.01$.

$$S = \frac{(\Delta O/O)}{\Delta I/I}$$

2.2. Routes of exposure, uptake factors and biotransformation factors

The following human exposure pathways are included in this study: ingestion of dust, food, and drinking water, and inhalation of air. Vestergren et al. (2008) considered additional exposure pathways associated with consumer products such as contact with treated clothes and impregnation sprays, however, these pathways played an insignificant role in the overall exposure to PFOS, PFOA, and their precursors and are therefore not considered in the present study. For each of the pathways considered, intakes are estimated on a per-day basis normalized to body weight (i.e. intakes in units of pg/kg/d). To calculate the contribution of precursors to total PFAA exposure, concentrations of precursors are converted to their respective PFAAs on a molar basis, and in the case of a diPAP with twice the same chain length (e.g., 6:2/6:2 diPAP) the molar concentration is multiplied by two. A summary of the employed literature data of PFAA and precursor concentrations (5th percentile, median, and 95th percentile) measured in dust, air, food, and drinking water can be found in Tables S2–S6. A detailed description of the intake estimations for each exposure pathway can also be found in the Supplementary data.

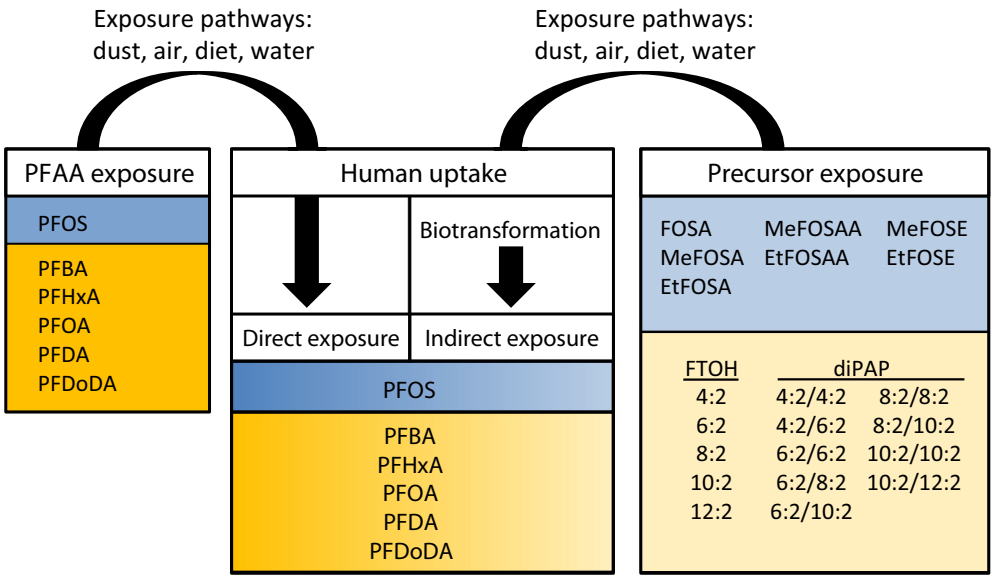

Fig. 1. Schematic of direct and indirect (precursor) exposure pathways for PFOS and PFCAs.

Gastrointestinal (GI) uptake factors are based on rodent studies and were calculated as the fraction of an oral dose recovered in tissues or blood. Uptake factors for the low-, intermediate-, and high-exposure scenarios were previously estimated to be 0.66, 0.80, and 0.91, respectively, for PFOA and PFOS (Trudel et al., 2008). These uptake factors were used for PFOS precursors by Vestergren et al. (2008) due to lack of rodent data for PFOS precursors and are used in the present study. Uptake factors for FTOH were previously reported as 0.27, 0.38, and 0.56, respectively (based on various in vivo and in vitro studies), for the three exposure scenarios (Vestergren et al., 2008) and these values are used in the present study. Due to lack of information for other PFCAs, we use the same uptake factors as for PFOS and PFOA. For diPAPs, the bioavailability in rats was reported to be highly variable depending on the chain length (D'Eon and Mabury, 2011). For example, the bioavailability for 4:2/4:2 diPAP was estimated to 190%, whereas for 10:2/10:2 diPAP the bioavailability could not be calculated because it was not observed in the blood after dosing. The 10:2/10:2 diPAP was, however, reported to be bioavailable to humans as it was detected in human blood samples (D'Eon et al., 2009; Yeung et al., 2013a). As these reports do not give a coherent picture of diPAP uptake factors, the assumption is made here that uptake factors for all diPAPs are the same as for the PFAAs, i.e. 0.66, 0.80, and 0.91 for the three exposure scenarios, respectively. The previously reported bioavailability in rats for the 6:2/6:2 diPAP is therewith comparable with the assumed uptake factor in the intermediate scenario of the present study. For exposure through inhalation the assumption is made that there is complete absorption of the PFAAs and precursors (Vestergren et al., 2008).

Biotransformation of PFOS precursors (EtFOSE and FOSA) to PFOS has been observed in *in vivo* experiments in rats with reported biotransformation factors of 0.095, 0.20 and 0.32 (Seacat, 2000; Seacat et al., 2003; Xie et al., 2009), however, the biotransformation of FOSA to PFOS is likely greater (reported as >0.32), as discussed by Martin et al. (2010). These factors represent the variation of biotransformation factors of precursors to PFOS. As there is no further literature data on biotransformation factors of PFOS precursors, we use these factors for all PFOS precursors in the low-, intermediate-, and high-exposure scenarios, respectively. Biotransformation of fluorotelomer-based compounds (FTOH and PAPs) has been shown to produce multiple PFCAs in *in vivo* and *in vitro* studies, however, metabolism of e.g. 8:2 FTOH or 8:2/8:2 diPAP produced predominantly PFOA and only to a minor extent other chain length PFCAs, such as PFNA (D'Eon and Mabury, 2011; Martin et al., 2005). Therefore, odd carbon number PFCAs are not included in this study. We make the assumption that 4:2-telomer based precursors are metabolized only to PFBA, 6:2-telomer based precursors to PFHxA, 8:2-telomer based precursors to PFOA, 10:2-telomer based precursors to PFDA, and 12:2-telomer based precursors to PFDoDA. Biotransformation factors for FTOHs were earlier estimated by Vestergren et al. (2008) based on literature data as 0.0002, 0.005, and 0.017 for the low-, intermediate-, and high-exposure scenarios, respectively. These factors represent the variation of biotransformation factors of telomer based precursors to PFCAs. Biotransformation factors for diPAPs have been determined using rats, and were shown to be chain-length dependent (D'Eon and Mabury, 2011). DiPAPs with a chain length ≤6:2/6:2 had a biotransformation factor of 0.01, while longer chain length (>6:2/6:2) diPAPs had biotransformation factors around 0.1. These biotransformation factors were used in the intermediate-exposure scenario. As there is no additional literature data available, biotransformation factors for diPAPs in the low-, and high-exposure scenario are chosen as a factor of 10 lower and higher, respectively, compared to the intermediate-exposure scenario. All the model input parameters for estimating the precursor contribution to PFOS and PFCA exposure in the three exposure scenarios are provided in Tables S7–S9 in the Supplementary data.

2.3. Estimating the isomer pattern of total PFOS exposure

Several studies have reported isomer patterns of PFOS and its precursors in different exposure media (Table S10). In Canadian dust samples collected in 2007–2008, Beesoon et al. (2011) reported an isomer pattern of 70% linear and 30% branched PFOS isomers. Although PFOS precursors were detected in the dust samples, no information regarding isomer patterns was provided for these chemicals. Therefore, the basic assumption is made here that the isomer ratio of precursors in dust was 70% linear and 30% branched. However, additional scenarios with varying linear/branched isomer ratios of precursors in dust are also discussed in Section 3.2 including Fig. 4 below. Gebbink et al. (submitted for publication) reported the PFOS isomer pattern in food homogenates representing the general Swedish diet in 2010 as 92% linear and 8% sum branched PFOS. In these same food samples, branched FOSA was below detection limit, but using half the detection limit as hypothetical branched FOSA concentration, a ratio of 98% linear and 2% branched FOSA was estimated. PFOS and FOSA isomer patterns in drinking water collected from several European countries were comparable, i.e., 60% linear PFOS and 58% linear FOSA (Filipovic and Berger, in

press; Ullah et al., 2011). In outdoor air samples, Jahnke et al. (2007) reported linear to branched GC/MS patterns for MeFOSE that were comparable to an ECF standard (although isomers were not quantified); therefore, the basic assumption is made here that PFOS and precursor isomer ratios in air samples are 70/30 linear/branched. Nevertheless, the isomer ratio of both PFOS and its precursors is also varied in different scenarios. Intermediate-exposure scenario parameters are used in order to determine the PFOS isomer pattern that the general adult population is exposed to through the above mentioned pathways. For isomer-specific biotransformation factors and uptake factors different scenarios are discussed in Section 3.2 and in Fig. 4 below. Exposure to linear and branched isomers of PFCAs produced by ECF is not estimated in this study as literature data on PFCA isomers in human exposure pathways is not available or extremely limited.

2.4. Estimating serum PFAA concentrations based on total intakes

Human serum PFAA concentrations are dependent on the pharmacokinetic parameters for the PFAAs as well as the intake rate. Serum concentrations are estimated using a 1st order one-compartment pharmacokinetic (PK) model. The model predicts PFAA serum concentrations as a function of the dose, elimination rate, and volume of distribution, and has been described by Thompson et al. (2010). For the dose estimates, the daily PFAA exposures from direct and indirect intake are used from the intermediate-exposure scenario (Table 1). For PFBA and PFHxA elimination rates ($T_{½}$) and volumes of distribution (V_d), are taken from Chang et al. (2008) and Russell et al. (2013) (PFBA: $T_{½}$ = 0.0086 y, V_d = 220 mL/kg; PFHxA: $T_{½}$ = 0.088 y, V_d = 200 mL/kg). Several studies have estimated elimination half-lives for PFOS and PFOA (Bartell et al., 2010; Brede et al., 2010; Olsen et al., 2007; Wong et al., 2014) and of these reported elimination half-lives the highest and lowest are used to estimate a range of serum concentrations (PFOS: min = 4.2 y, max = 5.4 y; PFOA: min = 2.3 y, max = 3.8 y). Volumes of distribution for PFOS and PFOA are estimated as 230 and 170 mL/kg, respectively (Thompson et al., 2010). For PFDA and PFDoDA elimination half-lives and/or volumes of distribution are not available and serum concentrations are therefore not estimated.

3. Results and discussion

3.1. Direct versus indirect exposure to PFOS

The estimated intakes for PFOS and all individual precursors (assuming no biotransformation) are provided in Table S11. Including biotransformation of precursors, the daily exposures to total PFOS (direct and indirect) are estimated as 89 pg/kg/d, 410 pg/kg/d, and 1900 pg/kg/d for the low-, intermediate-, and high-exposure scenarios, respectively (Table 1, Fig. 2). Of these total PFOS exposures, the relative importance of precursors increases from the low- (11%) to the high-exposure scenario (33%), although the precursor contribution in the high-exposure scenario might be underestimated (see section on PFOS precursor biotransformation factors, Section 2.2) (Tables S12–S14). The relative contribution of each individual intake pathway to the total PFOS daily exposures is displayed in Fig. 3. Direct exposure to PFOS through food consumption is found to be the dominant exposure pathway in the low- and intermediate-exposure scenarios, 86% and 66%, respectively. In the high-exposure scenario, important sources of PFOS still include direct exposure via diet (43%) but also direct exposure via ingestion of drinking water (11%) and dust (13%) and precursor exposure via air inhalation (19%) and dust ingestion (14%). The sensitivity analysis reveals that the GI uptake fraction and PFOS concentration in the diet are the most influential parameters affecting the total PFOS exposure in all exposure scenarios (Fig. S1). The concentration of PFOS in food is today well defined with a large number of studies reporting on PFOS in human diet, but there are only few animal studies reporting the GI uptake fraction.

Table 1
Estimated daily exposures to PFOS and PFCA homologues (pg/kg/d) through direct and indirect intake pathways.

PFAA	Exposure pathway	Exposure scenario		
		Low	Intermediate	High
PFOS	Direct	79	350	1200
	Indirect	10	65	690
	Total	89	410	1900
PFBA	Direct	6.3	19	180
	Indirect	0.01	0.10	4.8
	Total	6.3	19	190
PFHxA	Direct	14	55	340
	Indirect	0.54	7.9	170
	Total	15	63	520
PFOA	Direct	38	200	1100
	Indirect	5.7	75	1900
	Total	44	270	3000
PFDA	Direct	23	48	230
	Indirect	1.3	19	440
	Total	24	67	660
PFDoDA	Direct	22	48	130
	Indirect	0.17	2.7	45
	Total	23	51	180

The estimated total PFOS exposures for all three scenarios are 1–2 orders of magnitude lower compared to estimates reported earlier for adults (Fig. 2) (Trudel et al., 2008; Vestergren et al., 2008). Also, the relative contribution of precursors to total PFOS exposure in the three exposure scenarios differs from the earlier study by Vestergren et al. (2008). In the present study, the precursor contribution in the low-exposure scenario is higher and in the high-exposure scenario lower compared to earlier estimations. However, the relative importance of the different exposure pathways (e.g., diet, dust, air) in the three exposure scenarios is comparable to earlier estimations (Vestergren et al., 2008). The observed differences in total intakes and patterns between the present and earlier estimations could be the result of several factors. A major factor is the overall declining concentrations of PFOS and its precursors in human diet (Gebbink et al., submitted for publication; Johansson et al., 2014; Ullah et al., 2014) and potentially also in other exposure media due to the phase out by 3 M in 2002. This is also reflected in decreasing trends in human serum (Glynn et al., 2012; Yeung et al., 2013b). However, these recent temporal changes in concentrations in PFOS and its precursors cannot fully explain the 1–2 orders of magnitude differences in intake estimates between the present study and Vestergren et al. (2008). Another important factor is the improvement of analytical methods resulting in more accurate (i.e., generally lower) PFOS concentrations in the major exposure pathway, food (Vestergren et al., 2012). Furthermore, different assumptions are made for some parameters in the intake estimations in this study compared to Vestergren et al. (2008). For example, Vestergren et al. (2008) assumed biotransformation factors of PFOS precursors in the low- and high-exposure scenarios as 0.01 and 1, respectively, whereas in this study the lowest and highest biotransformation factors reported in the literature are used for the low- and high-exposure scenarios, i.e., 0.095 and 0.32, respectively. This can to a large extent explain the differences found for the relative importance of precursors in the low- and high-exposure scenarios between the two studies.

A total of seven PFOS precursors are included in the estimation of precursor contribution to PFOS exposure via different exposure pathways. Among the four exposure pathways included in this study, literature data are available for most of the selected precursors in air and dust samples. In studies monitoring PFASs in food and drinking water samples, data on precursors are limited to FOSA. Although other precursors have been detected in specific food items (e.g., MeFOSAA and EtFOSAA in herring collected in 2011) (Ullah et al., 2014), these precursors were below the detection limit in food homogenates representing the general diet in 2010 (Gebbink et al., submitted for publication). Exposure to precursors other than FOSA via consumption of specific food

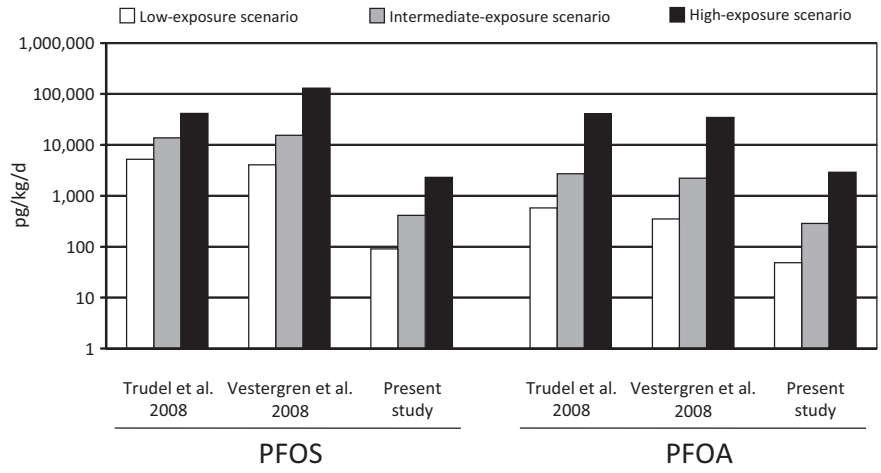

Fig. 2. Estimated PFOS and PFOA daily exposures of adults (pg/kg/d) reported by Trudel et al. (2008), Vestergren et al. (2008), and the present study. The estimated exposures reported by Vestergren et al. and the present study represent the sum of direct and indirect (precursor) intakes, while the estimation by Trudel et al. is only based on direct PFOS and PFOA exposure.

items likely contributes insignificantly to total PFOS exposure as the dietary contribution of precursors was estimated as <2% of the total PFOS exposure (Fig. 3). Biomonitoring studies reported the presence of other PFOS precursors in human blood that are not included in this study. For examples, the German population was exposed to perfluorooctane sulfonamidoethanol-based phosphate esters (SAmPAPs), although the detection frequency and concentrations in human serum were low (Yeung et al., 2013b). There have been no studies to date focusing on the exposure pathways that contribute to the presence of SAmPAPs in human blood.

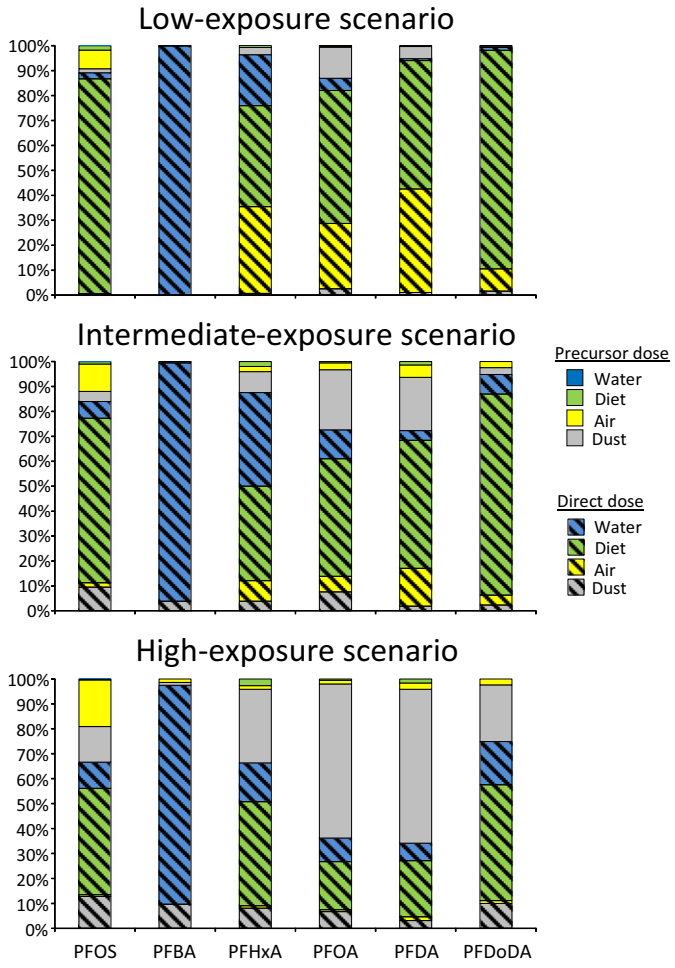

Fig. 3. Relative contribution (%) of estimated direct and precursor intakes to total PFOS, PFBA, PFHxA, PFOA, PFDA, and PFDoDA daily exposures via multiple pathways in the low-, intermediate, and high-exposure scenarios.

Based on our estimated PFOS exposures, our initial hypothesis, that PFOS exposures with up-to-date data would result in lower intakes compared to earlier estimations, is verified. This change in total PFOS exposures is in line with changes observed in temporal trend monitoring studies. However, other factors, such as improvement of analytical methods, contribute to lower estimated PFOS exposures. The hypothesis that precursors are more important compared to earlier estimations is accepted in the low- and intermediate-exposure scenario, however, not in the high-exposure scenario. The rejection of the hypothesis in the high-exposure scenario can to a large extent be explained by the lower biotransformation factor used in this scenario compared to earlier estimations (0.32 vs 1). There are still uncertainties in the estimation of PFOS intakes as well as in the contribution of precursors. For example, not all precursors included in this study have been reported in all exposure media, and there are precursors which have not been investigated in any of the human exposure pathways (e.g., SAmPAPs). Also, there are still large uncertainties regarding uptake and biotransformation factors for PFOS and individual precursors. A better understanding of these parameters would allow for a more accurate estimate of precursor intake as an indirect source of PFOS exposure.

3.2. Exposure to linear and branched PFOS isomers

The isomer pattern (linear and sum branched isomers) of total human exposure to PFOS is investigated using the intermediate-exposure scenario with the assumptions regarding the PFOS and precursor isomer patterns in dust and air and regarding biotransformation efficiency mentioned in Section 2.3. The isomer pattern of total PFOS exposure including all investigated intake pathways is estimated as 84% linear and 16% sum branched isomers, which is largely influenced by diet (especially fish, which is often enriched in linear isomers; Ullah et al., 2014) being the most important exposure pathway for PFOS (Fig. 3). Based on this estimate, the isomer pattern of total PFOS exposure is strongly enriched with the linear isomer compared to both ECF PFOS (70% linear) and the isomer pattern found in human serum (48–83% linear) (Beesoon et al., 2011; Glynn et al., 2012; Gützkow et al., 2012; Karrman et al., 2007; Rylander et al., 2009; Zhang et al., 2013b). A considerable uncertainty in this estimation is the isomer pattern of precursors in dust and of PFOS and precursors in air samples. Therefore, the isomer pattern of total PFOS exposure is also estimated according to different scenarios (Fig. 4A and B). Varying

the isomer pattern of precursors in dust from 100% linear to 100% branched isomers has only a minor effect on the isomer pattern of total PFOS exposure, i.e., changing it from 85% to 81% linear PFOS (Fig. 4A). Varying the isomer pattern of PFOS and precursors in air from 100% linear to 100% branched isomers results in an overall decrease of the linear PFOS isomer from 88% to 75% (Fig. 4B). Regardless of these two scenarios with up to 100% branched isomers in dust or air, the isomer pattern of total PFOS exposure remains enriched with linear PFOS compared to ECF PFOS or the isomer pattern generally found in human serum. When comparing the estimated PFOS isomer pattern of the total exposure based only on direct PFOS exposure (Fig. 4A and B, red line) relative to PFOS and precursor exposure (blue line), only a small deviation is seen, indicating that direct PFOS exposure dominates the overall PFOS isomer pattern or that both pathways (direct and indirect exposure) lead to a similar PFOS isomer pattern.

Additional uncertainties in estimating the PFOS isomer pattern of the total exposure are differences in uptake and biotransformation rates between linear and branched precursor isomers. Both *in vivo* and *in vitro* experiments have shown that branched precursor isomers are degraded faster relative to the linear isomer (Benskin et al., 2009b; Peng et al., 2014; Ross et al., 2012), however, no isomer-specific biotransformation factors have been provided. In the intermediate-exposure scenario in the present study, the biotransformation fraction of precursors to PFOS is estimated at 0.2 for both branched and linear isomers. However, the influence of a potentially higher percentage biotransformation of branched precursors to branched PFOS is further investigated with the assumption that the PFOS and precursor isomer pattern in dust and air are 70/30 linear/branched and equal uptake for all isomers (Fig. 4C). With biotransformation factors of >0.2 for the biotransformation of branched precursors to branched PFOS (relative to 0.2 for the linear precursor isomers), the isomer pattern in total PFOS exposure intake reflects the isomer pattern found in human serum. However, human serum isomer patterns cannot be explained even when complete biotransformation of branched precursors to branched PFOS is assumed. For both PFOS and its precursors, faster uptake of branched isomers relative to the linear isomers was observed in rats and fish

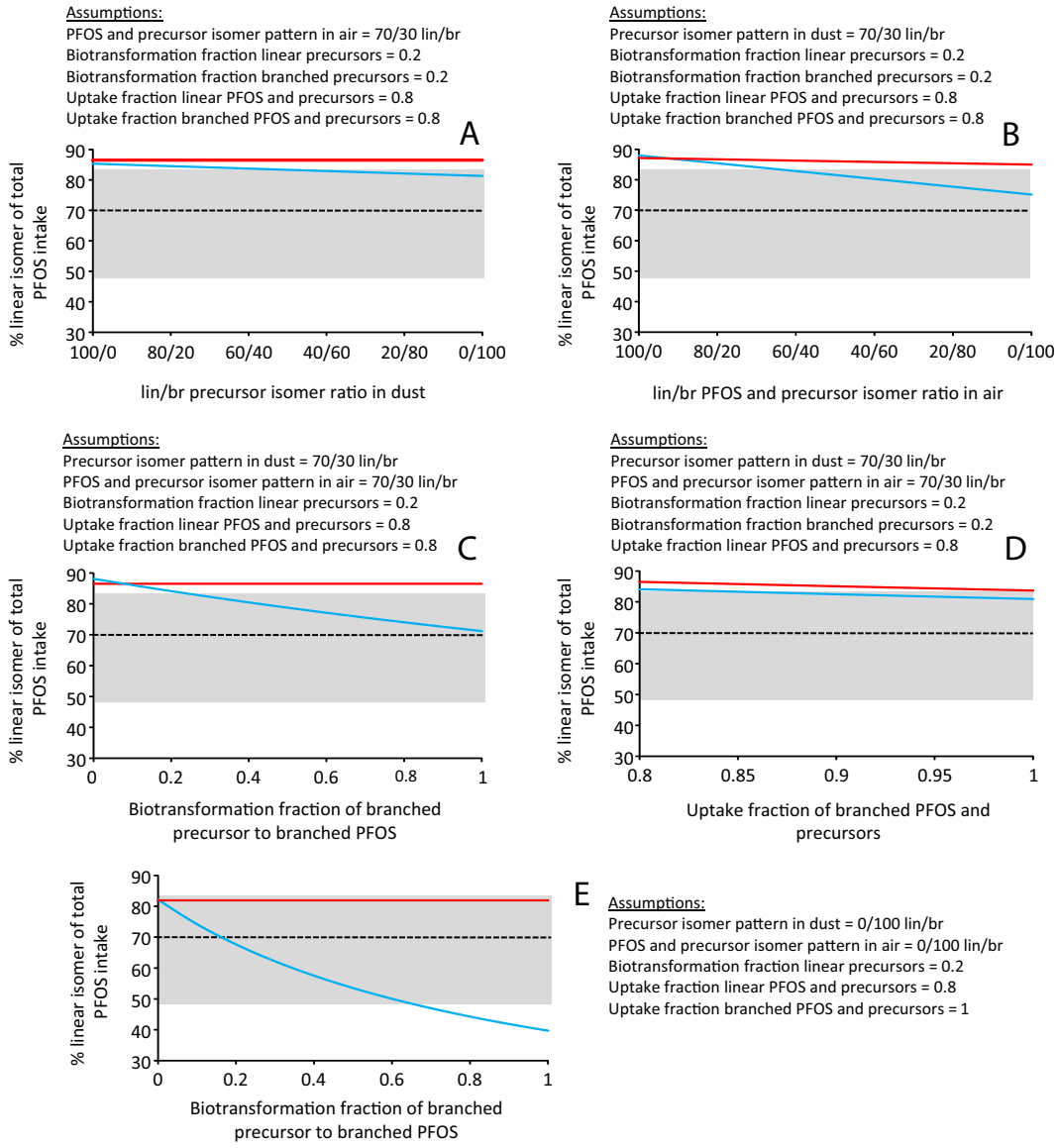

Fig. 4. Estimated % linear isomer of total PFOS exposure based on direct PFOS intake (red line) and PFOS and precursor intake (blue line) in the intermediate-exposure scenario. Estimations of % linear isomer are made with varying linear/branched ratios of precursors in dust (A), varying linear/branched ratios of PFOS and precursors in air (B), varying biotransformation fractions of branched precursors to branched PFOS (C and E), and varying uptake fractions for branched PFOS and precursors (D). The dotted line represents the linear/branched ratio of ECF PFOS, and the grey area represents the range of % linear PFOS reported in human serum.

(Benskin et al., 2009a; Peng et al., 2014). In the intermediate-exposure scenario in the present study, the uptake fractions of PFOS and its precursors are estimated at 0.8 for both branched and linear isomers. The influence of a potentially higher uptake efficiency for branched isomers compared to linear isomers is further investigated with the assumption that the PFOS and precursor isomer pattern in dust and air are 70/30 linear/branched and biotransformation fractions are 0.2 (Fig. 4D). Greater uptake of branched PFOS and precursors (>0.8) compared to the linear isomers had little impact on the isomer pattern of total PFOS intake. Completely efficient uptake of branched isomers (relative to 0.8 for linear isomers) only changed the isomer pattern of total PFOS intake from 84% to 81% linear PFOS. In an extreme scenario, with the assumption that the precursor isomer patterns in dust and PFOS and precursors in air are 100% branched and that there is complete uptake for branched isomers, an isomer pattern of total PFOS exposure that covers the whole range of human serum isomer patterns is observed with a biotransformation yield of branched isomers between 20% and 70% (Fig. 4E). This is, however, a highly improbable scenario as there is evidence of both linear and branched precursor isomers being present in air samples (Jahnke et al., 2007).

Faster uptake of branched PFOS and precursors compared to linear PFOS and precursors, as was seen in rats and fish (Benskin et al., 2009a; Peng et al., 2014) would result in an enrichment of branched PFOS relative to linear PFOS. However, as increasing uptake efficiency and thus uptake rate was shown only to have little impact on the isomer pattern of total PFOS intake, it seems unlikely that uptake of branched isomers alone would result in isomer patterns that are enriched with branched PFOS as seen in human sera. Faster biotransformation of branched precursors relative to linear isomers (Benskin et al., 2009b) as well as faster urinary elimination of linear precursors relative to branched precursors in humans as was seen for FOSA (Zhang et al., 2013a) would result in increasing formation of branched PFOS relative to linear PFOS originating from indirect exposure. If this was a dominant pathway influencing the isomer pattern in humans then enrichment of branched PFOS would be expected relative to the isomer pattern of the total exposure. However, as discussed above (Fig. 4), it is unlikely that biotransformation of precursors can fully explain the PFOS isomer pattern difference between total exposure and human serum, due to the low contribution of precursors to total PFOS exposure, which was estimated to be 16% in the intermediate-exposure scenario (Table S13).

Another process that may alter the PFOS isomer pattern in human serum relative to the total exposure are isomer-specific differences in elimination half-lives between PFOS isomers. Both in rats and humans the major branched isomers are excreted faster relative to linear PFOS via urine (Benskin et al., 2009a; Zhang et al., 2013a). If this was the dominant elimination route, then the isomer pattern of total PFOS exposure (estimated as 84% linear) would become even more enriched with linear PFOS in humans. However, the PFOS elimination half-life calculated from blood serum measurements (representing overall human elimination through all processes) is shorter compared to the half-life estimated only from urinary excretion (Olsen et al., 2007; Zhang et al., 2013a), indicating that there may be other significant elimination processes for PFOS, such as faecal excretion. Nevertheless, it is highly unlikely that isomer-specific faecal excretion not only compensates for the enrichment of linear isomers in humans through urinary excretion but even turns PFOS elimination into a process that explains the enrichment of branched isomers in human serum relative to total exposure.

Based on our findings, our initial hypothesis that the isomer pattern of total PFOS exposure can help to explain the isomer pattern found in human serum is rejected. Furthermore, current knowledge on isomer-specific differences in pharmacokinetics and metabolism of PFOS and/or precursors combined with the present data cannot explain the difference in the isomer pattern of the intake relative to the pattern in human serum. This discrepancy between PFOS isomer patterns in external and internal exposure could potentially be explained by: i) inaccurate estimation of the daily exposure (e.g., due to unknown precursors, missing or poorly quantified exposure pathways and/or poorly quantified isomer ratios of PFOS and precursors) or ii) an incomplete understanding of the human pharmacokinetic processes (e.g., biotransformation and elimination kinetics of precursors, intermediates and PFOS isomers).

3.3. Direct versus indirect exposure to PFCAs

The estimated daily intakes for all PFCAs and individual precursors (assuming no biotransformation) are provided in Table S11. Based on these intakes and biotransformation factors for precursors as given in Section 2.2, the highest total daily exposures among individual PFCAs are estimated for PFOA with 44 pg/kg/d, 270 pg/kg/d, and 3000 pg/kg/d for the low-, intermediate-, and high-exposure scenarios, respectively (Table 1, Fig. 2). Direct PFOA intake is dominant in the low- and intermediate-exposure scenarios (87% and 73% of total exposure, respectively), while in the high-exposure scenario precursor-based (indirect) intake is more important, contributing 64% to the total exposure (Tables S12–S14). Lower daily exposures are estimated for PFHxA and PFDA, ranging from 15 to 520 pg/kg/d for PFHxA and from 24 to 660 pg/kg/d for PFDA, depending on the exposure scenario (Table 1). For both PFHxA and PFDA, direct intake is dominant in the low- and intermediate-exposure scenarios, contributing between 72% and 96% of the total exposures. In the high-exposure scenario, direct PFHxA intake is still dominant (66%), whereas for PFDA the major daily exposure (66%) originates from precursor-based intakes. The lowest daily exposures are estimated for PFBA and PFDoDA, ranging between 6.3 and 190 pg/kg/d for PFBA and between 23 and 180 pg/kg/d for PFDoDA, depending on the exposure scenario (Table 1). For both PFBA and PFDoDA, daily exposures originate almost entirely from direct intakes regardless of the scenario (i.e., 75%–99%). Based on these results, our hypothesis that the estimated total exposure to PFOA is greater than to other PFCA homologues, and that contributions of direct and indirect exposure vary widely by homologue, is verified. Furthermore, the exposure scenario has a strong influence on the estimated relative importance of direct and indirect intakes, with precursors becoming more important the higher the exposure scenario (Table 1).

The relative contributions of each individual intake pathway (direct or indirect exposure and four different exposure media) to the total daily exposures are provided in Fig. 3 and Tables S12–S14 for individual PFCAs. Direct exposure to PFBA via drinking water consumption is estimated to be the primary exposure pathway in all exposure scenarios (88–99%) (although data on PFBA in other exposure pathways, such as dietary intake, is limited). Direct exposure via food is estimated to be the major exposure pathway for PFHxA, PFOA, PFDA and PFDoDA in the low- (41–88% of total exposure) and intermediate- (38–86%) exposure scenarios. In the high-exposure scenario, direct dietary exposure is estimated to be the major exposure pathway only for PFHxA and PFDoDA (42 and 47%, respectively), while for PFOA and PFDA precursor exposure via dust ingestion is estimated to be the dominant pathway (62% for both pathways).

Sensitivity analysis reveals that the GI uptake fraction for PFCAs and diPAPs is the most influential parameter affecting the calculated total exposure to all individual PFCAs in all exposure scenarios (Figs. S2–S6). However, there is a large uncertainty regarding this parameter for PFCAs as well as for diPAPs (see Section 2.2). For PFBA, the concentration in water and volume of water consumed are the most sensitive parameters in all three exposure scenarios after the GI uptake fraction. These parameters are quite well constrained. For PFHxA, PFOA, PFDA, and PFDoDA, concentrations in water, food, or air are influential parameters in the low- and intermediate-exposure scenarios, whereas levels in dust, amount of dust ingested and biotransformation factors for PAPs become more influential in the high-exposure scenario. Levels of individual PFCAs in different exposure media and FTOHs in air can be measured with a high level of certainty. On the other hand, concentrations of diPAPs in dust, the amount of dust ingested, and biotransformation factors for diPAPs are poorly constrained.

The precursor contribution to PFCA exposure has previously only been determined for PFOA, and it should be noted that the daily exposure estimates for PFOA in the current study are roughly one order of magnitude lower for each exposure scenario compared to earlier estimates (Fig. 2) (Trudel et al., 2008; Vestergren et al., 2008). The relative contribution of precursors to total PFOA exposure is higher in the present study in all three exposure scenarios compared to the earlier estimations (Vestergren et al., 2008). These differences between the present and earlier studies are likely the result of one or several of the following factors: i) reduced emissions over time and therewith lower levels of PFOA and its precursors in exposure media (US EPA, 2006; Wang et al., 2014), ii) improvement of analytical methods resulting in more accurate (i.e., generally lower) PFOA concentrations in the major exposure medium, food (Vestergren et al., 2012), iii) more literature data became available on PFOA and precursors in the exposure media included in the present study (e.g., diPAPs were not included in the study by Vestergren et al. (2008)), and iv) different exposure pathways are included in the various studies. As for PFOS, our initial hypothesis, that reexamination of total PFOA exposure with up-to-date data would result in lower calculated daily exposures, is verified. This change in total PFOA exposures is in line with changes observed in temporal trend monitoring studies. The hypothesis that precursors play a more important role compared to earlier estimations is accepted for all exposure scenarios. The scarcity of data on uptake and biotransformation factors for individual PFCAs and their precursors create uncertainties in the estimations of total human exposure to PFCAs as well as precursor contribution to this exposure. Addressing these knowledge gaps should be a key priority in future research on human exposure to PFCAs.

3.4. Modelling PFAA levels in human serum from estimated total daily exposures

Concentrations of PFDA and PFDoDA in human serum cannot be modelled based on the estimated exposures as serum elimination half-lives and volumes of distribution for these PFAAs are currently not available. On the other hand, these parameters are available for PFBA, PFHxA, PFOA, and PFOS (see Section 2.4). Based on the estimated daily exposure, the modelled PFBA and PFHxA concentrations in serum are 0.0039 and 0.014 ng/g, respectively (Fig. 5). Literature data on PFBA and PFHxA in human serum from European and North American countries is extremely limited. In human serum from the USA, PFBA and PFHxA concentrations are higher compared to the modelled serum concentrations, which could be due to local high exposure to PFBA and PFHxA in the USA study, or incorrect model parameterization for these substances. The modelled PFOA concentration in serum based on total daily PFOA exposure ranges between 1.9 and 3.2 ng/g, which is in good agreement with concentrations reported in serum samples, although there were some studies reporting on higher PFOA concentrations (Fig. 5). Based on the estimated total daily PFOS exposure, the modelled concentration ranges between 4.0 and 5.1 ng/g. This is generally lower compared to the measured concentrations in serum samples collected during and after 2007 in North America, Europe and Asia (Fig. 5). The reported higher PFOS levels in serum samples relative to the modelled concentrations can be explained by the long elimination half-lives of PFOS in humans (i.e., serum contains PFOS derived from historic exposure) (Section 2.4) together with the decreasing temporal trends in exposure media such as food items (Johansson et al., 2014) and in human serum (e.g., Glynn et al., 2012). Other factors could be that uptake and biotransformation factors are underestimated or that certain populations are (locally) more exposed to PFAAs and precursors than was estimated using the available literature data. The measured PFAA concentrations in serum between 2007 and 2011 originate partly from exposure prior to 2007, which was likely higher compared to the exposure post 2007 estimated in the present study. The decrease in human serum is steeper for PFOS compared to PFOA, thus a larger discrepancy between modelled and measured levels is expected and also observed for PFOS (Fig. 5). In fact, Glynn et al. (2012) reported PFOS and PFOA concentrations in serum in 2010 (originating largely from exposure 2007–2010) of 6.8 and 1.7 ng/g, respectively, which are close to the modelled serum concentrations. Thus, despite the uncertainties in the estimation of daily exposures (see sections above) and additional uncertainties in the modelling such as the volumes of distribution and elimination half-lives, a good match was obtained between modelled and measured values for both PFOS and PFOA. This lends confidence in our values for daily exposures and the estimated relative contribution of precursor intake to total PFAA exposure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.10.013.

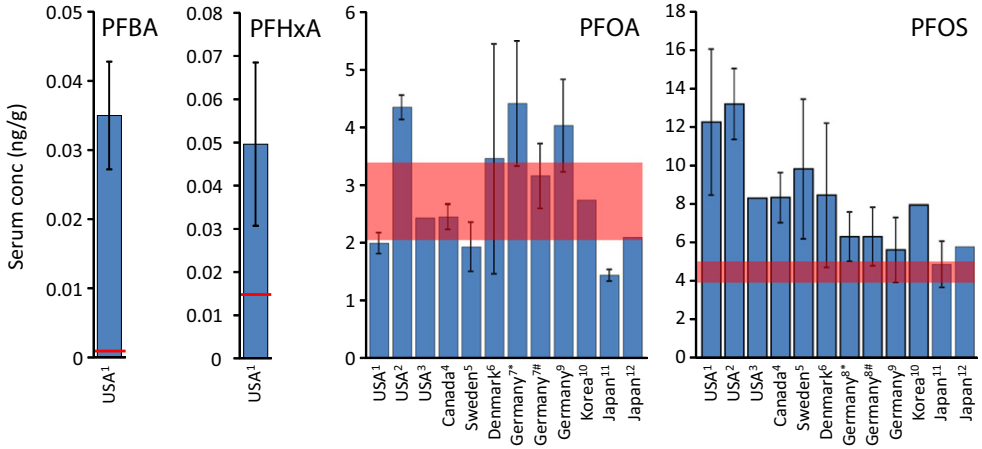

Fig. 5. Modelled (red line) and literature (blue bars) PFBA, PFHxA, PFOA, and PFOS concentrations in human serum (ng/g). The red area represents the range of PFOA and PFOS concentrations estimated with the minimum and maximum elimination half-lives. Intermediate-exposure scenario parameters are used for the modelled concentrations, literature concentrations in serum are the average (±SD, if provided) of reported concentrations in samples that were taken during and after 2007 ([1]Lee and Mabury, 2011;[2]Kato et al., 2011; [3]Olsen et al., 2012; [4]Fisher et al., 2013; [5]Glynn et al., 2012; [6]Nordström Joensen et al., 2013; [7]Yeung et al., 2013a (*Munster, #Halle); [8]Yeung et al., 2013b; [9]Schröter-Kermani et al., 2013; [10]Ji et al., 2012; [11]Okada et al., 2013; [12]Yamaguchi et al., 2013).

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