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Impacts of daily intakes on the isomeric profiles of perfluoroalkyl substances (PFASs) in human serum

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ABSTRACT

Perfluoroalkyl substances (PFASs) have been well studied in human daily intake for assessment of potential health risks. However, little is known about the isomeric compositions of PFASs in daily intake and their impacts on isomeric profiles in humans. In this study, we investigated the occurrence of PFASs with isomeric analysis in various human exposure matrices including foodstuffs, tap water and indoor dust. Perfluorooctanesulfonate (PFOS) and/or perfluorooctanoate (PFOA) were predominant in these exposure matrices collected in Tianjin, China. In fish and meat, linear (*n*-) PFOA was enriched with a percentage of 92.2% and 99.6%, respectively. Although *n*-PFOS was higher in fish (84.8%) than in technical PFOS (ca. 70%), it was much lower in meat (63.1%) and vegetables (58.5%). Dietary intake contributed >99% of the estimated daily intake (EDI) for the general population. The isomeric profiles of PFOA and PFOS in human serum were predicted based on the EDI and a one-compartment, first-order pharmacokinetic model. The isomeric percentage of *n*-PFOA in the EDI (98.6%) was similar to that in human serum (predicted: 98.2%, previously measured: 99.7%) of Tianjin residents. The results suggest direct PFOA intake plays an important role in its isomeric compositions in humans. For PFOS, the predicted *n*-PFOS (69.3%) was much higher than the previously measured values (59.2%) in human serum. This implies that other factors, such as indirect exposure to PFOS precursors and multiple excretion pathways, may contribute to the lower percentage of *n*-PFOS in humans than of technical PFOS.

1. Introduction

Perfluoroalkyl substances (PFASs), including perfluorocarboxylates (PFCAs) and perfluorosulfonates (PFSAs), are highly fluorinated aliphatic compounds with high thermal and chemical stabilities as well as high surface activity (Buck et al., 2011; Kissa, 2001; Smart, 1994). They have been manufactured for over 60 years and are commonly used in various commercial and household products (Buck et al., 2012). As a result, PFASs, particularly perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA), have been ubiquitously detected in the environment and in humans (Wang et al., 2015). Numerous studies have documented their links to many negative health effects in humans (Beesoon and Martin, 2015; Eriksen et al., 2013; Gump et al., 2011; Hoffman et al., 2010; Joensen et al., 2013; Nelson et al., 2010; Steenland et al., 2010; Whitworth et al., 2012). Due to their persistence, widespread distribution and potential health risks, several PFASs such as PFOS are listed as environmentally persistent organic pollutants (Lindstrom et al., 2011; Wang et al., 2009).

There are two main manufacturing processes for PFASs, namely electrochemical fluorination (ECF) and telomerization. PFOS-related chemicals (i.e. PFOS and its precursors) are produced solely by the ECF method (Jiang et al., 2015; Martin et al., 2010). The percentage of *n*-PFOS present in commercial products is mostly in the range 67–82% (Benskin et al., 2010b; Gao et al., 2015; Jiang et al., 2015; Zhang et al., 2014). Unlike PFOS, the two manufacturing methods lead to different isomeric patterns in PFOA-related products. The ECF PFOA is generally accepted as a complex mixture of ca. 70–80% linear (*n*-) and 20–30% branched (*br*-) isomers, whereas telomerization produces almost 100% linear geometry (Benskin et al., 2010a; Zhang et al., 2013b). Recent studies have reported that technical PFOA products in China share a similar percentage of *n*-PFOA (73–83%) as the historical 3 M ECF products (78%) (Jiang et al., 2015; Shi et al., 2015). Li et al. (2015) reported that ECF is still the major method for manufacturing of PFOA and related chemicals in China. In recent years, the telomerization PFOA precursors, such as fluorotelomer alcohols (FTOHs) and FTOH-based polyfluoroalkyl phosphate esters (PAPs), have attracted greater concerns due to their potential to degrade to PFOA (D'eon and Mabury, 2011; Gebbink et al., 2015c; Vestergren et al., 2008).

PFAS isomers have been widely found in biota and even in humans (Gao et al., 2015). Animal studies have shown that there are toxicological differences between *n*- and *br*-isomers of PFASs (Hickey et al., 2009; Loveless et al., 2006; O'Brien et al., 2011). Relative to *n*-isomers, *br*-isomers are less hydrophobic and most have weaker protein binding

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affinities (Beesoon and Martin, 2015; Greaves and Letcher, 2013). Thus, various isomers of PFASs may have different interaction affinities with molecular receptors, inducing different toxic effects (Beesoon and Martin, 2015). In addition, this difference could also give rise to different pharmacokinetics of the isomers, and finally result in their different accumulation potentials in humans (Benskin et al., 2010a).

Disposition of PFAS isomers was studied in experimental animals (De Silva et al., 2009a; O'Brien et al., 2011) and wildlife (Fang et al., 2014b; Gebbink and Letcher, 2010; Greaves and Letcher, 2013). In general, preferential enrichment of *n*- over *br*-isomers of PFOA or PFOS was observed in animal-based studies, in which *n*-isomers often contributed >90% of PFOA and >70% of PFOS (Fang et al., 2014b; Greaves and Letcher, 2013). Recently, human biomonitoring studies investigated the occurrence of PFOA and PFOS isomers in human blood and/or serum (Gebbink et al., 2015b; Jiang et al., 2014; Liu et al., 2015; Zhang et al., 2013b; Zhang et al., 2014). Results from these studies consistently showed that *n*-PFOA was overwhelmingly predominant with a percentage of 95.8–100%; while the percentage of *n*-PFOS (48–70%) was much lower than that in technical PFOS products, although it was still the major isomer of PFOS (Zhang et al., 2013b; Zhang et al., 2014). The isomeric profile of PFOA in humans was similar to that in wildlife, which can be explained by the preferential accumulation of *n*-PFOA in biota (Fang et al., 2014b). However, the isomeric profile of PFOS in human serum was different from that in wildlife (Beesoon and Martin, 2015). The underlying mechanisms accounting for this difference are not fully understood to date (Gebbink et al., 2015a). Separate studies by Zhang et al. and Martin et al. suggested that humans may have different metabolic mechanisms from wildlife, or that humans may be exposed to some PFOS precursors, for which *br*-isomers might be preferentially transformed to *br*-PFOS in human body (Martin et al., 2010; Zhang et al., 2013b).

It was widely reported that daily intakes by consumption of food, drinking water, and ingestion of dust, are the major pathways for exposure to PFASs by the general population (Gebbink et al., 2015a; Kato et al., 2015; Miralles-Marco and Harrad, 2015). Among them, diet was suggested as the main exposure route to these compounds (Domingo, 2012; EFSA, 2012). Thus, it is assumed that the isomeric compositions in these exposure matrices could influence the isomeric profiles of PFASs in the human body. However, to date, there is limited information available regarding the isomeric compositions of PFASs in these matrices (Gao et al., 2015; Gebbink et al., 2015a; Yu et al., 2015a, 2015b). Moreover, the impacts of PFASs in daily intakes on the isomeric patterns in humans are rarely investigated (Miralles-Marco and Harrad, 2015).

The objectives of this study were to investigate the impacts of daily intake of PFASs from multiple exposure media on their isomeric profiles in humans. Eleven PFAS homologs including the isomers of PFOA and PFOS were measured in foodstuff, tap water, and indoor dust samples, collected from Tianjin, China during 2013–2014. The isomeric profiles in human serum were predicted using a one-compartment, first-order pharmacokinetic model and compared with the measured profiles in Tianjin residents.

2. Materials and methods

2.1. Sample collection and preparation

Twenty one composite food items categorized as vegetables (including 58 vegetable samples which were pooled as 5 vegetable types, i.e. $n_{type} = 5$ and $n_{sample} = 58$), fruits ($n_{type} = 4$ and $n_{sample} = 36$), meat ($n_{type} = 5$ and $n_{sample} = 49$) and fish ($n_{type} = 7$ and $n_{sample} = 23$) (For details, see Table S1), were collected from traditional open-air markets or supermarkets in Tianjin in June 2013. For each food type, multiple samples collected from different markets were pooled as one composite sample. Twelve indoor dust samples were collected by sweeping floors from offices and residential homes in Tianjin in January–October 2014. Nine tap water samples were collected from residential homes in Tianjin in September 2014. Foodstuffs were packed with aluminum foil and stored at −20 °C. Indoor dust samples were kept cool and dry, while drinking water samples were pretreated upon arriving at the laboratory.

2.2. Chemicals and standards

PFAC-MXB is a mixed standard solution which contains the target compounds: perfluorohexanoate (PFHxA), perfluoroheptanoate (PFHpA), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), Perfluorotetridecanoate (PFTrDA), perfluorobutane sulfonate (PFBS), perfluorohexanesulfonate (PFHxS), perfluorooctanesulfonate (PFOS). The mass labeled internal standard MPFAC-MXA is a mixture of M_4-PFBA, M_2-PFHxA, M_2-PFOA, M_5-PFNA, M_2-PFDA, M_2-PFUnDA, M_2-PFDoDA, M_4-PFHxS, and M_4-PFOS.

The relative percentage of *n*- and *br*-isomers in BrPFOSK (78.8% *n*-PFOS, 10% *iso*-PFOS, 1.2% *1m*-PFOS, 1.9% *3m*-PFOS, 2.2% *4m*-PFOS, 4.5% *5m*-PFOS, 0.71% m_2-PFOS) and TPFOA (79% linear, 9% *iso*-PFOA, 3% *3m*-PFOA, 4% *4m*-PFOA, 4.5% *5m*-PFOA) were based on ^{19}F-NMR analysis. Abbreviated *m* refers to the perfluoromethyl branch for the monomethyl branched isomers, and the number preceding indicates the carbon number on which the branch resides (e.g., 1-perfluoromethyl-PFOS is *1m*-PFOS); m_2-PFOS is the sum of all diperfluoromethyl isomers of PFOS. The chemical structures of the different isomers of PFOA and PFOS are listed in Table S2. All PFAS standards were purchased from Wellington Laboratories (Guelph, ON, Canada). Milli-Q water was used throughout the sample process. Methanol, dichloromethane, and formic acid were of HPLC grade and obtained from Dikma Technology Inc., USA.

2.3. Sample extraction

Food samples were extracted using an ion pair method described by Hansen et al. (2001) with some modifications. An aliquot of 12.5 g (wet weight, ww) homogenized vegetables or fruits, or 5 g (ww) meat or fish, was added to polypropylene (PP) tubes (50 or 15 mL) and spiked with 1 or 2 ng of internal standard (MPFAC-MXA), respectively, and was then mixed thoroughly on a vortex. After that, 1 mL of 0.5 M TBA solution (pH 10), and 2 mL of 0.25 M sodium carbonate buffer were added to the tube. After thorough mixing, the extraction was carried out by addition of 8 mL of MTBE (methyl *tert*-butyl ether) and the mixture was shaken at 250 rpm for 20 min. The organic layer was separated from the aqueous layer by centrifugation at 10,000 rpm for 10 min, and then transferred to a new 15 mL PP tube. The extraction procedure was repeated once again with 8 mL of MTBE. For vegetable and fruit samples, the extracts from two portions of samples (12.5 g/each) were pooled as one sample. The solvent was evaporated to dryness with a gentle stream of nitrogen and reconstituted in 5 mL of methanol. The samples were subjected to further clean-up using carbon solid phase extraction (SPE; Pesti-Carb, 1000 mg/6 mL for vegetables and fruits, 500 mg/6 mL for meat and fish, Agela Technologies, China). The Pesti-Carb cartridges were preconditioned by passing through 5 mL of 0.1% NH_4OH/methanol, followed by 5 mL of water, and 5 mL of methanol at a rate of 1–2 drop(s) per second. All food sample extracts were loaded on the preconditioned Pesti-Carb cartridges and collected. The samples were further eluted by 5 mL of methanol.

For dust samples, the method developed by Powley et al. (2005) was adopted with minor modifications. Briefly, 2 ng of MPFAC-MXA was added to 2 g of dust sample in a 50 mL PP tube. Methanol (5 mL) was added and the tube was vortexed for 30 s before shaking for 10 min. After that, the tube was sonicated for 10 min at 40 °C, and centrifuged at 3000 rpm for 10 min. The extraction procedure was repeated twice as described above. The extracts were combined in a new 15 mL PP tube, evaporated to 5 mL with gentle nitrogen, diluted in 250 mL of water, and subjected to preconditioned SPE cartridge (Cleanert PEP,