Isomer Profiling of Perfluorinated Substances as a Tool for Source Tracking: A Review of Early Findings and Future Applications

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Contents

1 Introduction

The ubiquitous detection of perfluorinated acids (PFAs) and their precursors (PFA precursors) in the global environment has led to concern over their effects in humans and wildlife. This is exacerbated by evidence of developmental toxicity (Lau et al. 2007; Apelberg et al. 2007; Fei et al. 2008), along with persistence,

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chain length-dependent bioaccumulation potential (Houde et al. 2006), and long-range transport potential (Wallington et al. 2006; Wania 2007; Armitage et al. 2006, 2009a, b). In the over half-century of global perfluorochemical manufacturing, the two most commonly used synthetic methods have produced products with very different isomeric purities. Despite the fact that both branched and linear PFA and PFA-precursor isomers exist in the environment, quantitative analysis of these chemicals is, for the most part, still conducted by eluting all isomers together and integrating them as a single peak. This practice has continued despite the fact that emerging literature suggests that more accurate and informative data can be generated by isomer-specific analysis.

The extent to which perfluoromethyl branching patterns affect the physical, chemical, and biological properties of perfluorinated substances is of increasing scientific interest. It is hypothesized that branching patterns may affect properties such as environmental transport and degradation, partitioning, bioaccumulation, pharmacokinetics, and toxicity. It may even influence total PFA quantification, thus perhaps leading to questions about the accurateness of current human and environmental exposure assessments. Of particular focus in the current chapter is the measurement and interpretation of isomer signatures in the environment to gain new knowledge on emission sources, to differentiate between historical versus current exposure sources, or to identify direct versus indirect pathways of exposure for humans and wildlife. To do this effectively requires adequate analytical methods and a fundamental knowledge of the properties that may affect the environmental fate of individual isomers.

2 Isomer Nomenclature

PFA and PFA-precursor acronyms and empirical formulae are listed in Table 1. While a comprehensive numbering system was recently proposed for all isomers of perfluoroalkyl sulfonates and carboxylates (Rayne et al. 2008b), herein we have adopted an earlier, more rudimentary, system developed by Langlois and Oehme (2006) and modified by Benskin et al. (2007) for the limited number of isomers actually present in the commercially manufactured PFA and PFA-precursor formulations (see Section 3). Using perfluorooctane sulfonate (PFOS, Table 1) as an example, linear, perfluoroisopropyl, and *t*-perfluorobutyl are abbreviated as *n*-, *iso*-, and *tb*-PFOS, respectively. For the remaining monomethyl-branched isomers, *m* refers to a perfluoromethyl branch and the number preceding it indicates the carbon position on which the branch resides. Likewise, dimethyl-substituted-branched isomers are labeled as m_2 and the preceding numbers refer to the locations of the CF_3 branching points. For example, 5-perfluoromethyl-PFOS is abbreviated as 5*m*-PFOS, while 5,3-perfluorodimethyl-PFOS is abbreviated as 5,3m_2-PFOS. The same nomenclature system was adopted for perfluoroalkyl carboxylates (PFCAs); however, it should be noted that 1*m*-PFCAs do not exist, since the carbon in the 1-position corresponds to the carboxylate moiety.

Table 1 Acronyms and empirical formulas for perfluoroalkyl sulfonates, sulfonamides, and carboxylates

Chemical	Formula	Acronyms	Cas no.[a]
Perfluoroalkyl sulfonates			
Perfluorobutane sulfonate	$F(CF_2)_4SO_3^-$	PFBS	375-73-5
Perfluoropentane sulfonate	$F(CF_2)_5SO_3^-$	PFPeS	2706-91-4
Perfluorohexane sulfonate	$F(CF_2)_6SO_3^-$	PFHxS	355-46-4
Perfluoroheptane sulfonate	$F(CF_2)_7SO_3^-$	PFHpS	375-92-8
Perfluorooctane sulfonate	$F(CF_2)_8SO_3^-$	PFOS	1763-23-1
Perfluorodecane sulfonate	$F(CF_2)_{10}SO_3^-$	PFDS	335-77-3
Perfluoroalkyl sulfonamides			
N-Methyl perfluorooctanesulfonamidoethanol	$F(CF_2)_8SO_2N(CH_3)(CH_2CH_2OH)$	NMeFOSE	24448-09-7
N-Ethyl perfluorooctanesulfonamidoethanol	$F(CF_2)_8SO_2N(CH_2CH_3)(CH_2CH_2OH)$	NEtFOSE	1691-99-2
Perfluorooctanesulfonamide	$F(CF_2)_8SO_2NH_2$	PFOSA	754-91-6
N-Ethyl perfluorooctanesulfonamide	$F(CF_2)_8SO_2N(CH_2CH_3)H$	NEtFOSA	4151-50-2
N-Methyl perfluorooctanesulfonamide	$F(CF_2)_8SO_2N(CH_3)H$	NMeFOSA	31506-32-8
Perfluorooctanesulfonamidoethanol	$F(CF_2)_8SO_2NH(CH_2CH_2OH)$	FOSE	10116-92-4
Perfluorooctanesulfonamidoacetate	$F(CF_2)_8SO_2NH(CH_2C(O)OH)$	FOSAA	2806-24-8
N-Ethyl perfluorooctanesulfonamidoacetate	$F(CF_2)_8SO_2N(CH_2CH_3)(CH_2C(O)OH)$	NEtFOSAA	2991-50-6
N-Methyl perfluorooctanesulfonamidoacetate	$F(CF_2)_8SO_2N(CH_3)(CH_2C(O)OH)$	NMeFOSAA	2355-31-9
Perfluorocarboxylates			
Trifluoroacetate	$F(CF_2)C(O)O^-$	TFA	2966-50-9
Perfluoropropanoate	$F(CF_2)_2C(O)O^-$	PFPrA	422-64-0
Perfluorobutanoate	$F(CF_2)_3C(O)O^-$	PFBA	375-22-4
Perfluoropentanoate	$F(CF_2)_4C(O)O^-$	PFPeA	2706-90-3
Perfluorohexanoate	$F(CF_2)_5C(O)O^-$	PFHxA	307-24-4
Perfluoroheptanoate	$F(CF_2)_6C(O)O^-$	PFHpA	375-85-9
Perfluorooctanoate	$F(CF_2)_7C(O)O^-$	PFOA	335-67-1
Perfluorononanoate	$F(CF_2)_8C(O)O^-$	PFNA	375-95-1

Table 1 (continued)

Chemical	Formula	Acronyms	Cas no.[a]
Perfluorodecanoate	$F(CF_2)_9C(O)O^-$	PFDA	335-76-2
Perfluoroundecanoate	$F(CF_2)_{10}C(O)O^-$	PFUnA	2058-94-8
Perfluorododecanoate	$F(CF_2)_{11}C(O)O^-$	PFDoA	307-55-1
Perfluorotridecanoate	$F(CF_2)_{12}C(O)O^-$	PFTrA	72629-94-8
Perfluorotetradecanoate	$F(CF_2)_{13}C(O)O^-$	PFTA	376-06-7

[a]For sulfonates and carboxylates, the CAS number is for the protonated form, e.g., $F(CF_2)_7C(O)OH$ (=PFOA)

3 Historical and Current Manufacturing Sources of Perfluoroalkyl Isomers

Although the various synthetic routes and their estimated contributions to the global environmental mass balance of perfluorochemicals have been recently reviewed (Lehmler 2005; Paul et al. 2009; Prevedouros et al. 2006), here we focus on the relevance of perfluorochemical manufacturing to isomer profiles and the implications for source tracking. The major production of perfluorochemicals has historically occurred either by Simons electrochemical fluorination (ECF) or by telomerization. Telomerization is a synthetic process that results in an isomerically pure product which retains the structure of the starting material (typically linear), whereas ECF results in a mixture of branched and linear isomers and by-products. ECF was used to produce all 3M-manufactured perfluorooctane sulfonyl fluoride (PFOSF, $C_8F_{17}SO_2F$)-based products since 1949 (Paul et al. 2009) and the majority of 3M perfluorooctanoic acid since 1947 (Prevedouros et al. 2006). Although 3M phased out their perfluorooctyl-based chemistries in 2002, the company continues to manufacture perfluorobutyl-based products by this method (Parsons et al. 2008). Telomerization, which was originally developed by DuPont (Kissa 2005), saw minor use beginning in the 1970s for the production of PFOA; however, it was not until the 2002 phase out of 3M ECF PFOA that DuPont began the large-scale manufacturing of PFOA by this alternative technique. Telomerization continues to be the dominant production method today for producing PFOA and perfluorononanoic acid (PFNA); however, Prevedouros et al. (2006) indicated that minor ECF manufacturing of ammonium perfluorooctanoate (APFO) has continued since 2002 in Asia and Europe. Although it is not clear how much ECF production continues today, ECF is generally regarded as the "historical" manufacturing process whereas telomerization represents the "current" production method (De Silva and Mabury 2004, 2006).

It is only germane to note that other synthetic routes to branched PFCAs have been reported in the patent literature, as reviewed elsewhere (Lehmler 2005). For example, liquid phase direct fluorination (LPDF) can produce minor quantities of branched isomers of perfluoroalkyl substances and this may explain the small quantities of branched isomers in PFOA purchased from supplier Sigma–Aldrich/Fluka (Steinheim, Switzerland) (Table 2). However, it is unclear what contribution, if any, these minor manufacturing sources make to global PFA loadings.

The telomerization process involves free radical addition of a starting telogen (e.g., perfluoroethyl iodide, CF_3CF_2I) with an unsaturated taxogen (e.g., tetrafluoroethylene, $CF_2{=}CF_2$), thereby lengthening the perfluoroalkyl moiety by units of CF_2CF_2 (Kissa 2005). The major product of this reaction is typically an eight-carbon, straight-chain perfluoroalkyl iodide which is then subjected to oxidation with oleum to form PFOA (Savu 1994) or carboxylation to form PFNA, the latter of which is used by several companies in the United States, France, and Japan (Prevedouros et al. 2006) for the manufacturing of polyvinylidene fluoride. Fluoroalkyl iodides can also be reacted to form fluorotelomer

Table 2 Principally manufactured PFOS/PFOA isomer compositions, compared to specialty chemical isomer compositions determined by ^{19}F NMR. Note that in some cases, companies listed are the suppliers and not necessarily the manufacturers

Principally manufactured isomer profiles (wt%)			Specialty chemical isomer profiles (wt%)							
Isomer	3M ECF PFOA[a]	3M ECF PFOS[b]	PFOS-TCI[c]	PFOS-matrix[d]	PFOS-Sigma–Aldrich/Fluka[e]	T-PFOS-Wellington[f]	br-PFOS-Wellington[g]	PFOS-Sigma–Aldrich/Fluka[h]	PFOS-Oakwood[i]	PFOA-Sigma–Aldrich/Fluka[j]
Lot #	Assumed equivalent in all lots (Reagen et al. 2007)		GJ01	P15D	436098/1	TPFOS0405	brPFOSK1106	Batch # 312421000	Batch # 008577, lot # XO8M	n/a
Normal	77.6	70	67.0	68.3	78.9	68.9	78.8	82.2	72.4	98.9
Internal monomethyl	12.6	17.0	18.7	17.9	9.3	17.9	–	9.8	17.7	
Isopropyl	9.0	10.3	9.6	10.9	10.0	10.8	10.0	10.0	9.4	
Alpha	0.1	1.6	3.2	1.2	1.1	1.9	1.2	1.2	3.4	
t-butyl	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.4	0.4	
Dimethyl	0.1	0.2	1.4	1.3	0.5	0.3	0.6	0.5	–	
Total branched	22.0	29.3	33.1	31.7	21.1	31.1	21.1	21.4	30.9	1.1

n/a – not available
[a]St. Paul, MN, USA (Loveless et al. 2006)
[b]St. Paul, MN, USA (Kestner 1997)
[c]Portland, OR, USA (Arsenault et al. 2008b)
[d]Columbia, SC, USA (Arsenault et al. 2008b)
[e]Milwaukee, WI, USA, mean of $n = 2$ measurements (Arsenault et al. 2008b)
[f]Guelph, ON, Canada (Wellington Laboratories 2005)
[g]Guelph, ON, Canada (Wellington Laboratories 2007)
[h]Buchs, Switzerland (Vyas et al. 2007)
[i]West Columbia, SC, USA (Vyas et al. 2007)
[j]Steinheim, Switzerland (White et al. 2009)

olefins ($F(CF_2)_nCH{=}CH_2$), alcohols ($F(CF_2)_nCH_2CH_2OH$), and fluoroacrylate monomers ($F(CF_2CF_2)_nCH_2CH_2OC(O)CHR{=}CH_2$), which are subsequently incorporated into polymeric material and/or surfactants for consumer product applications. Although telomerization retains the geometry of the starting telogen and thus produces a more isomerically pure product than ECF, telomerized products usually contain chain-length impurities, which can be both even and/or odd chain lengths and varying from 4 to 15 carbons (Prevedouros et al. 2006). Despite this, there are reports in the scientific and patent literature of odd numbered and branched-chain perfluoroalkyl iodides being produced by telomerization using branched telogens (e.g., $(CF_3)_2CI$) and single-carbon taxogens (Haszeldine 1953; Grottenmuller et al. 2003; Balague et al. 1995; Millauer 1974; Katsushima et al. 1970).

In comparison to telomerization, ECF results in numerous by-products, including branched and linear isomers of various even and odd chain lengths (Fig. 1; Table 3). This method was used by 3M for perfluorination of *n*-octanoyl halide

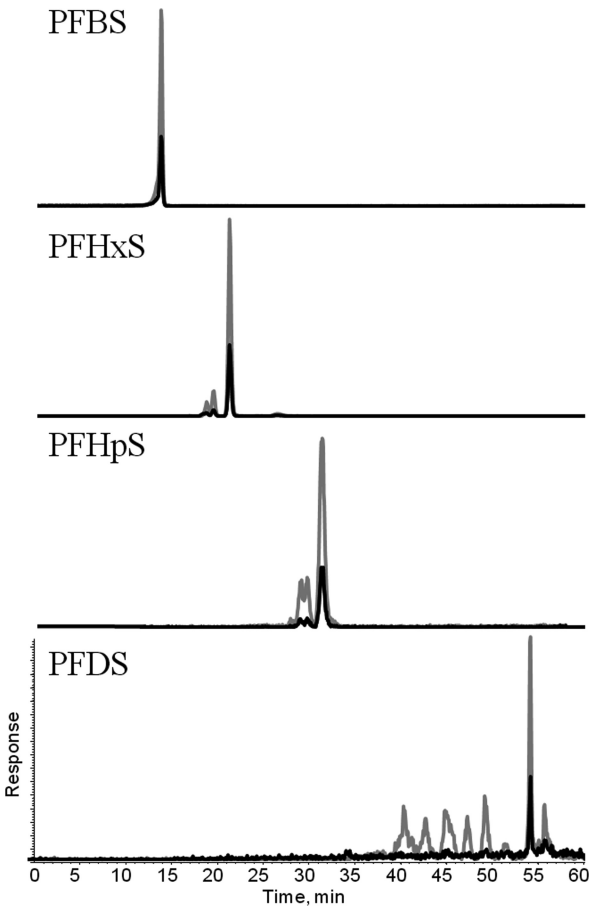

Fig. 1 LC–MS/MS chromatograms of residual perfluoroalkyl sulfonates in 3M ECF PFOS. Perfluorobutane sulfonate (PFBS; *m/z* 299/80, *grey*; *m/z* 299/99, *black*), perfluorohexane sulfonate (PFHxS; *m/z* 399/80, *grey*; *m/z* 399/99, *black*); perfluoroheptane sulfonate (PFHpS, *m/z* 449/80, *grey*; *m/z* 449/99, *black*); perfluorodecane sulfonate (PFDS, *m/z* 599/80, *grey*; *m/z* 599/99, *black*) Note increase in branched isomer content with chain length. Other sulfonates were not monitored

Table 3 Impurities and branched isomer content in 3M ECF PFOS and PFOA

Impurity in 3M ECF PFOS (lot 217)	%Impurity (wt)	%Branched of the impurity	Impurity in 3M ECF PFOA (lot 332)	%Impurity (wt)	%Branched of the impurity
PFBS	1.2[a]	0[b]	PFHxA	0.73[c]	18[d]
PFPeS	1.3[a]	N/A	PFHpA	3.7[c]	N/A
PFHxS	4.7[a]	18[e]	PFNA	0.2[f]	65[f]
PFHpS	1.1[a]	28[g]	PFDA	0.0005[f]	54[f]
PFDS	N/A	75[h]	PFUnA	0.0008[f]	28[f]
PFOA	0.79[f]	19[f]	PFDoA	0.0008[f]	32[f]
PFNA	0.002[f]	70[f]			
PFDA	0.0005[f]	51[f]			
PFUnA	0.0002[f]	46[f]			
PFDoA	0.0004[f]	33[f]			

[a]Seacat et al. (2002)
[b]As determined by LC–MS/MS peak area, monitoring *m*/*z* 299/80 transition
[c]Butenhoff et al. (2002)
[d]As determined by LC–MS/MS peak area, monitoring *m*/*z* 313/269 transition
[e]As determined by LC–MS/MS peak area, monitoring *m*/*z* 399/80 transition
[f]Reagen et al. (2007)
[g]As determined by LC–MS/MS peak area, monitoring *m*/*z* 399/80 transition
[h]As determined by LC–MS/MS peak area, monitoring *m*/*z* 599/80 transition

$(H(CH_2)_7C(O)X$, X = Cl or F) to form $F(CF_2)_7C(O)F$, which was then subjected to base-catalyzed hydrolysis to yield PFOA. The primary use of PFOA was as an emulsifier in fluoropolymer manufacturing (Prevedouros et al. 2006). Similarly, ECF of *n*-octanesulfonyl fluoride was used to produce PFOSF, which was subsequently used as a starting material for various consumer and industrial chemical formulations. For example, base-catalyzed hydrolysis of PFOSF yields PFOS, which had minor uses, predominantly in fire-fighting foams and metal plating. It was also used intentionally to some extent in various consumer products and can be observed as an unintentional residual in many PFOSF-derived products. Reaction of PFOSF with ethylamine was used to form *N*-ethyl perfluorooctanesulfonamide (NEtFOSA) (Table 1), commonly marketed as an insecticide (Appel and Abd-Elghafar 1990). The major use of PFOSF was reaction with ethyl or methyl amine, followed by ethylene carbonate, to yield *N*-ethyl perfluorooctanesulfonamidoethanol (NEtFOSE) and *N*-methyl perfluorooctanesulfonamidoethanol (NMeFOSE), respectively (Table 1). NMeFOSE was subsequently polymerized with urethane, acrylate, and/or adipate reactants to yield polymeric surface treatment products (marketed under 3M's ScotchGard^{TM} brand) (3M Co. 1999). Paper protectors used in food packaging and commercial applications consisted of either NMeFOSE acrylate polymer or a mixture of 10% mono-, 85% di-, and 5% tri-phosphate esters of NEtFOSE (3M Co. 1999). It is unknown if the isomeric profile of PFOSF is preserved in subsequent consumer products that are synthetically derived from PFOSF (e.g., fluroacrylate polymers and phosphate esters). Furthermore, while the degradation of such

polymers or PFOSF derivatives has been hypothesized as a source of PFAs in the environment, it is unclear whether such degradation rates would be isomer specific. The isomer profile of residual impurities may reflect the affinity of certain isomers to undergo polymerization, or alternatively, to cause selective weakening of the fluorinated polymer and cause isomer-specific degradation. Analysis of short- and long-chain perfluoroalkyl sulfonate and carboxylate impurities in standards of 3M ECF PFOA and PFOS reveal branched content of up to 75% (Table 3). Unreacted residual monomers (<1–2%) reported in polymers containing PFOSF-derived materials (3M Co. 1999; Dinglasan-Panlilio and Mabury 2006) also contain significant quantities of branched material of various chain lengths (Kissa 2005; Simons 1949).

The above discussion is important because it is uncertain what contribution residual impurities make to overall human or environmental exposures; however, it may be possible to distinguish residuals from intentionally produced products based on isomer profile. For example, residual PFOA found in pre-2002 ScotchGard™ Fabric and Upholstery formula as well as Rug and Carpet protectors (presumed to be NMeFOSE acrylate polymer) lacks a strong 3*m*-PFOA isomer signal compared to the profile of a representative 3M ECF PFOA production lot (Fig. 2). Similarly, PFOS present in ScotchGard™ showed enrichment of monomethyl-branched isomers when compared to 3M ECF PFOS (Fig. 2). Such differences may be useful for elucidating the role of residuals in human and environmental exposure scenarios, although further validation is necessary.

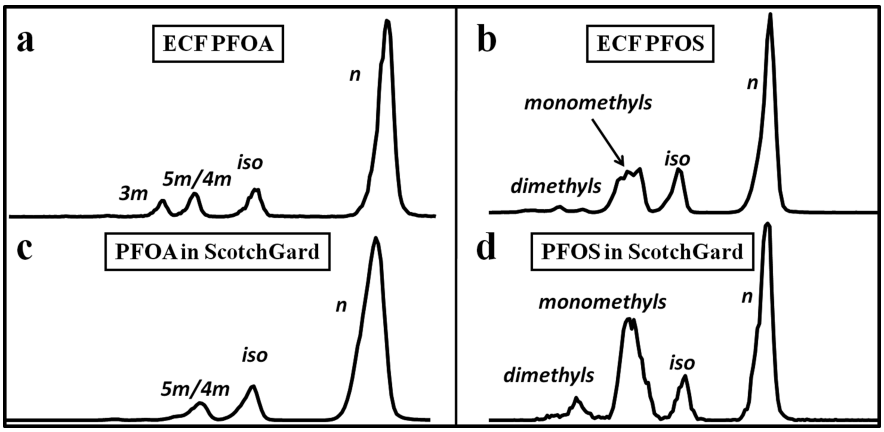

Fig. 2 Comparison of isomer profiles by LC–MS/MS of PFOA in 3M ECF standard (**a**), pre-2002 formula 3M ScotchGard™ Rug and Carpet Protector (**b**), PFOS in 3M ECF standard (**c**), and pre-2002 formula 3M ScotchGard™ Rug and Carpet Protector (**d**). For PFOA, trace represents *m*/*z* 413/369, while for PFOS, trace represents *m*/*z* 499/80. Note enrichment of *iso*-PFOA relative to *n*-PFOA in 3M ScotchGard™ and lack of 3*m*-PFOA isomer. Also notable is the apparent enrichment of PFOS monomethyl isomers relative to *n*-PFOS and *iso*-PFOS in ScotchGard™. PFOS and PFOA isomer profiles in pre-2002 3M ScotchGard™ Rug and Carpet Protector were identical to those found in pre-2002 3M ScotchGard™ Fabric and Upholstery Protector

In 2002, 16 companies were known to manufacture perfluorochemicals at 33 manufacturing sites worldwide (OECD 2002; Prevedouros et al. 2006). Of these, Asahi Glass, Clariant, Daikin, and DuPont produced fluorochemicals via telomerization, while Dyneon (a subsidiary of 3M), Bayer, Dainippon Ink & Chemicals, and Miteni were known to have or are currently producing fluorochemicals by ECF (Parsons et al. 2008). Little is known about production, use, or emissions of perfluorochemicals by these manufacturers; however, it is widely reported that 3M produced 85%, or more, of total worldwide volumes of APFO by ECF since 1949 (OECD 2002). ECF manufacturing by 3M took place in plants in Cottage Grove, MN (ECF PFOA pilot production only), Cordova, IL, Decatur, AL, and Antwerp (Belgium) (3M Co. 1999). All PFOS emissions from 1951 to 1964 are assumed to have occurred in the United States, however, as production in other plants increased from 1965 to 1974, this figure decreased to 75% and by 1975 only 50% of total emissions occurred from the United States (Armitage et al. 2009a). Although the isomer composition of ECF-fluorochemicals can vary from manufacturer to manufacturer (Vyas et al. 2007) (Table 2), isomer profiles of 3M ECF PFOS and PFOA were consistent between manufacturing locations and showed minimal inter-lot variability from year to year. For example, 3M ECF PFOS reportedly had a consistent isomer composition of 70% linear (standard deviation (SD) 1.1%) and 30% branched (SD 0.8%) in eight production lots over 10 years (Reagen et al. 2007). Likewise, 3M ECF PFOA had a consistent isomer composition of 78% linear (SD 1.2%) and 22% branched (SD 1.2%) in 18 production lots over a 20-year period, as determined by ^{19}F nuclear magnetic resonance (NMR). This batch-to-batch consistency may allow researchers to distinguish sources to the environment based on isomer profiles. It is important to note from a source-tracking perspective, however, that while 3M may have produced most of the historical global ECF PFOA, between 1992 and 2002, more than 95% of 3M ECF PFOA was being used by other companies for fluoropolymer manufacturing (Wendling 2003). DuPont, for example, used 3M ECF PFOA for fluoropolymer manufacturing, beginning in the 1950s (Prevedouros et al. 2006).

Of the 89 possible PFOS isomers described by Rayne et al. (2008b), only ~11 appear to be present in measurable concentrations in 3M standards (Arsenault et al. 2008a). The structures of these isomers are *n*, *iso*, 5*m*, 4*m*, 3*m*, 2*m*, 1*m*, *tb*, 4,4m_2, 5,3m_2, and 5,4m_2. While less effort has gone into the characterization of ECF PFOA, out of 39 possible PFOA isomers (Rayne et al. 2008b) it appears that *n*-, *iso*-, 5*m*-, 4*m*-, and 3*m*-PFOA make up 99.2% in 3M ECF standards with minor contributions (<0.8%) from 2*m*, *tb*, 4,4m_2, 5,3m_2, and 5,4m_2 (Loveless et al. 2006; Table 2). While other isomers are theoretically possible, these are unlikely to be present at measurable concentrations in the environment since they are virtually undetectable in the commercially manufactured material.

The isomer profile of 3M ECF perfluorooctane sulfonamides and sulfonamidoalcohols are also fairly consistent with 3M ECF PFOS, despite the additional synthetic production steps (Table 4). The isomer composition of these products reportedly varied from 70 to 75% straight-chain isomers, however, this could increase up to 80% linear in some cases depending on the final chemical form

Table 4 Isomer composition (relative weight %) of 3M perfluorooctane sulfonyl fluoride (PFOSF)-derived products determined by ^{19}F NMR

	FOSA[a]			PFOS[b]	NEtFOSE[a]	
Isomer	Lot 15312	TN-A-1584[c]	Lot 2353	Lot 217	Lot 30107	Mean ± 1 SD
Normal	67.3	70.9	67.1	70	69.9	69.1 ± 1.81
Monomethyl	17.9	15.2	18.2	17.0	17.4	17.2 ± 1.18
Isopropyl	9.9	9.1	9.4	10.3	10.7	9.90 ± 0.67
Alpha	3.7	3.2	3.5	1.6	1.6	2.72 ± 1.04
t-butyl	0.24	0.21	0.27	0.2	0.23	0.24 ± 0.02
Dimethyl	0.14	0.12	0.13	0.2	0.13	0.13 ± 0.01
Total branched	31.88	27.83	31.5	29.3	30.06	30.1 ± 1.63

[a]Korkowski and Kestner (1999)
[b]Kestner (1997)
[c]Lot number was not available for this standard

and customer specifications for the final product use. NMR characterization of 3M ECF perfluorooctane sulfonamide (FOSA; Table 1), PFOS, and NEtFOSE (Table 4) indicated reproducible batch-to-batch and product-to-product consistency in isomer profile. This may imply that directly emitted PFOS may be indistinguishable from precursor-derived PFOS based on isomer profile, provided the degradation pathways are not isomer selective (discussed in Section 6). This is perhaps unfortunate from a source-tracking perspective, since it may prevent the contributions of the various pathways (e.g., atmospheric transport and oxidation of precursors versus direct emission of PFAs) from being easily elucidated by isomer profile.

PFOSF-derived fluorochemicals can contribute to both perfluoro-carboxylate and sulfonate loadings via abiotic degradation (D'eon et al. 2006; Martin et al. 2006; Wallington et al. 2006; Plumlee et al. 2009) and to environmental PFOS concentrations via biotransformation (Tomy et al. 2004; Xu et al. 2004; Martin et al. 2005; Rhoads et al. 2008). Thus, PFOA isomer profiles in the environment (expected to be ∼80% linear if contribution is exclusively from ECF PFOA; Table 2) may be influenced by the isomer pattern of PFOSF-derived fluorochemicals such as perfluorooctane sulfonamides (∼70% linear; Table 4). If contributions from PFOSF-derived fluorochemicals to PFOA are significant, one might expect PFOA isomer profiles to be slightly enriched (i.e., up to 30% branched isomer content) in samples, relative to 3M ECF PFOA. However, not all branched PFOSF isomers are expected to degrade to the same corresponding branched perfluorocarboxylate. Atmospheric oxidation of alpha-branched perfluorooctyl sulfonamides (e.g. 1*m*-NEtFOSA, 1*m*-NMeFOSE) is expected to produce linear PFCAs due to loss of both the alpha carbon and its monoperfluoromethyl branch, provided degradation of branched chains proceeds via the same mechanism as the linear molecule.

Compared to what is known about the historical manufacturing of PFOS, surprisingly little is known about current production. Miteni (Italy) is known to be currently

producing perfluoroalkyl sulfonates and carboxylates by ECF, and according to documents recently submitted to the International Stockholm Convention on Persistent Organic Pollutants, China began the large-scale production of PFOSF products in 2003. By 2006, 15 Chinese enterprises were producing more than 200 tonnes (t) of PFOSF, approximately half of which was exported to Brazil, the EU, and Japan (Ruisheng 2008). While this is substantially less than the 3,665 t of PFOSF produced by the 3M Co. in 2000 alone (Paul et al. 2009), it is similar to the 260 t of APFO produced by 3M in 1999 (Fluoropolymer Manufacturing Group 2002 cited in Prevedouros et al. 2006). It is not currently clear how much PFOS is being produced by China or by what method (ECF vs. telomer). If isomer profiles in new Chinese PFOSF material are unique from other manufacturers and continue to increase to pre-2002 production levels, we could expect to see changes in environmental isomer patterns in the future. To our knowledge, this "new PFOS" has yet to be taken into account in models that estimate future global PFOS production; however, Paul et al. (2009) did estimate ~1,000 t/year PFOS/PFOSF manufactured globally since 2002, provided production by remaining companies has not increased.

Information recently presented at the Workshop on Managing Perfluorinated Chemicals and Transitioning to Safer Alternatives (Geneva, Switzerland, February 12–13, 2009) suggested that most manufacturers have begun substituting perfluorooctyl-based products with perfluorinated chains of four (Santoro 2009) and six (Shelton 2009; Shin-ya 2009) carbons in length. One such alternative, perfluorobutane sulfonate (PFBS), has demonstrated lower toxicity (Lieder et al. 2009) and faster elimination (Olsen et al. 2009) in rodents than its corresponding longer-chain homologs. However, PFBS is nevertheless still detectable in water, often in concentrations higher than PFOS or PFOA (Skutlarek et al. 2006; Ahrens et al. 2009). It has also been reported in children (Holzer et al. 2008), and its effects on humans are largely unknown. Residual PFBS impurities, a by-product of ECF PFOSF synthesis, did not appear to contain any branched isomers, despite the clear presence of branched C6, C7, and C10 perfluoroalkyl sulfonates in commercially manufactured material (Fig. 1). The rearrangement of the fluoroalkyl chain to form branched isomers tends to decrease with chain length (Vyas et al. 2007), and thus the lack of branched isomers in currently manufactured ECF PFBS (based on ^{19}F NMR analysis, Vyas et al. 2007), is not necessarily surprising; albeit this implies that differentiating between historical, residual, and current intentionally manufactured PFBS using isomer profiles will be difficult.

Other sources of branched PFAs may also contribute to environmental loadings. For example, thermolysis of fluoropolymers is known to be a potential source of PFAs in the environment (Ellis et al. 2001) and is thought to proceed via a carbene radical, which, while still requiring further investigation, may have the potential to form branched PFCAs. In fact, in a follow-up study by Ellis et al. (2003b), GC–MS analysis of aqueous polytetrafluoroethylene (PTFE) thermolysis extracts revealed some evidence of branched perfluorocarboxylate formation. No authentic branched standards were available at the time of this study, and therefore this finding should be re-examined using current isomer profiling methods.

4 Isomer-Specific Analytical Methodologies

4.1 Current Analytical Separation Methods

The earliest reported perfluoroalkyl isomer separations were conducted by Bastosa et al. (2001) in which GC–MS was used to partially separate a mixture of ECF NEtFOSA isomers in ant bait marketed under the name Sulfuramid^{TM}. 3M also reported HPLC–MS/MS separations of total branched from linear perfluoroalkyl carboxylates and sulfonates in human blood (Stevenson 2002) as well as ^{19}F NMR characterizations of technical mixtures (Loveless et al. 2006). These latter methods, while effective for characterizing the isomer composition in standards, lacked the sensitivity to be applied to environmental samples.

The first methods suitable for isomer-specific analysis in environmental samples were developed by De Silva and Mabury (2004), and employed GC-MS to chromatographically separate a range of perfluoroalkyl carboxylates (C8–C13). Their original method employed a 90-m ZB-35 column and was capable of separating seven PFOA isomers along with a suite of PFCAs up to and including PFTrA in less than 100 min. This method was later optimized by substituting in a 105-m Rtx-35 column (Restek Corp., Bellefonte, PA, USA), which reduced method time to under 80 min and allowed for the detection of an additional PFOA isomer (total of eight PFOA isomers) (De Silva and Mabury 2006). This has since been applied to several in vivo (De Silva et al. 2009a, c) and environmental monitoring (De Silva et al. 2009b) experiments. The advantage of GC–MS-based isomer analysis is, most obviously, not only the high chromatographic resolution associated with GC, but also that it is less prone to matrix effects which can hinder electrospray ionization (ESI) sources. Ionization efficiencies in GC–MS may have minimal differences based on comparison between pure standards of *n*-PFNA and *iso*-PFNA (De Silva and Mabury 2006). As such, the quantitative isomer composition of a sample may be possible by comparison of relative peak areas of the molecular ion. This approach is prone to errors in HPLC–ESI-MS methods because the relative peak areas are also affected by the physical properties of each isomer in the mixture. The major disadvantage of the GC–MS method is that the derivatization procedure is relatively laborious and that perfluoroalkyl sulfonates cannot be analyzed simultaneously because they are not efficiently derivatized with 2,4-difluoroaniline. Langlois and Oehme (Langlois et al. 2007) addressed this latter deficiency by developing a novel PFOS derivatization method in which PFOS was reacted with isopropanol and sulfuric acid to form volatile isopropyl derivatives. When a derivatized technical standard of PFOS was analyzed by GC–MS, 11 isomers were separated in under 8 min. This procedure proved viable for perfluorohexane sulfonate (PFHxS) and various PFCAs, however, chromatographic isomer separation was not evaluated for these latter compounds. Furthermore, it was unclear whether this method is suitable for application to environmental samples, since isomer-specific derivatization yield and stability were not investigated and no complex matrix was tested. A similar procedure producing silane derivatives for GC–MS analysis was recently used

to determine PFOS and PFOA in packaging materials and textiles (Lv et al. 2009). Derivatives were noted to be stable within 2 d and limits of detection were 13.9 and 1.6 ng/mL for silated PFOS and PFOA, respectively, but the method was not validated for isomer-specific analysis. Recently, Chu and Letcher (2009) developed an in-port derivatization GC–MS method for PFOS isomers, using tetrabutyl ammonium hydroxide to produce volatile butyl PFOS isomer derivatives. Application of this method to a technical standard resulted in the separation and identification of 11 PFOS isomers in <15 min, and while detection limits were notably higher than most current LC–MS/MS methods, the authors were able to validate the method using environmental samples from the Great Lakes and Arctic.

Isomer-specific PFOS-precursor analysis by GC was also conducted by De Silva et al. (2008) and Benskin et al. (2009b) (Fig. 3). The former method employed a 60-m DB-WAX (0.25 mm ID × 0.25 μm FT, Phenomenex, Torrance, CA, USA) column to provide near-baseline resolution of nine NEtFOSE isomers in under 15 min. The latter method employed an 80-m DB35-MS column (0.25 mm ID × 0.25 μm FT, Agilent Technologies (formerly J & W Scientific), Mississauga, ON, Canada) to achieve near-baseline separation of six major and two minor NEtFOSA isomers in under 40 min.

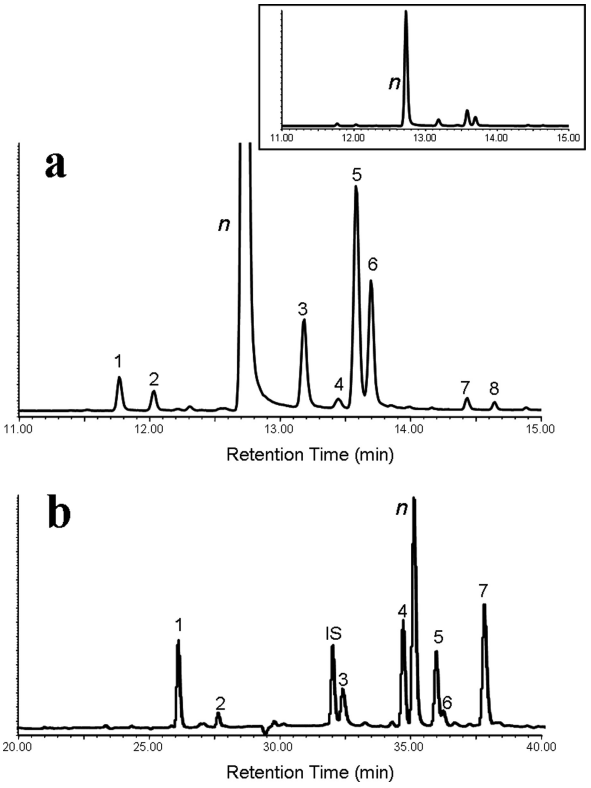

Fig. 3 **a** GC–(EI)MS separation of nine NEtFOSE isomers using *m/z* 448, 462, 562, and 540 ions on a 60-m DB-WAX. Peak #5 is tentatively identified as the isopropyl isomer. **b** Solid-phase microextraction–GC-ECD separation of eight NEtFOSA isomers on an 80-m DB35-MS column. IS indicates the internal standard, *n*-NMeFOSA

In 2004, Martin et al. (2004) presented early chromatograms of PFOS isomer separation by HPLC–MS/MS, using an octadecasilyl (C18) stationary phase. This was followed up in 2006 by Langlois and Oehme (2006), who carried out the first isomer-specific characterization of a technical PFOS standard using purified isomer fractions and HPLC–MS/MS with perfluorophenyl (PFP) and C18 columns. This relatively fast method (<30 min with PFP column for 10 isomers), was later used to examine FOSA isomer patterns in standards, as well as PFOA isomer patterns in standards, human blood, and water (Langlois 2006). Modification of the Langlois and Oehme (2006) method has since found application in the isomer-specific analysis of PFOS in human serum/plasma (Karrman et al. 2007) and Lake Ontario biota (Houde et al. 2008) as well as long-chain perfluorinated carboxylates in Lake Ontario biota (Furdui et al. 2008). Benskin et al. (2007) later improved isomer resolution and enabled wider analyte applicability using a linear perfluorooctyl (PFO) stationary phase and an acidified mobile phase to separate and detect all the major perfluoroalkyl carboxylate, sulfonate, and sulfonamides in a single injection. While the method was comprehensive, and had the added benefit of separating out PFHxS and PFOS interferences present in human serum, it was admittedly slow (115 min). Adjustments to the gradient and equilibration conditions of this method have decreased this time to 95 min (Benskin et al. 2009a) and it has since been applied to various in vitro (Benskin et al. 2009b) and in vivo (Benskin et al. 2009a; De Silva et al. 2009a; Sharpe et al. 2010) experiments, as well as (bio)-monitoring of human blood (Riddell et al. 2009) and ocean water (Benskin et al. 2009c).

Recently, ultra-pressure liquid chromatography (UPLC) has demonstrated promise in achieving simultaneous chromatographic separations of PFOS and PFOA isomers in less than 20 min (Arsenault et al. 2008b; Riddell et al. 2009; Wellington Labs 2008). While some co-elution appears to occur between 1*m*- and *n*-PFOS, and between 4*m*- and *iso*-PFOA isomers, these can likely be resolved using knowledge of isomer-specific collision-induced dissociation patterns (Langlois and Oehme 2006; Benskin et al. 2007), as described in Section 4.3. These methods also appear to suffer from co-eluting matrix interferences, and thus some work is still needed to refine them before they can be applied to environmental samples.

Despite improvements in PFA isomer separation methods, we still lack a single method that can provide high chromatographic resolution of *all* the major PFA isomers and their interferences in a reasonable amount of time (e.g., <30 min). The recent availability of isolated and characterized standards for the major PFOS and PFOA isomers will assist greatly in the further development of quantitative isomer-specific methods. However, another existing deficiency is that commercially available technical PFOS and PFOA standards do not have the same isomer profile as those which were historically manufactured by 3M, thus making comparisons between environmental isomer profiles and historical sources of PFOA and PFOS difficult. Some researchers have obtained standards as gifts from 3M, e.g., ECF PFOS and PFOA, and while these may indeed be very useful as a “gold standard” for use in source-tracking studies, these are known to contain many impurities which make them less useful for quantitative analyses.

4.2 Analytical Quantification Bias

Martin et al. (2004) provided preliminary evidence that PFOS isomer-specific collision-induced dissociation patterns could result in an analytical bias of unknown proportion unless the isomer profile in the sample was identical to the standard used for quantification. This hypothesized bias was quantified recently by Riddell et al. (2009), in which individual purified PFOS isomers were used to compare response factors, relative to the linear isomer. These results showed that regardless of the product ion used (*m*/*z* 80 or 99), at least one PFOS isomer (1*m*-PFOS monitored using *m*/*z* 80, 4,4m_2- and 4,5m_2-PFOS monitored using *m*/*z* 99) will be completely absent from the chromatogram. Considering that PFOS isomer profiles in biota can vary substantially, total PFOS analysis using *m*/*z* 80 or 99 product ions will lead to some inaccuracies, and possibly, incorrect conclusions to various hypotheses. To further examine this, Riddell et al. (2009) also quantified two human serum pools containing different PFOS isomer profiles (∼30–50% branched PFOS isomer content by LC–MS) using a characterized technical standard (21.1% branched PFOS by ^{19}F NMR) and isomer specific as well as total PFOS quantification methods. For sample A, total PFOS quantification resulted in *m*/*z* 80, overreporting by ∼30% compared to *m*/*z* 99, while quantification of sample B resulted in *m*/*z* 99, overreporting by ∼17% relative to *m*/*z* 80. When total branched PFOS was quantified separately from the linear isomer, the difference in values obtained from using *m*/*z* 80 and 99 for total branched isomer quantification was notably less than for total quantification methods, while consistent values were obtained for quantification of *n*-PFOS regardless of the product ion used (*m*/*z* 80 or 99). In the absence of methods which can quantify isomers individually, chromatographic separation of linear from "total branched" PFOS, followed by their independent quantification with a characterized technical standard, will provide improvement in the accuracy of total PFOS data.

Researchers should also be aware of a systematic bias that can be introduced when comparing isomer patterns in environmental samples at trace concentrations to ECF standards. As the concentration of branched isomers in a sample approaches the detection limit and disappears from chromatograms, the contribution of the linear isomer to total PFOA or PFOS may be incorrectly reported as 100% (Fig. 4). Any survey of isomer profiles should therefore take care to determine their "% linear dynamic range" – the concentration above which the isomer profile (or % linear calculation) of a standard stabilizes. Isomer profiles determined in samples that are below the concentration of the % linear dynamic range should only be reported with the necessary uncertainty identified, or flagged, as such. For example, Table 5 illustrates the results of Stevenson (2002), in which an ECF standard of PFOA at 0.5 and 10 ng/mL had % linear values of 81.2 and 74.7, based on LC–MS peak area, respectively, suggesting that % linear dynamic range likely lies somewhere in between these two concentrations. Alternatively, this bias may be diminished by reporting the ratio of each individually detected branched isomer to the *n*-isomer; thus permitting isomer-specific comparisons between studies.

Recently, the authors of several papers have utilized non-isomer-specific methods to assess the relative proportion of total branched from linear isomers in samples

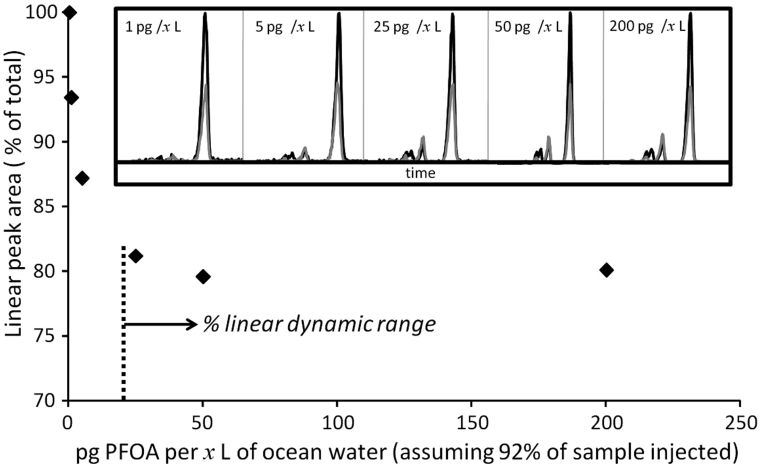

Fig. 4 The effect of decreasing concentration on PFOA isomer profile and the resulting contribution of linear PFOA to total PFOA peak area. Note that as the concentration falls outside the "% linear" dynamic range, the % contribution of linear PFOA becomes positively biased. Inset shows PFOA chromatograms for ECF standards at various concentrations. *Grey trace* represents *m*/*z* 413/369, *black trace* represents *m*/*z* 413/169

(Rylander et al. 2009a, b; Haug et al. 2009; Senthil Kumar et al. 2009). Although interesting observations have been made from this practice, caution is warranted as it can potentially lead to bias and overinterpretation of data, even when simply comparing peak areas. For example, when branched isomers are not baseline resolved from the linear isomer, it is unclear what contribution co-eluting branched isomers make to the signal of the *n*-isomer, which could potentially result in an overestimation of the true weight percent of the linear isomer in the mixture. Even in isomer-specific methods where near-baseline or baseline resolution is achieved, alpha-branched PFOS can still elute with *n*-PFOS and therefore contribute to the *m*/*z* 499/99 signal of this isomer (Riddell et al. 2009). For the purposes of qualitative assessment of relative branched content between samples, the above bias can be overcome by providing the corresponding branched content for a standard determined in the same manner, albeit this practice can also lead to overinterpretation (see Section 6.2), because the isomer content in standards supplied by specialty chemical manufacturers is usually not the same as historically manufactured fluorochemicals. For example, a sample with 30% branched PFOS content may appear enriched in branched isomers when compared to a Fluka standard (20% branched), despite the fact that it is indistinguishable from historically manufactured 3M ECF PFOS (30%). The numerous analytical methods (LC–MS, LC–MS/MS, and GC–MS) as well as different quantification techniques (monitoring single parent ion, single product ion, sum product ion, isomer-specific product ion) used for assessing branched isomer content can also make it difficult to compare branched content between studies. Nevertheless, this can again be overcome by providing the branched content of a characterized technical standard obtained in the same manner as the samples.

Table 5 PFOA isomer composition (%) in humans and standards. Values shown are means unless stated otherwise

References	Sample	*n*-	*Iso*-	IMM[a]	DM[b]	Other[c]	Total branched	Analysis
Stevenson (2002)	10 ng/mL 3M ECF PFOA	74.7					25.3	LC–MS/MS (C18, total ion count of *m/z* 369, 219, 169, 119). Branched content determined using relative sum product ions. Near-baseline separation of branched from linear
	0.5 ng/mL 3M ECF PFOA	81.2					18.8	
	Serum (Bioresource[d] Lot 020821)	99.7					<0.31	
	Serum (Lampire[e] Lot X324B)	84.0					16	
	Serum (Sigma[f] Lot 022K0965)	86.0					14	
	Serum (Golden West[g] Lot G01406042)	99.8					<0.21	
Keller et al. (2009)	Serum (SRM 1957, eight US States, 2004)	97.9					2.1	LC–MS/MS (C18 column, sum of *m/z* 369, 219, 169 product ions). Branched content determined using relative sum product ions. Extent of isomer separation unclear
Olsen et al. (2007)	3M ECF PFOA	78					22	LC–MS (C18, *m/z* 413). Branched content determined using relative peak areas. Extent of isomer separation unclear

Table 5 (continued)

References	Sample	*n*-	*Iso*-	IMM[a]	DM[b]	Other[c]	Total branched	Analysis
	Serum (occupationally exposed)	99 (range 94–99.9)					~1 (range 0.1–6.0)	
De Silva and Mabury (2006)	3M ECF PFOA	79.6	9.9	9.7		0.77	20.4	GC–MS (RTX-35, *m/z* 505). Branched content determined using relative peak areas. Nine PFOA isomers resolved in standard
	Serum (Sigma[f], Golden West[g])	98	1.5	0.5			2.1 (1.2–3.0)	
Benskin et al. (2007)	Serum (pregnant women, Edmonton, Canada, 2006)	>98					<2	LC–MS/MS (PFO, *m/z* 369). Branched content determined using relative peak areas. Eight PFOA isomers resolved in standard

[a]IMM – internal monomethyl branches (5*m*, 4*m*, 3*m*)
[b]DM – dimethyl branches
[c]Other – unidentified branched isomers
[d]Bioresource – Bioresource Technology Inc., Fort Lauderdale, FL
[e]Lampire – Lampire Biological Laboratories, Pipersville, PA
[f]Sigma – Sigma–Aldrich, Milwaukee, WI
[g]Golden West – Golden West Biologicals, Temecula, CA

4.3 Strategies for Isomer Separation by LC–MS/MS

For PFOS, current isomer separation techniques using PFP, PFO, or C18 stationary phases can typically and effectively separate dimethyl-branched isomers from internal monomethyl isomers (5*m*, 4*m*, 3*m*), and *iso*-PFOS from the linear isomer. However, separation of individual internal monomethyl-branched isomers from each other (5*m*, 4*m*, 3*m*) on these phases often proves challenging when using only the *m*/*z* 99, 80, or 499 (single MS) ions. Likewise, the alpha-branch isomer (1*m*-PFOS) tends to co-elute among internal monomethyl branches on PFO (Benskin et al. 2007), with the isopropyl branch (Karrman et al. 2007) or somewhere between isopropyl and linear (Houde et al. 2008) on PFP, or with *n*-PFOS, on C18 (Riddell et al. 2009). Fortunately, these co-eluting PFOS isomers can be resolved using knowledge of isomer-specific collision-induced dissociation (Langlois and Oehme 2006) in combination with less sensitive, albeit highly specific MS/MS transitions. As shown in Fig. 5a, the *m*/*z* 80 product ion provides good separation of *n*, *iso*, monomethyl, and dimethyl isomers on a PFO column, similar to that which has been previously obtained on C18 (Arsenault et al. 2008b) and PFP (Houde et al. 2008;

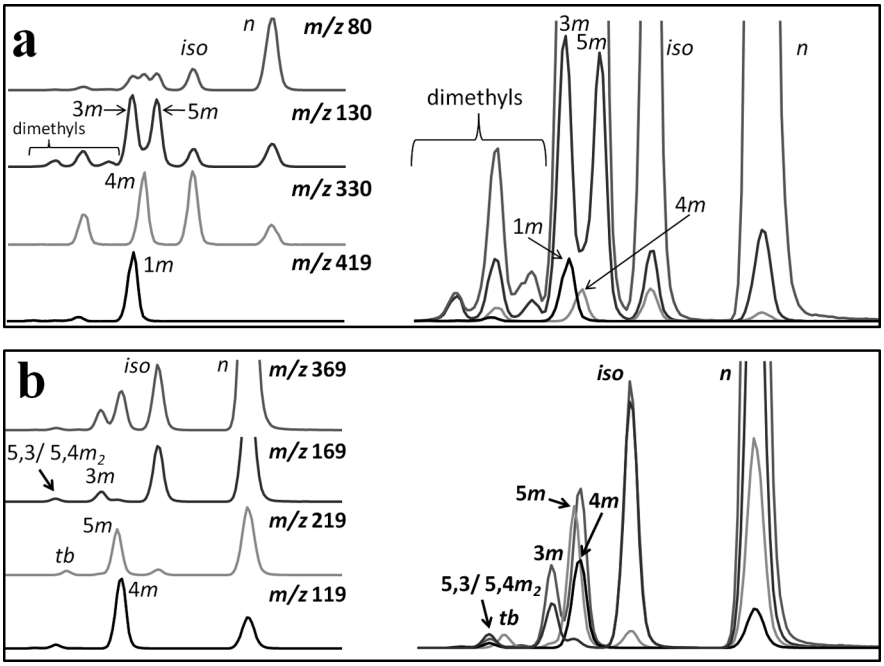

Fig. 5 **a** Recommended product ions for PFOS isomer-specific LC-MS/MS analysis: *m*/*z* 80 (*grey trace*): *n*, *iso*; *m*/*z* 130 (*dark grey trace*): 5*m*, 3*m*, *dimethyls*; *m*/*z* 330 (*light grey trace*): 4*m*; *m*/*z* 419: 1*m* (*black trace*). **b** Recommended product ions for PFOA isomer-specific LC-MS/MS analysis: *m*/*z* 369 (*grey trace*): *n*, *iso*; *m*/*z* 169 (*dark grey trace*): 3*m*, 5,3/5,4m_2; *m*/*z* 219 (*light grey trace*): 5*m*, *tb*; *m*/*z* 119 (*black trace*): 4*m*

Langlois and Oehme 2006) phases. With PFO, resolution of individual monomethyl branches is most easily accomplished using the *m*/*z* 130 product ion for 3*m* and 5*m* isomers and *m*/*z* 330 product ion for 4*m*-PFOS. A similar strategy can be adopted for the resolution of 1*m*-PFOS using *m*/*z* 419, since this is the only major isomer to produce this ion. Furthermore, 1*m*-PFOS does not produce an *m*/*z* 80 ion, therefore, provided that this ion is used for quantification of *iso*-PFOS and *n*-PFOS, 1*m*-PFOS should not cause any interference when using PFP or C18 phases. Although some minor isomers that are detectable in ECF PFOS standards also produce the *m*/*z* 419 ion (Fig. 5a), 1*m*-PFOS is the only isomer that has been detected to date in environmental samples that produces this highly specific product ion. A similar strategy can be employed for PFOA isomers using *m*/*z* 369, 169, 219, and 119 product ions as shown in Fig. 5b. Monomethyl PFOA isomers, 5*m*- and 4*m*-PFOA, elute essentially together but produce distinct *m*/*z* 219 (5*m*) and 119 (4*m*) ions, respectively, which permit their resolution.

5 Influence of Physical–Chemical Properties on Environmental Fractionation of Perfluoroalkyl Isomers

Among the most intriguing topics in perfluoroalkyl research today pertains to the mechanism(s) of long-range transport of PFAs to remote regions, such as the Arctic. Much of this discussion, and the associated environmental modeling, relies heavily on accurate knowledge of physical and chemical properties. While one hypothesis suggests atmospheric transport and degradation of volatile PFA precursors (Ellis et al. 2003a; Butt et al. 2007; Young et al. 2007), another proposes slow, long-range transport of PFAs in ocean water (Armitage et al. 2006, 2009a, b; Prevedouros et al. 2006; Wania 2007). A more recent third hypothesis, presented by McMurdo et al. (2008), is that PFOA has a higher pK_a than previously thought and thus atmospheric transport of PFOA (i.e., the protonated form) may occur due to partitioning from marine aerosols, and furthermore that fractionation of branched and linear PFOA isomers may occur because of this process. The authors suggest that, based on the greater surface activity of *n*-PFOA (Bernett and Zisman 1967), *n*-PFOA will become preferentially enriched on surface microlayers. Further fractionation of linear from branched PFOA isomers would then occur during the transfer of PFOA in aerosol droplets to the gas phase due to the (presumably) differing Henry's Law constants and pK_a of all the isomers. From model calculations, pK_a values close to 0 (Goss 2008a, b), 1.3 (Lopez-Fontan et al. 2005), 2.8 (Brace 1962), and 3.8 (Burns et al. 2008) have been predicted, while values of <1 (Cheng et al. 2009) and 1.3 (Kutsuna and Hori 2008) were derived from experimental measurements. In two recent studies, pK_as of $\leq$1.5 and $\geq$3.5 (Armitage et al. 2009a; inferred from McMurdo et al. 2008), and 2.8 and 3.8 (Ellis and Webster 2009), were suggested for total branched and linear PFOAs, respectively. This was followed by computational model estimations for the pK_as of individual branched isomers of PFOA, which ranged from –0.1 (5*m*- and 4*m*-PFOA) to −5.1 (1,1,2,2m_4-PFOA), with *n*-PFOA having a pK_a of −0.2

(Rayne et al. 2009). The lower values for most branched PFOA isomers are based on knowledge that electron-withdrawing CF_3 groups stabilize the carboxylate group, thus making most branched isomers stronger acids than the linear isomer. However, the inductive effect of the trifluoromethyl group is diminished as the distance from the carboxyl group increases and becomes negligible when the separation exceeds four alkyl units (Perrin et al. 1981; cited in Burns et al. 2008). Although helicity has also been suggested to influence the pK_a of *n*-PFOA (Burns et al. 2008), it is not clear to what extent a *lack* of helicity will influence branched isomer pK_as. Considering branching position alone, the suggestion of a significantly lower pK_a of "total branched" PFOA by Ellis et al. (2009) and Armitage et al. (2009a) requires that the majority of perfluoromethyl branches be situated alpha or beta to the carboxyl group. However, on the basis of monoperfluoromethyl isomers present in ECF PFOA, determined by ^{19}F NMR (Table 2), only 2*m*- and potentially 3*m*-PFOA have branching positions that should significantly influence the pK_a (Table 6); and the former isomer makes up only a scant 0.1% of 3M ECF PFOA. The quantities of 3*m*-PFOA have not been specifically reported, but total internal monomethyl branches (3*m*-, 4*m*-, and 5*m*-PFOA) constitute 12.6% of 3M ECF PFOA (Table 2) and 3*m*-PFOA is also readily identifiable in standards and in the environment. Thus, the partitioning processes described by McMurdo et al. (2008) could possibly be investigated by monitoring for a relative deficiency of 3*m*-PFOA in atmospheric samples over oceans or large lakes.

Overall, it is predicted that some enrichment of linear PFOA isomers may occur in the atmosphere as a result of the mechanism described by McMurdo et al. (2008). From a mass balance perspective, we speculate that the converse is unlikely and thus that ocean water PFOA isomer profiles should not be significantly influenced by isomer-specific partitioning to air. Any minor fractionation of isomers to aerosols or the atmosphere, although perhaps important as a global transport pathway, should not influence the bulk PFOA profile in the world's oceans, particularly in mid-latitude source regions. Our analyses of PFOA in Eastern Atlantic ocean water have

Table 6 Isomer composition (wt%) of ECF PFOA and predicted pK_a values

		pK_a		
	Isomer composition	Rayne et al. (2009)	Ellis and Webster (2009)	Armitage et al. (2009)
n-PFOA	77.6	−0.2	≥3.8	3.5
iso-	9	−0.1		
5*m*-		−0.1		
4*m*-	12.6[a]	−0.2	≤2.8[b]	1.5[b]
3*m*-		−1.3		
2*m*-	0.1	−1.7		
tb-	0.2	−0.3		

[a]Represents sum of 5*m*, 4*m* and 3*m* isomers
[b]Assumed to be average of all branched isomers

revealed a branched isomer profile (including 3*m*-PFOA) which was, in general, not significantly different to that of 3M ECF PFOA (Benskin et al. 2009c) (Table 7). Although this does not provide evidence *against* fractionation of PFOA isomers to marine aerosols and the atmosphere, it is strongly evident that such processes are unlikely to affect the overall isomer profiles in the world's oceans. Ultimately, more definitive evidence of selective atmospheric partitioning may be gleaned from PFOA isomer profiling in the atmosphere or in aerosols.

Other interesting differences in the physical−chemical properties of PFOA isomers imparted by perfluoroalkyl branching patterns are reported in the literature. For example, the mere ability to separate isomers by HPLC, or their derivatives by GC, implies differential hydrophobicity and vapor pressures, respectively (Langlois and Oehme 2006; Benskin et al. 2007; De Silva and Mabury 2004; Langlois et al. 2007). Vyas et al. (2007) also attributed a higher branched content in PFOSF, compared to PFOS standards, to selective removal of branched isomers during purification of the potassium salt. This is supported by the preparative-scale isolation of *n*-PFOS from branched isomers by successive recrystallization in water (Arsenault et al. 2008b) and carbonate buffer followed by centrifugation (Ochoa-Herrera et al. 2008), demonstrating that branched isomers are more water soluble than the linear chain – consistent with all HPLC elution orders on reversed-phase stationary phases. Furthermore, branching has also been observed to decrease melting point (Bernett and Zisman 1967), and in a separate study, to increase boiling point in perfluoroalkanes (Smart 2001).

More recently, De Silva et al. (2008) built on the work of Gauthier (2004) by measuring the *n*-octanol–water partition coefficients (K_{ow}) for nine isomers of 3M ECF NEtFOSE. The log K_{ow} values were statistically indistinguishable for seven branched isomers, including the isopropyl isomer, with a mean value of 5.41. However, isomer 4 (Fig. 3a) had a statistically higher K_{ow} of 5.58, and the *n*-isomer of NEtFOSE had a statistically lower log K_{ow} of 5.33. It is unclear whether the minor differences in these or other physical and chemical properties are sufficient to cause any significant differential transport or bioaccumulation potential. Similar studies may be warranted for other ECF chemical products and for other physical properties.

The subtle differences in the physical–chemical properties between branched and linear PFA isomers are also apparent in abiotic degradation studies. For example, Yamamoto et al. (2007) observed that three branched PFOS isomers degrade more rapidly than do the linear chain when subjected to UV light in the presence of water or alkaline 2-propanol. Similarly, Ochoa-Herrera et al. (2008) demonstrated that branched PFOS isomers could more readily undergo reductive dehalogenation by Ti(III)-citrate, in the presence of a vitamin B12 catalyst. In this study, *iso*- and 5*m*-PFOS were the most labile isomers, followed by 3*m*- and 4*m*-, 1*m*-, and finally *n*-PFOS. The authors suggested a decrease in C–C bond strength resulting from perfluorinated chain branching and/or the stabilization of radical intermediates imparted by branched structures as possible explanations for this observation. Ochoa-Herrera et al. (2008) also presented isomer-specific Gibbs free energies using ab initio calculations to predict the relative stability of the various isomers. The

Table 7 PFOA isomer composition (%) in environmental and biological samples and standards. Values shown are means unless stated otherwise

References	Sample	*n*-	*iso*-	IMM[a]	DM[b]	Other[c]	Total branched	Analysis
Benskin et al. (2009c)	3M ECF PFOA	77					23	LC−MS/MS (PFO, *m/z* 369, 219, 169, 119). Branched content determined using isomer-specific product ions. Ten PFOA isomers resolved in standard
	Atlantic Ocean (avg. 23 locations) (from N46° 17.257′ W06° 29.386′ to N01° 13.523′ W11° 57.961′)	78					22	
	Water, coastal Asia (avg. four locations)	77					23	
	Water, Tokyo Bay, Japan	90					10	
De Silva and Mabury (2004)	3M ECF PFOA	77				2.1	23	GC–MS (ZB-35, *m/z* 505). Branched content determined using relative peak areas. Seven PFOA isomers resolved in standard
	Polar bear (*Ursus maritimus*) (Greenland)	95					5.0 (2.8–9.8)	
	Polar bear (*Ursus maritimus*) (Canada)	100					nd[d]	
De Silva et al. (2009b)	3M ECF PFOA	78					22	GC–MS (RTX-35 or ZB-WAX, *m/z* 505). Branched content determined using relative peak areas. Eight PFOA isomers resolved in standard
	Char Lake surface water (Nunavut, Canada)	99	0.69	0.39			1.1	
	Amituk Lake surface water (Nunavut, Canada)	99	0.40	0.25			0.65	
	Lake Ontario surface water (Canada)	85–94	2.8–6.8	3.1–8.5			5.9−15	
	Ontario precipitation (Canada)	96	1.9	1.7			3.7	
	Dolphin plasma (*Tursiops truncatus*) (USA)	99	0.40	0.30			0.70	

Table 7 (continued)

References	Sample	*n*-	*iso*-	IMM[a]	DM[b]	Other[c]	Total branched	Analysis
	Lake Trout (*Salvelinus namaycush*) (Lake Ontario, Canada)	95	2.9	2.1			4.9	
	Mysis (*Mysis relicta*) (Lake Ontario, Canada)	99	0.69	0.40			1.1	
	Diporeia (*Diporeia hoyi*) (Lake Ontario, Canada)	99	0.79	0.42			1.2	
	Alewife (*Alosa pseudoharengus*) (Lake Ontario, Canada)	99	0.59	0.50			1.1	
	Sculpin (*Cottus cognatus*) (Lake Ontario, Canada)	99	0.69	0.40			1.1	
	Smelt (*Osmerus mordax*) (Lake Ontario, Canada)	99	0.6	0.24			0.83	
	Zooplankton (Lake Ontario, Canada)	98–99	0.99	0.39–0.79			1.4–1.8	
	Ringed seal (*Phoca hispida*) (Lake Ontario, Canada)	100					nd	
	Lake Ontario sediment (Canada)	97–98	0.98–1.4	0.59–1.5			1.6–2.8	
	Char Lake sediment (Nunavut, Canada)	95	2.9	2.1			4.9	
Furdui et al. (2008)	Trout (*Salvelinus namaycush*) (Lake Ontario, Canada)	100					nd	LC–MS/MS (C18 column, *m/z* 369). Branched content determined using relative peak areas. Extent of isomer separation unclear

Table 7 (continued)

References	Sample	*n*-	*iso*-	IMM[a]	DM[b]	Other[c]	Total branched	Analysis
Powley et al. (2008)	Arctic Cod (*Arctogadus glacialis*) (Canada)	100					nd	LC–MS/MS (C8 column, *m*/*z* 369). Branched content determined using relative peak areas. Extent of isomer separation unclear
	Bearded and ringed Seal (*Erignathus barbatus and Phoca hispida*) (Canada)	100					nd	

[a]IMM – internal monomethyl branches (5*m*, 4*m*, 3*m*)
[b]DM – dimethyl branches
[c]Other – unidentified branched isomers
nd – not detected

results indicated that after *n*-PFOS, 1*m*- and *iso*-PFOS were the most stable, followed by 3*m*-, 4*m*-, and 5*m*-PFOS. These data contrast those of Rayne et al. (2008a), in which branched isomers were all found to be more thermodynamically stable than *n*-PFOS; based on gas-phase enthalpies, entropies, and free energies of formation. If municipal or industrial water treatment facilities begin to apply such catalytic reductive or oxidative treatment procedures then some unique isomer profiles may be relevant in local environments.

The stability of perfluorinated radical intermediates may also influence the isomer-specific abiotic oxidation of ECF perfluoroalkyl sulfonamides. These are hypothesized to be a source of branched PFOS and perfluoroalkyl carboxylates (including PFOA) in the environment based on their occurrence in smog chamber studies with volatile precursors in the presence of Cl and OH radicals (D′eon et al. 2006; Martin et al. 2006) and indirect photolysis experiments with OH radicals (Plumlee et al. 2009). It should be noted that alpha-branched PFOA is unlikely to form from oxidation of alpha-branched perfluorooctyl sulfonamides by these processes (Ellis et al. 2004; Martin et al. 2006). Thus, while an absence of 2*m*-PFOA may be indicative of oxidation processes, it is only present at trace levels in 3M ECF PFOA (<0.1%) and has yet to be detected by current LC–MS methods, perhaps due to its unique collision-induced dissociation to *m*/*z* 85 (CF_3O^-) and 63 ($[CO_2F]^-$) product ions (Benskin et al. 2009a). Isomer-specific monitoring of PFA atmospheric deposition in remote regions may provide insight into this issue.

6 Characterization of Perfluoroalkyl Isomer Profiles in the Environment

6.1 PFOA Isomer Profiles

Especially relevant for regulation of fluorochemicals is the extent of the environmental PFA burden attributed to current-use fluorochemicals versus those whose source has largely been regulated or phased out. Early on, it was hypothesized that this could be assessed by monitoring isomer profiles in biological samples, since historical (pre-2002 phase out) releases of ECF fluorochemicals consisted of a mixture of isomers whereas current and historical manufacture of telomer-derived products has largely been of strictly the linear isomer (De Silva and Mabury 2006). However, due to the preferential excretion of branched isomers, it is possible that, at steady state, tissues of organisms exposed exclusively to ECF PFOA could take on isomer profiles that are predominantly linear (Benskin et al. 2009a; De Silva et al. 2009a, c). This evidence from rodents and fish thus raises ambiguity when attempting to ascribe manufacturing source based on PFOA isomer patterns in biological samples.

Notwithstanding, some information may be gained by examining isomer profiles in biological samples. For example, De Silva and Mabury (2004) examined PFCA isomer profiles in Arctic polar bear livers, from the south eastern Hudson Bay region

of Canada, and central eastern Greenland and found that Greenland bears showed some contribution from an electrochemical source (i.e., minor detectable branched isomers; Table 7), whereas Canadian bears had none detectable. Canadian bears had higher total concentrations of PFOA (mean 25 ng/g) compared to Greenland bears (9 ng/g), and thus the absence of branched isomers in Canadian bears cannot be explained by detection limits. Consistent with this observation, there were also no detectable branched PFOA isomers in seals (De Silva et al. 2009b) or cod (Powley et al. 2008) from the western and central Canadian Arctic. The discrepancy among polar bear populations may result from exposure to PFOA from two different sources or via different transport mechanisms. For example, Greenland bears may have PFOA isomer signatures similar to what is transported from the Arctic, which appear predominantly electrochemical in origin (Benskin et al. 2009c). Conversely, the strictly linear signature of Canadian polar bears may indicate less exposure to PFAs which have undergone long-range transport in oceans and more exposure to telomer-derived PFAs which have undergone atmospheric transport, since the atmosphere has been shown to deliver a highly linear profile of PFOA as evidenced by 99% *n*-PFOA in water and 95% *n*-PFOA in sediment from isolated remote Arctic lakes (De Silva et al. 2009b).

PFOA isomer profiles in samples (biotic and abiotic) from throughout North America also reveal a predominantly linear signature, albeit a "% linear" dynamic range was not defined in many of these studies, thus the % linear may be positively biased for some samples (see Section 4.2). Furdui et al. (2008) observed only *n*-PFOA in isomer profiles in Lake Ontario Lake Trout and suspended sediment. Consistent with this result, in a separate study De Silva et al. (2009b) observed predominantly *n*-PFOA (95%) in biological samples from Lake Ontario but substantially more branched PFOA isomers in surface water (85–94% linear), supporting the hypothesis of isomer-specific biological discrimination (De Silva et al. 2009c). In samples that contained branched isomers, *n*-, *iso*-, and 5*m*-PFOA were detected in humans, rainwater, Lake Ontario surface water and biota, and dolphins (Table 7). Of these, Lake Ontario surface water (87–93% linear PFOA) also contained 4*m*-PFOA and appeared to have the profile most similar to that of 3M ECF PFOA.

To date, the highest relative quantity of branched PFOA measured in environmental samples is in ocean water from the Atlantic and coastal Asia (Benskin et al. 2009c) (Table 7). In these samples, PFOA isomer profiles were, for the most part, consistent with a 3M ECF PFOA standard. The exception was in samples from Tokyo Bay which appeared to contain significant additional contributions from a linear (presumably telomer) source, but these samples also did not have a consistent ratio of *iso*-PFOA to other branched PFOA isomers, suggesting a potential additional source of *iso*-PFOA (also presumably telomer). This latter hypothesis is supported by the observation of single branched isomers (assumed to be isopropyl) in addition to linear isomers of PFNA, perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnA), and perfluorododecanoate (PFDoA) in Toyko Bay (absent in all other coastal Asian sampling locations), as well as recent data presented by Zushi et al. (2010) in Tokyo Bay sediment cores (see Section 6.3).

In humans, the PFOA isomer signature appears predominantly linear regardless of location and sex (Table 5). Serum from the background population and from occupationally exposed men and pregnant or non-pregnant women in four different studies showed consistently ≤2% total branched PFOA content (De Silva and Mabury 2006; Olsen et al. 2007; Benskin et al. 2007; Keller et al. 2009). Interestingly, the highest relative amount of branched PFOA in human serum is from unpublished data by 3M, in which a number of pooled human serum samples were analyzed by LC–MS/MS and branched content of up to 16% was observed, compared to 25.3% branched in a 10-ng/mL 3M ECF standard (Table 7). It should be noted that the apparent elevated quantity of branched isomers in this 3M ECF standard is likely a result of simply summing the responses of *m/z* 119, 169, 219, and 369 product ions and is therefore not representative of the actual weight % of branched isomers in 3M ECF PFOA, which is acknowledged as ∼20% (Reagen et al. 2007).

6.2 Perfluoroalkyl Sulfonate and Sulfonamide Isomer Profiles

The exclusive production of PFOS and PFOS precursors by ECF makes PFOS isomer signatures a potentially powerful tool for conducting exposure source determination experiments. Unlike PFOA, which has a predominantly linear isomer signature in humans, PFOS isomer profiles vary depending on geographic location and time of sample collection (Table 8). For example, in one of the earliest studies of PFOS isomer profiling in humans, contributions of the linear isomer to total PFOS ranged from ∼59 (Australia serum and UK plasma) to ∼68% (Sweden plasma) compared to a Fluka standard (78%) (Karrman et al. 2007). At the time, this apparent preferential accumulation of branched PFOS isomers was attributed to pharmacokinetic discrimination, however, this is contrary to what is observed for PFOS isomers in rodents (Benskin et al. 2009a; De Silva et al. 2009a), where the linear isomer was preferentially retained, albeit non-significantly relative to most branched isomers. Furthermore, PFOS standards manufactured by Sigma–Aldrich/Fluka (∼80% *n*-PFOS by ^{19}F NMR; Table 2) are known today to have lower branched isomer content than 3M ECF PFOS (∼70% *n*-PFOS by ^{19}F NMR, Table 2), thus a Fluka standard is a non-ideal reference standard, as we indicated earlier, and it is not clear if both these human samples would have been significantly different from 3M ECF PFOS. Nonetheless, the difference between the % linear values found in Australia/UK and Sweden implies that some factor, whether it be pharmacokinetic or source, is influencing the isomer profiles in these locations. Furthermore, Haug et al. (2009) also reported the apparent enrichment of branched PFOS isomers in a more recent survey of human blood samples from Norway. In this study, an 11% decrease in the relative proportion of *n*-PFOS was observed between 1976 (68% linear) and 2007 (57% linear), albeit the branched content in a reference standard was not provided. Interestingly, the same trend of decreasing branched content with time was also observed by Riddell et al. (2009) in human

Table 8 PFOS isomer composition (%) in humans. Values shown are means unless stated otherwise

References	Sample (description, location, year collected)	*n*-	*iso*-	5*m*/4*m*/3*m*	Dimethyls	Other branched	Total branched	Analysis/comment
Karrman et al. (2007)	PFOS standard (Fluka)	78.0	14.4[a]	8.0	0.6		23.0	LC–MS (C18, *m*/*z* 499). Branched content determined using relative peak areas. Separation of several branched isomers and near separation of branched from linear isomers
	Plasma (mixed age/gender, Sweden, 1997–2000)	68.1	18.0[a]	12.6	0.4	0.9	31.9	
	Serum (mixed age/gender, Australia, 2002–2003)	58.7	21.3[a]	17.1	0.8	2.9	42.1	
	Plasma (mixed age/gender, UK, 2003)	59.6	20.4[a]	17.7	0.5	2.5	41.1	
Haug et al. (2009)	Serum (*range*, mixed age/gender, Norway, 1976–2007)	53–78					22–47	LC–MS/MS (C8 column, *m*/*z* 499/499). Branched content determined using relative peak areas. Extent of isomer separation unclear
	Serum (mixed age/gender, Norway, 1976)	68					32	
	Serum (mixed age/gender, Norway, 2007)	57					43	
Keller et al. (2009)	Serum (SRM 1957, eight US States, 2004)	59					41	LC–MS/MS (C18 column, sum of *m*/*z* 80, 99, 130 product ions). Branched content determined using relative sum product ions. Extent of isomer separation unclear
	PFOS standard	77					23	LC–MS/MS (C8 column, *m*/*z* 80). Branched content estimated from peak height in chromatograms found in Keller et al. (2009). Branched isomers not baseline resolved
	Serum (SRM 1957, eight US States, 2004)	65					35	
	Milk (SRM 1954, several US states, 2006)	73					27	

Table 8 (continued)

References	Sample (description, location, year collected)	*n*-	*iso*-	5*m*/4*m*/3*m*	Dimethyls	Other branched	Total branched	Analysis/comment
Riddell et al. (2009)	Serum (SRM 1589a, Great Lakes region, 1996)	~70					~30	LC–MS/MS (PFO column, *m*/*z* 80). Total branched quantified separately from linear using characterized standard. Branched isomers baseline resolved from *n*-PFOS
	Serum (SRM 1957, eight US States, 2004)	~50					~50	
Benskin et al. (2007)	PFOS standard (Fluka)	76.0					24.0	LC–MS/MS (PFO column, *m*/*z* 80). Concentration using *n*-PFOS and technical PFOS (Fluka) standards. Branched isomers baseline resolved from *n*-PFOS
	Serum (pregnant women, Edmonton, Canada, 2006)	80.0					20.0	
Rylander et al. (2009b)	Plasma (*median*, delivering women, south central Vietnam, 2005)	83 (range 17–93)					17 (range 7–83)	LC-Q-TOF (C18, *m*/*z* 498.93). Branched content determined using relative peak areas. Branched appears to be separated from linear. Extent of co-elution with linear unclear
Rylander et al. (2009a)	Plasma (male, Norway, 2005)	67 (range 49–100)					33 (range 0–51)	LC-Q-TOF (C18, *m*/*z* 498.93). Branched content determined using relative peak areas. Branched appears to be separated from linear. Extent of co-elution with linear unclear
	Plasma (female, Norway, 2005)	70% (linear, range 56–100)					30 (range 0–44)	

[a] *iso*+ 1*m* isomer

serum standard reference materials (SRMs) collected in 1996 (SRM 1589a) and 2004 (SRM 1957) using isomer-specific quantification. SRM 1589a was collected across eight States and SRM 1957 was collected from the Great Lakes region, and it is unclear what geographical location-related factors may have influenced these profiles. Nonetheless, SRM 1589a (~30% branched) clearly had lower branched content than did SRM 1957 (~50% branched) and this was supported by the results of Keller et al. (2009), who also found SRM 1957 to contain elevated branched content (41%), although the branched content for a reference standard was not provided. Interestingly, a qualitative comparison of branched PFOS content in human serum (SRM 1957), human milk (SRM 1954), and a technical standard (unknown supplier) based on peak heights from chromatograms provided in Keller et al. (2009) indicates that the branched content in human milk may be quite similar to the reference standard and deficient in branched content relative to human serum (SRM 1957). It is unclear what factors might be influencing these isomer profiles and further investigation is needed; still, it is reasonable to hypothesize that the linear isomer, being more lipophilic, might partition to human milk to a greater extent than do branched isomers.

The results of Haug et al. (2009) are generally supported by those of Rylander et al. (2009a), who also examined human blood samples from Norway collected in 2005 and found a similar contribution of linear isomers; notwithstanding there was a small, albeit significant difference between men (67% linear, range 49–100%) and women (69% linear, range 56–100%), but again, these were not compared to a technical standard, thus it is difficult to say if these are similar to the ~70% linear content in 3M ECF PFOS or not. Isomer profiles of PFHxS, PFOS, and FOSA have also been examined in the serum of pregnant women from Edmonton, Canada (Benskin et al. 2007). Although up to six branched isomers were detected in a PFHxS standard from Fluka, endogenous interferences present in the serum (as discussed in Chan et al. 2009) hampered the elucidation of PFHxS isomer profiles, thus only a single branched PFHxS isomer was detected in addition to *n*-PFHxS. Two branched FOSA isomers were also observed, in addition to *n*-FOSA. PFOS isomer profiles in human serum were very similar (~80% linear based on quantification using an *n*-PFOS standard) to a Fluka standard (76%), suggesting that the branched isomer content was substantially lower than that of 3M ECF PFOS. This is generally consistent with recent data by Rylander et al. (2009b), in which the median contribution of the *n*-isomer to total PFOS in delivering women from south central Vietnam was 83% (range 17–93%), based on LC–MS/MS analysis; however, it is unclear if all branched isomers were fully resolved from the linear chain or how this percentage compared to that in a technical standard. Nonetheless, when taken at face value, it is interesting that samples from both of these studies were collected from pregnant or delivering women and both reported a deficiency in branched PFOS content relative to studies from Norway (Haug et al. 2009; Rylander et al. 2009a), Australia, and the UK (Karrman et al. 2007), which generally showed enrichment of branched content and did not involve pregnant or delivering women. While it is unknown what factor or combination of factors (e.g., source and pharmacokinetics) contribute to these differences, one possibility is that pregnancy reduces the body burden of branched

isomers in the mother by preferentially transferring branched PFOS to the fetus. At this time this hypothesis remains tentative, however, recent data have shown that branched PFOS isomers can preferentially cross the placental barrier relative to *n*-PFOS (Beesoon et al. 2009).

In contrast to humans, enrichment of branched PFOS in wildlife has not been frequently observed (Table 9). Lloyd et al. (2009) qualitatively observed enrichment of branched isomers in Red deer liver and Whitebait relative to a Fluka PFOS standard, while Powley et al. (2009) reported 50% branched PFOS in cod from the western Canadian Arctic, relative to Fluka PFOS (74%). In all other literature to date, PFOS isomer profiles in wildlife appear either similar or deficient in branched content relative to technical standards. For example, Chu and Letcher (2009) observed enrichment of *n*-PFOS in eggs from herring gull (94.5% *n*-PFOS) and double-crested cormorant (95.9% *n*-PFOS) from the Great Lakes, as well as in polar bear samples from the Norwegian Arctic (plasma, 82.4% *n*-PFOS) and Canadian Arctic (liver, 92.4% *n*-PFOS), compared to a technical standard from Wellington (65% *n*-PFOS). In these samples, dimethyl-branched isomers (3,5m_2, 4,5m_2, *tb*-, and 4,4m_2-PFOS) were not detectable, which is consistent with the results of Houde et al. (2008), who also found an absence of dimethyl-branched isomers and enrichment of *n*-PFOS in a Lake Ontario foodweb. In this study, the *n*-isomer accounted for more than 88% total PFOS in all biological samples, which was similar to that observed in sediment (81–89% *n*-PFOS) but contrasted with the composition in Fluka PFOS (77%) and Lake Ontario water (43–56% *n*-PFOS), the latter of which was noticeably deficient in *n*-PFOS. Powley et al. (2008) reported similar results in bearded and ringed seals from the western Canadian Arctic, which were both highly enriched in *n*-PFOS (96%) compared to a Sigma–Aldrich/Fluka standard (76%). Likewise, Senthil Kumar et al. (2009), observed 77–89% *n*-PFOS in a range of aquatic wildlife from GA, United States, and Lloyd et al. (2009) reported a qualitative deficiency in branched PFOS in Cromer crab and Carp roe, compared to a Fluka standard.

Although the deficiency in branched PFOS observed in most wildlife may be explained by preferential absorption or retention of the linear isomer, as observed to a minor extent in rodents (Benskin et al. 2009a; De Silva et al. 2009a) and significantly in fish (Sharpe et al. 2010) (see Section 7), it is also possible that in biological samples where total PFOS concentrations are extremely low, some branched isomers may be below detection limits, resulting in a positive bias in the % of total PFOS attributed to the linear isomer (see % linear dynamic range in Section 4.2). Nevertheless, deficiencies in branched content are still observed in samples containing total PFOS concentrations which are well above isomer detection limits in ECF standards, therefore there is a reasonable degree of confidence in these data.

Interestingly, the positive analytical bias discussed above, and what is known about the pharmacokinetics of PFOS isomers, does not explain the frequent observation of enriched branched isomer content in humans. One hypothesis is that preferential biotransformation of branched PFOS precursors (e.g., perfluorooctane sulfonamides) results in an enrichment of branched PFOS. Isomer-specific biotransformation was recently investigated using mixture incubations of various

Table 9 PFOS isomer composition (%) in environmental and wildlife samples. Values shown are means unless stated otherwise

References	Sample	*n*-	*iso*-	5*m*/4*m*/3*m*	1*m*	*tb* + dimethyls	Other branched	Total branched	Analysis/comment
Houde et al. (2008)	PFOS standard (unknown supplier)	76.9	10.6	5.1	3.9	3.6		23.2	LC–MS/MS (PFP column, *m*/*z* 80 or 99). Quantification using *n*-PFOS standard (Wellington) adjusted using branched isomer response factors from Riddell et al. (2009)
	Water (*range*, Lake Ontario, 2004)	43–56	22–28	17–21	3.9–8.0	1.0–2.0		44–57	
	Sediment (*range*, Lake Ontario, 1995–2002)	81–89	4.6–10	2.2–5.9	2.7–4.4			11–19	
	Zooplankton (*range*, Lake Ontario, 2004 and 2006)	95–100	0.1–1.0	0.4–3.0	0			0–5	
	Mysis (*Mysis relicta*) (*range*, Lake Ontario, 2001)	91–92	3.9–5.2	1.7–2.4	0			8–9	
	Diporeia (*Diporeia hoyi*) (*range*, Lake Ontario, 2002 and 2003)	95–96	2.0–2.8	0.4–0.6	0.7–1.1			4–5	
	Alewife (*Alosa pseudoharengus*) (*range*, Lake Ontario, 2002)	90–91	4.2–7.1	2.3–2.4	2.5–2.8			8–9	
	Smelt (*Osmerus mordax*) (*range*, Lake Ontario, 2002)	88–92	4.6–4.8	1.8–2.3	0.5–0.9	0.4–0.5		8–12	
	Sculpin (*Cottus cognatus*) (*range*, Lake Ontario, 2002)	91–92	4.6–4.8	1.8–2.3	0.9–1.1	0.2–0.3		8–9	
	Lake Trout (*Salvelinus namaycush*) (*range*, Lake Ontario, 2002)	88–93	2.8–7.1	2.5–4.1	0.9–1.1	0.2–0.3		7–12	

Table 9 (continued)

References	Sample	*n*-	*iso*-	5*m*/4*m*/3*m*	1*m*	*tb* + dimethyls	Other branched	Total branched	Analysis/comment
Powley et al. (2008)	PFOS standard (Fluka)	74.0						26.0	LC–MS/MS (C8 column, *m*/*z* 80). Branched content determined using relative peak areas. Extent of isomer separation unclear
	Cod (*Arctogadus glacialis*) (Western Canadian Arctic, 2004)	50.0						50.0	
	Bearded and ringed Seal (*Erignathus barbatus and Phoca hispida*) (Western Canadian Arctic, 2004)	96.0						4.0	
Senthil Kumar et al. (2009)	Aquatic wildlife (GA, USA, 2006, 2007)	81 (range 77–89)						19 (11–23)	LC–MS/MS (C18 column, *m*/*z* 80). Branched content estimated from concentrations of linear/branched isomers in Senthil Kumar et al. (2009). Unclear how quantification of branched PFOS was conducted or the extent of isomer separation

Table 9 (continued)

References	Sample	*n*-	*iso*-	5*m*/4*m*/3*m*	1*m*	*tb* + dimethyls	Other branched	Total branched	Analysis/comment
Lloyd et al. (2009)	PFOS standard (Fluka)	~71						~29	LC–MS/MS (PFO column, *m/z* 80). Branched content estimated from peak height in chromatograms found in Lloyd et al. (2009). Branched isomers not baseline resolved
	Whitebait	~39						~61	
	Roe deer liver	~42						~58	
	Cromer crab	~86						~14	
	Carp roe	~89						~11	
Chu and Letcher (2009)	PFOS Standard (T-PFOS, Wellington)	65	11.3	19.7	0.9	1.9	1.1[a]	35	GC–MS (DB-5 column, ion monitored dependent on isomer). Branched content determined using isomer-specific quantification
	Herring gull egg (*Larus argentatus*) (Great Lakes, 1989)	94.5	2.9	2.2	0.2	0.1	0.1[a]	5.5	
	Double-crested cormorant egg (*Phalacrocorax auritus*) (Great Lakes, 2003)	95.9	2.2	1.4	0.3	0.1	0.2[a]	4.1	
	Polar bear plasma (*Ursus maritimus*) (Norwegian Arctic, 2007)	82.4	4.1	10.3	2.8	0.1	0.4[a]	17.6	
	Polar bear liver (*Ursus maritimus*) (Canadian Arctic, 2007, 2008)	92.4	4.1	2.8	0.3	0.1	0.4[a]	7.6	

[a] 2*m*-PFOS

concentrations of a technical PFOS precursor (NEtFOSA isomers) with cytochrome P450 isozymes (CYPs) 2C9, 2C19, and human liver microsomes (Benskin et al. 2009b). Isomer-specific biotransformation rate constants were significantly different at all concentrations, and the rank orders of these rate constants were different with two different isozyme systems. Furthermore, when the ECF mixture was incubated with human liver microsomes (containing all of the major CYP isozymes), isomer-specific biotransformation and product formation were also observed. These data cannot be extrapolated directly to predict the extent of isomer-specific PFOS accumulation from precursors in an environmental exposure scenario, whereby constant exposure, biotransformation, and elimination processes will all combine to achieve a steady state. Thus, further in vivo experiments are necessary with PFOS precursors. However, based on this early evidence it is reasonable to speculate that preferential biotransformation of branched PFOS-precursor isomers may result in enriched branched PFOS isomer patterns, thereby providing a possible explanation for the high abundance of branched PFOS isomers in some humans and wildlife (Tables 8 and 9) and a potential biomarker for exposure to precursors. This precursor hypothesis currently remains tentative, however, it could be confirmed by measuring non-racemic proportions of PFOS isomer enantiomers in biological samples, as described in a proof-of-principle study by Wang et al. (2009). In this work, a chiral, alpha-branched PFOS (1*m*-PFOS) precursor was observed to biotransform enantioselectively when incubated with human liver microsomes. Based on these results, PFOS source exposure in humans and wildlife may be determined by examination of enantiomeric fractions, although a method for separation of PFOS enantiomers requires development before this hypothesis can be tested.

PFOS isomer profiles in coastal Asia and the Atlantic Oceans were also recently examined and found to be very similar or slightly enriched in branched isomers compared to 3M ECF PFOS (Benskin et al. 2009c). On the contrary, enrichment of *n*-PFOS (i.e., >70% linear content), in comparison to 3M ECF PFOS, was never observed in ocean samples. Differential PFOS isomer pK_a values are unlikely to affect environmental partitioning since all PFOS isomers will be ionized at environmentally relevant pH, and it is unclear to what extent differential surface activity alone may influence boundary layer (water–air) partitioning of *n*-PFOS. Surface layer enrichment of *n*-PFOS could potentially result in water samples collected below the surface layer being enriched to some extent with branched isomers, and while this hypothesis remains tentative at this time, differences have been observed in total PFOS concentrations between surface microlayer and sub-surface water samples (Ju et al. 2008).

Other possible explanations for branched PFOS isomer enrichment in ocean water include degradation of ECF polymeric material containing unique isomer signatures or alternatively preferential abiotic degradation (Ochoa-Herrera et al. 2008; Yamamoto et al. 2007) of branched PFOS precursors. This may also explain the relative abundance of branched PFOS isomers in Lake Ontario (Houde et al. 2008), discussed above. In comparison, PFOS isomer profiles from coastal Asian locations (Shanghai, Tokyo Bay, Tomakomai Bay, and Japan Sea) were fairly consistent with 3M ECF PFOS for all samples (Benskin et al. 2009c).

6.3 Perfluorocarboxylate Isomer Profiles Other than PFOA

The source of branched long-chain carboxylates (C > 8) is still uncertain. Recent analysis by 3M and by this study (Table 3) supports the assertion by Prevedouros et al. (2006) that branched isomers of C4–C7 and C9–C13 may be present as residuals in both 3M ECF POSF-derived products and 3M ECF PFOA. Global emissions in 2000 have been estimated for C6–C13 PFCAs (Prevedouros et al. 2006), however, it is still uncertain whether PFCAs other than C4, C6, C8, and C9 were ever intentionally produced for large-scale manufacturing. Interestingly, recent data suggest the possibility of long-chain (i.e., C11, C13) sources of isopropyl-branched isomers (De Silva et al. 2009b; Furdui et al. 2008; Zushi et al. 2010). Unlike ECF which produces a variety of branched isomers, formation of isopropyl perfluoroalkyl compounds is possible via the telomerization reaction pathway of an isopropyl telogen.

De Silva et al. (2009b) detected no branched PFNA in precipitation, Lake Ontario sediment, or most Lake Ontario Biota (mysis, zooplankton, trout, alewife) but one branched isomer (*iso*-PFNA) in ringed seals from Resolute Bay and a single polar bear from the Canadian Arctic. Examination of Arctic lake sediment revealed four branched PFNA isomers, including *iso*-PFNA, along with *n*-PFNA. The surface water of this lake contained only *iso*-PFNA and *n*-PFNA. In Lake Ontario surface water and sediment, only *iso*-PFNA and *n*-PFNA were observed. In contrast, two branched isomers of PFNA have consistently been detected in isomer-specific monitoring of human blood (Benskin et al. 2006; De Silva et al. 2006, 2009b). Given the large number of patents describing the synthesis of isopropyl-branched PFCAs via telomerization (Katsushima et al. 1970; Millauer 1974; Katsushima et al. 1976; also see supporting info of De Silva et al. 2009b), it is realistic to expect that these compounds have experienced significant production. De Silva et al. (2009b) suggested that the presence of multiple branched isomers (i.e., isopropyl and monomethyls) was most likely suggestive of ECF inputs, but that detection of only the isopropyl isomer in the absence of other branched isomers was ambiguous with respect to ECF versus an isopropyl telomer source.

The hypothesis of intentional isopropyl PFCA production is supported by PFCA isomer profiles in archived Lake Trout (1979–2004) from Lake Ontario and archived suspended sediment from the Niagara River (1980–2003) (Furdui et al. 2008), as well as archived sediment cores from Tokyo Bay (from 1950s to 2004) (Zushi et al. 2010). Of the perfluorocarboxylates monitored in these studies, only PFUnA and PFTrA-branched isomers were detected consistently. In Tokyo Bay, a consistent increase in the ratio of branched to linear PFTrA isomers was observed from 1988 to 2004, suggesting increase in branched isomer production, while the opposite trend was observed in suspended sediment from the Niagara River, where the ratio of branched to linear isomers of PFUnA and PFTrA decreased significantly from 1980 to 2002. This latter trend was also observed in Lake Ontario trout, however, the rate of decrease of branched PFTrA in fish was statistically different than in sediment, in contrast to PFUnA, where trends in fish and sediment were consistent. The presence of branched isomers has typically been interpreted as an ECF contribution, however, the authors cite patents describing synthesis of isopropyl PFCAs

by telomerization in both North America (Millauer 1974; Katsushima et al. 1970; cited in Furdui et al. 2008) and Japan (Katsushima et al. 1976; cited in Zushi et al. 2010) as evidence of isopropyl production sources in these regions. While the lack of branched PFOA in Lake Trout observed by Furdui et al. (2008) may be explained by the low bioaccumulation potential of most branched PFOA isomers (De Silva et al. 2009c), a subsequent study observed branched PFOA (two–four branched isomers) in all samples of Lake Ontario biota (2002, 2004, 2006), sediment (1998, 2002), and surface water (2001, 2002) (De Silva et al. 2009b). In addition, *iso*-PFNA was observed in surface water, sediment, and half of the biota samples (including trout). Interestingly, in this study isopropyl C9–C12 PFCAs were also observed, whereby PFUnA had notably higher branched isomer content (6–12%) than other long-chain PFCAs (<2%), consistent with the observation of the relatively high branched isomer content of PFUnA observed in Lake Trout (Furdui et al. 2008).

De Silva et al. (2009b) noted that Lake Ontario biota and dolphins from urban coastal areas in south-eastern United States and sporadic human blood samples contained an abundance of *iso*-PFUnA. Arctic samples, including Char Lake sediment, ringed seals, and polar bears had a different isomer profile in which *iso*-PFDoA (4–7% of total PFDoA) was dominant compared to *iso*-PFUnA (1–3%). In that study the authors speculated that atmospheric transport and oxidation of a precursor containing an isopropyl perfluoroundecyl moiety may be responsible. The same precursor could, presumably, also undergo biological transformation to yield *iso*-PFUnA, thus accounting for its presence at mid-latitudes that are heavily influenced by human activity. In coastal Asian waters a single branched isomer of PFNA, PFDA, PFUnA, and PFDoA was observed in addition to the respective linear isomer. There is currently a paucity of isomer-specific long-chain perfluorocarboxylate data to confirm whether these are consistent trends.

Benskin et al. (2007) examined perfluorocarboxylate (C9–C14) isomer profiles in pooled serum from pregnant Edmonton (Alberta, Canada) women and found, in addition to the linear isomer, two branched isomers of PFNA, and a single branched isomer of PFDA and PFUnA. In contrast, only linear isomers of PFDoA and PFTA were detectable. The peaks corresponding to branched isomers appeared to make up a relatively small component of the total concentrations based on relative LC–MS peak areas in several transitions. This is consistent with the observations by De Silva and Mabury (2006), who also detected two minor branched PFNA isomers and one minor branched PFUnA isomer in human serum, representing ∼1.6 and 2.3% of total PFNA and PFUnA concentrations, respectively.

7 Differences in Toxicity and Bioaccumulation of PFA Isomers

To date, most studies that examine biological properties of PFAs have not differentiated between the branched and linear structures. For PFOS, in vitro and in vivo experiments have typically relied on standards from Sigma–Aldrich/Fluka (∼20% branched) (Cui et al. 2009; Johansson et al. 2009), or 3M (∼30% branched) (Hu

et al. 2002; Luebker et al. 2005; Seacat et al. 2003), representing a difference in branched isomer content of ~10%. For those studies in which the manufacturer is not identified, or the branched content unknown, it is reasonable to predict that the variability among studies is less than 15%, given the difference in branched isomer content in technical standards (Table 2), provided a linear standard is not used. Although isomer-specific toxicity information is lost when using technical standards, this is likely the most environmentally relevant choice of standards for PFOS (and its precursors), considering most exposure sources (water, dust, food, etc.), and the internal dose of organisms (from biomonitoring studies) show that multiple isomers are always present.

Biological testing of PFOA has also made use of standards predominantly from 3M (80% linear) or Sigma–Aldrich (~99% linear). It is unclear which standard is the most relevant for toxicity testing. For example, in humans and higher trophic level organisms, even though linear PFOA dominates the internal dose, this does not necessarily mean that co-exposure does not also occur to the multiple branched isomers via food or house dust (for humans). Nonetheless, the few toxicological comparisons of branched and linear isomers have suggested that there may be only subtle toxicological differences between linear and total branched isomers. Furthermore, it is unclear whether the differences are a function of reduced biological activity or less bioavailability of the branched isomers. For example, Loveless et al. (2006) compared the responses of rats and mice following exposure to either a technical, 77.6% *n*-PFOA/22.4% branched PFOA isomer mixture, enriched branched isomer dose of 54% 3*m*-PFOA, 4% 4*m*-PFOA, and 42% *iso*-PFOA or a 100% *n*-PFOA dose. Peroxisomal beta-oxidation was least pronounced after administration of the enriched branched dose, results that contrast somewhat to those of Vanden Heuvel et al. (2006), in which branched and linear PFOA were both able to activate peroxisome proliferator receptor (PPAR)-α to a similar peak effect in vitro. Body weights of rats and mice in the Loveless et al. (2006) study were also approximately 20% lower in rats, exposed to the mixture of linear and branched or pure linear doses, compared to the branched-only dose; this further supports the opinion that *n*-PFOA may be slightly more toxic in vivo. However, the authors also observed that *n*-PFOA was preferentially absorbed relative to 3*m*/4*m*-PFOA and *iso*-PFOA at increasingly higher doses, suggesting that the increased potency of *n*-PFOA relative to branched, and branched + linear dosing regimens may simply be a result of decreased bioavailability of the branched isomers.

Other isomer-specific data in rodents and fish further corroborate the hypothesis that differences in toxicological response between branched and linear PFAs may be a result of differential bioavailability. For example, rats exposed to lower doses of PFHxS, PFOS, PFOA, and PFNA via a single gavage dose, or through a sub-chronic dietary exposure, showed varying degrees of selective retention of *n*-isomer, compared to the major branched isomers in ECF formulations (Benskin et al. 2009a; De Silva et al. 2009a). It should be noted that although most differences in excretion rates of PFOS isomers were not statistically significant, this could be reflective of the experimental design. For example, the single-dose exposure

(Benskin et al. 2009a) was likely not long enough to detect significant differences among most PFOS isomer rate constants. Likewise, in the sub-chronic exposure (De Silva et al. 2009a) PFOS isomer excretion rate constants were based only on a single animal. Despite these restrictions, some statistically significant differences were observed between *n*-PFOS compared to *tb*-PFOS and 4*m*-PFOS. It is likely that a longer depuration period along with a larger sample population would suggest preferential linear isomer retention compared to the major branched isomers in rodents, similar to observations by Sharpe et al. (2010) in fish. Rainbow trout exposed to PFOA and PFNA isomers through the diet showed a similar result, whereby the *n*-isomer was selectively retained in blood and tissues, relative to the majority of branched isomers (De Silva et al. 2009c). Similarly, Sharpe et al. (2010) demonstrated significant preferential accumulation of *n*-PFOS relative to branched isomers in rainbow trout and zebrafish. Also consistent with these results was the observation of a substantial enrichment of *n*-PFOS in Lake Ontario trout compared to water (Houde et al. 2008). Bioaccumulation factors calculated for *n*-PFOS in this study were estimated to be 3.4×10^4 L/kg, compared with 2.9×10^3 L/kg for the monomethyl-substituted isomers. The apparent difference in calculated values was attributed to enrichment of branched isomers in Lake Ontario water, however, it is not clear what is mediating this phenomenon. Possible explanations include preferential removal of *n*-PFOS to sediment or aerosols, albeit these hypotheses require further validation. Trophic magnification factors calculated for *n*-PFOS (4.6 ± 1.0), monomethyl-branched isomers (1.3 ± 0.17–2.6 ± 0.51), and dimethyl-branched isomers (no trophic magnification) also suggest that *n*-PFOS may preferentially biomagnify through the food chain, relative to branched isomers. Based on these results, it appears that exposure to any mixture of PFHxS, PFOS, PFOA, or PFNA isomers will result in enriched linear isomer profiles in a range of organisms.

Despite this general trend, there were some notable exceptions in which branched isomers were eliminated more slowly than the *n*-isomer of either PFOS or PFOA. The structure of the biopersistent PFOA isomers has not yet been determined, but the alpha-branch PFOS isomer (1*m*-PFOS) showed a remarkably long half-life (longer than the linear isomer) in male rats following single or sub-chronic dosing and was not significantly eliminated in female rats following sub-chronic dietary exposure. Interestingly, plots of half-life of linear and monomethyl-branched PFOS and PFOA isomers, in various species and dosing regimens, revealed a consistent structure–property relationship, whereby a relative decrease in pharmacokinetic half-life was observed as the branching point was moved from the perfluoroalkyl chain terminus (*n*-) to the 4*m*-position, whereas an increase in half-life was observed as the branching point moved from the 4*m*-position closer to the sulfonate or carboxylate group (Fig. 6).

While preferential elimination of branched PFHxS, PFOS, PFOA, and PFNA isomers reportedly occurs via the urine (Benskin et al. 2009a), it is still not clear what mechanism mediates this isomer-specific phenomenon. The sex hormone-mediated organic anion transporter (OAT) system plays an important role in the renal elimination of *n*-PFOA from male and female rats (Kudo et al. 2002). Katakura et al. (2007)

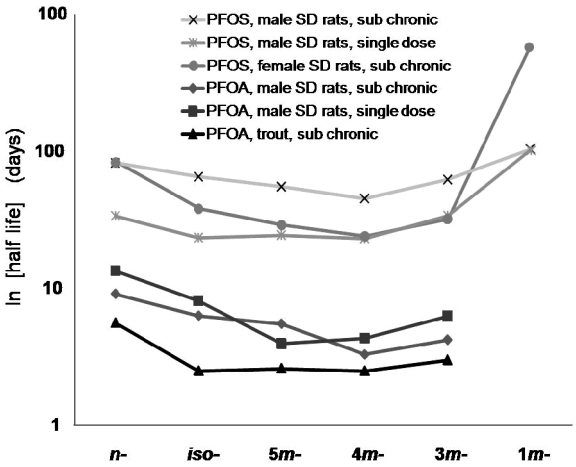

Fig. 6 Structure–property relationship between PFOS/PFOA isomers observed in rats (Benskin et al. 2009a; De Silva et al. 2009a) and fish (De Silva et al. 2009c). A relative decrease in half-life was observed as the branching point was moved from the perfluoroalkyl-chain terminus (*n*-) to the 4*m*-position. In contrast, an increase in half-life was observed as the branching point moved from the 4*m*-position closer to the sulfonate or carboxylate group regardless of sex, species, or dosing regimen. Note that while structure–property relationships between PFOS and PFOA isomers appear to be similar, half-lives for the individual branched PFOS isomers shown here were not statistically different from that of the *n*-isomer in either study

recently identified some of the specific transporters (oatp1 and OAT3) controlling the elimination of *n*-PFOA in rats, but it is still not clear if substrate–transporter binding is equivalent among isomers. In addition, while OAT3 was identified as mediating tubular uptake of *n*-PFOA and oatp1 with tubular reabsorption, the transporter responsible for tubular excretion of this PFA has not yet been identified. Sex differences in PFOA elimination in orally dosed fish have also been observed and are thought to be attributable to differences in renal transport activity (Lee and Schultz 2010). Clearly, there are many possibilities, and some transporters may have unique interactions with specific isomers. Only by probing the individual uptake of specific isomers by specific transporters can we obtain an accurate picture of the mechanism of elimination. It may be possible to correlate the preferential elimination of a given isomer in vivo to its affinity for renal uptake/excretion transporters and/or a lack of affinity for tubular reabsorption transporters.

Isomer-specific protein binding may also explain differential elimination rates in vivo. Branched PFAs with lower affinity for serum proteins could potentially undergo renal elimination to a greater extent than the linear isomer. Although it is known that *n*-PFOS and *n*-PFOA bind strongly to serum proteins (Jones et al. 2003; Ohmori et al. 2003), little is known about the binding affinity of branched isomers. Previous in vitro cytochrome P450 assays (Benskin et al. 2009b) are suggestive that differential protein binding can occur during the metabolism of PFA-precursor isomers, thus there is reason to suggest this could occur for PFA isomers

and serum proteins as well. Such experiments would complement OATP and in vivo pharmacokinetic studies to get a better overall picture of the mechanism(s) of isomer-specific biological handling.

8 Summary

The two major manufacturing techniques for perfluorochemicals can be distinguished based on the isomeric profile of their products. ECF (major use from 1950s to 2002) results in a product containing both linear and branched isomers, while telomerization (major use from 2002 to present) typically yields an isomerically pure, linear product. Among the most important questions today, which has implications for future regulation of these chemicals, is to what extent human and environmental exposure is from historical products (i.e., ECF) versus currently manufactured fluorochemicals (i.e., telomer). Perfluoroalkyl-chain branching can also affect the physical and chemical properties of these chemicals, which may influence their environmental transport and degradation, partitioning, bioaccumulation, pharmacokinetics, and toxicity. Unless perfluorinated substances are considered as individual isomers, much of this information will be overlooked or missed altogether, which could potentially lead to inaccuracies in human and environmental risk assessments.

In this review, we have highlighted novel findings, current knowledge gaps, and areas for improvement based on early experiments on the disposition of PFA and PFA-precursor isomers in the environment. We have also emphasized the wealth of information that can potentially be gleaned from future work in this area, which renders routine adoption of isomer-specific methodologies an attractive and logical next step in the progression of fluorochemical analysis. However, despite vast improvements in recent years, a fast and comprehensive method capable of separating all major PFA and PFA-precursor isomers, while removing interferences is still required before these methods become routine in most labs. Purified and characterized standards of PFOA and PFOS that have isomer profiles consistent with those of historically produced (i.e., 3M) PFOS and PFOA are also required. The limited data available on PFA isomer profiles that exist in the environment and the biological properties of each isomer suggest that examination of isomer profiles may yield clues on the source of PFA contamination to humans and the environment. For example, contributions from historical versus current PFOA emissions can be quantified by examining the isomer profile in abiotic samples. Similarly, residual PFOS/PFOA in pre-2002 consumer products may be distinguished from directly emitted PFOS/PFOA by the existence of slight differences in isomer profile. PFOS signatures may also have the potential to distinguish between indirect exposure (via precursors) versus direct exposure (via the sulfonate), based on findings of isomer-specific and/or enantiospecific biotransformation in vitro. Isomer-specific monitoring extended to longer-chain PFAs may also be informative in determining current and historical exposure sources. Finally, given the recent increase of

production of PFOSF-based chemicals, following their 2002 phase out, the ability of using isomer profiles to distinguish between historical and currently produced PFOS may also be possible.

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