# Chapter 3
# PFASs in the General Population

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**Abstract** Perfluoroalkyl and polyfluoroalkyl substances (PFASs) have been manufactured since the 1950s for use as surface protectants for textiles and leather treatment, as protection additives in food packaging and paper products, and in firefighting foams. Some PFASs are persistent in the environment and in people, and can be transported to remote regions. The main pathways of exposure to PFASs in humans include diet, drinking water, and indoor dust, but predictors of PFASs exposures are not clearly understood. Since 2002, changes in manufacturing practices appear to have reduced exposure to some of these PFASs both in the environment and in people,- but exposure to PFASs is still widespread. We review relevant research published up to the first quarter of 2014 to understand the demographic, geographic, and temporal differences that contribute to general population exposures to PFASs around the world. We also present data on exposures to PFASs in some vulnerable population groups (e.g., pregnant women, infants, young children).

**Keywords** Biomonitoring • Exposure assessment • PFOA • PFOS

## 3.1 Introduction

Polyfluoroalkyl chemicals (PFASs) have been manufactured since the 1950s (Buck et al. 2011). Because of their chemical inertness and heat stability, PFASs have been used extensively in a variety of industrial and commercial applications, such as surfactants, lubricants, paper and textile coatings, polishes, food packaging, and fire-retarding foams (Lau et al. 2007; Prevedouros et al. 2006).

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Some PFASs persist in the environment and in people, and can be transported to remote locations (Paul et al. 2009; Armitage et al. 2009; Ahrens 2011; Houde et al. 2006). Because of widespread exposure to certain PFASs in wildlife and people, and the potential adverse health impacts associated with such exposures (Lau et al. 2007; Steenland et al. 2010a), in 2002, 3M, the main worldwide manufacturer of perfluorooctane sulfonic acid (PFOS), discontinued the production of PFOS precursors and related compounds in the United States. PFOS is still produced in other countries (Paul et al. 2009; Pistocchi and Loos 2009). Other PFASs including perfluorooctanoic acid (PFOA), its salts, and precursors are also produced in other countries and still manufactured in the United States (Buck et al. 2011). However, efforts from U.S. industry and government exist to limit emissions of PFOA into the environment to reduce by 2015 the global emissions of PFOA and longer chain perfluoroalkyl acids (including their relevant precursors) to 95 % of the year 2000 levels (Buck et al. 2011; Prevedouros et al. 2006; US 2006). Similarly, regulatory and other initiatives intended to reduce environmental emissions of PFASs also exist in Canada and the European Union (Buck et al. 2011). All of these efforts appear to have reduced exposure to some of these PFASs not only in the ecosystem (Butt et al. 2007; Furdui et al. 2008; Hart et al. 2008) but also in people (Calafat et al. 2007a; Olsen et al. 2008; Haug et al. 2009) as discussed later in this chapter.

The main pathway(s) of exposure to PFASs in humans include diet (Ericson et al. 2008; Fromme et al. 2007a; Tittlemier et al. 2007; Yamaguchi et al. 2013; Holzer et al. 2011; Weihe et al. 2008; Vestergren et al. 2012; Bjermo et al. 2013; Dallaire et al. 2009), drinking water (Vestergren et al. 2012; Emmett et al. 2006; Holzer et al. 2008), and indoor dust (Vestergren et al. 2012; Kato et al. 2009a; Katsumata et al. 2006; Kubwabo et al. 2005; Martin et al. 2002; Moriwaki et al. 2003; Shoeib et al. 2005; Strynar and Lindstrom 2008; Fraser et al. 2012, 2013) although sources and routes of exposure to PFASs for children and adults may differ (Calafat et al. 2007a, b; Olsen et al. 2004a). Data on the actual levels of PFASs in people (i.e., biomonitoring data) can facilitate the exposure assessment because concentrations of these compounds in biological fluids represent an integrative measure of exposure to the target chemicals from multiple sources and routes. Blood (plasma, serum, or whole blood) is a commonly used biomonitoring matrix for assessing exposure to PFASs.

Biomonitoring data in combination with indirect measures of exposure (e.g., environmental monitoring, questionnaire information) are the most appropriate tools for exposure assessment and can provide useful information about differences in exposures by geography, demographic factors (e.g., age, sex), and socio-economic status, as well as time trends. Literature on population exposures to PFASs is exhaustive and cannot be covered comprehensively in this review. In this chapter, we present an overview of environmental exposures to PFASs in human populations based on available information up to the first quarter of 2014. Specifically, we discuss demographic, geographic, and temporal differences in exposures to PFASs among the general population. We also discuss exposures to PFASs in vulnerable population groups (e.g., pregnant women, infants, young children).

## 3.2 PFASs in General Population Studies

Exposure to PFASs has been estimated from the concentrations of the target PFASs in serum, plasma, or whole blood in numerous PFASs biomonitoring studies conducted around the world since the early 2000s (Haug et al. 2009; Yamaguchi et al. 2013; Holzer et al. 2011; Bjermo et al. 2013; Dallaire et al. 2009; Olsen et al. 2003, 2004b, 2005, 2012; CDC 2013a; Midasch et al. 2006; Fromme et al. 2007b, 2009; Vassiliadou et al. 2010; Schroter-Kermani et al. 2013; Ericson et al. 2007; Kannan et al. 2004; Yeung et al. 2013a, b; Harada et al. 2007; Toms et al. 2009; Haines and Murray 2012; Jin et al. 2007; Audet-Delage et al. 2013; Schecter et al. 2012; Pinney et al. 2014; Frisbee et al. 2010; Ingelido et al. 2010; Zhang et al. 2010; Wan et al. 2013; Ji et al. 2012; Bao et al. 2014; Pan et al. 2010; Kim et al. 2014). In Table 3.1, we present a selection of studies with a sample size of at least 100 participants, including two national surveys: the National Health and Nutrition Examination Survey (NHANES) (CDC 2013b), conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States, and the Canadian Health Measures Survey (CHMS) (Tremblay and Gorber 2007) administered by Statistics Canada. NHANES is designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews, physical examinations, and analysis of biological samples for environmental contaminants (CDC 2013b), including PFASs for Americans 12 years of age and older. Similar to NHANES, CHMS provides national data on indicators of general health, chronic and infectious diseases, and environmental biomarkers; PFASs exposure data are available for Canadians 20–79 years of age (Tremblay and Gorber 2007).

For the majority of the general populations examined, the four most commonly studied PFASs have been PFOS, PFOA, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) (Table 3.1). Generally, PFOS showed the highest serum concentrations followed by PFOA, while other PFASs are detected both at lower concentrations and frequencies. In occupational settings or in populations accidentally exposed to specific PFASs (Emmett et al. 2006; Holzer et al. 2008; Frisbee et al. 2010; Brede et al. 2010; Holzer et al. 2009; Wilhelm et al. 2009; Winquist et al. 2013; Hoffman et al. 2011; Seals et al. 2011; Shin et al. 2011a, b; Bartell et al. 2010; Steenland et al. 2009; Frisbee et al. 2009; Beesoon et al. 2013), the concentration patterns observed may differ from those reported among the general population. We will not cover occupational exposures (the main subject of Chap. 4), but will discuss some general aspects of accidental exposures later in this chapter.

**Table 3.1** Geometric mean/mean concentrations of PFOS, PFOA, PFHxS, and PFNA in serum (or plasma/whole blood) from select population studies (N > 100) around the world from 1974 to 2011

| | Concentration (ng/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Year(s) | PFOS | PFOA | PFHxS | PFNA | Age | Sample size | Location | Ref | |
| 1974 | 29.5 | 2.3 | 1.6 | – | 30–60 | 178 | Maryland, USA | Olsen et al. (2005) | |
| 1989 | 34.7 | 5.6 | 2.4 | – | 39–65 | 178 | Maryland, USA | Olsen et al. (2005) | e |
| 1994–1995 | 40.1 | 5.2 | 5.3 | – | 2–12 | 300[a] | USA | Olsen et al. (2004a) | |
| 1994–1995 | 35.2 | 4.7 | 3.9 | – | 2–12 | 298[b] | USA | Olsen et al. (2004a) | |
| 1999–2000 | 30.4 | 5.2 | 2.13 | 0.557 | 12–60 | 1,562 | USA, NHANES | CDC (2013a) | |
| 2000 | 31.0 | 4.2 | 2.2 | – | 65–96 | 238 | Washington, USA | Olsen et al. (2004b) | |
| 2000–2001 | 34.9 | 4.7 | 1.9 | – | 20–69 | 645 | USA | Olsen et al. (2012) | |
| 2002 | 12.9 | 3.0 | – | – | 20–36 | 119 | Shenyang, China | Jin et al. (2007) | |
| 2003–2004 | 20.7 | 3.95 | 1.93 | 0.966 | 12–60 | 2,094 | USA, NHANES | CDC (2013a) | |
| 2003–2004 | 22.3 | 6.8 | – | – | 5–84 | 105[a] | Northern Bavaria, Germany | Midasch et al. (2006) | d |
| 2004 | 18.68 | | | | 1>8 | 857 | Nunavik | Dallaire et al. (2009) | |
| 2004 | 10.9 | – | – | – | 18–39 | 120[b] | Nunavik | Audet-Delage et al. (2013) | d |
| 2005 | 13.5[c] | 5.7[c] | – | – | 14–67 | 356 | Southern Bavaria, Germany | Fromme et al. (2007b) | d |
| 2005–2006 | 20.7[c] | 32.6[c] | – | – | 0–12 | 6,536 | PFOA water contaminated area, USA | Frisbee et al. (2010) | |
| 2005–2006 | 19.3[c] | 26.3[c] | – | – | 12–18 | 5,934 | PFOA water contaminated area, USA | Frisbee et al. (2010) | |
| 2005–2006 | 19.2 | 32.9 | 3.3 | 1.4 | 12–80 | >65,000 | PFOA water contaminated area, USA | Frisbee et al. (2009) | |
| 2005–2006 | 17.1 | 3.92 | 1.67 | 1.09 | 12–60 | 2,120 | USA, NHANES | CDC (2013a) | |
| 2005–2007 | 13.2 | 7.8 | 5.1 | 1.4 | 6–8 | 353[b] | Great Cincinati, USA | Pinney et al. (2014) | |
| 2005–2009 | 13.2 | 5.7 | 3.0 | 1.7 | 6–8 | 351[b] | San Francisco Bay area, USA | Pinney et al. (2014) | |
| 2006 | 14.5 | 3.44 | 1.52 | 0.97 | 20–69 | 600 | USA | Olsen et al. (2012) | d |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2006 | 5.2 | 2.8 | 0.6 | – | 23–49 | 153[b] | Siegen, Germany | Holzer et al. (2008) | [d] |
| 2006 | 5.8 | 23.4 | 1.1 | – | 23–49 | 164[b] | Arnsberg, Germany, PFOA water contaminated area | Holzer et al. (2008) | [d] |
| 2006 | 9.7 | 5.8 | 2.2 | – | 18–69 | 103[a] | Brilion, Germany | Holzer et al. (2008) | [d] |
| 2006 | 10.5 | 25.3 | 2.5 | – | 18–69 | 101[a] | Arnsberg, Germany, PFOA water contaminated area | Holzer et al. (2008) | [d] |
| 2006–2007 | 26.0 | 11.0 | 2.6 | – | 14–88 | 105 | Lake Mohne, Germany | Holzer et al. (2011) | [d] |
| 2006–2008 | 10.6 | 1.39 | 0.57 | – | 18–75 | 233 | China | Pan et al. (2010) | [e] |
| 2007–2008 | 13.20 | 4.12 | 1.95 | 1.22 | 12–60 | 2,100 | USA, NHANES | CDC (2013a) | |
| 2007–2009 | 11.13 | 2.94 | – | – | 20–79 | 1,376[a] | Canada, CHMS | Haines and Murray (2012) | |
| 2007–2009 | 7.07 | 2.17 | – | – | 20–79 | 1,504[b] | Canada, CHMS | Haines and Murray (2012) | |
| 2008 | 8.21 | 3.5 | 1.84 | 1.45 | >20 | 140 | Korea | Ji et al. (2012) | |
| Unknown | 11.5[c] | 7.97[c] | 2.3[c] | 2.65[c] | 20–71 | 306 | Korea | Kim et al. (2014) | |
| 2008–2010 | 8.5 | 1.8 | – | – | 53–79 | 153[a] | Sweden | Bao et al. (2014) | [e] |
| 2009 | 4.10[c] | 2.85[c] | 1.20[c] | 1.20[c] | <13 | 300 | Texas, USA | Schecter et al. (2012) | |
| 2009–2010 | 9.32 | 3.07 | 1.66 | 1.26 | 12–60 | 2,233 | USA, NHANES | CDC (2013a) | |
| 2009–2010 | 5.8[c] | 2.1[c] | – | – | 16–76 | 607 | Japan | Yamaguchi et al. (2013) | |
| 2010 | 8.30 | 2.44 | 1.34 | 0.83 | 20–69 | 600 | USA | Olsen et al. (2012) | [d] |
| 2010–2011 | 7.65[c] | 3.24[c] | 1.08[c] | 0.95[c] | 16–63 | 153 | Hong Kong | Wan et al. (2013) | |
| 2010–2011 | 11.20[c] | 2.25[c] | 1.95[c] | 0.80[c] | 18–80 | 270 | Sweden | Bjermo et al. (2013) | |

[a]Only males
[b]Only females
[c]Median concentration
[d]Plasma
[e]Whole blood

### 3.3 Determinants of General Population Exposure to PFASs

Exposure to PFASs in the general population of developed countries and many developing countries is widespread, but the extent of such exposures may vary considerably (Yamaguchi et al. 2013; Vassiliadou et al. 2010; Kannan et al. 2004; Jin et al. 2007; Audet-Delage et al. 2013; Calafat et al. 2006a; Hemat et al. 2010). Comparing PFASs concentrations among populations is difficult because of differences in study design—including age, sex, and race of the populations examined—, years of sample collection, geographical location, and analytical methodologies used (e.g., isomeric profiles). Interestingly and despite these challenges, the ranges of concentrations of PFOS, PFOA, PFHxS, and PFNA are remarkably similar worldwide. For example, NHANES data in the United States during 1999–2010 are in agreement with those from American Red Cross donors in 2000–2010 (Olsen et al. 2012); from Canada in 2007 to 2008 (Haines and Murray 2012); from several European countries in 2005 to 2006 (Fromme et al. 2009), 2005–2009 (Haug et al. 2009; Vassiliadou et al. 2010; Ingelido et al. 2010) and 2010–2011 (Bjermo et al. 2013); and from China in 2009 (Zhang et al. 2010; Wan et al. 2013).

Research is ongoing to evaluate the determinants of exposure to PFASs, but exposures to PFASs may be associated with demographic factors such as age, sex and race. Racial differences in PFASs (e.g., PFOA, PFNA, PFHxS) serum concentrations were observed in the United States (Kato et al. 2011). For instance, regardless of age, Americans of Mexican descent had lower adjusted geometric mean serum concentrations of PFNA than non-Hispanic white and non-Hispanic black Americans (Kato et al. 2011). For PFHxS, non-Hispanic whites and non-Hispanic blacks had similar concentrations, and both were higher than for Mexican Americans; at older ages, however, concentrations were different only among Mexican Americans and non-Hispanic whites (Kato et al. 2011). These differences may reflect variability in exposures as a result of differences in lifestyle, diet (Holzer et al. 2011; Zhang et al. 2010; Halldorsson et al. 2008; Rylander et al. 2010), use of products containing PFASs, physiology (e.g., elimination) (Han et al. 2008), or a combination of these factors.

Higher concentrations of PFOS, PFOA, and PFHxS among males than among females have been reported in diverse adult populations around the world (Calafat et al. 2007a; Olsen et al. 2008; Bjermo et al. 2013; Dallaire et al. 2009; Fromme et al. 2007b, 2009; Vassiliadou et al. 2010; Ericson et al. 2007; Yeung et al. 2013a, b; Haines and Murray 2012; Ingelido et al. 2010; Ji et al. 2012; Kato et al. 2011), suggesting the possibility of sex-related exposure differences, perhaps in terms of lifestyle or diet. In North America, NHANES (Kato et al. 2011) and CHMS (Haines and Murray 2012) data suggested differences in PFASs concentrations according to sex. Canadian men had higher plasma PFOS and PFOA concentrations than women (Haines and Murray 2012). In the United States, males had higher adjusted geometric mean serum concentrations of PFOS, PFOA, and PFHxS than females regardless of age (Kato et al. 2011). In addition, males had higher adjusted geometric mean serum concentrations of PFOA, PFHxS, and PFNA than females regardless of race/

ethnicity. Differences in concentrations of PFOS, PFOA, PFNA, and PFHxS by sex appeared to be more pronounced in younger than in older Americans. These concentration trends may be related to sex-related differences in exposures to these PFASs even at an early age; they may also be related to physiological differences by sex, including differences in urinary elimination due to the renal resorption of perfluoroalkyl acids by organic anion transporters (Han et al. 2008). In addition, menses (Harada et al. 2005; Taylor et al. 2014), pregnancy (Yamaguchi et al. 2013; Monroy et al. 2008) and lactation (Bjermo et al. 2013; Kubwabo et al. 2013; Karrman et al. 2007a) may affect elimination of PFASs in females and also contribute to differences in PFASs exposure between men and women (Knox et al. 2011; Harada et al. 2004).

Increasing serum concentrations as people age are common for lipophilic persistent pollutants, such as polychlorinated biphenyls, but PFASs do not partition into fat deposits in the body (Conder et al. 2008). Nonetheless, suggestive associations between age and exposure to some PFASs have been reported, although without consistent trends among studies. Geometric mean serum concentrations of PFOS, PFOA, and PFNA did not differ significantly among age groups for Americans older than 12 years from NHANES 1999–2000 (Calafat et al. 2007a), in agreement with findings from several other studies outside the United States (Olsen et al. 2008; Vassiliadou et al. 2010; Ericson et al. 2007). By contrast, geometric mean serum concentrations of PFOS and PFNA tended to increase with age regardless of sex when combining data from four NHANES cycles (1999–2008) (Kato et al. 2011). In another study, PFOS concentration in pooled serum collected from over 2000 Australian donors between 2006 and 2007 was also significantly higher in adults (>60 years) than in children (Toms et al. 2009). The increase of production of PFASs since 1970s might have resulted in increased exposure over time for persons aged >30 years at the time of blood collection in the mid 2000s (Toms et al. 2009). Other studies also reported increase of PFASs concentrations with age (Haug et al. 2009; Yamaguchi et al. 2013; Bjermo et al. 2013; Dallaire et al. 2009; Holzer et al. 2008; Fromme et al. 2007b).

For PFHxS, however, the adjusted geometric mean serum and 95th percentile concentrations were higher for adolescents than for adults in NHANES (Kato et al. 2011). Higher concentrations of PFHxS in adolescents could be related to youth's increased contact with carpeted floors because PFHxS had been used for specific postmarket carpet-treatment applications (Olsen et al. 2004a); carpets and upholstered furniture are known to trap dust, which may also contain PFHxS (Vestergren et al. 2012; Kato et al. 2009a; Katsumata et al. 2006; Kubwabo et al. 2005; Martin et al. 2002; Moriwaki et al. 2003; Shoeib et al. 2005; Strynar and Lindstrom 2008; Fraser et al. 2012, 2013). The lack of consistent age trends for PFASs may be related to differences in early life—including in-utero—exposure to these compounds, ongoing exposures being much lower than previous historical exposures when production of the chemicals peaked, poor urinary elimination due to the renal resorption of perfluoroalkyl acids by organic anion transporters (Han et al. 2008), or a combination of these factors.

Even though exposure to PFASs is widespread, differences in exposures between urban and suburban locations or among various countries also exist (Yamaguchi et al. 2013; Vassiliadou et al. 2010; Kannan et al. 2004; Jin et al. 2007; Audet-Delage et al. 2013; Calafat et al. 2006a; Hemat et al. 2010). Factors such as the environment (e.g., air and water quality), diet, and other lifestyle choices which can vary considerably among regions and even within the same country (Fromme et al. 2009; Zhao et al. 2011; Martin et al. 2010; Trudel et al. 2008; Vestergren et al. 2008; Paustenbach et al. 2007; Washburn et al. 2005) likely play a role in the observed differences. Accidental exposure to certain PFASs (Brede et al. 2010; Oliaei et al. 2013; Post et al. 2013; Weiss et al. 2012; Lindstrom et al. 2011; Wilhelm et al. 2010; Renner 2009), mainly from contaminated drinking water, is one specific example of within country differences.

In the mid–Ohio River Valley in the United States, almost 70,000 residents living near a fluoropolymer production facility had mean PFOA serum concentrations much higher than the geometric mean serum concentration in NHANES participants during the same time period (Emmett et al. 2006; Frisbee et al. 2010; Winquist et al. 2013; Hoffman et al. 2011; Seals et al. 2011; Shin et al. 2011a, b; Bartell et al. 2010; Steenland et al. 2009; Frisbee et al. 2009). The increased PFOA concentration was associated with consumption of drinking water contaminated with PFOA (Emmett et al. 2006; Winquist et al. 2013; Hoffman et al. 2011; Seals et al. 2011; Shin et al. 2011a, b; Bartell et al. 2010; Steenland et al. 2009). A similar situation occurred in Arnsberg, Germany, where about 40,000 residents were exposed to PFOA-contaminated drinking water (Holzer et al. 2008; Brede et al. 2010; Holzer et al. 2009; Wilhelm et al. 2009). In another study from Germany, blood PFOS concentrations in a group of ten people who drank contaminated water from private wells were higher than among the general population (Weiss et al. 2012).

Of interest, exposure patterns in populations accidentally exposed to specific PFASs (Emmett et al. 2006; Holzer et al. 2008, 2009; Brede et al. 2010; Wilhelm et al. 2009; Winquist et al. 2013; Hoffman et al. 2011; Seals et al. 2011; Shin et al. 2011a, b; Bartell et al. 2010; Steenland et al. 2009; Beesoon et al. 2013; Weiss et al. 2012) can differ considerably from those reported among the general population (Emmett et al. 2006; Holzer et al. 2008, 2009; Brede et al. 2010; Wilhelm et al. 2009; Winquist et al. 2013; Hoffman et al. 2011; Seals et al. 2011; Shin et al. 2011a, b; Bartell et al. 2010; Steenland et al. 2009). Studies of such populations may be useful to both evaluate associations between exposures to PFASs and potential health effects (Frisbee et al. 2010; Barry et al. 2013; Darrow et al. 2013; Vieira et al. 2013; Lopez-Espinosa et al. 2011, 2012; Savitz et al. 2012; Innes et al. 2011; Stein and Savitz 2011; Nolan et al. 2010; Steenland et al. 2010b; Nolan et al. 2009; Stein et al. 2009) as well as the efficacy of interventions to remove the PFASs from the contamination source (e.g., water) (Pinney et al. 2014; Bartell et al. 2010; Rumsby et al. 2009). For instance, certain drinking water treatments including granular activated carbon adsorption can remove PFOA and other long chain PFASs from the potable water supply (Eschauzier et al. 2012; Flores et al. 2013; Rahman et al. 2014; Takagi et al. 2011) and effectively reduced exposure to PFOA in consumers of treated drinking water (Pinney et al. 2014; Bartell et al. 2010; Rumsby et al. 2009).

Biomonitoring concentrations provide an integrated measure of exposures through all potential sources and routes of exposure (Calafat et al. 2006b), but biomonitoring data may also be useful to identify potential exposure pathways. Synthesis of PFASs has employed electrochemical fluorization (ECF) or fluorotelomerization. ECF generates linear as well as branched isomers, but telomerization exclusively generates linear isomers (Vyas et al. 2007). In a standard product after ECF, the proportion of PFOS isomers was 70 % linear and 30 % branched; ECF PFOA had a consistent isomer composition of 78 % linear and 22 % branched (Benskin et al. 2010a). The presence of PFOS and PFOA branched isomers was first noted in 2001 (Hansen et al. 2001). Limited data exist on the toxicokinetics of the various isomers (Benskin et al. 2009a, b; De Silva et al. 2009), but the structural isomer patterns in humans may be useful for understanding the routes and sources of exposure to PFASs (De Silva and Mabury 2006; Karrman et al. 2007b; Benskin et al. 2010b).

In 70 blood samples collected in 1997–2003 from Sweden, the United Kingdom, and Australia, linear PFOS was the main isomer comprising 58–70 % of the total PFOS measured, depending on the location (Karrman et al. 2007b); similarly, linear PFOS was 53 % of the total PFOS measured in 20 Canadians' blood samples collected in 2007–2008 (Zhang et al. 2013a). Differences in isomeric distributions may relate to different isomer patterns in the source products or to country-specific differences in the major human exposure pathways (Karrman et al. 2007b). The different ratio of the PFOS isomers could also indicate differential uptake of the branched and linear PFOS isomers, and also reflect different renal clearances (Zhang et al. 2013a) or tranceplacental transfer (Hanssen et al. 2010) in humans.

From 1947 to 2002, worldwide production of PFOA was mainly by ECF and exposure to both linear and branched isomers likely occurred. Branched PFOA isomers were detected in 96.9 % of NHANES 1999–2000 participants sera, with a median (25th–95th percentiles) percentage of branched PFOA isomers of 4.2 % (2.7–9.9 %) (Kato et al. 2011). By contrast, only the linear PFOA isomer was detected among NHANES 2007–2008 participants (Kato et al. 2011). Similarly, in 16 pooled sera collected across the Midwest United States during 2004 and 2005, only between 1.6 and 2.3 % of the mean concentrations of PFOA, PFNA, and another PFAS, perfluoroundecanoate, were branched isomers (De Silva and Mabury 2006). The relatively high proportion of linear PFOA in serum in these studies may be partly due to exposure to and metabolism of fluorotelomer alcohols and olefins, two classes of PFASs synthesized by the telomerization process (Benskin et al. 2010a). Linear isomers of PFASs also predominated in wildlife during 1999–2003 (Butt et al. 2010). Together, the above findings suggest that telomer products may have contributed to PFOA burden after the phase-out of ECF products (Prevedouros et al. 2006; Ellis et al. 2004).

Paired blood and urine samples (N = 86) collected from Chinese adults in 2010 were analyzed for linear and branched PFOS and PFOA isomers (Zhang et al. 2013a). PFOS and PFOA concentrations in urine and blood were correlated, but the percentage of linear and branched isomers in the two matrices differed. The mean percentage of linear PFOS in blood (53 %) was significantly lower than in the ECF

standard (70 %), but the mean percentage of linear PFOA (97 %) was higher than in the ECF standard (78 %) (Zhang et al. 2013a). Interestingly, the mean percentage of linear isomers in urine (PFOS, 45 %; PFOA, 94 %) was lower than in blood (Zhang et al. 2013a) suggesting preferential excretion of the branched isomers of PFOA and PFOS in urine (Zhang et al. 2013a). Results from this study also suggested that perfluoroalkyl carboxylates (PFCAs) were excreted more efficiently in urine than their corresponding perfluoroalkane sulfonates of the same carbon chain-length. Also, although urinary excretion was a major elimination route for short PFCAs ($C \leq 8$), other routes of excretion likely contribute to overall elimination for longer PFCAs (e.g., PFOA), PFHxS and PFOS.

## 3.4 Temporal Trends in Exposure to PFASs

PFASs manufacturing started in the 1950s and peaked in the 1980s–1990s (Prevedouros et al. 2006; Paul et al. 2009). Estimates suggest that the global production volumes and environmental releases of PFOS and its precursors started to decrease in the mid 1990s, but voluntary emission reduction measures were not implemented before 1997 (Paul et al. 2009). Concerns about the potential environmental and toxicological impact of certain PFASs led to (a) several major changes in manufacturing practices (Prevedouros et al. 2006; Paul et al. 2009; Pistocchi and Loos 2009; US 2006), and (b) other initiatives to reduce environmental emissions of these compounds or their precursors (Buck et al. 2011). First, 3M Company, the main global manufacturer of perfluorooctanesulfonyl fluoride (POSF)-based materials (Prevedouros et al. 2006), including PFOS, PFOA and related compounds, phased out the production of these chemicals in 2000–2002. Furthermore, the US Environmental Protection Agency and eight leading global companies participated in a stewardship agreement to reduce emissions and product content of PFOA and related chemicals by 95 % by 2010 and to work toward their elimination by 2015 (US 2006). Canadian environmental and health authorities and five companies reached a similar agreement to restrict certain PFASs in products, and a European Union Marketing and Use Directive restricted the use of "perfluorooctane sulfonates" in the European Union (Buck et al. 2011). Last, PFOS was added to the persistent organic pollutants list of the Stockholm Convention in May 2009 as an Annex B substance (i.e., restricted in its use) (Ahrens 2011). All of these changes have impacted exposure to PFASs as discussed below.

Temporal trends have been investigated in the United States (Olsen et al. 2005, 2012; Kato et al. 2011), Germany (Schroter-Kermani et al. 2013; Yeung et al. 2013a, b), Norway (Haug et al. 2009), Sweden (Glynn et al. 2012), Australia (Toms et al. 2009), Japan (Harada et al. 2007), and China (Jin et al. 2007; Chen et al. 2009). Despite differences in design among studies—pools vs individual specimens, plasma vs serum, sample size, time period—, PFASs concentrations in people follow similar increasing trends from the 1970s to the mid 1990s because of the high production and widespread use of this class of compounds and their resulting

emissions (Prevedouros et al. 2006; Paul et al. 2009). For instance, participants in two community-based cohorts from Maryland in the United States had blood concentrations of PFOS, PFOA, and PFHxS, among other PFASs, significantly higher in 1989 than in 1974 (Olsen et al. 2005). In Japan, serum concentrations of PFOS and PFOA from urban females increased 3 and 14 times, respectively, between 1977 and 1995, before plateauing between 1991 and 2003 (Harada et al. 2004). In Chinese students, faculty members and university workers, median serum concentrations of PFOA and PFOS increased significantly from 1987 until 2002 (Jin et al. 2007). Similar time trends were observed in Sweden using pooled milk samples: PFOS and PFOA concentrations increased significantly from 1972 to 2000, and showed statistically significant decreasing trends during 2001–2008 (Sundstrom et al. 2011).

Compared to the late 1990s, serum concentrations of PFOS and PFOA have shown a downward trend worldwide since the 2000s. In a Norwegian study using 57 pooled samples collected from 1976 to 2007, serum concentrations of PFOS and PFOA in men increased ninefold from 1977 to the mid 1990s, then reached a plateau before starting to decrease around the year 2000 (Haug et al. 2009); PFOA concentrations decreased by about 40 % between 2000 and 2006 in Norwegian men 40–50 years old (Haug et al. 2009). Similarly, plasma concentrations of PFOS and PFOA in 420 samples collected from residents of two German cities decreased between 2000 and 2009 (Yeung et al. 2013a, b). Sera collected from Swedish primiparous women sampled three weeks after delivery in 1996–2010 also showed decreasing concentrations of PFOS and PFOA (Glynn et al. 2012). In the period from 2002 to 2009, PFOA concentrations in serum pools from Australians older than 16 years decreased by about 50 % (Toms et al. 2009). In American Red Cross donors, PFOA geometric mean serum concentrations decreased from 4.7 ng/mL (2000–2001) to 2.44 ng/mL (2010) (Olsen et al. 2012). Similar trends were observed among the US general population with geometric mean serum concentrations decreasing from 5.2 ng/mL (PFOA) and 30.4 ng/mL (PFOS) in 1999–2000 to 3.07 ng/mL (PFOA) and in 9.32 ng/mL (PFOS) in 2009–2010 (CDC 2013a) although from 2005 to 2008, PFOA adjusted concentrations appeared to increase for males but remained the same for females (Kato et al. 2011).

Compared with PFOS and PFOA, concentrations of PFNA in NHANES participants showed an upward trend, regardless of race/ethnicity since 1999–2000 (Kato et al. 2011). The geometric mean serum concentration of PFNA in the US general population increased more than twofold between 1999–2000 and 2009–2010 (CDC 2013a). In German residents, plasma concentrations of PFNA also increased during 2000–2009 while those of PFOS and PFOA decreased (Yeung et al. 2013a, b). Because PFNA was present as a reaction by-product in POSF-based materials (Prevedouros et al. 2006) which are no longer produced in the United States since 2000–2002, the observed PFNA concentration trends may be related to the degradation of volatile fluorotelomer alcohols (Ellis et al. 2004). These human data are also in agreement with wildlife data suggesting that concentrations of PFNA and certain longer chain-length PFASs show an upward trend in the same time period (Olsen et al. 2012; Yeung et al. 2013a; Glynn et al. 2012; Dietz et al. 2008).

## 3.5 Exposure to PFASs in Vulnerable Populations

Biomonitoring studies among pregnant women, infants, and young children are of interest because stressors, including chemical exposures, during these critical time periods may impact health later in life. Unfortunately, these segments of the population are poorly represented in general population biomonitoring surveys such as NHANES (CDC 2006) and CHMS (Haines and Murray 2012). For instance, to date, published data on background exposure to PFASs among pregnant women in the United States general population are limited to only 180 of 1,079 women 17–39 years of age who participated in 2003–2008 NHANES (Woodruff et al. 2011; Jain 2013). Information on background exposure to PFASs exist for pregnant women or newborns in other countries including Great Britain (Maisonet et al. 2012), Denmark (Kristensen et al. 2013; Fei et al. 2009), Norway (Ode et al. 2013), Sweden (Starling et al. 2014), Canada (Monroy et al. 2008; Hamm et al. 2010), China (Wu et al. 2012), and Japan (Washino et al. 2009). In Table 3.2, we present concentrations of PFASs in women during pregnancy or at delivery, or infants shortly after birth from select studies with sample sizes of at least 30 participants (Monroy et al. 2008; Karrman et al. 2007a; Maisonet et al. 2012; Kristensen et al. 2013; Fei et al. 2009; Ode et al. 2013; Starling et al. 2014; Hamm et al. 2010; Wu et al. 2012; Washino et al. 2009; Whitworth et al. 2012; Stein et al. 2012; Liu et al. 2011; Lee et al. 2013; Kim et al. 2011a; Inoue et al. 2004; Hanssen et al. 2013; Fromme et al. 2010),

Research has also shown that PFASs can be transported across the placenta and several PFASs have been detected in cord serum (Monroy et al. 2008; Hanssen et al. 2010; Glynn et al. 2012; Ode et al. 2013; Liu et al. 2011; Lee et al. 2013; Kim et al. 2011a; Inoue et al. 2004; Hanssen et al. 2013; Fromme et al. 2010; Arbuckle et al. 2013; Lien et al. 2013; Porpora et al. 2013; Zhang et al. 2011, 2013b; Chen et al. 2012; Gutzkow et al. 2012; Llorca et al. 2012; Beesoon et al. 2011; Kim et al. 2011b; Lien et al. 2011; Apelberg et al. 2007; Midasch et al. 2007; Needham et al. 2011). Furthermore, data on paired maternal and cord blood PFASs concentrations also exist for populations around the world (Monroy et al. 2008; Hanssen et al. 2010; Glynn et al. 2012; Ode et al. 2013; Liu et al. 2011; Lee et al. 2013; Kim et al. 2011a, b; Hanssen et al. 2013; Fromme et al. 2010; Porpora et al. 2013; Zhang et al. 2013b; Gutzkow et al. 2012; Beesoon et al. 2011; Midasch et al. 2007; Needham et al. 2011). Interestingly, the ratio of concentrations between maternal and infant's samples vary depending on the compound. For example, ratios between maternal and cord serum concentration were ~1 for PFOA but ~2 for PFOS (Monroy et al. 2008; Hanssen et al. 2010; Ode et al. 2013; Lee et al. 2013; Kim et al. 2011a, b; Fromme et al. 2010; Porpora et al. 2013; Zhang et al. 2013b; Gutzkow et al. 2012; Beesoon et al. 2011; Midasch et al. 2007) suggesting differences in the partition of these compounds. Taken together, these results suggest that PFAS exposure is ubiquitous in pregnant women and their newborns.

Although infants and young children are exposed to PFASs, data in these age groups are still rather limited (Olsen et al. 2004a; Toms et al. 2009; Schecter et al.

**Table 3.2** Median/geometric mean concentrations of PFOS, PFOA, PFHxS, and PFNA in vulnerable populations from select studies (N>30) around the world from 1978 to 2011

| | Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Year(s) | PFOS | PFOA | PFHxS | PFNA | Sample size | Sample type | Location | Ref |
| 1978–2001 | 15 | 2.1 | 0.24 | – | 263 | Maternal serum at delivery | South Sweden | Ode et al. (2013) |
| 1978–2001 | 6.5 | 1.7 | 0.2 | – | 263 | Umbilical cord serum | | Ode et al. (2013) |
| 1988–1989 | 21.1 | 3.6 | – | – | 343 | Maternal serum at 30 weeks | Denmark | Kristensen et al. (2013) |
| 1991–1992 | 19.6 | 3.7 | 1.6 | – | 447 | Maternal serum | Avon, Great Britain | Maisonet et al. (2012) |
| 1996–2002 | 33.7 | 5.3 | – | – | 1,240 | Maternal plasma | Denmark | Fei et al. (2009) |
| 2002–2005 | 4.9[a] | 1.2[a] | – | – | 428 | Maternal serum at delivery | Hokkaido, Japan | Washino et al. (2009) |
| 2003–2004 | 13.03 | 2.25 | 0.60 | 0.39 | 891 | Maternal plasma at middle of pregnancy | Norway | Starling et al. (2014) |
| 2004–2005 | 5.94[a] | 1.84[a] | – | 2.36[a] | 439 | Umbilical cord plasma | Taiwan | Chen et al. (2012) |
| 2004–2005 | 4.9[a] | 1.6[a] | – | – | 299 | Umbilical cord serum | Maryland, USA | Apelberg et al. (2007) |
| 2004–2005 | 16.6 | 2.13 | 1.82 | 0.73 | 101 | Maternal serum at 24–28 weeks | Canada | Monroy et al. (2 008) |
| 2004–2005 | 14.54 | 1.81 | 1.62 | 0.69 | 101 | Maternal serum at delivery | | Monroy et al. (2008) |
| 2004–2005 | 6.08 | 1.58 | 2.07 | 0.72 | 105 | Umbilical cord serum | | Monroy et al. (2008) |
| 2005–2006 | 1.6 | 1.3 | 0.5 | 0.5 | 71 | Maternal serum at delivery | South Africa | Hanssen et al. (2010) |
| 2005–2006 | 0.7 | 1.3 | 0.3 | 0.2 | 58 | Umbilical cord serum | | Hanssen et al. (2010) |
| 2005–2006 | 7.8 | 1.5 | 0.97 | – | 252 | Maternal serum at 15 weeks | Alberta, Canada | Hamm et al. (2010) |
| 2005–2008 | 4.443[a] | 1.469[a] | 0.579[a] | 0.359[a] | 100 | Umbilical cord serum | Ottawa, Canada | Arbuckle et al. (2013) |
| 2007 | – | 16.95 | – | – | 108 | Maternal serum | Guiyu, China | Wu et al. (2012) |
| 2007 | – | 8.70 | – | – | 59 | Maternal serum | Chaonan, China | Wu et al. (2012) |
| 2007–2008 | 4.99 | 1.22 | 0.34 | 0.28 | 123 | Maternal plasma at delivery | Norway | Gutzkow et al. (2012) |
| 2007–2008 | 1.52 | 0.88 | 0.12 | 0.20 | 123 | Umbilical cord plasma | | Gutzkow et al. (2012) |
| 2007–2009 | 3.2 | 2.4 | 0.5 | 0.6 | 44 | Maternal whole blood | Munich, Germany | Fromme et al. (2010) |

(continued)

**Table 3.2** (continued)

| | Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Year(s) | PFOS | PFOA | PFHxS | PFNA | Sample size | Sample type | Location | Ref |
| 2007–2009 | 3.2 | 1.9 | 0.5 | 0.6 | 38 | Maternal whole blood at delivery | | Fromme et al. (2010) |
| 2007–2009 | 1.0 | 1.4 | 0.2 | <0.4 | 33 | Umbilical cord blood | | Fromme et al. (2010) |
| 2008–2009 | 2.9 | 2.4 | – | – | 38 | Maternal serum at delivery | Rome, Italy | Porpora et al. (2013) |
| 2008–2009 | 1.1 | 1.6 | – | – | 38 | Umbilical cord serum | | Porpora et al. (2013) |
| 2009 | 2.92 | 1.264 | 0.068 | 0.483 | 50 | Maternal serum at delivery | Jinhu, China | Liu et al. (2011) |
| 2009 | 1.47 | 1.115 | 0.055 | 0.315 | 50 | Umbilical cord serum | | Liu et al. (2011) |
| 2011 | 9.37 | 2.62 | 1.21 | – | 70 | Maternal serum at delivery | South Korea | Lee et al. (2013) |
| 2011 | 3.18 | 2.08 | 0.57 | – | 70 | Umbilical cord serum | | Lee et al. (2013) |
| 2003–2004 | 1.59 | 0.73 | 1.64 | 0.35 | 20[b] | Dried blood spot, infant (newborn screening program) | New York, USA | Spliethoff et al. (2008) |
| 2007 | 2.1[a] | 0.9[a] | 0.4[a] | 0.3[a] | 98 | Dried blood spot, infant | Texas, USA | Kato et al. (2009c) |

[a]Geometric mean
[b]Pooled samples

2012; Pinney et al. 2014; Kato et al. 2009b) in part because of the difficulties in obtaining blood from newborns and young children. Using dry blood spots (DBS) or residual specimens can overcome this limitation. In the United States, DBS are collected routinely from newborns within 48 h of birth for the main purposes of screening for metabolic and other health disorders. A couple of studies relied on using residual newborn DBS stored by state public health departments to demonstrate exposure to PFASs including PFOS, PFOA, PFNA, and PFHxS in Texas (Kato et al. 2009c) and New York infants (Spliethoff et al. 2008) (Table 3.2).

Three studies, two in the United States and one in Australia, used residual serum specimens collected during routine health exams to evaluate exposure to PFASs among young children (Toms et al. 2009; Schecter et al. 2012; Kato et al. 2009b). In the first study, researchers used 936 samples collected from U.S. children participants in NHANES in 2001–2002 to prepare pools that were analyzed for several PFASs. Mean concentrations of PFOS, PFOA, PFNA, and PFHxS in these pools were similar regardless of age (3–5 or 6–11 years) or sex, but were higher than the mean concentrations reported in pools from adolescents and adults NHANES 2001–2002 participants (Kato et al. 2009b). In the second US study, PFASs were detected in serum collected in late 2009 from 300 Texas children from birth through 12 years of age, several years after phasing out the manufacture of POSF-based materials (Schecter et al. 2012). Of note, serum concentrations of PFOS, PFOA, PFNA, and PFHxS did not significantly differ by sex, unlike findings from adult populations (Calafat et al. 2007a; Olsen et al. 2008; Bjermo et al. 2013; Dallaire et al. 2009; Fromme et al. 2007b, 2009; Vassiliadou et al. 2010; Ericson et al. 2007; Yeung et al. 2013a, b; Haines and Murray 2012; Ingelido et al. 2010; Ji et al. 2012; Kato et al. 2011). By constrast, concentrations appeared to increase with age, perhaps because the older children experienced higher exposures to PFASs in the late 1990s–early 2000s when environmental levels of these compounds were higher. In another study (Toms et al. 2009), investigators examined the concentrations of several PFASs in pools made from individual sera collected in 2006–2007 in southeast Queensland, Australia from 2,420 male and female donors between birth to >60 years of age. PFOS, PFOA and PFNA were detected in all pools; PFOS was detected at the highest mean concentration followed by PFOA. Concentration differences by sex were not apparent among children <12 years, in agreement with the results from the Texas children (Schecter et al. 2012), and concentration patterns by age varied depending on the compound.

The relevance of sources and routes of exposure to certain PFASs in children may differ from those in adults. For example, investigators reported higher serum mean concentrations of selected PFASs, specifically PFHxS and 2-(N-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), from U.S. children than from adults (Olsen et al. 2004a). Me-PFOSA-AcOH is a known oxidation product of 2-(N-methyl-perfluorooctane sulfonamido) ethanol, which was used primarily in surface treatment applications for carpets and textiles (Olsen et al. 2003). PFHxS was used as a building block for compounds incorporated in fire-fighting foams and specific postmarket carpet treatment applications (Olsen et al. 2003). One explanation for the apparent greater mean concentrations of PFHxS and Me-PFOSA-AcOH

in children than in adolescents and adults was increased exposure among children resulting from increased contact with carpeted floors and upholstered furniture coupled with hand-to-mouth activity. Carpets and upholstered furniture are known to trap dust, which may contain PFHxS. In fact, the mean concentrations of PFHxS in house dust samples collected in North America were higher than for other PFASs (Kato et al. 2009a; Strynar and Lindstrom 2008; Beesoon et al. 2013) indoor dust concentration data on Me-PFOSA-AcOH were also relatively high (Kato et al. 2009a).

Unlike lipophilic persistent organic pollutants such as polychlorinated biphenyls, PFASs bind to plasma proteins (Butenhoff et al. 2012; Wu et al. 2009; Han et al. 2003). However, PFASs have also been detected in human milk (Kubwabo et al. 2013; Karrman et al. 2007a; Sundstrom et al. 2011; Barbarossa et al. 2013; Guerranti et al. 2013; Karrman and Lindstrom 2013; Croes et al. 2012; Fujii et al. 2012; Kadar et al. 2011; Karrman et al. 2010; Liu et al. 2010; Llorca et al. 2010; Nakata et al. 2009; von Ehrenstein et al. 2009; Tao et al. 2008; So et al. 2006; Lankova et al. 2013), albeit at concentrations approximately one order of magnitude lower than in serum. Therefore, breast milk can be a source of exposure to PFASs and nursing may reduce the PFASs body burden in lactating women (Pinney et al. 2014; Loccisano et al. 2013; Haug et al. 2011; Mondal et al. 2014).

## 3.6 Conclusions

Diet, drinking water, and indoor dust are important sources of human exposure to PFASs; in utero and lactational exposure to PFASs are also relevant for certain segments of the population. Comparing PFASs concentrations among populations is difficult because of differences in study design (e.g., age, sex, race of the populations examined), timing of sample collection, geographical location, and analytical methodologies used (e.g., isomeric profiles). Interestingly, the concentration ranges of the most commonly studied PFASs, PFOS and PFOA, are remarkably similar in people worldwide, although important differences may exist (e.g., accidental exposures; developed vs developing countries).

Due to regulatory and voluntary efforts to reduce emissions of PFASs, human exposure to some of the PFASs appears to have decreased since the early 2000s. However, PFASs are still ubiquitously detected in people around the world. Concerns remain regarding the importance of past and present exposure sources on the human body burden of PFASs and on the potential adverse health effects of such exposures. Age; diet; route, frequency, and magnitude of exposure; potential synergistic or antagonistic interactions among chemicals; and genetic factors, among others, are critical in determining health outcomes associated with exposure to PFASs and other environmental chemicals.

Biomonitoring efforts are important to facilitate the risk assessment of PFASs. Comprehensive biomonitoring programs, such as NHANES and CHMS, provide a reliable estimate of PFASs internal dose among the general population. In addition,

future research should continue to improve our understanding of (i) determinants of exposure to PFASs, (ii) PFASs toxicokinetics with emphasis on fetal and neonatal exposures, when susceptibility to potential adverse health effects of environmental chemicals may be highest, and (iii) specific populations with known source(s) of exposure to evaluate potential health effects as well as the efficacy of intervention strategies to reduce exposures.

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