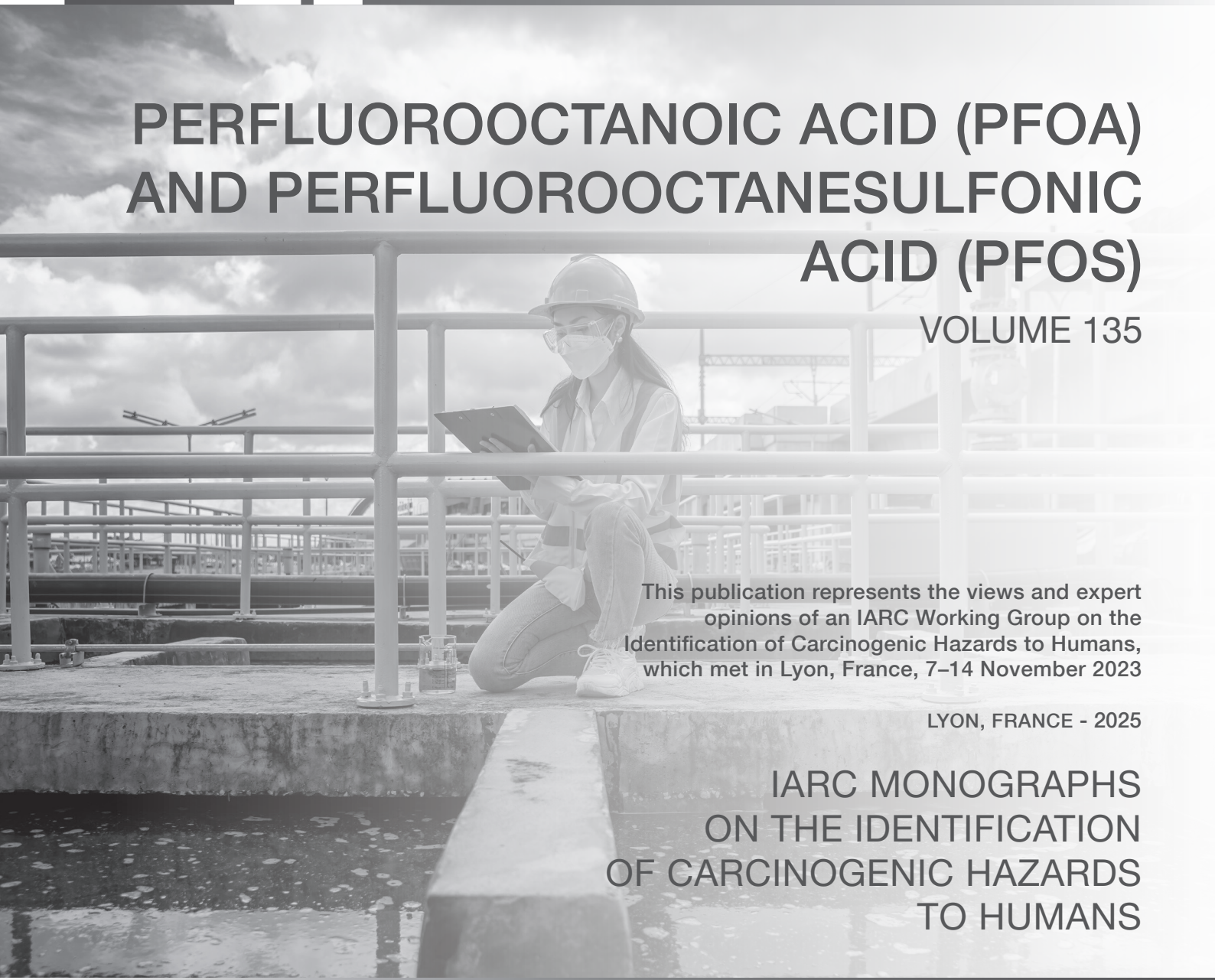
IARC MONOGRAPHS



PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

VOLUME 135

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 November 2023

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1. EXPOSURE CHARACTERIZATION

1.1 Identification of the agent

Because of their acidic nature, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) exist in the environment, and in aqueous solutions, in equilibrium with their conjugated bases, perfluorooctanoate and perfluorooctane sulfonate. Salts of PFOA and PFOS will dissociate in solution and in the human body (except the stomach) to produce the respective anions perfluorooctanoate and perfluorooctane sulfonate.

The terms "PFOA" and "PFOS" are used for both the acid and the deprotonated form in environmental or biological samples, if not otherwise specified.

All isomeric forms of PFOA and PFOS and their salts should be considered to be part of the definition of the agents considered in the present monograph.

1.1.1 Nomenclature and molecular information

(a) PFOA and its salts

The agents considered in the present monograph include PFOA and its salts (see Table 1.1 for a non-exhaustive list). PFOA and its salts exist as linear and branched isomers (see Fig. 1.1). Depending on the production method used, PFOA is present primarily as the linear isomer or as a mixture of linear (*n*-isomer) and branched isomers (see Section 1.2).

(b) PFOS and its salts

The agents considered in this present monograph include PFOS and its salts. Linear and branched isomers of PFOS and its salts exist (see Table 1.2). Depending on the production method, PFOS is present primarily as the linear isomer or as a mixture of linear and branched isomers (see Fig. 1.2).

1.1.2 Chemical and physical properties of the pure substances

Selected chemical and physical properties of PFOA and PFOS are presented in Table 1.3. [The Working Group noted that there is some inconsistency in the data reported for these agents. This may be attributed to a combination of factors, including the purity of the acid form used to conduct the measurement; the low water solubility of the pure acid forms; and their strong surface active properties, resulting in sorption to interfaces such as the water surface or the walls of a glass vessel to an extent that is unknown for other substances (Goss, 2008).] The salts of PFOA and PFOS are more soluble in water than are their acid forms. For example, the water solubility of PFOA is 9.5 g/L, whereas the water solubility of ammonium perfluorooctanoate (APFO) is

Table 1.1 Nomenclature and molecular information for PFOA isomers and selected salts

Chemical name	CAS No.	IUPAC name and synonyms	Molecular formula	Relative molecular mass
n-Perfluorooctanoic acid	335-67-1 (NCBI, 2023a)	2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluoro-octanoic acid PFOA; *n*-Perfluorooctanoic acid; Pentadecafluoro-1-octanoic acid; Pentadecafluoro-*n*-octanoic acid; Pentadecafluorooctanoic acid; Perfluorocaprylic acid; Perfluoroctanoic acid; Perfluoroheptanecarboxylic acid (NCBI, 2023a)	$C_8HF_{15}O_2$ (NCBI, 2023a)	414.07 (NCBI, 2023a)
branched-Perfluorooctanoic acid	207678-51-1 705240-04-6 1144512-18-4 909009-42-3 15166-06-0 1144512-35-5 1192593-79-5 1144512-36-6 1144512-34-4 35605-76-6 (Nielsen, 2012)	sb-Perfluorooctanoic acid (CDC, 2022), br-Perfluorooctanoic acid (e.g. Jin et al., 2020) [The Working Group noted that different sums of isomers have been used. The exact definition varies between studies and might include all or just some of the isomers.] (See Fig. 1.1 for the names of some isomers)	$C_8HF_{15}O_2$ (NCBI, 2023a)	414.07 (NCBI, 2023a)
Ammonium perfluorooctanoate	3825-26-1 207678-62-4 19742-57-5 13058-65-5 (Nielsen, 2012)	Ammonium perfluorocaprylate; Pentadecafluorooctanoic acid ammonium salt; Octanoic acid, pentadecafluoro-, ammonium salt, APFO (NCBI, 2023c)	$C_8H_4F_{15}NO_2$ (NCBI, 2023c)	431.10 (NCBI, 2023c)
Sodium perfluorooctanoate	335-95-5 207678-72-6 646-84-4 18017-22-6 1195164-59-0 (Nielsen, 2012)	Sodium perfluorocaprylate; Octanoic acid, pentadecafluoro-, sodium salt; Perfluorooctanoic acid sodium salt (NCBI, 2023d)	$C_8F_{15}NaO_2$ (NCBI, 2023d)	436.05 (NCBI, 2023d)
Potassium perfluorooctanoate	2395-00-8 207678-65-7 29457-73-6 (Nielsen, 2012)	Potassium, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octanoate; Octanoic acid, pentadecafluoro-, potassium salt (NCBI, 2023e)	$C_8F_{15}KO_2$ (NCBI, 2023e)	452.16 (NCBI, 2023e)

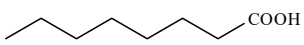
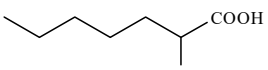
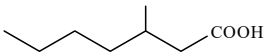
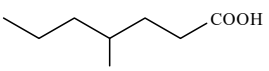
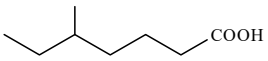
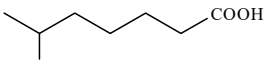
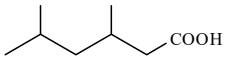
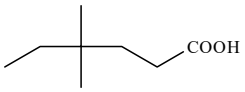
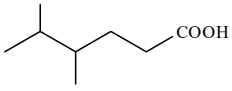
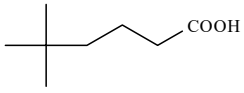
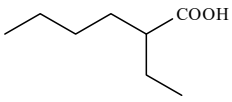
br, branched; CAS, Chemical Abstracts Service Registry; IUPAC, International Union of Pure and Applied Chemistry; PFOA, perfluorooctanoic acid; sb, sum of branched isomers.

> 500 g/L, at 20 °C (OECD, 2008). [The Working Group noted that other properties of the salts might be different from those of the acid form, but data are lacking.]

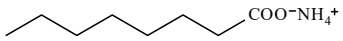
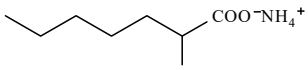
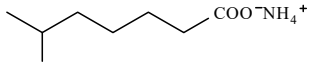
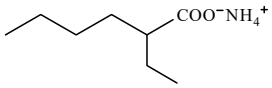
[The Working Group noted that even though the data on the pK_a of PFOA and PFOS were inconsistent, the values were in the range of that for weak to strong acids. In aqueous samples of low concentrations (e.g. drinking-water, bio-specimen), it can be assumed that both agents are mainly present in the deprotonated form.]

Fig. 1.1 Main salts and isomers of PFOA

a. PFOA isomers

Structure of carbon chain	CAS No.
	335-67-1 Linear PFOA
	207678-51-1 Perfluoro-2-methyl-heptanoic acid
	705240-04-6 Perfluoro-3-methyl-heptanoic acid
	1144512-18-4 Perfluoro-4-methyl-heptanoic acid
	909009-42-3 Perfluoro-5-methyl-heptanoic acid
	15166-06-0 Perfluoro-6-methyl-heptanoic acid
	1144512-35-5 Perfluoro-3,5-dimethyl-hexanoic acid
	1192593-79-5 Perfluoro-4,4-dimethyl-hexanoic acid
	1144512-36-6 Perfluoro-4,5-dimethyl-hexanoic acid
	1144512-34-4 Perfluoro-5,5-dimethyl-hexanoic acid
	35605-76-6 Perfluoro-2-ethyl-hexanoic acid

b. Ammonium salts of PFOA isomers (APFO)

Structure of carbon chain	CAS No.
	3825-26-1
	207678-62-4
	19742-57-5
	13058-06-5

c. Sodium salts of PFOA isomers

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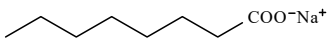
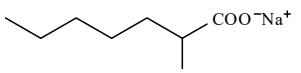
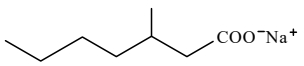
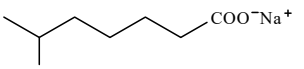
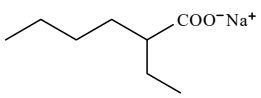
	335-95-5
	207678-72-6
	646-84-4
	18017-22-6
	1195164-59-0

d. Potassium salts of PFOA isomers

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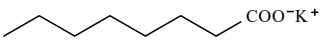
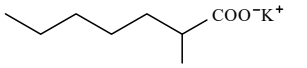
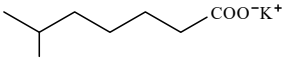
	2395-00-8
	207678-65-7
	29457-73-6

APFO, ammonium perfluorooctanoate; CAS, Chemical Abstracts Service; PFOA, perfluorooctanoic acid.
From Nielsen (2012), as cited in IARC (2016).

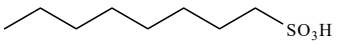
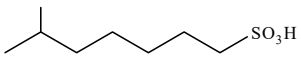
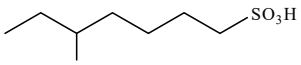
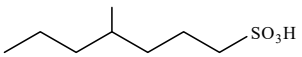
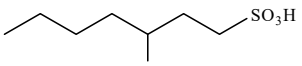
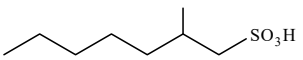
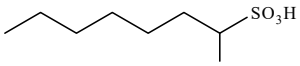
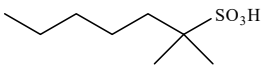
Table 1.2 Nomenclature and molecular information for PFOS isomers and selected salts

Chemical name	CAS No.	IUPAC name and synonyms	Molecular formula	Relative molecular mass
n-Perfluorooctane-sulfonic acid	1763-23-1 (NCBI, 2023b)	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluorooctane-1-sulfonic acid PFOS, *n*PFOS; Heptadecafluorooctane-1-sulfonic acid; Perfluorooctane sulfonate; Perfluorooctane-1-sulfonic acid; Perfluorooctylsulfonic acid; Heptadecafluoro-1-octanesulfonic acid; Heptadecafluorooctane sulfonic acid; 1-Perfluorooctanesulfonic acid (NCBI, 2023b; Royal Society of Chemistry, 2023)	$C_8HF_{17}O_3S$ (NCBI, 2023b)	500.13 (NCBI, 2023b)
Branched-Perfluorooctane-sulfonic acid	255831-20-0 747385-21-3 775554-63-7 740777-79-1 765246-09-1 927670-12-0 950669-24-6 950669-23-5 950669-22-4 950669-21-3 927670-09-5 (CAS, 2023)	sm-Perfluorooctanesulfonic acid (CDC, 2022), br-Perfluorooctanesulfonic acid (EFSA Panel on Contaminants in the Food Chain, 2018) [The Working Group noted that different sums of isomers have been used. The exact definition varies between studies and might include all or just some of the isomers.] See Fig. 1.2 for the names of some isomers.	$C_8HF_{17}O_3S$ (NCBI, 2023b)	500.13 g/mol (NCBI, 2023b)
Ammonium perfluorooctane-sulfonate	29081-56-9 (NCBI, 2023f)	Ammonium heptadecafluoro-1-octanesulfonate (NCBI, 2023f)	$C_8H_4F_{17}NO_3S$ (NCBI, 2023f)	517.16 g/mol (NCBI, 2023f)
Potassium perfluorooctane-sulfonate	2795-39-3 (NCBI, 2023h)	Potassium heptadecafluoro-1-octanesulfonate 1-Octanesulfonic acid, heptadecafluoro-, potassium salt (NCBI, 2023h)	$C_8F_{17}KO_3S$ (NCBI, 2023h)	538.22 g/mol (NCBI, 2023h)
Lithium perfluorooctane-sulfonate	29457-72-5 (NCBI, 2023g)	Lithium heptadecafluorooctanesulfonate Heptadecafluoro-1-octanesulfonic acid lithium salt (NCBI, 2023g)	$C_8F_{17}LiO_3S$ (NCBI, 2023g)	506.10 g/mol (NCBI, 2023g)

br, branched; CAS, Chemical Abstracts Service Registry; IUPAC, International Union of Pure and Applied Chemistry; PFOS, perfluorooctanesulfonic acid; sm, sum of perfluoromethylheptane sulfonate isomers.

Fig. 1.2 Main salts and isomers of PFOS

a. PFOS isomers

Structure of carbon chain	CAS No.
	1763-23-1 Linear PFOS
	255831-20-0 Perfluoro-6-methyl-heptanesulfonic acid
	747385-21-3 Perfluoro-5-methyl-heptanesulfonic acid
	775554-63-7 Perfluoro-4-methyl-heptanesulfonic acid
	740777-79-1 Perfluoro-3-methyl-heptanesulfonic acid
	765246-09-1 Perfluoro-2-methyl-heptanesulfonic acid
	927670-12-0 Perfluoro-1-methyl-heptanesulfonic acid
	950669-24-6 Perfluoro-1,1-dimethyl-hexanesulfonic acid
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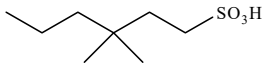
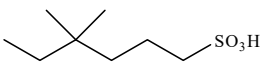
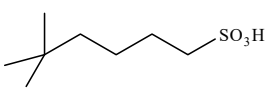
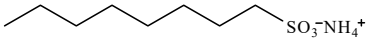
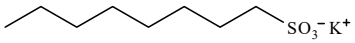
	950669-22-4 Perfluoro-3,3-dimethyl-hexanesulfonic acid
	950669-21-3 Perfluoro-4,4-dimethyl-hexanesulfonic acid
	927670-09-5 Perfluoro-5,5-dimethyl-hexanesulfonic acid

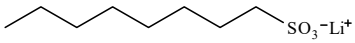
b. Ammonium salt of PFOS

Structure of carbon chain	CAS No.
	29081-56-9

c. Potassium salt of PFOS

Structure of carbon chain	CAS registry number
	2795-39-3

d. Lithium salt of PFOS

Structure of carbon chain	CAS No.
	29457-72-5

CAS, Chemical Abstracts Service; PFOS, perfluorooctanesulfonic acid.
From Langlois and Oehme (2006); Miralles-Marco and Harrad (2015).

Table 1.3 Chemical and physical properties of pure PFOA and PFOS in acid form

Property	PFOA	PFOS
Boiling-point	192 °C (US EPA, 2017a; NCBI, 2023a)	258–260 °C (US EPA, 2017a)
Melting-point	54.3 °C (IARC, 2016; ATSDR, 2021)	84 °C [The Working Group noted that these are predicted data (US EPA, 2023a)]
Vapour pressure	[0.0421 hPa] at 25 °C (ATSDR, 2021; NCBI, 2023a), [0.700 hPa] at 25 °C (US EPA, 2017a)	[0.003 hPa] at 25 °C (US EPA, 2017a; NCBI, 2023b)
Water solubility	9.5 g/L at 25 °C (IARC, 2016; US EPA, 2017a; ATSDR, 2021)	680 mg/L at 25 °C (US EPA, 2017a; NCBI, 2023b)
Density	1.8 g/cm^3 at 20 °C (IARC, 2016; ATSDR, 2021)	1.84 g/cm^3 [The Working Group noted that these are predicted data (US EPA, 2023a)]
log K_{ow} (octanol/water partition coefficient, *P*)	Not measurable, since PFOA forms multiple layers in an octanol/water mixture (ATSDR, 2021)	Not measurable, since PFOS forms multiple layers in an octanol/water mixture (ATSDR, 2021; NCBI, 2023b)
log K_{oc} (organic carbon/water partition coefficient)	2.06 (US EPA, 2017a)	2.57–3.14 (US EPA, 2017a; ATSDR, 2021)
Conversion factor	1 ppm = 16.94 mg/m^3, 1 mg/m^3 = 0.059 ppm, at 25 °C and 101 kPa	1 ppm = 20.45 mg/m^3; 1 mg/m^3 = 0.049 ppm, at 25 °C and 101 kPa
Physical description	White to off-white powder (ATSDR, 2021)	White powder (ACS, 2019); also reported as off-white to grey liquid (NCBI, 2023b)
Stability	When heated to decomposition, it emits toxic vapours of hydrogen fluoride. Perfluoroalkyl carboxylates are resistant to direct photolysis and reaction with acids, bases, oxidants, and reductants (IARC, 2016; ATSDR, 2021).	When heated to decomposition, it emits toxic vapours of sulfur oxides and fluorine (NCBI, 2023b). Perfluoroalkyl sulfonates are resistant to direct photolysis and reaction with acids, bases, oxidants, and reductants (ATSDR, 2021).

PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; ppm, parts per million.

1.1.3 Technical grade and impurities

(a) PFOA

Before 2002, PFOA, which was produced mainly by the electrochemical fluorination (ECF) method, was reported to have a consistent isomer composition of 78% ± 1.2% linear isomers and 22% ± 1.2% branched-chain isomers in 18 production lots tested over a 20-year period. PFOA produced by ECF was reported to contain the following impurities: perfluorohexanoate, 0.73%; perfluoroheptanoate, 3.7%; perfluorononanoate, 0.2%; perfluorodecanoate, 0.0005%; perfluoroundecanoate, 0.0008%; and perfluorododecanoate, 0.0008%. From 2002 onwards, PFOA, which is produced mainly by the telomerization method, is typically an isomerically pure, linear product (Benskin et al., 2010a; IARC, 2016).

(b) PFOS

PFOS and its salts are mainly produced by ECF. This ECF-produced PFOS comprises 11 different isomers, including the linear isomer (approximately 70%) and various branched isomers (approximately 30%) (Naile et al., 2010). Some of these isomers (specifically those with branched chains) are chiral, and the environmental fate and behaviour of PFOS may vary according to its isomeric and enantiomeric composition (Miralles-Marco and Harrad, 2015). The following impurities were reported in a commercial sample of potassium perfluorooctanesulfonate (purity, 86.9%): homologues with fewer carbons (C2–C7, predominantly C6), 9.38%; metals (calcium, magnesium, sodium, nickel, and iron), 1.45%; inorganic fluoride, 0.59%; molecules containing perfluorinated sulfur(VI) (sulfur hexafluoride), 0.68%; PFOA,

0.33%; nonafluoropentanoic acid, 0.28%; hydrocarbon sulfonate salts, 0.15%; terminal cyclopentyl PFOS, 0.11%; heptafluorobutyric acid, 0.1%; and trifluoroacetic acid, 0.015% (Seacat et al., 2003).

1.2 Production and uses

1.2.1 Production process

PFOA and PFOS have been manufactured by ECF and fluorotelomerization. During ECF, an organic acyl or sulfonyl fluoride backbone structure is dissolved in a solution of aqueous hydrogen fluoride (Buck et al., 2011; ATSDR, 2021; ITRC, 2022c). All the hydrogens on the molecule are then replaced with fluorines when a direct electrical current is passed through the solution. Perfluoroacyl fluorides produced by ECF are hydrolysed to form the perfluorocarboxylic acid, which is then separated via distillation. The ECF process results in a mixture of linear and branched isomers, with 78% and 70% linear forms of PFOA and PFOS, respectively (Buck et al., 2011; ATSDR, 2021; ITRC, 2022c).

Fluorotelomerization produces primarily linear perfluorocarboxylic acids with an even number of carbon atoms, which includes PFOA. The process begins with the preparation of pentafluoroiodoethane from tetrafluoroethene. Tetrafluoroethene is then added to the product at a molar ratio that gives a product of the desired chain length, before the product is oxidized to form the carboxylic acid (Buck et al., 2011; ATSDR, 2021; ITRC, 2022c).

1.2.2 Production volume

Production of perfluoroalkyl carboxylates began in 1947, initially by ECF. By 2000, ECF was still the leading process, accounting for the majority (80–90%) of the production of APFO – a salt of PFOA – worldwide, which was approximately 260 tonnes in 1999 (Prevedouros et al., 2006). Global production of perfluorooctane sulfonyl fluoride (POSF) – a production precursor of PFOS – was estimated to be 96 000 tonnes (or 122 500 tonnes, including wastes, largely disposed of through land farming/landfilling or incineration) between 1970 and 2002. One major company based in the United States of America (USA) manufactured most of the POSF, using ECF, accounting for about 78% of global production in 2000 (Paul et al., 2009). [The Working Group noted that data on production volumes were limited, particularly after 2002 (see below).]

In the USA, the manufacture and import of PFOA and PFOS has been phased out; however, some existing stocks may remain. PFOS was phased out of production by its primary manufacturer between 2000 and 2002 (US EPA, 2016) and was not reported in the 2006 or 2012 Chemical Data Reporting effort (US EPA, 2023e). Before 2006, production volume ranges in the USA were reported as follows: PFOA, [5–227] tonnes in 1986, 1994, 1998, and 2002; APFO, [5–227] tonnes in 1986, 1990, 1994, and 1998, and [227–454] tonnes in 2002; and PFOS, [5–227] tonnes in 1994 and 2002 (ATSDR, 2021). In 2006, the United States Environmental Protection Agency (US EPA) invited eight major leading companies manufacturing PFOA to join the 2010/2015 PFOA Stewardship Program. All participating companies reported meeting the goals of this programme, which included eliminating emissions by 2015 (US EPA, 2022). As of November 2016, PFOA and PFOS are no longer used in food contact applications sold in the USA (US FDA, 2023). For regulatory agency guidelines on the production and use of PFOA and PFOS that might explain changes over time, see Section 1.5.

Since 2002 there has been a geographical shift in industrial production (particularly fluoropolymer-production sites) from North America, Europe, and Japan to some countries in Asia, especially China (Wang et al., 2014). Zhang et al. (2012) report PFOS production in China of 247 tonnes

in 2006 and about 100 tonnes in 2008, with the majority used in metal plating (30–40 tonnes/year) and aqueous film-forming foam (AFFF) (25–35 tonnes/year), as well as the production of sulfluramid insecticides (4–8 tonnes/year). During 2004–2012, 480 tonnes of PFOA and its salts were produced in China using the ECF process (Li et al., 2015). China has also implemented a phase-out of PFOA and PFOS, with the Chinese Ministry of Environmental Protection restricting and banning different uses (OECD, 2023a). Brazilian imports of *N*-ethyl perfluorooctane sulfonamide (*N*-EtFOSA), a PFOS precursor, for the production of sulfluramid between 2005 and 2015 were almost exclusively from China; imports of *N*-EtFOSA peaked at > 1.3 tonnes in 2012, and exports increased to around 2 tonnes per year in 2012 (Löfstedt Gilljam et al., 2016). [The Working Group noted that these data were not for PFOS itself, but might give some indication of use or production in these geographical regions where data for PFOS itself are lacking.]

1.2.3 Uses

The unique properties of per- and polyfluoroalkyl substances (PFAS), including PFOA and PFOS, have led to extensive uses in a wide variety of diverse applications. These properties, including the "ability to lower the aqueous surface tension, high hydrophobicity, high oleophobicity, non-flammability, high capacity to dissolve gases, high stability, extremely low reactivity, high dielectric breakdown strength, good heat conductivity, low refractive index, low dielectric constant, ability to generate strong acids, operation at a wide temperature range, low volatility in vacuum, and impenetrability to radiation" (Glüge et al., 2020) facilitate nearly 300 different uses and functions. For the more than 1400 PFAS evaluated by Glüge et al. (2020), uses fell within 20 industry branches (e.g. chemical industry and electroplating) and 44 other use categories (e.g. cleaning compositions and personal care products). [However, the Working Group noted that the uses identified by Glüge et al. (2020) are summarized across all 1400 PFAS; some uses may not be applicable to PFOA and PFOS.] PFOA and PFOS may be present in industrial and consumer products as main ingredients, or as unreacted raw materials, undesired reaction by-products, or cross-contaminants along production and supply chains (OECD, 2015a; Glüge et al., 2020). PFOA and APFO are used in chemical manufacturing processes, industrial products and processes, and consumer products. As a processing aid, APFO has been used extensively to manufacture fluoropolymers, such as polytetrafluoroethylene (PTFE) (Buck et al., 2011). Applications for fluoropolymers containing PFOA, as well as direct uses for PFOA, include household products with non-stick coatings (e.g. cookware); textiles for outdoor or personal protection applications (e.g. firefighter turnout gear); personal care products (e.g. cosmetics, sunscreens, dental floss); seals and gaskets used in the aviation and aerospace industries; coatings for cables and wires; electronics, solar panels and electrolyte fuel cells; fluoropolymer fabrication materials used in food processing (e.g. liners for grills and ovens); carpets; cleaning and impregnating agents; construction materials (e.g. chipboard and oriented strand board); and surface coatings conferring stain-, oil- and water resistance on carpets, textiles, leather products, and paper or cardboard packaging used in food and feed contact paper and board (e.g. popcorn bags, pizza boxes, fast food containers) (Kotthoff et al., 2015; Bečanová et al., 2016; ATSDR, 2021; Ramírez Carnero et al., 2021; ITRC, 2022a). [The Working Group noted that the concentration of PFOA varied by application and product. For example, in fluoropolymer-based consumer products (e.g. non-stick cookware or textiles) PFOA may be present in a chemically bound form or at lower concentrations than in products in which PFOA is an intentionally added ingredient.]

With some applications that overlap those of PFOA, such as waxes (e.g. car, shoe, floor, ski), carpets, and packaging used for food and feed (Kotthoff et al., 2015; Nordic Council of Ministers, 2017), PFOS has additionally been used in the semiconductor industry; as a hydraulic fluid additive in the aviation and aerospace industries; as an etchant and antireflective coating in photolithography processes; and in the fabrication of imaging devices (e.g. cameras, mobile phones, and printers) (ITRC, 2022a). During electroplating processes in metal finishing and plating operations, PFOS has been used as a mist-suppressing agent to prevent workers' exposure to aerosols and mists; however, in the USA, the US EPA National Emissions Standards for Hazardous Air Pollutants (NESHAP) mandated that use of PFOS-based mist-suppressants in chromium electroplating be discontinued by 2015 (Office of the Federal Register, 2012). Similar phase-outs of PFOS for this application have occurred in other countries (Ramírez Carnero et al., 2021; ITRC, 2022a); however, this application is still permitted in the European Union (EU) (Swedish Chemicals Agency, 2020). PFOS is also present in a variety of building and construction materials, including paints and varnishes; insulation (phenolic foam); dyes and ink; and in wetting, levelling, and dispersing agents (ITRC, 2022a).

PFOS together with other PFAS have been used extensively in class B firefighting foams known as AFFFs. [The Working Group noted that AFFFs were designed to meet firefighting performance criteria; formulations of PFAS have changed over time and by manufacturer (Leeson et al., 2021).] These foams were developed in the 1960s to extinguish liquid fuel fires by efficiently suppressing flammable liquid vapour, suffocating the fire hazard, and preventing re-ignition (Rosenfeld et al., 2023). AFFF containing PFOS was manufactured in the USA from the late 1960s until 2002; however, other fluorotelomer-based AFFF manufactured from the 1970s until 2016 contained precursors of PFOA. Although newer formulations of class B foams exist, the legacy products have been used during fire response, training, and equipment maintenance activities by the military, airport and municipal fire departments, and oil and gas production and refining industries worldwide (Prevedouros et al., 2006; ITRC, 2022b).

PFAS that are known to convert into PFOA and PFOS, frequently referred to as "precursors", are used in a variety of settings (see Section 1.4(d)). Although a detailed description of these uses and functions is beyond the scope of the present monograph, examples include the semiconductor and electronics industry; personal care products, coatings for medical devices, apparel, pharmaceutical equipment; and the pesticide sulfluramid (Löfstedt Gilljam et al., 2016; Glüge et al., 2020; ITRC, 2022a).

1.3 Detection and quantification

General considerations

(a) Analytical method terminology

Analytical methods used for PFAS consist of targeted, non-targeted, and total fluorine analysis approaches. Targeted analyses refer to methods for a pre-defined, known list of analytes for which authentic chemical standards exist. Non-targeted analyses are capable of identifying suspect and unknown analytes in a sample, often through mass spectrometry. Analyte identity can then be confirmed using authentic chemical standards, and unknown analytes can be tentatively identified through matching to existing chemical libraries (US EPA, 2023b). Total fluorine methods quantify the fluorine (often organic fluorine) present in a sample, regardless of chemical structure, and thus are unable to differentiate between chemical structures of analytes (Schultes et al., 2019).

Some methods are able to differentiate between linear and branched isomers. [The Working Group noted that some recent studies

of PFOA and PFOS differentiate between linear and branched isomers. For example, linear, secondary-branched, and tertiary-branched isomers of PFOA and PFOS can be resolved by high-resolution differential ion mobility-mass spectrometry (DMS-MS) (Ahmed et al., 2019).] Isomer profiling can be used in the quantitative assessment of manufacturing source (Benskin et al., 2010b).

[The Working Group noted that, in the papers reviewed for PFOA and PFOS exposure, multiple approaches were used to report the lowest concentration of a chemical analyte. These commonly include the limit of detection (LOD), which describes the lowest concentration identifiable by the analytical instrumentation, and the limit of quantification (LOQ), which describes the lowest concentration that can be determined by means of a given analytical procedure with the established accuracy, precision, and uncertainty. The Working Group noted that some studies reported lowest measurable concentrations as LODs, whereas others reported LOQs. This makes comparison between studies more challenging at the lower end of the concentration range studied.]

Liquid chromatography-mass spectrometry (LC-MS), commonly used for the analysis of PFOA and PFOS, is a sophisticated analytical technique that requires the purchase and maintenance of an expensive instrument. [The Working Group noted that, consequently, access to PFOA and PFOS analyses can be challenging for regions or populations with limited resources, such as low- or middle-income countries (LMICs), and may explain the paucity of available data in some regions of the world.]

(b) Potential for cross-contamination

Consideration of numerous potential sources of cross-contamination (also referred to as "background interference") of PFOA and PFOS have been documented in the context of sample collection and analysis (Method 533, US EPA, 2023b; MDEQ, 2018). Potential sources of PFAS cross-contamination in the typical sampling environment include water used for washing or decontamination and materials used within the sampling environment (MDEQ, 2018).

In a laboratory setting, analytical instrumentation (e.g. mass spectrometry) and laboratory equipment or materials often have fluoropolymer (e.g. PTFE) components that may contain PFOA (Method 533, US EPA, 2023b; MDEQ, 2018). [The Working Group noted that cross-contamination issues may affect the concentrations of PFOA and PFOS in samples and blanks alike. This may contribute to the high LOQs reported in some studies.]

1.3.1 Air

Several methods have been reported for the quantification of PFOA and PFOS in indoor and/or outdoor air using both active and passive air-sampling techniques, and some examples are presented in Table 1.4. These methods generally rely on a combination of sampling media to collect both gas and particle-bound PFOA and PFOS. Most reported active air sampling methods apply a filter (glass fibre or quartz) to capture the particle phase, followed by an adsorbent resin to bind the gaseous-phase PFAS. Few active air-sampling methods reported the use of filters only to capture particle-bound PFAS, or sorbent only to capture both gas- and particle-bound PFAS on the same sampling medium. The passive sampling methods use a compact-design sampler containing a sorbent-impregnated, polyurethane foam (PUF) disc to sample PFAS from both the gaseous and particle phases. Therefore, active sampling methods with two independent sampling media can differentiate between gas- and particle-bound PFAS concentrations, whereas passive sampling methods can only provide PFAS concentrations as the sum of concentrations in the two phases. In general, sampling media (filters and PUF discs)

Table 1.4 Selected analytical methods for the measurement of PFOA and PFOS in air

Sample matrix	Sampler type	Sample collection method	Instrument (LOD)[a]	Reference
Air emissions from stationary sources	Active (flow rate not specified – minimum sample of 3 m^3)	Gas- and particle-bound PFAS collected on a sampling train of GFF or QFF, a packed column of adsorbent material	HPLC-MS/MS (PFOA, 0.35 ng/m^3; PFOS, 0.43 ng/m^3)	EPA-OTM-45 US EPA (2021)
Indoor and outdoor air	Active (flow rate of 6.4 m^3/h)	Gas- and particle-bound analytes collected using GFFs (particle phase) and glass columns with a PUF–XAD-2–PUF sandwich (gaseous phase)	HPLC-TOF/MS (1 pg/m^3)	Barber et al. (2007)
Outdoor air	Active (flow rate of 1.1 m^3/h)	Particle-bound analytes collected using GFF	HPLC-TOF/MS (PFOA, 0.2 pg/m^3; PFOS, 0.4 pg/m^3)	Jahnke et al. (2007)
Outdoor air, $PM_{2.5}$	Active (flow rate of 30 m^3/h)	$PM_{2.5}$-bound analytes collected on QFF	HPLC-MS/MS (0.14 pg/m^3)	Beser et al. (2011)
Indoor and outdoor air	Passive	Gas- and particle-bound analytes collected on sorbent (XAD-4)-impregnated PUF disc samplers	HPLC-MS/MS (PFOA, 0.47 pg/m^3; PFOS, 0.02 pg/m^3)	Shoeib et al. (2010, 2011)
Indoor air and personal breathing zone	Active (flow rate of 0.12 m^3/h)	ISOLUTE ENV+ sorbent (hydroxylated polystyrene–divinylbenzene copolymer) cartridge	HPLC-MS/MS (PFOA, 73 pg/g extract; PFOS, 38 pg/g extract)	Nilsson et al. (2013b)
Outdoor air, $PM_{2.5}$	Active (flow rate of 30 m^3/h)	$PM_{2.5}$-bound analytes collected on QFF	HPLC-HRMS (PFOA, 0.18 pg/mL extract; PFOS, 0.11 pg/mL extract)	Kourtchev et al. (2022)

GFF, glass-fibre filters; h, hour(s); HPLC, high-performance liquid chromatography; HRMS, high-resolution mass spectrometry; ISOLUTE ENV+, commercial solid-phase extraction column; LOD, limit of detection; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NR. not reported; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; $PM_{2.5}$, particulate matter with diameter < 2.5 µm; PUF, polyurethane foam; QFF, quartz fibre filters; SIP, sorbent-impregnated polyurethane; TOF, time-of-flight; XAD, commercial resin.

[a] Using electrospray ionization in negative ion mode.

are extracted with an organic solvent (mostly methanol), followed by clean-up using filtration, centrifugation, or solid-phase extraction (SPE). Instrumental analysis is usually carried out using LC-MS with an electrospray ionization (ESI) source, operated in negative ion mode. [The Working Group noted that the LC-MS methods reported for the analysis of PFOA and PFOS in air had low instrumental LODs and were appropriate for trace level detection of these chemicals in air samples.]

EPA-OTM-45 is a standardized method that can be used to measure air emissions of PFOA and PFOS from stationary emission sources. In this method, a sampling train of glass fibre or quartz filter is applied, followed by a packed column of adsorbent material to collect both gaseous-phase and particulate-bound target analytes. The samples are then extracted with methanol/5% ammonium hydroxide, cleaned-up and concentrated using SPE and quantified using LC-MS/MS. The method detection limits (MDLs) for PFOA and PFOS were 0.43 ng/m^3 and 0.35 ng/m^3, respectively (US EPA, 2021).

[The Working Group noted that most of these methods have been developed for environmental measurements, and there has been no validated method using personal samplers developed for occupational exposure measurements.]

1.3.2 Water

Several methods have been developed to measure PFOA and PFOS concentrations in water. Some selected methods are summarized in Table 1.5.

The US EPA Methods 537.1 (published in 2009) and 533 (published in 2019) describe methods to analyse PFOA and PFOS in drinking-water (US EPA, 2019; Shoemaker and Tettenhorst, 2020). Water samples are fortified with surrogate standards and passed through a solid-phase sorbent cartridge to extract the PFAS and surrogates. The extract is concentrated, and isotopically labelled performance standards are added. Extracts are analysed by LC-MS/MS. LODs were reported as 0.53 and 1.1 ng/L for PFOA and PFOS, respectively. Interlaboratory comparisons have reported coefficients of variation (CVs) between laboratories of 23% for PFOA and 33–40% for PFOS isomers (van der Veen et al., 2023). An earlier interlaboratory comparison reported substantially higher CVs: 118% for PFOA and 95% for PFOS in water samples (van Leeuwen et al., 2006).

The US EPA has also validated SW-846 Method 8327 using external standard calibration and LC-MS/MS for the analysis of PFOA and PFOS (and other PFAS) in surface water, groundwater, and wastewater effluent (US EPA, 2023c).

In 2023, a draft version was published of US EPA Method 1633, which had already been finalized for the aqueous matrices wastewater, surface water, and groundwater (US EPA 2023d).

Some examples of low detection limits reported for PFOA and PFOS detected via various methods were: PFOA, 0.3 ng/L in demineralized water and 0.5 ng/L in natural spring water (Janda et al., 2019); 0.10 ng/L (Song et al., 2023); PFOA, 0.1 ng/L, and PFOS, 0.5 ng/L (Chen et al., 2016); and PFOA, 0.01 ng/L, and PFOS, 0.01 ng/L (Zheng et al., 2023). [The Working Group noted that detection limits have changed as the methodology for sample processing and detection has improved over time. Differences in LODs might also be explained by the use of different methods to derive these LODs.]

1.3.3 Soil, sediment, consumer products, and foods

Several analytical methods for the quantification of PFOA and PFOS in soil, sediment, dust, and consumer products have been reported. Because of the large variability in sample matrices, the analytical methods involved various extraction techniques, including solvent extraction, ultrasonic extraction, ion-pair

Table 1.5 Selected analytical methods for the measurement of PFOA and PFOS in water

Sample matrix	Sample preparation	Instrument	LOD	Reference
Drinking-water	Adsorb on polystyrene divinylbenzene; elute with methanol; reconstitute in water/methanol with ^{13}C-PFOA internal standards	HPLC-MS/MS	PFOA, 0.53 ng/L; PFOS, 1.1 ng/L	Shoemaker and Tettenhorst (2020) US EPA Method 537.1
Drinking-water	Adsorb on polystyrene divinylbenzene; elute with methanol containing ammonium hydroxide; reconstitute in water/methanol with ^{13}C-PFOA internal standards	HPLC-MS/MS	PFOA, 3.4 ng/L; PFOS, 4.4 ng/L	US EPA (2019) US EPA Method 533
Reagent water, surfacewater, groundwater, and wastewater effluent	Uses US EPA Method 3512 – dilute and filter; does not use SPE or carbon clean-up steps, which is a significant difference from the other US EPA methods	LC-MS/MS	PFOA, 10 ng/L; PFOS, 10 ng/L (LOQ)	US EPA (2023c) US EPA Method 8327
Drinking-water, groundwater and surface water (fresh water and sea water)	No pretreatment; adsorb on WAX SPE cartridges, elute with methanol, evaporate with nitrogen gas	HPLC-MS/MS	PFOA, 10 ng/L; PFOS, 2.0 ng/L (LOQ)	ISO (2009) ISO Method 25101
Wastewater, surface water, groundwater, landfill leachate	Glass fibre filtration of total suspended solids; aqueous samples with ≤ 50 mg of suspended solids must not be filtered; aqueous sample: spiking with isotopically labelled standards, SPE, and carbon clean-up	HPLC-MS/MS	PFOA, 0.54 ng/L; PFOS, 0.63 ng/L	US EPA (2023d) US EPA Method 1633 (draft version as of November 2023, finalized for the aqueous matrices: wastewater, surface water, and groundwater)[a]
Non-filtered waters, e.g. drinking-water, natural water (fresh water and sea water) and wastewater	Adsorb on high-purity mixed-mode WAX sorbent; elute with methanol	LC-MS/MS	PFOA, 0.31 ng/L; PFOS, 0.29 ng/L	ISO (2019) ISO Method 21675; Jones and Harden (2022)
Drinking-water	Adsorb on WAX SPE cartridges, elute with 1% ammonium hydroxide in methanol; concentrate to dryness; reconstitute in methanol	LC-MS/MS	PFOA, 0.01 ng/L; PFOS, 0.01 ng/L	Zheng et al. (2023)

HPLC, high-performance liquid chromatography; ISO, International Organization for Standardization; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MS/MS, tandem mass spectrometry PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; SPE, solid-phase extraction; US EPA, United States Environmental Protection Agency; WAX, weak anion exchange.

[a] US EPA recommends the use of Method 1633, and it is currently the only PFAS method that has been validated in multiple laboratories for aqueous matrices that include wastewater, surface water, groundwater, and landfill leachate, as well as for soil, sediment, biosolids, and fish and shellfish tissue.

extraction and dispersive SPE. Sample clean-up methods also varied, from filtration after pH control, to SPE and QuEChERS ("quick, easy, cheap, effective, rugged, safe"). LC-MS-ESI was the method of choice for the analysis of PFOA and PFOS. A summary of these methods is provided in Table 1.6.

The standard test method ASTM D7968 can be used for the determination of PFOA and PFOS in soil samples. The method uses solvent extraction with methanol:water (50:50) under basic conditions, followed by filtration, acidification, and then LC-MS/MS analysis. The MDLs were 6.2 and 18.8 ng/kg for PFOA and PFOS, respectively (ASTM International, 2017).

The United States Food and Drug Administration (US FDA) published a validated method C-010.02 for the analysis of 16 PFAS chemicals, including PFOA and PFOS, in various food items. Target PFAS are extracted from the food samples using acetonitrile and formic acid. After extraction, a modified QuEChERS technique is performed for clean-up, and further SPE is required for clean-up of complex samples. The cleaned extracts are then analysed using LC-MS/MS, with MDLs of 12–24 ng/kg for PFOA and 7–28 ng/kg for PFOS, in the different food items tested (US FDA, 2021b).

1.3.4 Human biospecimens

In early studies on exposed workers, total serum fluorine was used as a surrogate variable for PFOA exposure (e.g. Gilliland and Mandel, 1996). [The Working Group noted that using a total fluorine approach as a surrogate for PFOA is not an accurate quantification method for an individual analyte.] In 2001, LC-MS/MS was used for the first time for the analysis of PFOA and PFOS in biological samples (Hansen et al., 2001). At present, mainly targeted methods are used for the analysis of PFOA and PFOS in whole blood, serum, and plasma. Non-targeted mass spectrometry-based methods, lacking the ability to quantify concentrations, are also used (e.g. Chang et al., 2023). [However, these methods provide semiquantitative intensity levels that allow ranking of participants within a study.] A selection of methods for the analysis of PFOA and PFOS in human biospecimens is shown in Table 1.7. The usual sample preparation step before extraction is protein precipitation (for example, with acetonitrile). An aliquot of the supernatant is analysed using LC-MS/MS. Isotopically labelled internal standards may be used. Typical instrumental LODs are < 0.1 ng/mL for PFOA and PFOS, although higher values were reported in earlier publications (e.g. 10 ng/mL for PFOA; Sottani and Minoia, 2002), and lower values in more recent ones (e.g. 0.023 ng/mL for PFOA and 0.033 ng/mL for PFOS; Gao et al., 2018).

A method for determination of PFOA and PFOS (and other PFAS) in human serum, plasma, and whole blood described the use of methanol for protein precipitation and online SPE-LC-MS/MS. LODs for PFOA in serum, plasma, and whole blood were 0.018, 0.009, and 0.045 ng/mL, respectively, whereas the corresponding LODs for PFOS were 0.009 ng/mL for all three matrices (Poothong et al., 2017).

Earlier interlaboratory comparisons indicated quite large CVs, for example, 51% and 20% for PFOA and 24% and 32% for PFOS, in plasma samples (van Leeuwen et al., 2006; Longnecker et al., 2008). More recently, one interlaboratory comparison reported CVs ranging from 9% for PFOA and from 9% to 38% for PFOS isomers (van der Veen et al., 2023). An interlaboratory comparison and training exercise carried out for four rounds, involving 21 laboratories across Europe, included several PFAS (Nübler et al., 2022). For PFOA, the relative standard deviation improved from 12% to 6% from the second to the fourth round, and the relative standard deviation for PFOS was 11–12% in both rounds. [The study by van Leeuwen et al. (2006) was nearly 20 years old and involved the use of different extraction

Table 1.6 Selected analytical methods for the measurement of PFOA and PFOS in soil, sediment, dust, consumer products, and foods

Sample matrix	Sample preparation	Instrument (LOD)[a]	Reference
Soil	Solvent extraction with methanol:water (50:50) under basic conditions (pH ~9–10, adjusted with ~20 µL NH_4OH), followed by filtration, and acidification (pH ~3–4, adjusted with ~50 µL acetic acid)	HPLC-MS/MS (PFOA, 6.2 ng/g; PFOS, 18.8 ng/g)	ASTM International (2017)
Soil, sediment, and sludge (PFOA)	Solvent extraction with acetonitrile/0.2 M NaOH	HPLC-MS/MS (PFOA, 1 ng/g)	Powley et al. (2005)
Soil (PFOA)	Ultrasonic extraction with acetonitrile/water mixture	HPLC-MS/MS (PFOA, 180 fg on column)	Washington et al. (2008)
Soil and biosolids	Ultrasonic extraction with methanol containing 1% NH_4OH	HPLC-MS/MS (0.02–0.5 ng/g)	Sepulvado et al. (2011)
Soil and riverine sediment	Ion pair extraction with 0.5 M TBAS and 0.25 M sodium carbonate buffer (pH 10)	HPLC-MS/MS (soil: PFOA, 0.34 ng/g; PFOS, 0.32 ng/g; sediment: PFOA, 0.30 ng/g)	Lorenzo et al. (2015)
Sediment and sludge	Ultrasonic extraction with methanol and 1% acetic acid	HPLC-MS/MS (sediment: PFOA, 0.01 ng/g; PFOS, 0.1 ng/g; sludge: PFOA, 1.0 ng/g; PFOS, 0.9 ng/g)	Higgins et al. (2005)
Marine sediment	Ultrasonic extraction with methanol	HPLC-MS/MS (PFOA, 0.01 ng/g; PFOS, 0.05 ng/g)	Wang et al. (2018b)
Lake sediment	Solvent extraction with acetonitrile/0.2 M NaOH	HPLC-MS/MS (PFOA, 0.02 ng/g; PFOS, 0.05 ng/g)	Guo et al. (2016)
Marine plastic litter	Ultrasonic extraction with hexane	HPLC-MS/MS (PFOA, 0.03 ng/g; PFOS, 0.01 ng/g)	Gómez et al. (2021)
Sewage sludge	Ion pair extraction with 0.5 M TBAS and 0.25 M sodium carbonate buffer (pH 10)	HPLC-MS/MS (PFOA, 0.6 ng/g; PFOS, 5 ng/g)	Zhang et al. (2010)
Asphalt	Ultrasonic extraction with methanol and 1% NH_4OH	HPLC-MS/MS (PFOA, 0.6 ng/g; PFOS, 0.7 ng/g)	Srivastava et al. (2022)
Indoor dust	Ultrasonic extraction with acetonitrile	HPLC-MS/MS (PFOA, 2.3 ng/g; PFOS, 4.6 ng/g)	Kubwabo et al. (2005)
Indoor dust	Solvent extraction with methanol followed by filtration	Online SPE-HPLC-TOF/MS (PFOA, 0.03 ng/g; PFOS, 0.01 ng/g)	Padilla-Sánchez and Haug (2016)
Home garden produce (e.g. tomato, pepper, apples)	Dispersive SPE using magnesium sulfate and acetonitrile with 1% NH_4OH	HPLC-MS/MS (PFOA, 0.03 ng/g; PFOS, 0.01 ng/g)	Scher et al. (2018)
Food (various items)	Solvent extraction with acetonitrile plus formic acid, followed by QuEChERS clean-up; further SPE clean-up on WAX sorbent cartridges is required for complex food matrices	HPLC-MS/MS (PFOA, 0.012–0.024 ng/g; PFOS, 0.007–0.028 ng/g)	US FDA (2021b) (Validated US FDA method number C-010.02)
Food (various items)	Ultrasonic extraction with acetonitrile plus NaOH, followed by clean-up on WAX sorbent cartridges	NanoLC – Orbitrap MS (PFOA, 0.001–0.3 ng/g; PFOS, 0.001–0.3 ng/g)	Zacs et al. (2023)

Table 1.6 (continued)

Sample matrix	Sample preparation	Instrument (LOD)[a]	Reference
Microwave paper packaging	FUSLE with ethanol	HPLC-QTOF/MS (PFOA, 1.53 ng/g; PFOS, 0.63 ng/g)	Monge Brenes et al. (2019)
Consumer products (papers and textiles)	Solvent extraction with methanol	HPLC-MS/MS (papers: PFOA, 0.040 μg/m^2, PFOS, 0.038 μg/m^2; textiles: PFOA, 0.12 μg/m^2; PFOS, 0.15 μg/m^2)	Robel et al. (2017)
Consumer products (e.g. waterproofing agents, textiles, paints, cookware, waterproofing agents, firefighting foams, electronics)	Ultrasonic extraction with methanol	HPLC-QTOF/MS (NR)	Herzke et al. (2012)
Consumer products (e.g. textiles (outdoor materials), carpets, cleaning and impregnating agents, leather samples, baking and sandwich papers, paper baking forms and ski waxes)	Depending on the matrix procedures using ion pair extraction, acidic–alkaline sequential extraction or SPE with WAX were applied	HPLC-MS/MS (0.1–0.5 ng/g)	Kotthoff et al. (2015)

FUSLE, focused ultrasonic liquid extraction; HPLC, high-performance liquid chromatography; LOD, limit of detection; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NaOH, sodium hydroxide; NH_4OH, ammonium hydroxide; NR, not reported; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; QTOF, quadrupole time-of-flight; QuEChERS, Quick, Easy, Cheap, Effective, Rugged, and Safe; SPE, solid-phase extraction; TBAS, tetrabutylammonium hydrogen sulfate; TOF, time-of-flight; WAX, weak anion exchange.
[a] Using electrospray ionization (ESI) in negative ion mode.

and instrumental techniques, which led to the large variation and high z-scores.]

Reported serum-to-plasma ratios for PFOA and PFOS were approximately 1:1, whereas serum- or plasma-to-whole blood ratios were approximately 2:1 (Ehresman et al., 2007; Poothong et al., 2017). In the past, total PFOS was normally presented, but in more recent publications PFOS isomers have been distinguished, separating linear and the sum of branched forms; LODs in serum have also improved (e.g. Li et al., 2022c) (see Table 1.7). The method reported by Li et al. (2022c) can be applied for the analysis of PFOA and PFOS in urine; the resulting LODs were 0.01 ng/mL for PFOA and 0.01–0.02 ng/mL for PFOS isomers (Li et al., 2022c).

Similar methods are used for breast milk or colostrum. Existing methods for sample preparation and analysis of PFAS concentrations in human breast milk were reviewed by Macheka-Tendenguwo et al. (2018). SPE is more popular, owing to higher recovery, shorter analysis times, simpler procedures, and less use of solvents (e.g. Kärrman et al., 2007; Abdallah et al., 2020) than in other techniques, such as liquid–liquid extraction (LLE). The LOQ for each PFAS in colostrum and breast milk has been reported as 0.01 ng/mL. In two replication sets with in-house controls (n = 6 each), relative standard deviations were 28% and 11.1% for PFOA, and 20.2% and 8.8% for PFOS, respectively (Blomberg et al., 2023).

Table 1.7 Selected analytical methods for the measurement of PFOA and PFOS in human biospecimens

Sample matrix	Sample preparation	Instrument (LOD)	Comments	Reference
Whole blood	Adding of labelled internal standards; solvent extraction with acetonitrile; carbon–acetic acid, filtration; addition of performance standards $^{13}C_8$-PFOA and $^{13}C_8$-PFOS, with 2 mM ammonium acetate	HPLC-MS/MS (PFOA, 0.4–0.7 ng/mL; PFOS, 0.01–0.1 ng/mL)		Hardell et al. (2014)
Plasma and serum	Protein precipitation with acetonitrile; ^{13}C-labelled PFOA internal standards	LC-MS/MS (PFOA LOQ, 0.5 ng/mL)	Validated to meet US FDA guidelines for bioanalytical methods	Flaherty et al. (2005)
Plasma	Labelled internal standards; protein precipitation with acetonitrile; shaking, centrifugation	LC-MS/MS (PFOA, 0.4 ng/mL; PFOS, 0.5 ng/mL)		Li et al. (2018)
Plasma	Protein precipitation with acetonitrile; reconstitution in MeOH; filtration	HPLC-ESI-MS/MS (PFOA LOQ, 0.5 ng/mL; PFOS LOQ, 0.1 ng/mL)		Tsai et al. (2020)
Plasma	Addition of ^{13}C-labelled PFAS compounds; addition of acetonitrile to precipitate proteins; vortex mixing, centrifugation	LC-HRMS (PFOA, 0.01 µg/L; PFOS, 0.43 µg/L)		Goodrich et al. (2022)
Plasma, serum, and whole blood	Protein precipitation with MeOH, mixing, centrifugation	HPLC-MS/MS (PFOS, 0.009 ng/mL; PFOA, 0.009 ng/mL plasma; 0.018 ng/mL serum; 0.045 ng/mL whole blood)	Validated for human plasma, serum, and whole blood	Poothong et al. (2017)
Serum	Sample with internal standard and TBAS solution mixed; MTBE added and shaken; centrifugation; separation ×2; reconstitution in MeOH; vortex mixing; filtration	HPLC-MS/MS (PFOA, 1.0 ng/mL; PFOS, 1.7 ng/mL)		Hansen et al. (2001)
Serum	Ion-pair extraction	HPLC-MS/MS (PFOA, 10 ng/mL)		Sottani and Minoia (2002)
Serum	Proteins precipitated with formic acid; SPE clean-up	HPLC-MS/MS (PFOA, 0.2 ng/mL; PFOS, 0.2 ng/mL)		Kuklenyik et al. (2005)
Serum	Acidification with HCl, addition of hexanoic acid and THF; vortex-shaking, centrifugation	LC/QQQ MS/MS (2–20 pg/mL)		Luque et al. (2012)
Serum	Dilution with ultrapure water and isotope internal standards in MeOH, centrifugation	HPLC-MS/MS (PFOA, 0.023 ng/mL; PFOS, 0.033 ng/mL)		Gao et al. (2018)
Serum	Alkaline digestion followed by two-stage SPE purification using polymeric HLB and graphitized non-porous carbon cartridges	LC-MS/MS (NR)	Fully validated (2002/657/CE decision) and accredited (ISO 17025 standard)	Mancini et al. (2020)

Table 1.7 (continued)

Sample matrix	Sample preparation	Instrument (LOD)	Comments	Reference
Serum	Precipitation using acetonitrile by vigorous shaking; all sample batches include chemical blanks and three quality control samples	LC-MS/MS (PFOA, 0.09 ng/mL; *n*-PFOS, 0.2 ng/mL; 3/4/5m-PFOS, 0.01 ng/mL)		Li et al. (2022c)
Breast milk, serum	Proteins precipitated with formic acid; SPE clean-up	HPLC-MS/MS (PFOA, 0.2 ng/mL milk; 0.1 ng/mL serum; PFOS, 0.3 ng/mL milk; 0.4 ng/mL serum)		Kuklenyik et al. (2004)
Breast milk	LLE; purification by two successive SPE; reconstitution in fluorometholone solution as external standard in MeOH/water	LC-HRMS (PFOA, 0.003 ng/mL; PFOS, 0.002 ng/mL)		Kadar et al. (2011)
Breast milk	LLE with acetonitrile; purification by dispersive SPE using C18 sorbent; shaking and centrifugation; reconstitution in MeOH; filtration	HPLC-MS/MS (PFOA LOQ, 0.006 ng/mL; *n*-PFOS LOQ, 0.005 ng/mL; br-PFOS LOQ, 0.010 ng/mL)		Lankova et al. (2013)
Semen, serum	Samples were spiked with mass-labelled extraction standard, TBAS solution, $NaHCO_3/Na_2CO_3$ buffer solution and MTBE; shaking; extraction ×2 with MTBE; all three extracts combined, evaporated to dryness under nitrogen at 40 °C, and reconstituted with MeOH	HPLC-MS/MS (PFOA LOQ, 0.004–0.010 ng/mL semen; 0.020 ng/mL serum; PFOS LOQ, 0.004–0.010 ng/mL semen; 0.020 ng/mL serum)		Pan et al. (2019)
Urine and serum	For urine, add isotope-labelled internal standard and ammonium acetate buffer including β-glucuronidase, and subsequently formic acid; for serum, isotope-labelled internal standard was added, and formic acid; samples vortexed	SPE-HPLC-MS/MS (PFOA, 0.1 ng/mL; PFOS, 0.1 ng/mL)		Kato et al. (2018)
Urine	Precipitation using acetonitrile by vigorous shaking for 30 min; all sample batches include chemical blanks and three quality control samples	LC-MS/MS (PFOA, 0.01 ng/mL; *n*-PFOS; 0.01 mL; 3/4/5m-PFOS, 0.02 ng/mL)		Li et al. (2022c)
Hair, nail, urine, serum	For hair and nails: soaking in water, washing twice with acetone, air-drying, grinding to powder, extraction by various organic solvents, cleaning by WAX cartridge, elution with 9% NH_4OH in MeOH, concentration to dryness under nitrogen gas and reconstitution in water/MeOH (v/v; 1/1), filtration	HPLC-MS/MS (PFOA, 0.03 ng/g hair; 0.04 ng/g nail; 0.02 ng/mL serum; 1.07 ng/L urine; PFOS, 0.03 ng/g hair; 0.05 ng/g nail; 0.02 ng/mL serum; 2.09 ng/L urine)		Wang et al. (2018a)

Table 1.7 (continued)

Sample matrix	Sample preparation	Instrument (LOD)	Comments	Reference
Dried blood spots	Punch samples desorbed in ultrapure water, sonicated, and extracted into MTBE with labelled internal standards; dried then reconstituted in MeOH	HPLC-ESI-MS/MS (PFOA, 0.4 ng/mL; PFOS, 0.2 ng/mL)	LODs expressed in units of whole blood equivalents	Spliethoff et al. (2008)
Dried blood spots	Punch samples desorbed into MeOH with labelled internal standards; mixed, sonicated, centrifuged	SPE-HPLC-MS/MS (PFOA, 0.0075 ng/mL; PFOS, 0.03 ng/mL)		Poothong et al. (2019)
Placental tissue	Shaking with MeOH and MPFOA for 5 min, freeze-drying, homogenized with acetonitrile, centrifuged	HPLC-MS/MS (PFOA, 0.03 ng/g; PFOS, 0.03 ng/g)	Linearity, selectivity, accuracy (trueness and precision) and sensitivity validated according to US FDA guidelines	Martín et al. (2016)

br-, branched chain; C18, octadecyl alkyl substituent; ESI, electrospray ionization; HCl, hydrochloric acid; HLB, hydrophilic–lipophilic-balanced; HPLC, high-performance liquid chromatography; ISO, International Organization for Standardization; LC-HRMS, liquid chromatography-high-resolution mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC/QQQ-MS/MS, liquid chromatography/triple quadrupole-tandem mass spectrometry; LOD, limit of detection; LOQ, limit of quantification; LLE, liquid–liquid extraction; MeOH, methanol; min; minute(s); MPFOA, perfluoro-*n*-[1,2,3,4-$^{13}C_4$]octanoic acid; MS/MS, tandem mass spectrometry; MTBE, methyl *tert*-butyl ether; $NaHCO_3$/Na_2CO_3, sodium bicarbonate/sodium carbonate; NH_4OH, ammonium hydroxide; NR, not reported; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; *n*-PFOS, linear perfluorooctanesulfonic acid; 3/4/5m-PFOS, corresponds to the sum of branched isomers 3m-PFOS, 4m-PFOS, and 5m-PFOS; SPE, solid-phase extraction; TBAS, tetra-*n*-butylammonium hydrogen sulfate; THF, tetrahydrofuran; US FDA, United States Food and Drug Administration; v/v, volume per volume; WAX, weak anion exchange.

Thomsen et al. (2010) reported a different method, with internal standards and acetonitrile added, followed by mixing and centrifugation. After the addition of formic acid, the supernatant is analysed by online column-switching LC-MS/MS.

Dried blood spots have been used to assess PFOA and PFOS exposure (Spliethoff et al., 2008). Detection limits as low as 0.0075 ng/mL for PFOA and 0.030 ng/mL for PFOS, estimated for the corresponding serum concentrations, have been reported.

PFOA and PFOS concentrations have also been measured in placental tissue (Martín et al., 2016), hair, and nails (Wang et al., 2018a).

1.4 Occurrence and exposure

Introduction to occurrence and exposure

(a) Life cycle and practices involved in end-of-life and disposal

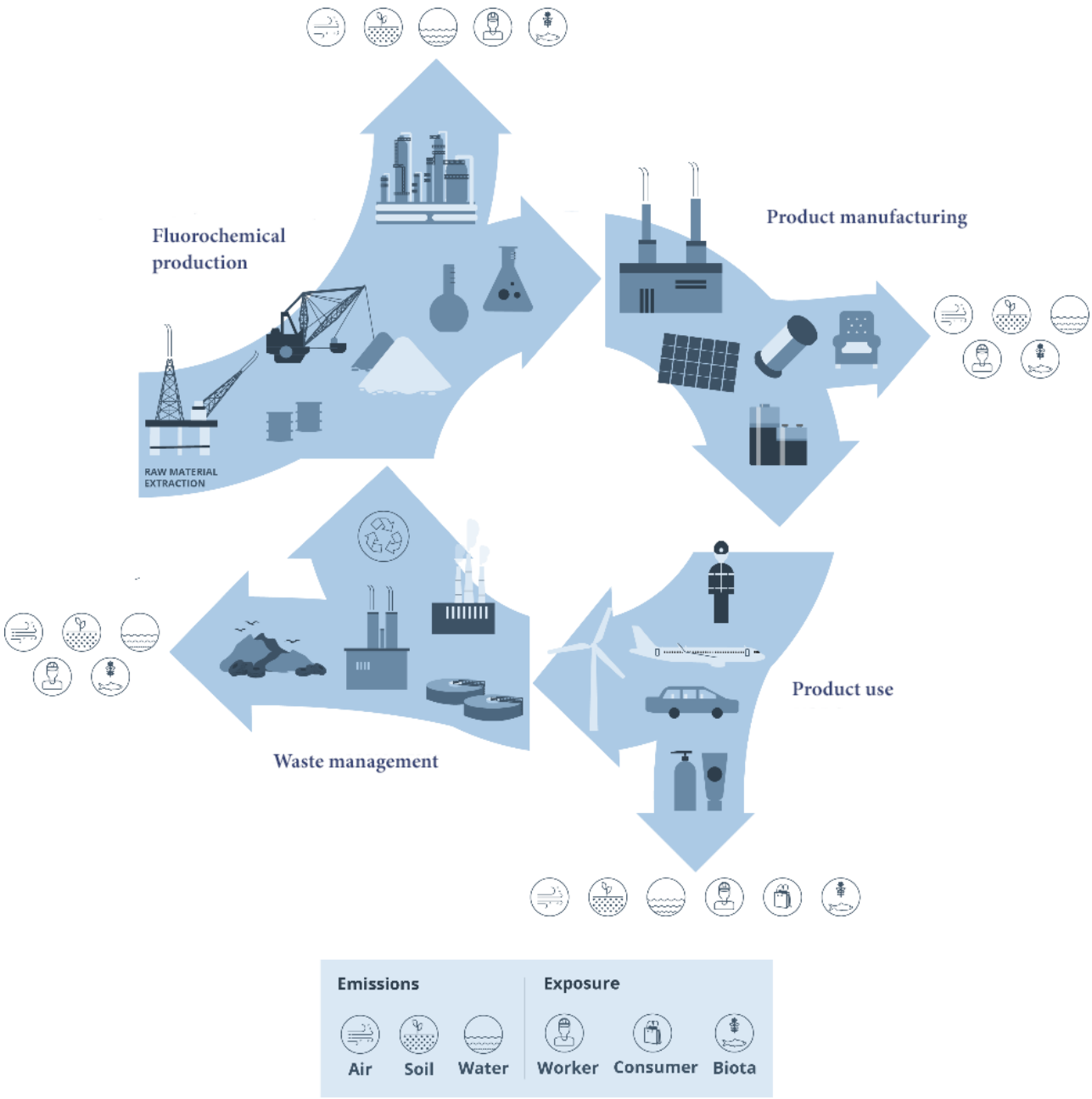
The occurrence of PFOA and PFOS in the environment is influenced by the chemical life cycle, including during fluorochemical production; secondary manufacturing processes (e.g. products containing fluorochemicals or processes using fluorochemicals); product use; and management of waste (industrial waste, products containing PFOA and PFOS, and materials contaminated with PFOA or PFOS) (see Fig. 1.3). The presence of PFOA and PFOS in consumer and industrial products, as well as environmental media subject to remediation, creates avenues for inadvertent, repeated cycles of contamination (Stoiber et al., 2020).

The available approaches to managing large quantities of PFAS wastes include landfilling, incineration, and wastewater treatment (US EPA, 2020). Landfills have been used historically for disposal at perfluorochemical facilities (ATSDR, 2021). The presence of PFAS in leachate from landfills has been documented in several countries, including Australia, China, Germany, and the USA (Stoiber et al., 2020). Incineration of products containing PFOA or PFOS generally requires temperatures of > 800 °C, using a scrubber to remove hydrogen fluoride. Although limited, experimental studies have indicated that incineration can break down PFOA and PFOS (Stoiber et al., 2020; ATSDR, 2021). Liquid wastes are treated with precipitation, decanting, or filtering to separate solids, followed by landfill or incineration of the solids and discharge of the liquids to a wastewater treatment facility (ATSDR, 2021). The US EPA interim guidance also lists underground injection as a possible means of disposal (US EPA, 2020).

In some settings, PFOA- or PFOS-contaminated waste products, including food wastes and sludge from municipal wastewater treatment, have been dispersed over land, for example, by land application of biosolids or composts (Kenny, 2021; ITRC, 2022a). Land application of these products may contribute to the contamination of crops and livestock and the continued cycle of contamination (Stoiber et al., 2020; Kenny, 2021).

[The Working Group acknowledged that in geographical regions with restrictions and phase-out of PFOA and PFOS production and use (e.g. Europe and the USA), trends towards decreases in PFOA and PFOS concentrations in human biospecimens (mainly in serum) have been observed (see Section 1.4.3); however, no clear patterns of declining trends have been observed for abiotic and environmental samples from the same regions. Decreasing concentrations in humans may be influenced by the removal of certain PFAS from consumer products and associated reductions in direct exposure (Land et al., 2018). Persistent levels in the environment may reflect the re-circulation of historically manufactured and released PFOA and PFOS and potentially the breakdown of their precursors.]

Fig. 1.3 Life cycle of PFOA and PFOS



PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.
Adapted from European Environment Agency (2021).

(b) Persistence and mobility

The carbon–fluorine bond is one of the strongest bonds known in nature and makes PFAS extremely resistant to degradation in the natural environment. PFOA and PFOS are among the most environmentally persistent organic chemicals and are, therefore, under the Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) definition for persistence, classified as "very persistent (vP)" (Cousins et al., 2020).

Unlike other known persistent organic pollutants, PFOA and PFOS are highly mobile in the environment. They are quite soluble in water, and thus can be carried to remote regions through oceanic currents and long-range atmospheric currents. They can also vertically infiltrate sediment layers and move across the water column (ECHA, 2023).

(c) Global and temporal trends

PFOA and PFOS have been detected in environmental media worldwide, including in remote areas like the Arctic, Antarctic, and Mount Everest (Cai et al., 2012; ATSDR, 2021; Miner et al., 2021; Garnett et al., 2022). Estimations of total global annual emissions of PFOA-based products show that emissions steadily increased from 1960 to 2002 and quickly decreased from 2002 to 2012, followed by an increase from 2012 to 2015. The same trend was observed for PFOS-based products (OECD, 2015a). The estimated oceanic transport of PFOA to the Arctic for the period 1951–2004 was greater than the estimated atmospheric transport (Prevedouros et al., 2006). The deposition into soil from the atmosphere and subsequent transport pathways, such as leaching, also contribute to the widespread distribution of these substances in the environment (ATSDR, 2021). Retention by soil is expected to be low (Prevedouros et al., 2006). In the environment, most PFOA and PFOS are estimated to be in ocean water, and smaller amounts are present in freshwater and sediments. The presence of PFOA and PFOS in groundwater is widespread (Johnson et al., 2022).

The presence of PFOA and PFOS in snow and ice core samples indicates their atmospheric deposition from production and/or use (see Section 1.4(c)(i) below). Likewise, sediment cores reflect time trends corresponding to initial production and subsequent changes in patterns of production and use (Section 1.4(c)(ii)).

(i) Snow and ice cores

In a snow core from the Mount Muztagata glacier (western Tibet, China) showed a steady increase in PFOA and PFOS from 1983 to 1999. A more recent (1996–2007) core from Mount Zuoqiupo glacier (south-eastern Tibet) contained lower concentrations of PFOA and PFOS, with no clear trend. Differences in concentrations were attributed to different upwind sources affecting the respective study sites (e.g. sources in Europe or central Asia for Mount Muztagata and sources in India for Mount Zuoqiupu) (Wang et al., 2014).

In glacial ice cores from Svalbard, Norway, representing deposition from 1990 to 2005, higher concentrations of PFOA and PFOS were detected in the layers representing 1997–2000, the period that coincides with the peak production of these compounds (Kwok et al., 2013).

In the eastern Antarctic, a firn core representing the period from 1958 to 2017, showed PFOA levels peaking in 1997–2000. Subsequently there was a short decline, then an increase from 2003 to 2013 with no sign of a decrease, despite recent global restrictions on PFOA production and use (Garnett et al., 2022). [The Working Group noted this may be attributed to increasing production of fluorochemicals in emerging Asian economies, which probably offsets emission reduction in North America and Europe, and may account for the higher concentrations observed in the later years represented in the firn core. PFOS was not detected in any of the studied samples.]

(ii) Sediment cores

In a sediment core containing deposits from the 1950s to 2004, in Tokyo Bay, Japan, concentrations of PFOA increased consistently from 1994 to 2004, which is generally consistent with the PFOA production and usage profile during this period in Japan (Zushi et al., 2010). PFOS concentrations decreased gradually after the early 1990s, whereas concentrations of some PFOS precursors decreased rapidly in the late 1990s. This trend could reflect the shift in PFOS industrial production processes after the phase-out of POSF-based products in 2001 (Zushi et al., 2010). Another study on three sediment cores from Lake Ontario, Canada, (1952–2005) reported a marked increase in PFOA and PFOS concentrations from the mid-1970s to 2005, which is generally in line with PFOA and PFOS production and usage profiles (Yeung et al., 2013). In a sediment core from the Bering Sea, covering almost 70 years of deposition, PFOS concentrations generally showed an upward trend since 1952 and peaked in about 2003, after which concentrations dropped to a lower level until 2015. This largely coincides with the production and usage history of PFOS. Conversely, PFOA concentrations showed a more fluctuating pattern among layers, which was explained by its vertical mobility in pore water (Lin et al., 2020a). [The Working Group noted that although the temporal trends in PFOS concentrations in dated sediment cores reflect PFOS production and usage history, temporal trends in PFOA concentrations can be influenced by its vertical mobility in pore water and thus may not adequately reflect changes in its production and use in certain geographical areas.]

(d) Precursor compounds

In the present monograph, "precursor compounds" refers to PFAS that are known to break down or transform into PFOA or PFOS in the environment or biota, including humans. Precursors include, but are not limited to, fluorotelomer alcohols (FTOH) and polyfluoroalkyl phosphate diesters (diPAP) for PFOA; and perfluorooctane sulfonamides (e.g. *N*-EtFOSA), perfluorooctane sulfonamidoacetic acids (e.g. *N*-EtFOSAA) and perfluorooctane sulfonamidoethanols (e.g. *N*-EtFOSE) for PFOS (Gebbink et al., 2015). While estimates vary by exposure scenario, it has been estimated that a substantial proportion of the body burden of PFOA and PFOS may originate from intake of precursors (Vestergren et al., 2008; Gebbink et al., 2015) (see also Section 4.1). While direct exposure to PFOA and PFOS may decline as a result of regulation or voluntary efforts, production and use of precursors may contribute to ongoing exposure from the breakdown of precursors. Breakdown of precursors has also resulted in PFOA and PFOS contamination in remote areas with no direct sources of pollution (ATSDR, 2021).

1.4.1 Environmental occurrence

(a) Air and dust

The atmospheric environment is not only an important compartment for the transport of PFOA and PFOS, but it is also an exposure pathway for PFOA and PFOS (Liu et al., 2018a). Air is a mixture of particles, gases, and dust. The sources and levels of PFOA and PFOS in outdoor and indoor air differ, and the characteristics of PFOA and PFOS are described here for outdoor air, indoor air, and settled dust separately.

(i) Outdoor air

The sources of PFOA and PFOS in outdoor air include direct emissions from the fluorochemical industry and products containing fluorochemicals (Butt et al., 2010), long-range transport via the gas phase, and degradation of PFAS precursors (McMurdo et al., 2008). Sampling time and location varied among multiple studies; representative concentrations are presented in Table 1.8.

Table 1.8 Occurrence of PFOA and PFOS in outdoor air

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Camoiras González et al. (2021)	15 countries in Africa[a], 2017–2019	118, meteorological station, PAS, 3 mo/sample, 2 yr	LC-MS/MS, (LOQ: PFOA, 13 pg/PUF disc; PFOS, 12 pg/PUF disc)	207 (< 13–1190)	148	185 (< 12–2480)	97.7	pg/PUF disc	Long sampling time. Good reflection of PFAS levels in Africa.
	7 countries in Asia[b], 2017–2019	46, meteorological station, PAS, 3 mo/sample, 2 yr		271 (83.1–965)	183	139 (27.3–634)	101		Long sampling time. Good reflection of PFAS levels in Asia.
	10 countries in Group of Latin America and Caribbean[c], 2017–2019	101, meteorological station, PAS, 3 mo/sample, 2 yr		257 (58.9–655)	233	376 (< 12–2260)	192		Long sampling time. Good reflection of PFAS levels in Group of Latin America and Caribbean countries.
	9 countries in Pacific Islands subregion[d], 2017– 2019	43, meteorological station, PAS, 3 mo/sample, 2 yr		181 (< 13–417)	165	297 (< 12–827)	266		Long sampling time. Good reflection of PFAS levels in Pacific Islands subregion.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Chaemfa et al. (2010)	UK, July to October 2007	15, background and city centre area, PAS, 2–3 mo/sample	LC-TOF-MS (LOD: PFOA, 27 pg/sample; PFOS, 3.9 pg/sample)	[2657 (< 27–27 000)]	[400]	[53.5 (< 3.9–720)]	[6.5]	pg/sample per day	Long sampling time. Good reflection of PFAS levels in north-western England.
	UK–Norway, June to October 2006	11, background and semi-rural/ rural area, PAS, 2–3 mo/sample		[139 (< 27–1200)]	[< 27]	[3.0 (< 3.9–7.7)]	[< 3.9]		Long sampling time. Good reflection of PFAS levels in UK–Norway transect.
	Europe, June to November 2006	23, ranged from background to city centre area, PAS, 2–3 mo/sample		[117 (< 27–540.0)]	[< 27]	[10 (< 3.9–69.0)]	[< 3.9]		Long sampling time. Good reflection of PFAS levels in Europe.
Dreyer et al. (2015)	Geesthacht, Germany, December 2007 to May 2008	11, semirural, AAS, 14–21 days/sample, 2 sample/mo	HPLC-MS/MS, (LOQ: PFOA, 10 pg/sample; PFOS, 10 pg/sample)	0.7 (0.1–4.8)	NR	0.65 (0.2–3.5)	NR	pg/m^3	Sampling time in each month was relatively limited. Partially reflects PFAS levels in semirural area.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Guo et al. (2018)	Shanghai, China, December 2013 to January 2015	18, urban area (reflects long-range transported PFAS from northern or eastern continental China and surrounding seas), AAS, 24 h/sample, 28.3 L/min	HPLC-MS/MS, (LOD: PFOA, 0.35 pg/L; PFOS, 1.30 pg/L)	145.6	101.0 (71.3–230.0)	24.2	24.1 (14.2–29.0)	pg/m^3	Sampling time collected in every month was limited. Partially reflects PFAS levels in urban area in winter.
Lin et al. (2020a)	Xiamen, China, December 2016 to September 2018	13, eastern coastal China and commercial/residential area, AAS, 2–3 days/sample, 0–1 sample/mo, 20 L/min	LC-MS/MS (minimum MQL: PFOA, 0.089 pg/m^3 ; PFOS, 0.174 pg/m^3)	[3.21] (0.211–7.47)	[0.72]	[2.79] (< 0.315–15.7)	[1.50]	pg/m^3	Sampling time in each month was relatively limited. Partially reflects PFAS levels in commercial/residential area in Xiamen.
	Delhi, India, December 2017 to May 2018	2, commercial and residential area, AAS, 2–3 days/sample, 0–1 sample/mo, 20 L/min		[0.42] (< 0.367–1.07)	[0.38]	[0.63] (ND to 1.33)	[0.61]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in commercial/residential area in Delhi.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Lin et al. (2020a) (cont.)	Beijing, China, May 2017 to January 2018	7, rural (surrounded by forest; near some residents), AAS, 2–3 day/sample, 0–1 sample/month, 20 L/min		[0.68] (< 0.182–2.81)	[0.41]	[0.53] (< 0.350–1.16)	[0.41]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in rural area in Beijing.
	Yuxi, China, August 2016 to April 2017	7, rural (fewer residents and low traffic density), AAS, 5 days/sample, 0–1 sample/mo, 20 L/min		[0.12] (< 0.091–0.393)	[0.07]	[0.11] (ND to 0.209)	[0.09]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in rural area in Yuxi.
	Wenchuan, China, May 2017 to October 2017	3, rural (mountain areas), AAS, 2–3 days/sample, 0–1 sample/mo, 20 L/min		[0.70] (0.365–1.22)	[0.66]	[0.57] (ND to 1.37)	[0.47]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in mountain area in Wenchuan.
	Tsukuba, Japan, July to December 2017	5, rural (fewer residents and low traffic density), AAS, 4 days/sample, 0–1 sample/mo, 20 L/min		[0.51] (< 0.124–3.01)	[0.28]	[0.19] (< 0.24–0.709)	[0.14]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in rural Japan.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Lin et al. (2020a) (cont.)	Jinju, Republic of Korea, April 2017 to January 2018	6, rural (fewer residents and low traffic density), AAS, 3–4 days/sample, 0–1 sample/mo, 20 L/min		[1.47] (0.212–7.84)	[0.65]	[0.39] (ND to 1.16)	[0.38]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in rural Jinjiu.
	Nanjing, China, September 2017 to July 2018	7, urban (industrial area), AAS, 3–5 day/sample, 0–1 sample/mo, 20 L/min		[5.71] (0.695–26.8)	[2.73]	[2.10] (ND to 17.1)	[0.76]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in industrial area in Nanjing.
	Gujarat, India, December 2016 to November 2017	12, urban (western coastal India, residential area), AAS, 2–5 days/sample, 0–1 sample/mo, 20 L/min		[0.28] (ND to 2.06)	[0.17]	[0.37] (ND to 1.81)	[0.35]		Sampling time in each month was relatively limited. Partially reflects PFAS levels in residential area in Gujarat.
Lin et al. (2022)	Karachi, Pakistan, December 2012 to January 2013	18, urban (near industrial area and garbage dumping sites), AAS, 24 h/sample, 16.7 L/min	LC-MS/MS, (MQL: PFOA, 1.0 pg/m^3; PFOS, 0.2 pg/m^3)	2.01 (0.85–8.70)	1.6	1.69 (0.64–3.17)	1.55	pg/m^3	Sampling time was relatively long. Reflects PFAS levels in urban areas.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Liu et al. (2023)	Pearl River Delta, China, May to July and October to December 2018	186, urban, AAS, 24 h/sample, 100 /min in summer and 1.05 m^3/min in winter	HPLC-MS/MS (LOD: PFOA, 0.0025 ng/mL; PFOS, 0.0003–0.0016 ng/mL)	10.80 (1.02–56.53)	6.05 (3.71–13.04)	45.19 (3.90–378.06)	24.18 (11.94–44.18)	pg/m^3	Sampling time for each sample was limited, but sample sites were representative and sample size was large. Partially reflects PFAS levels in an urban area in the Pearl River Delta.
Seo et al. (2019)	Hyung-san River, Gyeongju and Pohang, Republic of Korea, September 2014	8, urban (near wastewater treatment plants), AAS, 18–24 h/sample, 700 L/min	LC-MS/MS (MDL: PFOA, 0.13 pg/m^3; PFOS, 0.13 pg/m^3)	48.66	43.09	90.52	99.03	pg/m^3	Total sampling time was long. Reflects PFAS levels near wastewater treatment plants in the Republic of Korea.
Wang et al. (2021)	Shandong, China, November 2017	12, urban (fluorochemical industry park), AAS, 20 h/sample, 800 L/min	LC-MS (LOD: PFOA, 0.06 pg/m^3; PFOS, 0.13 pg/m^3; LOQ: PFOA, 0.31 pg/m^3; PFOS, 0.31 pg/m^3	1610 (42.8–9730)	451	1.24 (< 0.31–2.74)	1.01	pg/m^3	Long total sampling time. Reflects PFAS levels at source.

Table 1.8 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow, and duration)	Analytical method (reporting limits)	PFOA		PFOS		Unit	Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)		
Yu et al. (2018)	Coastal areas of the Bohai Sea, China, May 2015 to April 2016	48, urban (large emission of PFAS, economic zones), AAS, 48 h/sample, 2 sample/mo, 300 L/min	HPLC-MS/MS (LOD: PFOA, 0.01 pg/m^3; PFOS, 0.02 pg/m^3; LOQ: PFOA, 0.05 pg/m^3; PFOS, 0.05 pg/m^3)	27.0 (0.1–362.9)	[26.2] [(15.0–34.8)]	[1.8] (< 0.05–11.1)	[1.4] [(1.0–2.1)]	pg/m^3	Sampling time in every month was relatively limited, but number of samples was large. Partially reflects PFAS levels in an urban area.
	Coastal areas of the Yellow Sea, China, May 2015 to April 2016	35, urban (large emission of PFAS, economic zones), AAS, 48 h/sample, 2 sample/month, 300 L/min		30.5 (0.6–524.8)	[18.3] [(13.3–46.1)]	[0.6] (< 0.05–8.6)	[0.8] [(0.5–0.9)]		Sampling time in each month was relatively limited, but number of samples was large. Partially reflects PFAS levels in an urban area.
Zhou et al. (2021)	North Carolina, USA, 2018–2019	60, suburban residential areas and on or near university campuses, AAS, 6 days/sample, 3 mo, 10.0 L/min	HPLC-MS/MS (LOD: PFOA, 0.0067 pg/m^3; PFOS, 0.0047 pg/m^3; MDL: PFOA, 2.86 pg/m^3; PFOS, 0.18 pg/m^3)	(< 0.005–14.06)	NR	(< 0.004–4.75)	NR	pg/m^3	Long sampling time. Good reflection of PFAS levels in North Carolina.

AAS, active air sampler; h, hour(s); HPLC, high-performance liquid chromatography; IQR, interquartile range; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MDL, method detection limit; min, minute(s); mo, month(s); MQL, method quantification limit; MS/MS, tandem mass spectrometry; ND, not detected; NR, not reported; PAS, passive air sampler; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PUF, polyurethane foam; TOF, time-of-flight; UK, United Kingdom; USA, United States of America.

[a] Including Democratic Republic of the Congo, Egypt, Ethiopia, Ghana, Kenya, Mali, Mauritius, Morocco, Nigeria, Senegal, Togo, Tunisia, Uganda, United Republic of Tanzania, Zambia.

[b] Including Cambodia, Indonesia, Lao People's Democratic Republic, Mongolia, Philippines, Thailand, Viet Nam.

[c] Including Antigua and Barbuda, Argentina, Barbados, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay.

[d] Including Fiji, Kiribati, Marshall Islands, Niue, Palau, Samoa, Solomon Islands, Tuvalu, Vanuatu.

In general, PFOA and PFOS levels differ according to the surroundings of the sampling sites. Air collected near fluorochemical industrial sites (Yu et al., 2018; Wang et al., 2021), wastewater treatment plants (Seo et al., 2019), and in industrial areas (Lin et al., 2020a) was highly contaminated by PFOA and PFOS, whereas air collected from areas that were remote from exposure sources and had fewer residents and less traffic had lower levels of PFOA and PFOS (Lin et al., 2020a). For example, the average concentration of PFOA in air samples from the fluorochemical industry park in Shangdong, China, was 1610 pg/m^3 (Wang et al., 2021); however, in coastal areas of the Bohai Sea, China, which is more than 100 km from the industry park, the average PFOA concentration was 27.1 pg/m^3 (Yu et al., 2018). This concentration is higher than that in the Pearl River Delta, China, (average 10.8 pg/m^3) (Liu et al., 2023), a coastal area that is farther from fluorochemical industries than is the Bohai Sea.

PFOA and PFOS levels in outdoor air vary widely worldwide, and it is also difficult to compare concentrations when the results are expressed in different units. One study conducted in 2017–2019 used the same method for four regions in LMICs (Camoiras González et al., 2021). The median concentration of PFOA in Africa (148 pg/PUF disc) was similar to that in the Pacific Islands (165 pg/PUF disc), but lower than that in Asia (183 pg/PUF disc) and the Group of Latin America and the Caribbean (GRULAC) (233 pg/PUF disc). The median concentrations of PFOS in Africa (97.7 pg/PUF disc) and Asia (101 pg/PUF disc) were similar, higher levels were observed in GRULAC (192 pg/PUF disc), and the highest levels were found in the Pacific Islands (266 pg/PUF disc) (Camoiras González et al., 2021).

In Asia, PFOA and PFOS levels were mainly reported for samples from China, and some information was available from Pakistan, Japan, India, and the Republic of Korea. Concentrations of PFOA and PFOS in areas remote from exposure sources were similar in China, Japan, India, and the Republic of Korea, and most median concentrations were < 5 pg/m^3 (Lin et al., 2020a, 2022). However, mean PFOA concentrations in highly polluted zones such as industrial areas or areas near fluorochemical industry parks varied from 23.8 pg/m^3 to 1610 pg/m^3, with a maximum of 9730 pg/m^3 (Guo et al., 2018; Seo et al., 2019; Lin et al., 2020a; Wang et al., 2021).

Across Europe and the United Kingdom (UK), PFOA concentrations in outdoor air have been relatively low. According to sampling campaigns conducted in the UK, Norway, and other countries in Europe, more than half of the samples did not contain PFOA and PFOS at concentrations above the detection limits (27 pg/sample per day for PFOA and 3.9 pg/sample per day for PFOS), although in north-west England, the median values for PFOA and PFOS were 400 and 6.5 pg/sample per day, respectively (Chaemfa et al., 2010). Maximum concentrations of PFOA and PFOS in the particle phase measured in Geesthacht, Germany, were both < 5 pg/m^3 (Dreyer et al., 2015).

Available data on PFOA and PFOS levels in outdoor air in other countries or regions including the USA were limited. For example, the production of PFOA and PFOS was phased out in the USA nearly 20 years ago, and in one study in which particulate matter with diameter < 2.5 µm ($PM_{2.5}$) samples were collected from five sites in North Carolina, USA, it was reported that most PFOA and PFOS concentrations were < 1 pg/m^3 (Zhou et al., 2021).

[The Working Group noted that these data suggest that, in the absence of an emission source, levels of PFOA and PFOS in outdoor air are low.]

(ii) Indoor air

The sources of PFOA and PFOS in indoor air include consumer products, building materials, and outdoor air (Winkens et al., 2017; Janousek et al., 2019). The results of previous studies have

suggested that PFOA and PFOS concentrations in indoor air exceed those in outdoor air (Goosey and Harrad, 2012). However, there were only a few studies in which PFOA and PFOS levels in indoor air were reported. The studies were conducted in Canada, the USA, Europe, and China, with samples collected from multiple sites, including bedrooms, homes, offices, cars, living rooms, and a laboratory and hallway (see Table 1.9). The median PFOA concentrations in indoor air collected from bedrooms in Canada (21 pg/m^3) (Shoeib et al., 2011) and eastern Finland (15.2 pg/m^3) (Winkens et al., 2017) were similar to those in living rooms (24 pg/m^3) and offices (18 pg/m^3) in the UK (Goosey and Harrad, 2012), but lower than median values in living rooms (56 pg/m^3), cars (76 pg/m^3), offices (96 pg/m^3), and school classrooms (89 pg/m^3) in Ireland (Harrad et al., 2019). The median PFOS concentrations in bedrooms in Canada (< 0.02 pg/m^3) (Shoeib et al., 2011) and eastern Finland (1.24 pg/m^3) (Winkens et al., 2017), and in living rooms in Ireland (< 0.4 pg/m^3) (Harrad et al., 2019) were similar, and lower than those in living rooms (11 pg/m^3) in the UK (Goosey and Harrad, 2012), and in cars (13 pg/m^3), offices (8.9 pg/m^3), and school classrooms (9.3 pg/m^3) in Ireland (Harrad et al., 2019), and much lower than those in offices in the UK (55 pg/m^3) (Goosey and Harrad, 2012). [These findings suggest that the function of these spaces might influence the concentrations of PFOA and PFOS, but more data are needed to confirm these influences.] In addition, one study at the University of North Carolina, USA, found that the floor waxing process in a laboratory and hallway increased mean PFOS concentrations from < 0.22 pg/m^3 before waxing to 8.88 pg/m^3 during waxing (Zhou et al., 2022).

[The Working Group noted that the available data on PFOA and PFOS levels in indoor air and their determinants were sparse.]

(iii) Settled dust

PFOA and PFOS are widely detected in dust samples because of continuous releases from consumer products (Jian et al., 2017; Zhu et al., 2023). de la Torre et al. (2019) evaluated 65 samples of house dust from three European countries. The median concentrations of PFOA in these dust samples from Belgium, Italy, and Spain were similar (1.54 ng/g, 1.56 ng/g and 1.00 ng/g, respectively), and median concentrations of PFOS in dust samples from these three countries were also low (0.77 ng/g, 0.33 ng/g, and 0.03 ng/g, respectively) (Table 1.10) (de la Torre et al., 2019). A study that collected dust samples from 184 homes in North Carolina, USA, and 49 fire stations in the USA and Canada showed that the median concentration of PFOA in dust samples collected from fire stations (17.6 ng/g) was higher than that from homes (7.9 ng/g) (Table 1.10) (Hall et al., 2020). Likewise, the median concentration of PFOS in fire stations (64.5 ng/g) was much higher than from homes (4.4 ng/g). Another study measured levels in 81 dust samples from homes in Indiana, USA, and found similar median concentrations of PFOA (5.9 ng/g) and PFOS (10 ng/g) (Zheng et al., 2023).

(b) Water

PFOA and PFOS are generally not removed from source water during standard water treatment (Wee and Aris, 2023). They have been detected in surface water, groundwater, wastewater, and in raw and finished drinking-water. Although the global extent of water contamination by PFOA and PFOS has not been completely characterized, PFOA and PFOS have been measured in water sources on all continents (Kurwadkar et al., 2022). Studies on highly contaminated water are discussed in subsection (iv).

Table 1.9 Occurrence of PFOA and PFOS in indoor air

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow and duration)	Analytical method (reporting limits)	PFOA concentration (pg/m³)		PFOS concentration (pg/m³)		Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)	
Goosey and Harrad. (2012)	Birmingham, UK, September 2008 to March 2009	20, living room, PAS, 1.0 m³/day PFOA; 0.8 m³/day PFOS, 28–35 days/sample	HPLC-MS/MS (NR)	52 (< 1.9–440)	24	38 (< 1.0–400)	11	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in homes.
		12, offices, PAS, 1.0 m³/day PFOA; 0.8 m³/day PFOS, 28–35 days/sample		58 (< 1.9–200)	18	56 (12–89)	55	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in homes.
Harrad et al. (2019)	Dublin, Galway, and Limerick, Ireland, August 2016 to January 2017	34, living room, PAS, 60 days/sample 1.0 m³/day PFOA; 0.8 m³/day PFOS	HPLC-MS/MS (LOD: PFOA, 0.3 pg/m³; PFOS, 0.4 pg/m³)	72 (< 0.3–386)	56	14 (< 0.4–208)	< 0.4	Long sampling time. No. of samples was large. Good reflection of PFAS levels at selected sites.
		31, cars, PAS, 60 days/sample		162 (1.2–790)	76	22 (< 0.4–152)	13	
		34, offices, PAS, 60 days/sample		153 (< 0.3–1210)	96	89 (< 0.4–1290)	8.9	
		28, school classrooms, PAS, 60 days/sample		210 (< 0.3–728)	89	188 (< 0.4–1590)	9.3	
Shoeib et al. (2011)	Vancouver, Canada, 2007–2008	59, bedroom, PAS, 4 wk/sample	LC-MS/MS, MDL, 0.47 pg/m³, 0.02 pg/m³	113 (3.4–2570)	21	(< 0.02, < 0.02)	< 0.02	Long sampling time. No. of samples was large. Good reflection of PFAS levels in bedrooms.
Winkens et al. (2017)	Kuopio, eastern Finland, 2014–2015	57, bedroom, PAS, 21 days/sample	LC-MS/MS (MDL: PFOA, 4.48 pg/m³; PFOS, 0.47 pg/m³)	21.2 (< 4.48–99.8)	15.2	1.33 (< 0.47–5.04)	1.24	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in bedrooms.

Table 1.9 (continued)

Reference	Location and collection date	Characteristics of sampling (number, sites, sampler, time, flow and duration)	Analytical method (reporting limits)	PFOA concentration (pg/m³)		PFOS concentration (pg/m³)		Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)	
Zhou et al. (2022)	University of North Carolina, USA, August to September 2019	3, laboratory and hallway, before floor waxing, AAS, 16/min, 24 h/sample	HPLC-MS/MS (MDL: PFOA, 0.82 pg/m³; PFOS, 0.25 pg/m³)	[12.69]	NR	[< 0.22]	NR	Sampling time and size were limited.
		3, laboratory and hallway, during floor waxing, AAS, 16/min, 18 h/sample		[8.83]	NR	[8.88]	NR	Sampling time and size were limited.
		3, laboratory and hallway, after floor waxing, AAS, 16/min, 24 h/sample		[8.17]	NR	[< 0.22]	NR	Sampling time and size were limited.

AAS, active air sampler; h, hour(s); HPLC, high-performance liquid chromatography; IQR, interquartile range; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MDL, method detection limit; min, minute(s); MS/MS, tandem mass spectrometry; NR, not reported; PAS, passive air sampler; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; UK, United Kingdom; USA, United States of America; wk, week(s).

Table 1.10 Occurrence of PFOA and PFOS in dust

Reference	Location and collection date	Characteristics of sampling (number, sites)	Analytical method (reporting limits)	PFOA concentration (ng/g dust)		PFOS concentration (ng/g dust)		Comments
				Mean (range)	Median (IQR)	Mean (range)	Median (IQR)	
de la Torre et al. (2019)	Belgium, September 2016 to January 2017	Homes (n = 22)	HPLC-MS/MS (LOQ: PFOA, 0.11 ng/g; PFOS, 0.04 ng/g)	NR (0.31–24.2)	1.54	NR (< 0.04–6.81)	0.77	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in dust.
	Italy, September 2016 to January 2017	Homes (n = 22)		NR (0.21–53.0)	1.56	NR (< 0.04–11.9)	0.33	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in dust.
	Spain, September 2016 to January 2017	Homes (n = 21)		NR (0.42–12.5)	1.00	NR (< 0.04–2.45)	0.03	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in dust.
Hall et al. (2020)	Fire stations, USA and Canada, 2015 and 2018	Fire stations (n = 49)	HPLC-MS/MS (MDL: PFOA, 1.60 ng/g dust; PFOS, 1.44 ng/g dust)	NR	17.6	NR	64.5	No. of samples was relatively large. Good reflection of PFAS levels in dust.
	North Carolina, USA, 2014–2016	Homes (n = 184)	HPLC-MS/MS (MDL: PFOA, 0.26 ng/g dust; PFOS, 0.20 ng/g dust)	NR	7.9	NR	4.4	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in dust.
Zheng et al. (2023)	Indiana, USA, August to December 2020	Homes (n = 81)	HPLC-MS/MS (MDL: PFOA, 0.01 ng/g dust; PFOS, 0.02 ng/g dust)	(< 0.01–1900)	5.9	(< 0.02–1100)	10	Long sampling time. No. of samples was relatively large. Good reflection of PFAS levels in dust.

HPLC, high-performance liquid chromatography; IQR, interquartile range; LOQ, limit of quantification; MDL, method detection limit; MS/MS, tandem mass spectrometry; NR, not reported; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; UK, United Kingdom; USA, United States of America.

(i) Surveys of surface water

Examples of PFOA and PFOS measurements in surface waters (lakes or rivers) are presented in Table S1.11 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). Mean values of PFOA and PFOS were generally below or in the low nanograms-per-litre range in locations without any reported PFAS pollution source. One example of higher levels reported downstream of an industrial source was in Alabama, USA, where values reported were 598 µg/L for PFOA and 144 µg/L for PFOS (ATSDR, 2021). Reported concentrations in ocean water were generally well below the nanogram-per-litre range (see Table S1.11).

Kurwadkar and colleagues reviewed levels of PFAS substances in surface water, groundwater and wastewater (Kurwadkar et al., 2022). They included information on the Asia–Pacific region, collected under the Second Global Monitoring Report on Persistent Organic Pollutants, which showed that PFOS detection was becoming more frequent. Levels of PFOS ranged from not detected to 47 ng/L in China; from 0.02 to 230 ng/L in Japan; from 0.12 to 33 ng/L in the Republic of Korea; from 0.39 to 42 ng/L in the Philippines; and from not detected to 54 ng/L in Thailand (United Nations Environment Programme, UNEP, as cited in Kurwadkar et al., 2022). Limited data were available for most of South America and Africa.

Muir and Miaz (2021) assembled an extensive summary of PFOA and PFOS measurements and total emissions for rivers across the world. There was a high degree of variability but widespread detectable levels of PFOA, with the highest concentrations identified in Europe in the River Po, Italy (200 ng/L); in Asia, in the Hokkesantanigawa River, Japan (360 ng/L); and in China in numerous rivers (e.g. the Daling River, 233 ng/L). Estimated riverine emissions of PFOA to the sea exceeded 1000 kg/year for many rivers, with estimates for the Yangtze River reaching 10 000 to 40 000 kg/year.

For PFOS, high concentrations were reported for the Llobregat and Besos rivers in Spain (> 250 ng/L) and the Ganges in India (142 ng/L) (Muir and Miaz, 2021). Riverine emissions of PFOS to the sea were estimated to have exceeded 2000 kg/year for the Pearl and Xi Rivers in China, and the Saint Lawrence River in North America. [The Working Group noted that several of these measurements were taken in the early 2000s and may not represent more recent riverine discharges.]

In a meta-analysis of publications on PFAS in wastewater treatment plant effluent streams, some indications of trends over time were presented (Cookson and Detwiler, 2022). Multiple results in China indicated a clear upward trend during 2006–2019 for both PFOA and PFOS. In the data for the USA, a clear downward trend was evident for PFOA over the period 2004–2020, but there was no overall trend for PFOS.

In a systematic review, Land et al. (2018) observed declining trends in PFOA and PFOS levels in Tokyo Bay between 2004 and 2006; in marine and fresh waters on the west coast of the Republic of Korea between 2008 and 2012; and in Bohai Bay on the east coast of China between 2011 and 2013.

Across the USA and across Europe there were many sources of data on PFAS surface-water contamination, from both local government monitoring and research projects, and many of these sources have been assembled into an online searchable resource (Dagorn et al., 2023; Environmental Working Group, 2023; PFAS Project Laboratory, 2023). These maps show the widespread locations where PFOA and PFOS are detectable in the USA and across Europe but do not provide summary exposure data for PFOA and PFOS.

PFOA and PFOS have been detected in many rainwater samples collected from urban and rural areas of Europe, Asia, and North

America. Levels near local emission sources can be very high, for example, PFOA concentrations measured in rainwater near to a fluoropolymer plant in China (median, [615 ng/L]; maximum, 2752 ng/L) (Liu et al., 2017). Dispersion has been very widespread, with detectable concentrations of [0.22 ng/L] for PFOA and [0.006 ng/L] for PFOS reported in Antarctica (Casas et al., 2021). Reported urban rainfall levels tended to be up to about 10 ng/L, and rural levels were generally < 1 ng/L (see Table S1.11).

PFOA and PFOS have been detected in both coastal and sea and ocean waters, with lower concentrations in ocean waters (see Table S1.11). PFOA and PFOS have been found to be substantially concentrated in sea foam and rising mist, which can be blown inland and contaminate surface water (Sha et al., 2022). Muir and Miaz conducted an extensive review of measurements from ocean and coastal waters, lakes, and rivers, and incorporated 29 500 measurements of 87 individual PFAS analytes, including PFOA and PFOS (Muir and Miaz, 2021). During 2015–2019, concentrations in seas were highest for PFOA in the Bohai and Yellow seas (median, 9.0 ng/L) and for PFOS in the Indian Ocean (median, 0.087 ng/L). The lowest concentrations were found in the Mediterranean Sea for PFOA (median, 0.001 ng/L) and in the Arctic Sea for PFOS (0.02 ng/L). Comparison of surveys conducted in 2000–2009, 2010–2014, and 2015–2019 revealed clear upward trends in concentrations of PFOA in the Bohai Sea, Yellow Sea, and East China Sea, and a steep decline in the Mediterranean. For PFOS, upward trends were evident in the Indian Ocean. [The Working Group noted, as did the authors, that deriving medians across studies with different sampling sites, design, and timing of sample collection, as well as different method detection limits (MDLs), introduces considerable uncertainty for assessing contrasts across space and time.]

PFOA and PFOS have been detected in fresh snow at levels that were very low in remote areas such as Antarctica (Xie et al., 2020) and higher in China (Shan et al., 2015), see Table S1.11 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). For PFOA and PFOS concentrations measured in snow and ice core samples, see Section 1.4(c)(i).

(ii) Groundwater

Some examples of PFOA and PFOS concentrations measured in groundwater are presented in Table S1.11 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). The occurrence of PFAS in groundwater from different areas in the world, including Australia, China, India, and islands of Malta has been described in a review (Xu et al., 2021a). PFOA was the dominant PFAS detected in three of the eight locations studied. For instance, in rural areas of eastern China, PFOA concentrations ranged from 7 to 175.2 ng/L, with a mean value of 90.8 ng/L (Chen et al., 2016). Also in China, but in the alluvial–pluvial plain of the Hutuo River, PFOA concentrations ranged from 0 to 1.76 ng/L (mean, 0.63 ng/L) in groundwater (Liu et al., 2019). PFOA was found at concentrations in the range of 0–8.03 ng/L (mean, 1.46 ng/L) in groundwater from valleys in Gozo on the Maltese Islands (Sammut et al., 2019). In the case of PFOS, higher concentrations than those of other PFAS were found only in 13 shallow monitoring bores surrounding legacy landfills in Melbourne, Australia, with a range of 1.3–4800 ng/L and mean value of 413.3 ng/L (Hepburn et al., 2019).

In 2019, 254 samples were collected from five aquifer systems in the eastern USA to evaluate PFAS occurrence in groundwater used as a source of drinking-water. In this study, PFOA and PFOS represent two of the three most frequently detected PFAS in public-supply wells,

with 2.4% ($n = 6$) of the samples containing PFOA plus PFOS at concentrations of > 70 ng/L, and median concentrations detected were 4.6 ng/L and 6.7 ng/L for PFOA and PFOS, respectively (McMahon et al., 2022).

In a study developed in Sweden, a national screening for perfluorinated pollutants in drinking-water was performed. The most abundant individual PFAS in surface and groundwater supplies was PFOS, followed by PFOA (Holmström et al., 2014).

[The Working Group noted that some studies did not report on PFOA and PFOS separately.]

(iii) Drinking-water and drinking-water supplies

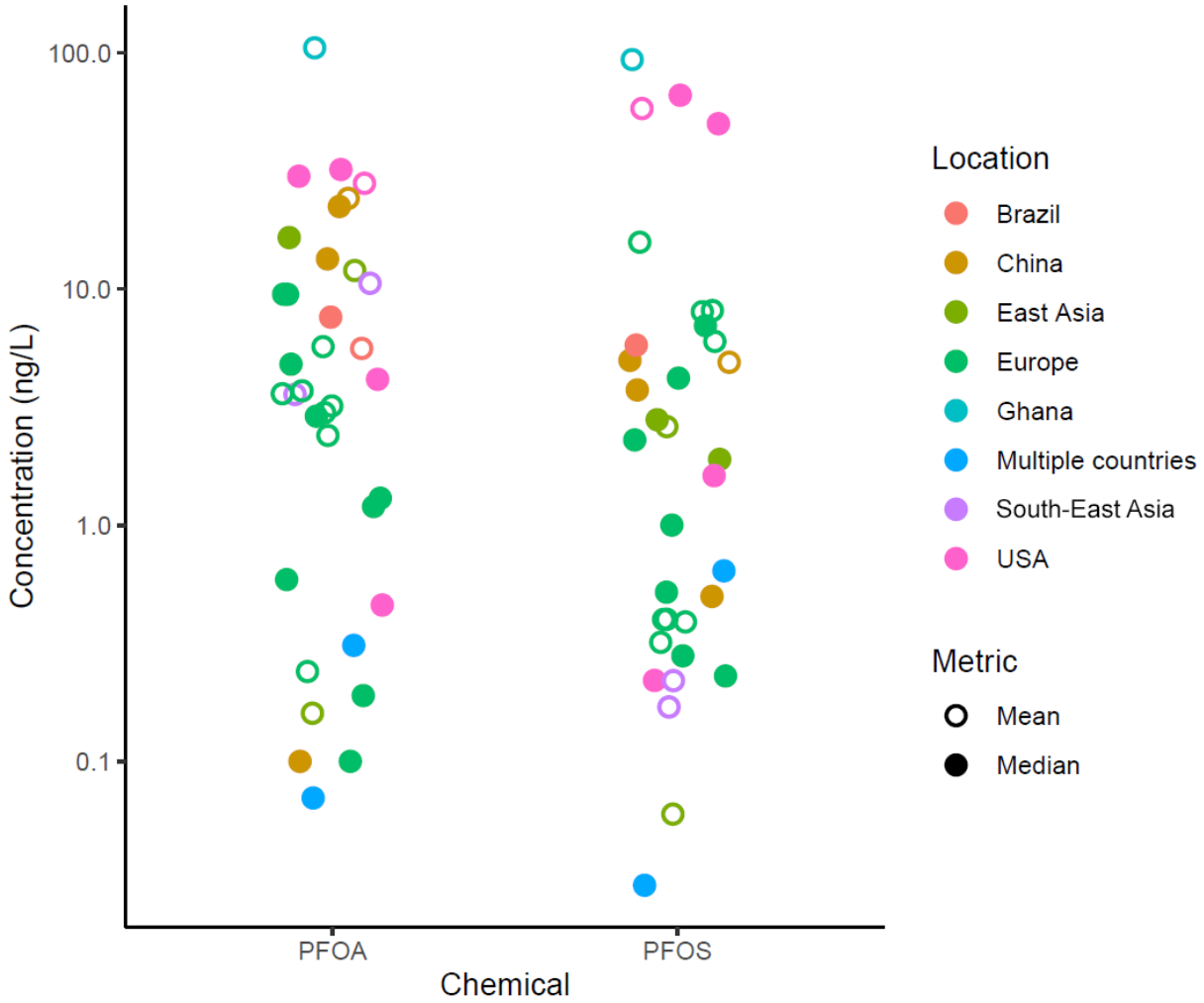
PFOA and PFOS have been measured in drinking-water (e.g. tap water, bottled water) in various locations (Fig. 1.4; Table S1.11, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). [The Working Group noted that mean concentrations in drinking-water from sites without any known contamination were usually below 10 ng/L (Fig. 1.4; see also Section 1.4.1(b)(iv) for concentrations measured at sites with reported contamination sources).]

Domingo and Nadal (2019) reviewed the scientific literature on PFAS exposure via drinking-water and highlighted that most information was coming from the EU, USA, and China. They reported on water sampling efforts in Europe (France, Italy, Sweden, Spain, Norway, Belgium, and the Faroe Islands), the Americas (USA, Canada, Brazil), and Asia (China, Japan, Afghanistan, India, and the Republic of Korea), Africa, and Australia. Levels of PFOA and PFOS in drinking-water and drinking-water sources ranged from non-detectable to > 500 ng/L.

There have been few formal efforts to characterize PFOA and PFOS levels in drinking-water sources on a national or international level. Because communities draw drinking-water from both surface and groundwater sources, large-scale efforts focus on water used for drinking-water supplies, regardless of whether this is surface or groundwater. In 2013–2015, the US EPA required 6000 public water systems (PWS) to test for PFOA and PFOS (and four other PFAS) in source water under the Third Unregulated Contaminant Monitoring Rule (UCMR 3) programme (US EPA, 2017b). The prevalence of PFOA at levels above the minimum reporting levels (MRLs) was low (0.09% of samples from 0.3% of PWS were above the MRL of 20 ng/L), as was that of PFOS (0.3% of samples from 0.9% of PWS exceeded the MRL of 40 ng/L) (US EPA, 2017b). Levels of PFOA reported ranged from 20 to 349 ng/L (median, [32 ng/L]); levels of PFOS ranged from 41 to 1800 ng/L (median, [66 ng/L]); the frequency of detection of these chemicals increased over the reporting period (Guelfo and Adamson, 2018). Detectable levels of PFOA and PFOS spanned three orders of magnitude, with PFOS levels being higher than those of PFOA (US EPA, 2017b). On the basis of these detections, it was estimated that more than 6 million people in the USA had drinking-water that exceeded 70 ng/L for the sum of PFOA and PFOS (Hu et al., 2016). Detection of PFOA and PFOS was significantly associated with nearby military firefighting training areas, AFFF-certified airports, and wastewater treatment plants. Detectable PFOA was also associated with major industrial sites that produced or used PFOA and/or PFOS (Hu et al., 2016).

More recently, UCMR 5, being conducted in 2023–2025, is measuring 29 PFAS with lower MRLs (4 ng/L for PFOA and PFOS) and in a larger number of PWS than UCMR 3 (US EPA, 2024). In initial data available up to October 2023 for 10 020 samples from 3072 PWS, PFOA was reported to be above the MRL in 6.1% of samples and 9.5% of PWS, and PFOS was detected at above the MRL in 6.4% of samples and 9.5% of PWS.

Fig. 1.4 Examples of PFOA and PFOS concentrations in drinking-water from sites without known sources of contamination



LOD, limit of detection; LOQ, limit of quantification; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; USA, United States of America.
Selected publications, see Table S1.11 for detail and references (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). When available, the median was plotted. When values were below the LOQ or LOD, the LOQ or LOD was plotted instead. Note the logarithmic scale.

(iv) Local major contamination of drinking-water sources

Fluorochemical manufacture and use of fire-fighting foams are associated with PFOA and PFOS contamination of drinking-water around the world. Some examples are described below.

The first such contamination identified was from a facility manufacturing PTFE in Parkersburg, West Virginia, USA, which contaminated surface water and drinking-water supplies in West Virginia and Ohio, with more than 80 000 people supplied with water contaminated with PFOA to varying extents. Levels of PFOA in water supplies measured since the early 2000s ranged from 10 to 100 ng/L in the least-contaminated water district to up to 10 µg/L in the most-contaminated water district (Shin et al., 2011a). Modelling of the water contamination indicated

progressive increases in contamination from the 1950s to 2000, when emissions were curtailed (Shin et al., 2011a). In a series of measurements from 62 private wells used for drinking-water in the same area, the median PFOA concentration was 200 ng/L (range, 6–13 300 ng/L) (Hoffman et al., 2011).

In Veneto, Italy, groundwater used for drinking-water was contaminated by chemical production; PFOA was the main contaminant, together with a mixture of mainly shorter-chain PFAS. In 152 samples collected from the contaminated area in 2013, the PFOA concentration was above the LOQ in 90% of samples, with a median concentration of 319.5 ng/L (maximum, 1475 ng/L), and the PFOS concentration was above the LOQ in 78% of samples, with a median concentration of 18 ng/L (maximum, 117 ng/L) (Pitter et al., 2020).

Firefighting foams and their use at airports and air force bases have resulted in PFAS contamination, particularly PFOS, in drinking-water. In Ronneby, Sweden, about one third of a community of 28 000 people were supplied with contaminated drinking-water in which PFOS was measured at 8000 ng/L and PFOA at 100 ng/L before the waterworks was closed (Xu et al., 2021b).

In Australia, PFOA and PFOS were detected in groundwater near a military base in Williamtown, New South Wales, at concentrations of 1800 ng/L and 5560 ng/L, respectively (Kurwadkar et al., 2022).

(c) Soil

Soil has been highlighted as a global sink for and long-term source of PFOA and PFOS (Brusseau et al., 2020). The estimated half-lives of PFOA and PFOS in soil are at least tens of years, although the true half-lives may be longer, because no significant degradation was noticeable during the experiments that have been conducted (UNEP, 2006, 2017). PFOA and PFOS can reach the soil directly, or via degradation of their precursors, from various input sources including: application of biosolids as fertilizers; the use of PFAS-based firefighting foams; leaching from contaminated asphalt and concrete affected by the extensive use of AFFF in firefighting training centres and airfields; seepage of leachate from landfills; discharge of effluents from wastewater treatment plants; contaminated irrigation water; contaminated discharge from fluorochemical industries; and atmospheric deposition (Costello and Lee, 2020; Abou-Khalil et al., 2022; Panieri et al., 2022; Douglas et al., 2023). Brusseau et al. (2020) comprehensively reviewed the literature on PFAS in soil. Both PFOA and PFOS were ubiquitously distributed globally in soil, with or without nearby point sources. The median for maximum concentrations of PFOA and PFOS reported globally in soil near primary point sources was 8722 and 83 ng/g, respectively, whereas the median for maximum background soil (i.e. no direct input sources) concentrations worldwide was 2.7 and 2.7 ng/g, respectively (Brusseau et al., 2020). The highest reported concentration of PFOA in soil (50 000 ng/g) was measured in soil contaminated with AFFF from a US military site (Brusseau et al., 2020), and the highest PFOA concentration (460 000 ng/g) was measured at firefighting training grounds in Australia (CRCCARE, 2018). Regarding background soil levels, the highest PFOA concentration of 47.5 ng/g was measured in soil from Shanghai, China (Li et al., 2010), and the highest PFOS concentration of 162 ng/g was reported for Alnabru, Norway (NEA, 2017). Table 1.12 provides a summary of selected studies on the occurrence of PFOA and PFOS in soil and lists PFOA and PFOS concentrations from various sites with different sources of contamination, as well as background concentrations from non-contaminated sites.

A systematic review of concentrations of 12 PFAS (including PFOA and PFOS) in 1042 soil samples from 15 countries on 6 continents reported significantly higher Σ_{12}PFAS levels (dominated by PFOA and PFOS) in the northern

Table 1.12 Occurrence of PFOA and PFOS in soil

Location and collection date	No. of samples	PFOA concentrations (ng/g)	PFOS concentrations (ng/g)	Comments	Reference
Antarctica, 2010	3	< MQL	Range, 0.31–0.54 Mean, [0.45]		Llorca et al. (2012a)
Australia, NR	6	Range, 13.6–58.1 Mean, 34.5	Range, 2180–15 300 Mean, 7800	AFFF use at airport sites	Bräunig et al. (2019)
Australia, NR	3	Range, 0.33–0.39 Mean, 0.36	Range, 6.4–7.2 Mean, 6.8	No direct input sources	Bräunig et al. (2019)
Africa					
Uganda, 2015	18	Range, 0.25–0.91	Range, 0.6–3.0	No direct input sources	Dalahmeh et al. (2018)
Asia					
China, 2009	32	Range, < 0.05–34.2 Mean, 2.5	Range, 0.68–189 Mean, 22.6	Soil around a fluorochemical-manufacturing plant	Wang et al. (2010)
China, NR	86	Range, < 0.1–0.9 Mean, 0.2	Range, 0.02–2.4 Mean, 0.3	No direct input sources	Pan et al. (2011)
Nepal, 2010	14	Range, < 0.1–0.26	Range, < 0.09–0.13	No direct input sources	Tan et al. (2014)
Republic of Korea, 2009	13	Range, < 0.2–3.4 Mean, 2.2	Range, < 0.2–1.7 Mean, 0.8	No direct input sources.	Naile et al. (2013)
Europe					
Germany, 2006	1	650	8600	Soil affected by contaminated industrial waste	Wilhelm et al. (2008)
Norway, 2008	39	Range, < 1.0–141.5 Median, 12.8 GM, 16.0	Range, 24.5–11 923 Median, 641 GM, 516.6	Fire training sites (n = 4)	SFT (2008)
Norway, 2016	9	< 0.01	Range, < 0.02–7.06 Median < 0.02	No direct input sources	Skaar et al. (2019)
Sweden, 2011–2012	45	Range, < 0.1–219 Median, 1.4 GM, 2.6	Range, < 0.5–8520 Median, 39 GM, 42.5	AFFF-contaminated soil near a military airport	Filipovic et al. (2015a)
Sweden, NR	31	Range, < 0.02–0.57 Median, < 0.02 Mean, 0.04	Range, < 0.02–1.7 Median, 0.3 Mean, 0.43	No direct input sources	Kikuchi et al. (2018)
North America					
USA, 2010	6	Range, 0.29–0.54 Median, 0.33	Range, 0.93–2.1 Median, 1.4	No direct input sources	Scher et al. (2018)
USA, 2019	2469	Range, 0.07–50 000 Median, 1.4 GM, 2	Range, 0.09–373 000 Median, 18 GM, 22	Sites affected by AFFF use	Brusseau et al. (2020)

Table 1.12 (continued)

Location and collection date	No. of samples	PFOA concentrations (ng/g)	PFOS concentrations (ng/g)	Comments	Reference
South America					
Tierra del Fuego, Argentina, 2010	30	Range, < MQL–1.5 Mean, 0.3	Range, < MQL–5.4 Mean, 1.4	No direct input sources	Llorca et al. (2012a)

AFFF, aqueous film-forming foam; GM, geometric mean; MQL, method quantification limit; NR, not reported; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; USA, United States of America.

hemisphere, which was attributed to greater PFAS emissions, compared with the southern hemisphere (Lv et al., 2023). On a continental scale (from highest to lowest), mean concentrations of PFOA were ranked, North America > Asia > Europe > Africa > Oceania > South America, and mean PFOS concentrations were ranked, North America > Africa > Europe > Asia > Oceania > South America (Lv et al., 2023).

A meta-analysis of PFAS soil-to-groundwater concentration ratios for samples collected from 324 sites where AFFF was used across 56 military installations throughout the USA demonstrated that soil is a significant reservoir for PFAS at these contaminated sites (Hunter Anderson et al., 2019). Moreover, analysis of PFAS depth profiles in the soil indicated significant retention of PFOA and PFOS in the vadose zone over decades, serving as a significant long-term source of PFAS in groundwater (Guo et al., 2020; Lv et al., 2023). In a recent study of temporal trends in PFAS concentrations in soil samples from eastern China, it was reported that PFOA concentrations increased by 86.4% between 2011 and 2021, whereas PFOS concentrations decreased by 28.2% during the same period. The distinct difference between PFOA and PFOS in terms of temporal changes in soil concentrations during the studied decade was attributed to the fact that PFOS was added to the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2009, while PFOA was added later in 2019 (Cheng et al., 2023).

(d) Food

PFOA and PFOS are introduced into foods in various ways, mainly depending on the food origin, but also on packaging (Schaider et al., 2017) and processing (Choi et al., 2018). Plant-based foods may be contaminated via atmospheric deposition or uptake from water and soil, including from use of sewage sludge as fertilizer (Ghisi et al., 2019). A study on crops grown in outdoor lysimeters demonstrated uptake of PFOA and PFOS, including in various edible parts of the crop (Felizeter et al., 2021). Uptakes vary both between and within species and may partly be explained by different plant properties (Costello and Lee, 2020). PFOA and PFOS become incorporated into animal-based foods because animals are exposed to these PFAS via water, feed, soil, and air (Death et al., 2021). [The Working Group noted that there was a lack of data on the contributions of different sources of PFOA and PFOS contamination in foods. This may be of more importance for source tracking and reduction than for exposure characterization.]

Concentrations of PFOA and PFOS have been determined in various food products, including food for infants such as formula and baby food, in a range of studies worldwide (Mikolajczyk et al., 2023). Some studies on processed food were available (e.g. Jogsten et al., 2009; Jeong et al., 2019; Genualdi et al., 2022; Vendl et al., 2022), but most of the data were based on the analysis of raw food products. In general, most data were available for fish and seafood, but there have been an increasing number of studies on other food groups during recent years (Domingo and Nadal, 2017; Jian et al., 2017; Pasecnaja et al., 2022). PFOA and PFOS concentrations detailed in selected studies and reports are presented in Table S1.13 and Table S1.14, respectively (see Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636).

Reporting limits varied to a large extent between studies (Pasecnaja et al., 2022). [The Working Group noted that high reporting limits, especially when considering data generated in the early 2000s, have resulted in low detection frequencies, resulting in challenges when comparing studies.] As a result of an increasing focus on the need for more sensitive methods, lower reporting limits have been observed in more recent studies (e.g. Lacina et al., 2011; Vestergren et al., 2012; Sadia et al., 2020). For example, in the study by Vestergren et al. (2012),

in which a particular effort had been made to increase sensitivity, the method limit of quantification (MLQ) ranged between 1.8 and 9.6 pg/g for PFOA, depending on food type, and between 1.5 and 8.0 pg/g for PFOS. In comparison, in the study by Clarke et al. (2010), for example, the LOQ for both PFOA and PFOS was 1000 pg/g. [The Working Group noted that because levels of PFOA and PFOS are low in many food products, improvements in MLQ have an impact on detection frequencies (EU, 2022).]

The studies presented in supplementary Table S1.13 and Table S1.14 were published recently, present data from different regions worldwide, and include information on several food categories. As an example, a study on 266 samples collected during 2018–2019 from 26 countries located in Africa, Asia (excluding China), and Latin America included data on several food groups and had high detection rates (Fiedler et al., 2022). The mean concentrations of PFOA in vegetables, fish and other seafood, beef, chicken, milk, and eggs were 7.58, 12.4, 6.44, 4.61, 0.99, and 8.34 pg/g, respectively. The corresponding mean concentrations of PFOS in the same food groups were 2.45, 124, 37.6, 5.80, 22.1, and 45.6 pg/g, respectively. [The Working Group noted that with the low LOQ in this study, PFOA and PFOS contamination was detected more frequently.]

The mean concentrations in samples from Europe (EFSA Panel on Contaminants in the Food Chain, 2020) and China (Fan et al., 2021) were in general higher than those from Africa, Asia (excluding China), and Latin America (Fiedler et al., 2022), but detection frequencies in studies in the USA were too low to compare, except for fish and seafood (US FDA, 2022a; Young et al., 2022). For example, the mean concentrations of PFOA in eggs were 106 and 150 pg/g in samples from Europe (EFSA Panel on Contaminants in the Food Chain, 2020) and China (Fan et al., 2021), respectively, while the mean concentration in the study on samples from Africa, Asia (excluding China), and Latin America was 8.34 pg/g (Fiedler et al., 2022).

For PFOS, the highest mean concentrations were generally seen in fish and seafood, when compared with other food groups (see Table S1.13 and Table S1.14, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). For example, the mean concentration of PFOS in fish and shrimp from China was 2760 pg/g, whereas the mean concentration in meat and meat products was 300 pg/g (Fan et al., 2021). This was in line with data reported in review papers (Domingo and Nadal, 2017; Jian et al., 2017; Pasecnaja et al., 2022). These observations were supported by the results of a study that found PFOS to be very bioaccumulative (bioaccumulation factor, > 5000) and also biomagnifying (trophic magnification factor, > 1) in a freshwater food web in Canada (Munoz et al., 2022). For PFOA, among various countries, the mean concentrations were highest in China across all food groups, with the highest concentrations found in fish and meat (see Table S1.13 and Table S1.14, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636).

In a study on more than 500 composite samples of locally caught freshwater fish collected across the USA in 2013–2015, the median concentration of total PFAS (of which PFOS constituted 74%) was more than 200 times as high as the levels found in commercially relevant fish analysed by the US FDA in 2019–2022 (Barbo et al., 2023). The median and 90th percentile concentrations of PFOS in locally caught freshwater fish fillets across the USA were 8410 pg/g and 41 400 pg/g, respectively (Barbo et al., 2023), whereas the concentrations reported by the US FDA were generally in the low hundreds of picograms per gram, or less (Barbo et al., 2023).

Elevated concentrations of PFOA and PFOS in food have been reported in areas with known PFAS contamination (e.g. Hölzer et al., 2011; Langberg et al., 2022; Lasters et al., 2022). For instance, elevated concentrations of PFOA and PFOS were measured in hen eggs from private gardens situated within a 10 km radius of a fluorochemical-production plant in Antwerp, Belgium (Lasters et al., 2022). The highest concentrations were observed for PFOS (130–241 000 pg/g), and decreasing concentrations were observed with increasing distance from the plant (Lasters et al., 2022). This was in line with the results of a study showing increasing PFOA and PFOS concentrations in eggs of hens exposed to increasing concentrations in drinking-water (Wilson et al., 2021). In Lyon, France, PFOS concentrations in home-produced eggs near a fluorochemical-production facility were higher than in commercially produced eggs: home-produced, median, [965 pg/g] and range, 105–5240 pg/g; commercially produced, median, [113 pg/g] and range, 34–650 pg/g (Préfète du Rhône, 2023).

Environmental contamination may also result in elevated levels in dairy products. In a study on two dairy farms in the USA with known contamination of groundwater, samples were collected between 2018 and 2021. Milk samples from one of the two farms contained PFOS at elevated concentrations. PFOS concentrations of up to 4.22 ng/g were reported in the milk from this farm, while retail milk and control milk did not contain PFOS at detectable levels (US FDA, 2021a)

Food from wild game species may also contain elevated levels of PFOA and PFOS (Death et al., 2021). The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (EFSA Panel on Contaminants in the Food Chain, 2020) reported that edible offal from game animals contained mean levels of PFOA and PFOS that were more than 10 and 100 times, respectively, as high as in any other food group.

In a study from China that included food samples from two provinces, Hubei (n = 121) and Zhejiang (n = 106), geographical differences were observed between regions and sampling sites (Zhang et al., 2017a). PFOS levels were higher in Hubei than in Zhejiang, particularly for food of animal origin. This was expected because PFOS was produced in Hubei province. The concentrations of PFOA were similar in the two regions.

Temporal trends for abiotic and biological environmental samples, including food items, were evaluated in a systematic review by Land et al. (2018). Both non-significant and decreasing trends were observed for PFOS, depending on region and study. Non-significant trends were predominant for PFOA. The authors concluded that, despite interventions to reduce exposure to PFOA and PFOS, no clear temporal trends have been observed globally, probably because of the high persistence of these compounds in the environment. [There were no available data from the southern hemisphere and Asia.]

(e) Consumer products

PFOA and PFOS are present in numerous consumer products; for example, textiles, outdoor clothing, cleaning products, paints, coatings, carpets, floor coverings, floor polish, leather, cosmetics, printing inks, adhesives, ski wax, and lubricants (Glüge et al., 2020). However, it is often not clear if they were added intentionally, are impurities of other components, or are degradation products (Glüge et al., 2020). Also, PFOA has been used as a processing aid when manufacturing fluoropolymers used, for example, in non-stick cookware. Residues of PFOA may thus be present in these products (Sinclair et al., 2007).

The amount of available data on PFOA and PFOS in consumer products is considerably smaller than that on these compounds in food and drinking-water, and almost all data have been published in the last decade. [The Working Group noted that results are reported in different metrics, e.g. ng/g or μg/m^2, which makes com-

parison challenging.] Below, selected studies on consumer products available on the market in different regions worldwide are presented.

PFOA and PFOS were determined in 115 randomly selected consumer products (textiles, carpets, cleaning and impregnating agents, leather, baking and sandwich papers, paper baking forms, and ski waxes) purchased in Germany in 2010 (Kotthoff et al., 2015). Detection frequencies varied between product categories. For PFOA and PFOS, respectively, the detection frequencies were 100% and 100% for outdoor textiles, 78% and 100% for nanosprays and impregnation sprays, 88% and 100% for ski wax, and 30% and 90% for carpets. PFOA was also found in 100% of the gloves, 100% of textiles for awnings, and 63% of leather products. PFOS was detected in 69% of paper-based food contact materials. PFOA and/or PFOS were detected in < 50% of the remaining products (wood glue and cleaners). For PFOA, the highest median (and maximum) concentrations were observed in ski wax and nano- and impregnation sprays, 15.5 (maximum, 2033.1) and 15.9 (maximum, 28.9) ng/g, respectively (Kotthoff et al., 2015). The highest median (and maximum) levels of PFOS were observed in outdoor textiles and leather with concentrations of 9.5 (maximum, 35.4) and 5.6 (maximum, 5.6) μg/m^2, respectively.

PFOA and PFOS were determined in 25 samples of consumer products available to private consumers in Japan and purchased between 1981 and 2009 (car wash/coating products, sprays for fabrics and textiles, insecticides, rust inhibitors, and paints) (Ye et al., 2015). PFOA was found in one sample of spray for fabrics and textiles (36 ng/g) and one rust inhibitor (11 ng/g), and PFOS was observed in one sample of spray for fabrics and textiles (59 ng/g) (Ye et al., 2015). In a study in Norway, PFOA and PFOS were determined in 45 samples of furniture textile, carpet, clothing, and food contact materials (Vestergren et al., 2015). All samples were imported from China and purchased in Norway in 2012–2013. PFOA was found in 26 samples, at concentrations between 0.005 (carpet) and 0.91 μg/m^2 (curtain). PFOS was detected at 1.7 μg/m^2 in one carpet sample (Vestergren et al., 2015).

Seventeen samples of paper and cardboard food packaging materials purchased from retailers and grocery stores in Egypt in 2013 were analysed for PFAS (Shoeib et al., 2016). PFOA and PFOS were detected in 79% and 58% of the samples, at median concentrations of 2.40 ng/g and 0.29 ng/g, respectively.

In a study in the USA, PFAS were determined in 61 samples of furnishings, apparel, and bedding purchased in 2020 (Rodgers et al., 2022). PFOA and PFOS were detected in seven and one product, respectively. The maximum concentration of PFOA was 22.5 ng/g, and the concentration of PFOS was 2.1 ng/g in the one product in which it was detected (Rodgers et al., 2022). PFAS were determined in 160 textile products purchased in Albany, New York, USA, between 2016 and 2019 (Zhu and Kannan, 2020). PFOA was detected in 20% of the products, at a maximum concentration of 32.7 μg/m^2, whereas PFOS was found in 3.8% of the products, at a maximum concentration of 0.167 μg/m^2 (Zhu and Kannan, 2020). PFOA and PFOS were determined in 32 textile samples purchased in Thailand; mean concentrations were 2.74 μg/m^2 (range, 0.31–14.14 μg/m^2) and 0.18 μg/m^2 (range, 0.02–0.46 μg/m^2), respectively (Supreeyasunthorn et al., 2016).

PFOA was determined in sunscreens and cosmetics, primarily from Japan, for which fluorinated compounds were listed as ingredients. Among these products, 8 of 9 sunscreens and 13 of 15 cosmetics contained PFOA at concentrations above the LOQ; concentrations ranged from 3.7 to 5700 ng/g (Fujii et al., 2013). A wide range of PFAS were determined in 38 cosmetics and personal care products for which organofluorine compounds were listed as ingredients and that were available on the North American market in 2020–22 (Harris et al., 2022). PFOA and PFOS

were found at levels above the LOQ in 65.8% and 26.3% of the samples, respectively. The median (and maximum) concentrations of PFOA and PFOS were 13.6 ng/g (28 600 ng/g) and < LOQ (16.5 ng/g), respectively (Harris et al., 2022). In another study in which PFOA and PFOS concentrations were determined in cosmetics (n = 29, 12 from the USA and 17 from Canada) available on the North American market in 2020, PFOS was detected in only two Canadian samples, at concentrations of 15.5 and 6.6 ng/g (Whitehead et al., 2021). In a study on 43 different cosmetics for which PFAS were listed as ingredients and that were available on the European market in 2020, PFOA was detected in only one foundation/beauty balm cream, at a concentration of 112 ng/g, and PFOS was not detected (Pütz et al., 2022).

[The Working Group noted that there were few data available on the same products at different time points; it was thus not feasible to evaluate potential time trends and the effects of regulations and voluntary phase-outs (see Section 1.5).]

The results of these studies demonstrated that PFOA and PFOS are commonly present in a wide range of consumer products. In several of the studies, PFOA and/or PFOS were most frequently detected in textiles and fabrics at concentrations between the LOD and 35 μg/m^2. Also, in some of the studies on cosmetics, detection frequencies were high, and concentrations detected were up to micrograms per gram product.

1.4.2 Occupational exposure

Populations with occupational exposure are generally recognized as having some of the highest levels of exposure to PFOA and PFOS (Christensen and Calkins, 2023). In occupational settings, the exposure route of greatest importance is typically assumed to be inhalation, but dermal uptake and ingestion of dust may also contribute, depending on the workplace conditions (De Silva et al., 2021).

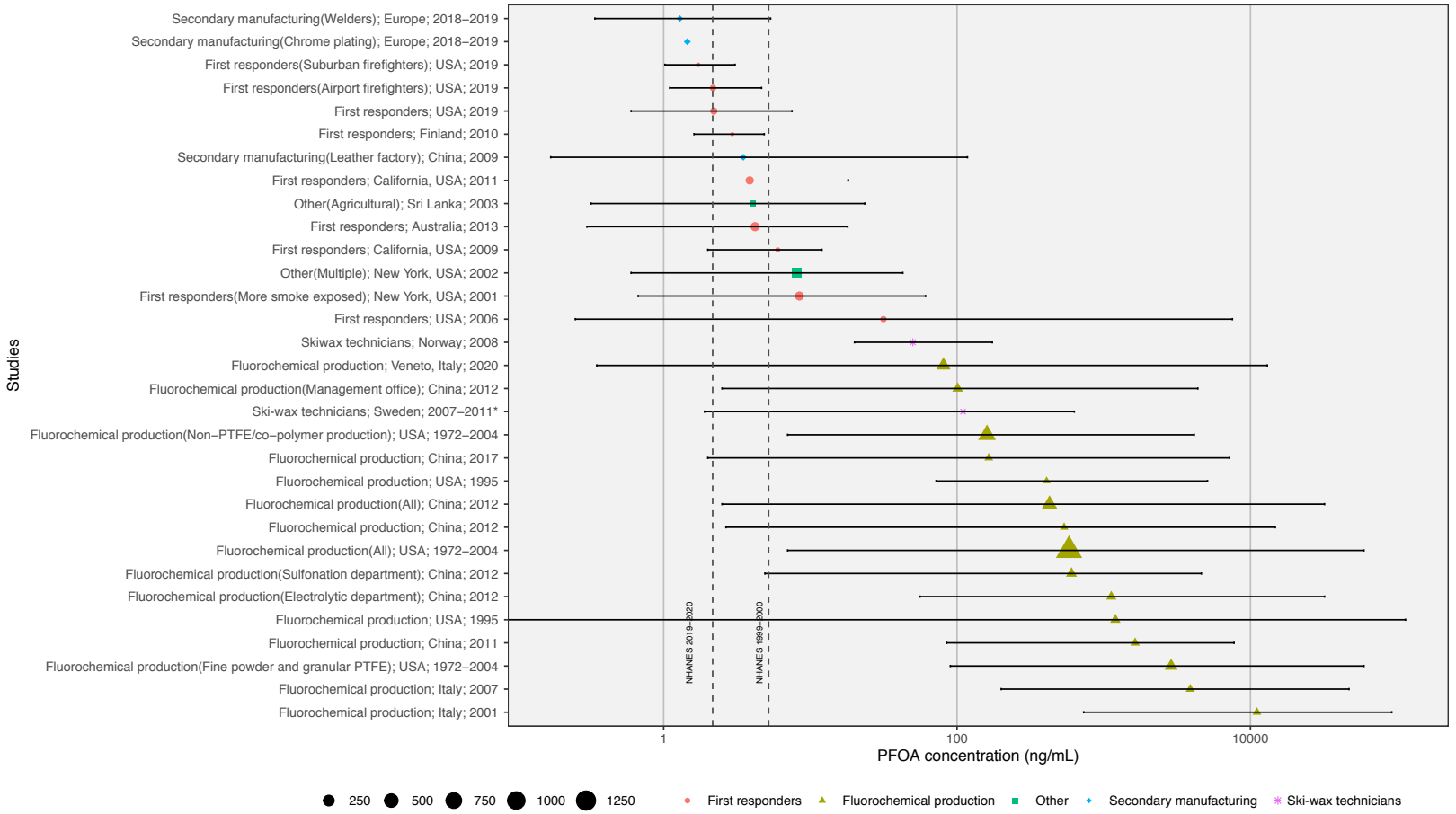
Occupational exposure to PFOA and PFOS may result from fluorochemical-production processes; use of PFAS as a processing aid in other manufacturing settings; use of PFOS as a mist suppressant to reduce exposure to other chemical hazards; contact with products containing PFOA or PFOS, as well as precursor compounds; and contact with contaminated environmental media or waste infrastructure (see Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). The information regarding determinants of exposure was limited, but indicated that processing conditions, such as high temperature, low pH, and use of PFAS in dry powder form, are linked to elevated PFAS exposure in fluorochemical-manufacturing settings (Freberg et al., 2010; Kaiser et al., 2010; Christensen and Calkins, 2023). Limited data on bulk and dust monitoring suggested that dust present in speciality textile-manufacturing settings, such as those producing flame-retardant or water-repellent materials, increases the risk of PFAS exposure (Sha et al., 2018; Christensen and Calkins, 2023). For non-manufacturing industries, such as retail and office buildings, factors including the building's age, the presence of carpeting, and the extent of ventilation are strongly linked to PFAS exposure (Langer et al., 2010; Sha et al., 2018; Christensen and Calkins, 2023).

In this section, occupational exposures are first described using biomonitoring data, followed by industrial hygiene samples, and work environment samples.

(a) Biomonitoring data

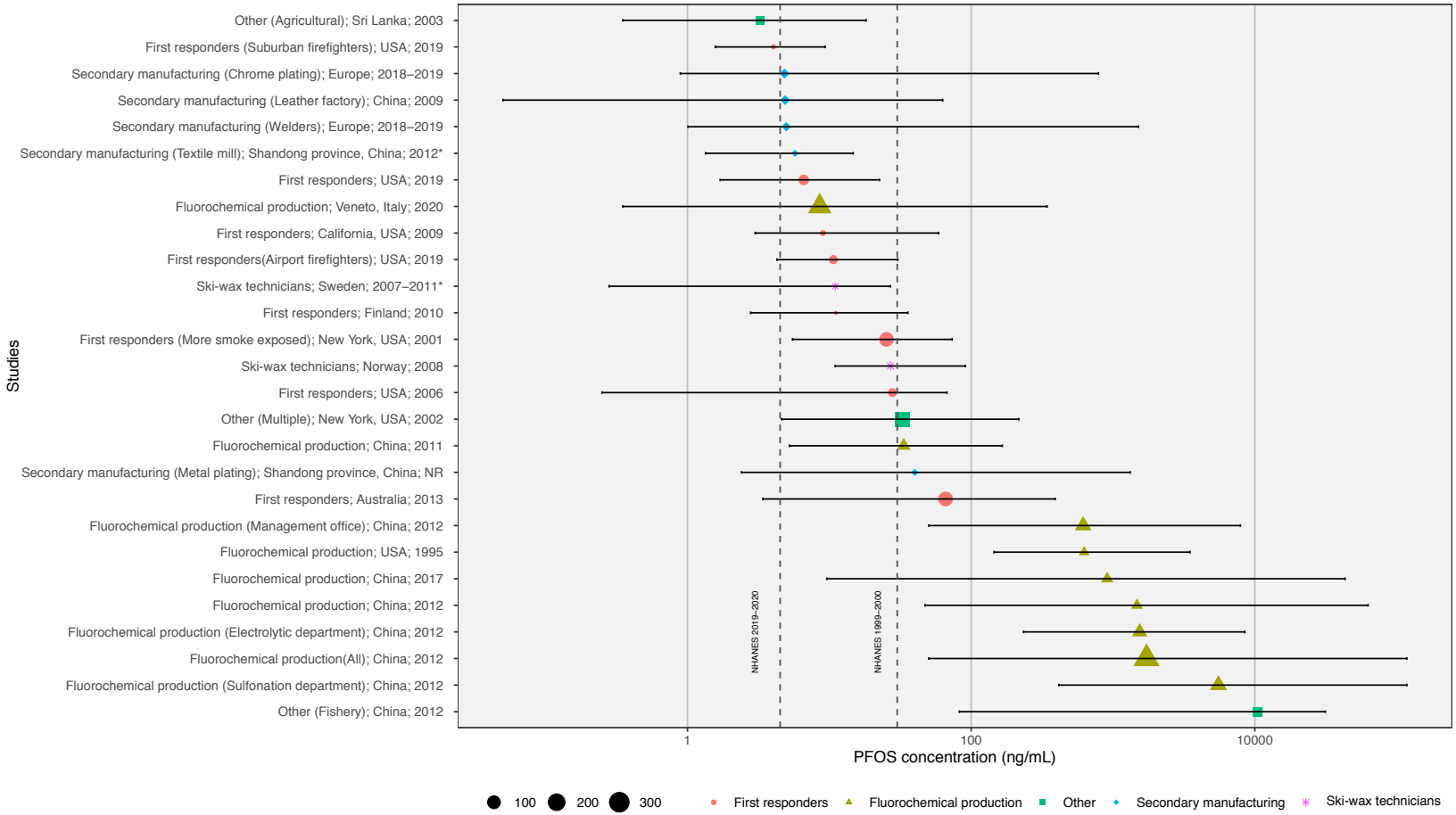
Biomonitoring has been used to assess exposure to PFOA and PFOS in different settings. Fluorochemical-production workers have some of the highest serum PFOA and PFOS concentrations reported in the literature (see Fig. 1.5 and Fig. 1.6; and Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization,

Fig. 1.5 Examples of PFOA concentrations in serum, plasma, and whole blood in occupationally exposed populations



NHANES, National Health and Nutrition Examination Survey; PFOA, perfluorooctanoic acid; PTFE, polytetrafluoroethylene; USA, United States of America. *Whole blood. Statistics include median, minimum, and maximum concentrations (ng/mL), the most recent year of sample collection is indicated. See Table S1.15 for detail and references (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). [The Working Group noted that these values are thought to be representative of the literature on occupational exposure. For studies in which data were reported for multiple subgroups, only selected groups are included.] Concentrations from the adult general population study NHANES are given for the years 1999–2000 and 2019–2020 for comparison (see Section 1.4.3).

Fig. 1.6 Examples of PFOS concentrations in serum, plasma, or whole blood in occupationally exposed populations



NHANES, National Health and Nutrition Examination Survey; PFOS, perfluorooctanesulfonic acid; USA, United States of America. *Whole blood.
Statistics include median, minimum, and maximum concentrations (ng/mL), the most recent year of sample collection is indicated. See Table S1.15 for detail and references (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). [The Working Group noted that these values are thought to be representative of the literature on occupational exposure. For studies in which data were reported for multiple subgroups, only selected groups are included.] Concentrations from the adult general population study NHANES are given for the years 1999–2000 and 2019–2020 for comparison (see Section 1.4.3).

online only, available from: https://publications.iarc.who.int/636). In samples collected in the year 2000 from 25 PFOA-production workers at a site in Italy, Costa et al. (2009) reported a geometric mean concentration of PFOA in serum of 11 700 ng/mL (range, 1540–86 300 ng/mL) (Costa et al., 2009). However, the highest reported PFOA serum concentration (114 100 ng/mL) was in a sample collected in 1995 from a male worker at a US facility that produced APFO, the ammonium salt form of PFOA (Olsen et al., 2000). In a study by Fu et al. (2016) of fluorochemical-production workers from a chemical plant in Hubei province, China, serum samples collected from 101 workers in the sulfonation department contained some of the highest concentrations of PFOS, with a mean of 14 002 ng/mL (range, 416–118 000 ng/mL). PFOA was also reported in this study; however, concentrations were higher for workers in the electrolytic department than in the sulfonation department, peaking at 32 000 ng/mL (Fu et al., 2016).

Using blood samples collected from workers at a fluoropolymer-manufacturing facility in West Virginia, USA, between 1972 and 2004, Woskie et al. (2012) constructed a job-exposure matrix (JEM) to retrospectively assess exposure spanning from 1950 to 2004. This facility used a process to manufacture certain fluoropolymers, such as PTFE, that involved the use of APFO as a surfactant in the polymerization of tetrafluoroethylene (TFE). Serum PFOA concentrations were highest in workers with tasks involving fine powder and granular PTFE (mean, 5470 ng/mL; range, 90–59 400 ng/mL), whereas workers involved in non-PTFE production (no use of APFO or PFOA) had the lowest serum concentrations (mean, 240 ng/mL; range, 7–4140 ng/mL). However even the latter experienced exposure that far exceeded that of the general population. For example, for the period 2000–2004, the geometric mean serum concentration for non-PTFE (no use of APFO or PFOA) production workers was 140 ng/mL, whereas the median serum concentration for the local community in 2005–2006 was 40 ng/mL, and geometric mean concentrations in adults aged > 20 years in the National Health and Nutrition Examination Survey (NHANES) were about 4–5 ng/mL between 1999–2000 and 2003–2004 (Woskie et al., 2012). Trends over time also differed by job category in modelled output, with exposures in fine powder/granular PTFE chemical operators peaking in 1980 (median serum concentration, > 6000 ng/mL), just before the implementation of exposure control measures. However, workers with only intermittent or background exposure to PFOA experienced higher exposure in 2000 (median serum concentration was estimated at nearly 1600 ng/mL), corresponding with peak production (Woskie et al., 2012).

Exposure in first responders (including firefighters), the second most frequently characterized worker population, is typically described as resulting from interactions with products containing PFAS, most notably AFFF, but exposure from turnout gear or the built environment has also been the subject of recent research (Peaslee et al., 2020; Young et al., 2021). Inhalation, dermal contact, and ingestion (e.g. via hand-to-mouth contact) are potential exposure routes because of contact with the product as well as with dust or air at the fire station and response scene (Mazumder et al., 2023; Rosenfeld et al., 2023). The highest serum concentrations of PFOS were reported among 149 firefighters working at AFFF training facilities in Australia; the mean PFOS concentration was 74 ng/mL (range, 3.4–391 ng/mL), compared with a mean concentration of 12 ng/mL for the general population in Australia. In this study, employment before the 2003 phase-out of PFOS-based AFFF at the facilities was positively associated with PFOS concentrations in serum samples collected in 2013. PFOA was not elevated in this population, with mean serum concentrations of 4.6 ng/mL (range, 0.3–18 ng/mL) (Rotander et al., 2015).

Results from other studies of firefighters suggest that there are differences by type of firefighter, firefighting activity, and geography. PFOS concentrations were higher in airport firefighters, (median, 10.69 ng/mL; range, 4.28–30.42 ng/mL) than in suburban firefighters (median, 4.04 ng/mL; range, 1.57–9.34 ng/mL) from the same geographical region; however, no difference was observed for PFOA (Leary et al., 2020). Burgess et al. (2023) compared serum concentrations collected from firefighters in municipal fire departments in three distinctly different regions of the USA and reported concentrations that were elevated above those reported in NHANES for branched PFOS (sm-PFOS, sum of perfluoromethylheptane sulfonate isomers) in all four departments, as well as linear PFOS (*n*-PFOS) and linear PFOA (*n*-PFOA) in two departments (Burgess et al., 2023). In contrast, PFOS levels were similar to those from NHANES for a sample of 101 male municipal firefighters in California, USA (Dobraca et al., 2015), and lower than those from NHANES in 138 volunteer municipal firefighters in New Jersey, USA (Graber et al., 2021).

In plasma from first responders from New York State and National Guard employees who responded to the collapse of the World Trade Center, New York City, USA, in the terrorist attack of 11 September 2001, PFOA concentrations were approximately twofold those of the general population. In this study, Tao et al. (2008a) used samples collected 6 months to 2 years after the collapse to assess exposure to PFAS categorically according to more and less exposure to smoke or dust. They observed higher PFOA concentrations in smoke-exposed individuals than in dust-exposed individuals, with the highest levels occurring in the group that was more highly exposed to smoke (mean, 10.21 ng/mL; range, 0.67–61 ng/mL). Background PFOA concentrations for 2001–2002 in the USA ranged from a median of 4.7 ng/mL for the full population to a mean of 6.98 ng/mL for non-Hispanic White men (see Section 1.4.3 for exposure in the general population). PFOS was detected in all samples, with mean concentrations ranging from 22.9 to 33.9 ng/mL across the study groups; however, concentrations were not elevated above those in the general US population (median, 25.8 ng/mL) or in the general population in two US cities (in Portland, Oregon, the median was 26.0 ng/mL, and in Boston, Massachusetts, the median was 29.5 ng/mL) (Tao et al., 2008a).

There were few available biomonitoring data for other worker populations. In the Human Biomonitoring for Europe (HBM4EU) project, samples collected in 2018–2019 contained median PFOS concentrations of 4.97 ng/mL (maximum, 1513 ng/mL) in welders and 4.83 ng/mL (maximum, 789 ng/mL) in metal plating workers – an exposure that is anticipated to have resulted from the use of PFOS as a mist suppressant in chrome plating baths (Göen et al., 2024). Shi et al. (2016) reported a median serum PFOS concentration in metal plating workers in China of 40 ng/mL (range, 2.4–1323 ng/mL) (Shi et al., 2016). In a study of workers in shoe and leather-related industries (2011) from the same region of China, mean serum concentrations were 6.93 ng/mL (range, 0.17–117.77 ng/mL) and 14.18 ng/mL (range, 0.05–31.66 ng/mL) for PFOA and PFOS, respectively (Zhang et al., 2011). In a separate study of textile factory workers (2009) in another region of China, the mean blood concentration of PFOA was 5.46 ng/mL (range, 2.35–10.93 ng/mL), and that of PFOS was 5.73 ng/mL (range, 1.34–14.75 ng/mL) (Lu et al., 2014). In the same study, mean concentrations measured in barbers, who may be exposed through the use of products containing PFOA and PFOS, were 3.18 ng/mL (range, 0.78–12.18 ng/mL) and 2.56 ng/mL (range, 0.44–7.72 ng/mL) for PFOA and PFOS, respectively (Lu et al., 2014). PFOA concentrations measured in whole blood from ski-wax technicians working with teams competing in World Cup events in Europe between 2007 and 2011

ranged from 1.9 to 630 ng/mL (mean, 130 ng/mL) (Nilsson et al., 2013a). In this population, for which samples were collected at multiple time points across multiple ski seasons, PFOA concentrations increased in technicians with "low" initial concentrations, but decreased or remained at steady-state in technicians with "high" initial concentrations (Nilsson et al., 2010, 2013a). The median PFOS concentration (12.2 ng/mL) was not elevated when compared with exposure in the general population (Nilsson et al., 2010).

In studies of agricultural workers in China and Sri Lanka, as well as retail and office workers in the USA, concentrations of PFOA and PFOS have been reported that are similar to those in the corresponding general population (see Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636) (Guruge et al., 2005; Fraser et al., 2012; Zhou et al., 2014; Wu et al., 2019; Clarity et al., 2021), with the exception of commercial fishery workers in China, for whom the potential for a large dietary exposure through consumption of employer-provided fish probably contributed to the mean serum PFOS concentration of 11 400 ng/mL (range, 82.6–31 400 ng/mL) (Zhou et al., 2014).

Although biomonitoring data collected over time and by occupation or industry were relatively limited, the available data indicated the potential for exposure to PFOA and PFOS in diverse occupational settings, including primary (e.g. fluorochemical production) and secondary (e.g. metal plating, textile mill) manufacturing, public safety (e.g. firefighters) and services (e.g. ski-wax technicians, barber). The exposure characterization was the most robust for fluorochemical-production workers, followed by first responders. Although the magnitude of exposure in these populations differed substantially, there was evidence for intrapopulation differences in exposure by task or activity, with higher concentrations being measured in workers with tasks or activities involving known contact with materials containing PFOA or PFOS.

[The Working Group noted that blood concentrations across occupational populations differ by orders of magnitude. For example, median concentrations of PFOA and PFOS reported for fluorochemical-production workers are often 100 to 10 000 times as high as those of firefighters, depending on the study. The Working Group also noted that PFOA and PFOS have primarily been measured in worker populations with a known source of exposure (e.g. manufacturing of fluorochemicals, use of AFFF); the absence of data for the many occupations with the potential for PFOA and PFOS exposure is not evidence of the absence of exposure.]

(b) Industrial hygiene samples

Characterization of PFOA and PFOS in the work environment, for example through air samples, is limited by the availability and consistency of methods (see Section 1.3) and comparable data. Although large variability exists in the reported concentrations, measures of the work environment, including samples of workplace air, dust, surfaces, and other work-related materials, frequently contain higher concentrations of PFOA and PFOS in facilities engaged in manufacturing or use of PFAS-laden products (such as fluorochemical production, secondary manufacturing, firefighting, and ski-wax application) than in other occupational environments (such as offices, schools, retail stores, and hotels). In these studies, measurement of PFOA and PFOS is often accompanied by measurement of related or precursor compounds (see Section 1.4), such as fluorotelomer alcohols (e.g. 8:2 FTOH), fluorotelomer sulfonic acids (e.g. 8:2 FTS), sulfonamides (e.g. *N*-EtFOSA), and phosphoric acid diesters (e.g. 8:2 diPAP) (Christensen and Calkins, 2023). Precursor compounds such as these may transform in the environment or the body to PFOA, PFOS, or other PFAS (Kolanczyk et al., 2023). For

additional information on the toxicokinetics of PFOA and PFOS, see Section 4.1.

Occupational exposure at a chemical plant in Hubei province, China, was described by Gao et al. (2015) as indicating higher concentrations of PFOS than PFOA in indoor dust, with geometric mean concentrations of 830 ng/g dust (range, LOD to 658 343 ng/g dust) and 360 ng/g dust (range, 41.3–85 139 ng/g dust), respectively. However, the reverse was observed in total suspended particles, with geometric means of 0.4 ng/m^3 (range, 0.03–78 ng/m^3) and 0.94 ng/m^3 (range, 0.04–1123 ng/m^3) for PFOS and PFOA, respectively (Gao et al., 2015). At a facility producing APFO and PFOA in the USA, Kaiser et al. (2010) reported an 8-hour time-weighted average (TWA) median air concentration of 34 µg/m^3 (range, 4–65 µg/m^3) measured near the process sumps. Concentrations were higher at lower pH and water levels. They also reported that the sublimation rate measured for PFOA (360 µg/hour) was higher than that for APFO (0.302 µg/hour) (Kaiser et al., 2010).

In the studies on ski-wax technicians, personal breathing zone samples collected over three ski seasons spanning 2007 to 2010 contained higher concentrations of 8:2 FTOH (a precursor to PFOA) than PFOA, with concentrations ranging from 0.834 to 997 µg/m^3 and from 0.027 to 14.9 µg/m^3 for 8:2 FTOH and PFOA, respectively. Area aerosol samples did not contain FTOH; however, PFOA concentrations were higher in the inhalable fraction than the respirable fraction, with mean concentrations of 16 µg/m^3 (range, 2.11–52.8 µg/m^3) and 9.91 µg/m^3 (range, 0.62–26.8 µg/m^3), respectively (Nilsson et al., 2013b). The metabolism of FTOH to PFOA in workers' blood was supported by the presence of FTOH degradation products, 5:3 FTCA and 7:3 FTCA, in the blood of workers in this study (Nilsson et al., 2013a). Although concentrations were lower, Freberg et al. (2010) reported a similar relationship between inhalable and respirable fractions, with PFOA concentrations ranging from 5.1 to 35 ng/m^3 and 5.6 to 38 ng/m^3 in inhalable and respirable fractions, respectively. PFOA was detected at higher concentrations in powder wax (median, 2.7 µg/g product; range, 0.29–12 µg/g) than in solid block wax (median, 0.68 µg/g product; range, < LOQ to 3.8 µg/g). PFOS was not detected in any dust samples and was only detected in a few of the powder ski-wax samples (maximum, 0.149 µg/g) (Freberg et al., 2010).

Hall et al. (2020) reported higher concentrations of PFOA and PFOS in dust samples collected from 49 fire stations across the USA and Canada than in samples from 184 homes in North Carolina, with median (and maximum) concentrations in fire stations and homes of 17.6 ng/g dust (maximum, 791 ng/g dust) and 7.9 ng/g dust (2350 ng/g dust) for PFOA, respectively and 64.5 ng/g dust (74 370 ng/g dust) and 4.4 ng/g dust (2810 ng/g dust) for PFOS, respectively (Hall et al., 2020). Within fire stations, concentrations of the PFOS precursor, *N*-ethyl-perfluorooctane sulfonamido acetic acid (*N*-EtFOSAA), in dust were higher in living areas (median, 87.5 ng/g dust; range, 0.748–1800 ng/g dust) than in gear storage (median, 7.84 ng/g dust; range, < MDL to 299 ng/g dust) or the apparatus bay (median, 3.51 ng/g dust; range, < MDL to 159 ng/g dust) (Young et al., 2021). Using silicone wristbands worn while on- or off-shift, Levasseur et al. (2022) reported that PFOS concentrations while on-duty and responding to fires were 2.5 times as high as off-duty exposures; however, PFOA concentrations while on-duty and responding to fires were lower than off-duty exposures (Levasseur et al., 2022). When analysing textiles used in new firefighter personal protective equipment (PPE), Maizel et al. (2023) detected PFOA and PFOS in 7 of 20 textiles tested, with concentrations all < 2 ng/g. However, the highest concentrations were reported for precursor compounds, including 6:2 fluorotelomer methacrylate (mean, 1570 ng/g), 6:2 FTOH (mean, 613 ng/g), and 6:2 fluorotelomer sulfonic acid (mean, 393 ng/g). In

a separate study of PPE worn by firefighters, sets of used and unused turnout gear thermal liners, moisture barriers, and outer shells were analysed. PFOS levels were largely below the LOD, but PFOA was detected at higher concentrations than other PFAS, with the highest concentration measured in a used thermal liner from trousers worn in 2014 (850 ppb) (Peaslee et al., 2020).

Area air and dust collected over 17 days in 2014 from a speciality, water-repellent textile-manufacturing facility in China were analysed for PFOA, PFOS, and numerous precursor compounds. Heydebreck et al. (2016) reported higher concentrations in the gas phase than the particle phase in air samples, with generally lower concentrations in settled dust. Fluorotelomer alcohols (8:2 FTOH and 10:2 FTOH) were the dominant analytes measured in workplace air, with the highest concentrations reported for 8:2 FTOH from heat setting (91.3 μg/m^3) and drying (87.7 μg/m^3) operations in one of the workshops, two processes that occur after the durable water-repellent coating has been applied to the textile. PFOA was the ionic PFAS measured at the highest concentrations in workplace air, with highest concentrations measured during the drying operation in the same workshop (8.48 ng/m^3). PFOS was generally below the method detection limit (5.33 ng/g) (Heydebreck et al., 2016).

Some studies have described exposure in occupational environments where the exposure sources are similar to sources for the general public, such as through direct contact or contact with dust from consumer products (e.g. clothing) or the built environment (e.g. carpets). In these settings, exposures vary across studies of classrooms, offices, and retail stores. In the UK, Goosey and Harrad (2011) reported higher concentrations of PFOS in dust collected from classrooms (mean, 980 ng/g dust; range, 22–3700 ng/g dust) than from offices (mean, 370 ng/g dust; range, 20–1000 ng/g dust). Concentrations of PFOA were variable in classrooms, (mean, 310 ng/g dust; range, 18–1700 ng/g dust), and in offices (mean, 550 ng/g dust; range, < LOD to 6000 ng/g dust) (Goosey and Harrad, 2011). PFOA has been reported to be the predominant compound in samples analysed for perfluoroalkyl carboxylic and sulfonic acids from electronic shops, offices, libraries, and internet cafés (Besis et al., 2019), and to be present at higher concentrations in office than in residential settings. However, this is not the case for PFOS (D'Hollander et al., 2010; Goosey and Harrad, 2011; Fraser et al., 2012). In office settings, Fraser et al. (2012) reported a strong positive association between FTOHs measured in office air and serum PFOA concentrations measured in office workers, with geometric mean air concentration of 8:2 FTOH of 9.92 ng/m^3 (range, 0.28–70.6 ng/m^3).

In the only study of dermal exposure, skin exposure to the pesticide sulfluramid (*N*-EtFOSA), a precursor of PFOS, in pesticide manufacturing workers during an 8-hour shift was measured at six different locations across the body. Exposure was greatest on the hands, with a mean of 89.7 μg/day, followed by the left leg (73.0 μg/day) and arms (72.1 μg/day); however, there was substantial variability (Machado-Neto et al., 1999).

(c) Protection measures to limit exposure

Approaches to reducing occupational exposures are commonly categorized into the hierarchy of controls – an effectiveness-based hierarchy of actions. This framework categorizes elimination and substitution as the most effective risk management measures, with PPE considered the least effective because of reliance on correct and consistent use by individual workers (NIOSH, 2023). Effective control measures have been documented in research studies involving fluorochemical-production facilities and ski waxing. For both industries, the use of local exhaust ventilation near the exposure source was linked to reductions in PFAS exposure. Other measures that led to reductions included

maintaining pH levels above 7 to reduce volatilization potential and wetting PFAS-containing dry powders at fluorochemical-production facilities, and replacing powder wax with block wax at ski-waxing facilities (Christensen and Calkins, 2023). The retrospective assessment by Woskie et al. (2012) demonstrated that, despite increases in production between 1980 and 2000, incorporation of exposure controls such as engineering and PPE resulted in decreasing serum concentrations in workers in the most highly exposed job category (Woskie et al., 2012). [The Working Group noted that the implementation of effective control measures may affect occupational exposures, including those relevant to epidemiological studies. In this case, samples collected after the implementation of effective controls may not be representative of exposures that occurred under prior conditions (and vice versa).]

1.4.3 Exposure of the general population

The general population is exposed via multiple sources to PFOA and PFOS and, given their widespread use, environmental contamination, and long persistence, both compounds are detectable in the blood of virtually all people tested (OECD, 2015b). Serum or plasma are the most common biological matrices used in biomonitoring campaigns. Long-chain PFAS such as PFOA and PFOS are not commonly measured in urine or breast milk samples, because of the lack of sensitivity of most available analytical tools (Worley et al., 2017) (see Section 1.3.4).

Measured levels in whole blood, serum or plasma are useful indicators of exposure since they reflect accumulated intake from all sources and, given the long half-lives of PFOA and PFOS, they are quite stable indicators of body burden (see also Section 4.1). Where people are exposed to a local substantial source of PFOA or PFOS, such as contaminated drinking-water, or occupational exposure, such exposure will be the main source (Pitter et al., 2020). For the general population not living close to a major point source, measured serum levels will reflect diverse exposure sources, including food, water, air, indoor dust, and consumer products. Also, individual serum levels will vary, reflecting not only degree of intake but individual variability in efficiency of uptake, distribution, and excretion (Section 4.1).

(a) Human exposure estimation

The general population is exposed via the diet, drinking-water, household dust, consumer products, and inhalation of contaminated air (Sunderland et al., 2019; De Silva et al., 2021). [The Working Group noted that the data presented in this section mainly draw from studies performed after 2000. Extrapolation to earlier points in time was difficult because of the sparse data available before 2000.] When drinking-water is contaminated by a specific pollution source with high emissions, drinking-water is the main exposure source. For example, in the Mid-Ohio Valley "C8" study population in the USA, the principal PFOA exposure source was drinking-water. In the most highly contaminated water district, the population's PFOA serum levels were 17-fold those in the water district with the lowest contamination, and drinking-water was the main contributor to the total body burden (Steenland et al., 2009).

For general populations without a recognized emission source or not living in a highly contaminated location, several studies have sought to estimate the relative importance of different exposure sources, and these are summarized in Table 1.16 and Table 1.17. Some of the studies have in addition estimated the possible pathways of exposure. There was some variability in the dietary contribution but, in all cases, diet has been estimated to be the most important exposure source. Exposure can derive both from the food being contaminated from uptake during growing or grazing, and from migration from food packaging materials (see Section 1.4.1(d)).

Table 1.16 Estimated relative contribution (%) of various routes of exposure to total PFOA in the general population

Location, sampling time	Relative contribution of exposure route (%)							Comments	Reference
	Oral				Inhalation	Dermal	Via precursors		
	Diet	Dust	Water	Food packaging					
Germany, 2005; Japan, 2004	85	6	1	3			2–8		Vestergren et al. (2008); Vestergren and Cousins (2009)
Norway, 2008	84	5	11		0.13				Haug et al. (2011)
USA, 2003/2004	66	9	24		< 1	< 1			Lorber and Egeghy (2011)
North America, Europe, Republic of Korea, Japan 2007/2008	47	8	12		6		27[a]		Gebbink et al. (2015)
Republic of Korea, 2009	41		37		22		5		Tian et al. (2016)
China, 2013/2014	> 99		< 1						Shan et al. (2016)
Finland, 2005/2006, 2010/2011, 2014/2015	95	< 2.5			< 2.5			Children aged 10 years	Balk et al. (2019)
Ireland, 2016/2017/2018	NR	1	37		62			Adults	Harrad et al. (2019)
	NR	3	74		23			Children	
Norway, 2013/2014	92	4			3	< 1			Poothong et al. (2020)

NR, not reported; PFOA, perfluorooctanoic acid.; USA, United States of America.
[a] Value given for the intermediate exposure scenario; estimated contribution varied according to exposure scenario from 13% to 64%.

In 2020, the European Food Safety Authority made an assessment of exposure of the European population to several PFAS, including PFOA and PFOS, on the basis of data available concerning the presence of these PFAS in different food categories and on consumption data (EFSA Panel on Contaminants in the Food Chain, 2020). For the lower-bound scenario, which was considered the most realistic by the panel, median dietary exposure to PFOA was estimated to range between 0.17 and 0.41 ng/kg body weight (bw) per day for different age categories (Table 1.18). Median dietary exposure to PFOS for the same scenario was estimated to range between 0.36 and 1.34 ng/kg bw per day. Similar average intakes were estimated in the Netherlands: 0.2 ng/kg bw per day for PFOA and 0.3 ng/kg bw per day for PFOS (Noorlander et al., 2011). In both studies and for both compounds, mean dietary exposure was highest for toddlers (defined as children aged 1–3 years).

In a study conducted in the USA in 2020 (Zheng et al., 2020), the occurrence and distribution of PFAS, including PFOA and PFAS, was determined in the childcare environment (dust and nap mats), and children's exposure

Table 1.17 Estimated relative contribution of various routes of exposure to total PFOS in the general population

Location	Relative contribution of exposure route (%)							Comments	Reference
	Oral				Inhalation	Dermal	Via precursors		
	Diet	Dust	Water	Food packaging					
USA, 2003/2004	72	6	22		< 1	< 1			Egeghy and Lorber (2011)
Norway, 2008	96	1	1		2				Haug et al. (2011)
North America, Europe, Republic of Korea, Japan 2007/2008	66	10	7		2		16[a]		Gebbink et al. (2015)
Republic of Korea, 2009	93		4		3				Tian et al. (2016)
China, 2013/2014	100		< 1						Shan et al. (2016)
Finland, 2005/2006, 2010/2011, 2014/2015	95	< 2.5			< 2.5			Children aged 10 years	Balk et al. (2019)
Ireland, 2016/2017/2018	NR	21	30		49			Adults	Harrad et al. (2019)
	NR	55	35		10			Children	
Norway, 2013/2014	75				3				Poothong et al. (2020)

PFOS, perfluorooctanesulfonic acid; USA, United States of America.
[a] Value given for the intermediate exposure scenario; estimated contribution varied with exposure scenario from 11% to 33%.

through dust ingestion and dermal absorption was estimated. The estimated daily intake of PFOA through dust ingestion for toddlers was 0.03 ng/kg bw per day (median value). In the case of dermal absorption, the estimated daily intake was 0.002 ng/kg bw per day (median value). For PFOS, the equivalent values were 0.002 and 0.001 ng/kg bw per day, respectively (Zheng et al., 2020). A modelling exercise for US children and adults considered both direct exposure to PFOS and exposure to precursors. Median adult intake was 4.2 ng/kg bw per day, about half of which was from precursors. This estimate was validated by comparing with intake calculated from a one-compartment pharmacokinetic model with a range of values for the volume of distribution (V_d). With the more plausible V_d values (see Section 4.1), agreement was quite close (Egeghy and Lorber, 2011).

For some individuals, a considerable part of the intake could be from personal care products and cosmetics (Husøy et al., 2023). [The Working Group noted that recent data suggested that dermal uptake is likely to be higher than was previously assumed (see Abraham and Monien, 2022, and Section 4.1).]

(b) Biomonitoring data for the general population (serum and plasma)

Repeated population surveys with the aim of measuring PFOA and PFOS concentrations in serum or plasma, or in archived blood samples,

Table 1.18 Median dietary exposure to PFOA and PFOS for different age groups in the population of Europe

Age group[a]	Dietary exposure (ng/kg bw per day)[b]	
	PFOA	PFOS
Infants	0.19	0.36
Toddlers	0.41	1.34
Other children	0.30	1.02
Adolescents	0.17	0.53
Adults	0.18	0.58
Elderly adults	0.17	0.59

bw, body weight; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.
[a] Age ranges: infants, < 12 months; toddlers, ≥ 12 to < 36 months; other children, ≥ 36 months to < 10 years; adolescents, ≥ 10 to < 18 years; adults: ≥ 18 to < 65 years; elderly, ≥ 65 to < 75 years; very elderly, ≥ 75 years.
[b] Only the lower-bound estimates are presented since these were considered to be more realistic by the European Food Safety Authority Panel.
From EFSA Panel on Contaminants in the Food Chain (2020).

have permitted exposure trends to be observed in several countries (Fig. 1.7). For most studies, estimated total PFOS or PFOA concentrations are presented, but more recent studies present concentrations of isomers, distinguishing linear and different branched isomers, more commonly for PFOS than PFOA (e.g. NHANES, 2023).

In Japan between 1983 and 1999, results for PFOA showed a clear trend, with geometric mean concentrations in men rising from [2.5 to 11] ng/mL, and in women from [1.8 to 8.1] ng/mL, corresponding to a mean annual increase of 0.49 and 0.42 ng/mL, respectively. For PFOS, there was no clear trend, with mean concentrations in the range of approximately [15–23] ng/mL for men and [13 to 19] ng/mL for women (Harada et al., 2007).

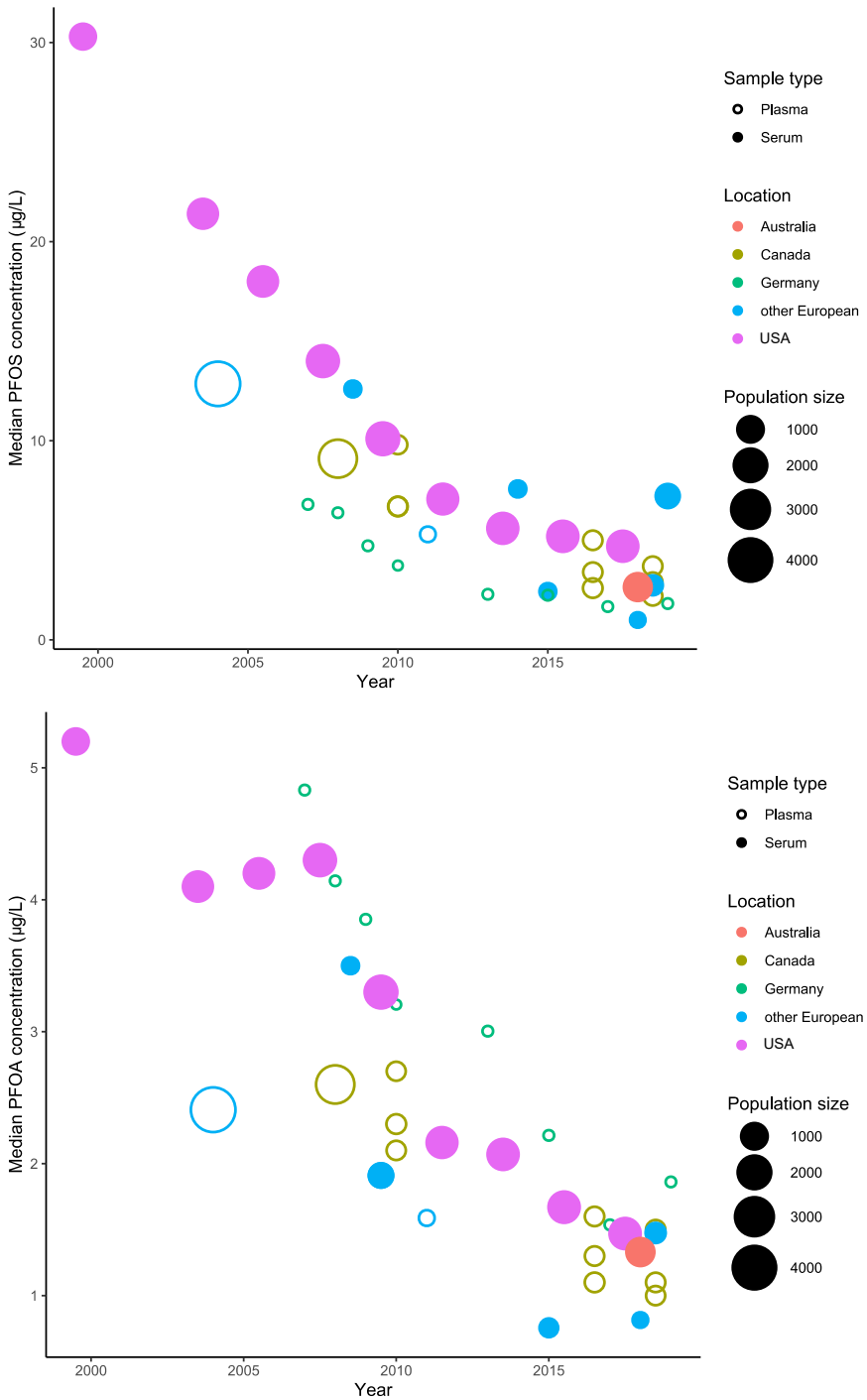
In China, in the region of Shenyang, the results of a study from 2006 showed mean PFOS concentrations of 142 ng/mL (range, 31.7–225 ng/mL) for men and 170 ng/mL (range, 80.4–310 ng/mL) for women (Yeung et al., 2006). Concentrations of PFOS in a previous study (Jin et al., 2003) were 40 ng/mL (range, 5.32–145 ng/mL) for men and 45.5 ng/mL (range, 10.6–142 ng/mL) for women. On this basis, PFOS concentrations measured in the study conducted in 2006 were 3–4 times as high as those reported in the previous study (Yeung et al., 2006).

In the USA, analysis of archived blood samples collected in 1974 (serum) and 1989 (plasma) from volunteer participants in a large community health study indicated an increase in PFOA concentrations from median values of 2.3 µg/L in 1974 to 5.6 µg/L in 1989; for PFOS, the equivalent figures were 29.5 µg/L in 1974 and 34.7 µg/L in 1989 (Olsen et al., 2005).

A unique study reporting PFOA and PFOS concentrations in the same 59 individuals over a long time period in Tromsø, Norway, showed clear trends (Nøst et al., 2014). Samples were collected in five rounds – in 1979, 1986, 1994, 2001, and 2007 – and for both PFOA and PFOS, average concentrations peaked in 2001. Correlations were high between each pair of subsequent rounds for both PFOA and PFOS (Spearman correlation, ρ, in the range 0.6–0.8; all $P < 0.05$), indicating some stability in exposure as determined by single measurements (Nøst et al., 2014).

Trends towards falling concentrations in the last 20–30 years have been shown in several countries (Fig. 1.7). For example, data from the USA derived from NHANES, a large national biomonitoring programme with repeated sampling cycles that has included PFAS in monitoring campaigns

Fig. 1.7 Median PFOA and PFOS concentrations reported in blood samples from the adult general population in several countries



PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; USA, United States of America.
Data aggregated from HBM4EU (2023), CDC (2023), and Government of Canada (2023).

since 1999, have shown this trend very clearly. For PFOA, geometric mean serum concentrations were 5.2 µg/L in 1999–2000, close to 4 µg/L between 2003 and 2008, then declined steadily in subsequent rounds, falling to 1.42 µg/L in 2017–2018. Equivalent trend data were observed for PFOS, with geometric mean serum concentrations of 30.4 µg/L in 1999, falling in each survey, down to 4.3 µg/L in 2017–2018 (Kato et al., 2011; NHANES, 2023). A similar pattern with downward trend was reported for PFOA and PFOS concentrations measured in archived blood spots collected in 1997–2007 from infants in New York, USA (Spliethoff et al., 2008).

A decreasing trend was also observed in Australia (Toms et al., 2014; Eriksson et al., 2017), Japan (Okada et al., 2013), and in several countries in the EU (Fig. 1.7).

In Norway, a steady increasing trend for PFOA concentrations in serum was observed from 1977 (0.58 µg/L) up to the 1990s (5.2 µg/L in 1993), then a decline to 2.7 µg/L in 2006. For PFOS, serum concentrations rose from 3.8 µg/L in 1977 to 33 µg/L during the 1990s, falling to 12 µg/L by 2006 (Haug et al., 2009).

In Germany, data from archived plasma samples from 20 participants (10 men and 10 women) randomly chosen from the monitoring programmes in Münster between 1982 and 2010 were analysed; PFOA concentrations were found to be highest in 1986 (7.4 µg/L) and decreased from 2007 (5.2 µg/L) to 2010 (3.1 µg/L), but in other years there were no clear trends. For PFOS, the pattern was clearer, rising from 15.4 µg/L in 1982 to 28.6 µg/L in 1989, and subsequently falling steadily to 12.7 µg/L in 2005 and 3.8 µg/L in 2010 (Schröter-Kermani et al., 2013).

A similar pattern of decline since 2000 is evident in data assembled from many recent smaller studies across Europe. In the HBM4EU project, data were assembled across 12 European countries, combining 32 different surveys. The surveys were not all directly comparable because of variation in the age and sex composition, but together they provided a picture of falling serum levels over time and exposure ranges between countries at the same points in time (HBM4EU, 2023). In this European project, although early studies were sparse (with only one study including data from 2000), PFOA body burdens were comparable to US NHANES results, with PFOA concentrations in the range of 3 to 6 µg/L up to around 2010, falling to 1 to 2 µg/L in recent years. For PFOS, levels in the EU were somewhat lower than in the USA, being mainly between 6 and 10 µg/L around 2010 for the European data, falling to between 1 and 3 µg/L in recent years (CDC, 2023; HBM4EU, 2023) (Fig. 1.7).

Exposure data for teenagers in this EU project suggested that exposure levels were significantly higher in north and west Europe than in the south and east. Concentrations of PFOA and PFOS were significantly higher in boys than in girls, and significantly higher concentrations were found in teenagers from households with a higher education level. In the same EU project, the consumption of seafood and fish at least twice per week was significantly associated with a 21% (95% CI, 12–31%) increase in PFOS concentrations. The same trend was observed for PFOA but was not statistically significant (Richterová et al., 2023).

PFOA and PFOS levels have been shown to vary by age and sex (Frisbee et al., 2009; Kato et al., 2011; Pitter et al., 2020; NHANES, 2023). Serum levels are consistently higher in males than females, reflecting differences in excretion (with women excreting additionally via menstruation, pregnancy and lactation), and possibly differences in intake and pharmacokinetics (see Li et al., 2022c, and Section 4.1). By age, serum levels measured in cross-sectional surveys showed some differences, with older people having higher serum levels. This may reflect variation in the routes of exposure according to age and biological changes, but the time trends of exposure would also be important, given the long half-lives in people. Infants can have high levels from

maternal and lactational transfer that fall in the post-lactation period (Fromme et al., 2010).With emissions and ambient levels falling, higher levels in older people will in part reflect the fact that they were exposed at earlier time periods when intake was likely to be higher (Nøst et al., 2014). In NHANES data for 1999–2000 and 2003–2004, a modest increasing slope was evident in PFOS levels from age 12 to ≥ 60 years, but no slope was evident for PFOA (Calafat et al., 2007). In the Mid-Ohio C8 population, which had a wider age range, there was a clear increasing trend from age < 10 to ≥ 80 years for PFOS levels in males, but for females the trend was decreasing until age 30–39 years, then rising thereafter (Frisbee et al., 2010). For PFOA, concentrations in females are lower than in males in most age groups, but both males and females show a similar pattern, with a minimum at around age 30 years.

NHANES also provided information on ethnicity: there were some small differences between White and Black people, but PFOS levels were markedly lower for Hispanic people, with smaller differences for PFOA (Calafat et al., 2007).

[The Working Group noted that although there were differences between countries, the overall pattern in general population serum or plasma samples across the world has been a rise in concentrations since the earliest measurements in the 1970s, reaching a peak in the 1990s or close to 2000. Subsequently, trends towards falling serum concentrations have been observed for both PFOA and PFOS. The most notable difference between countries was a higher level of PFOS in earlier samples from the USA compared with other countries.]

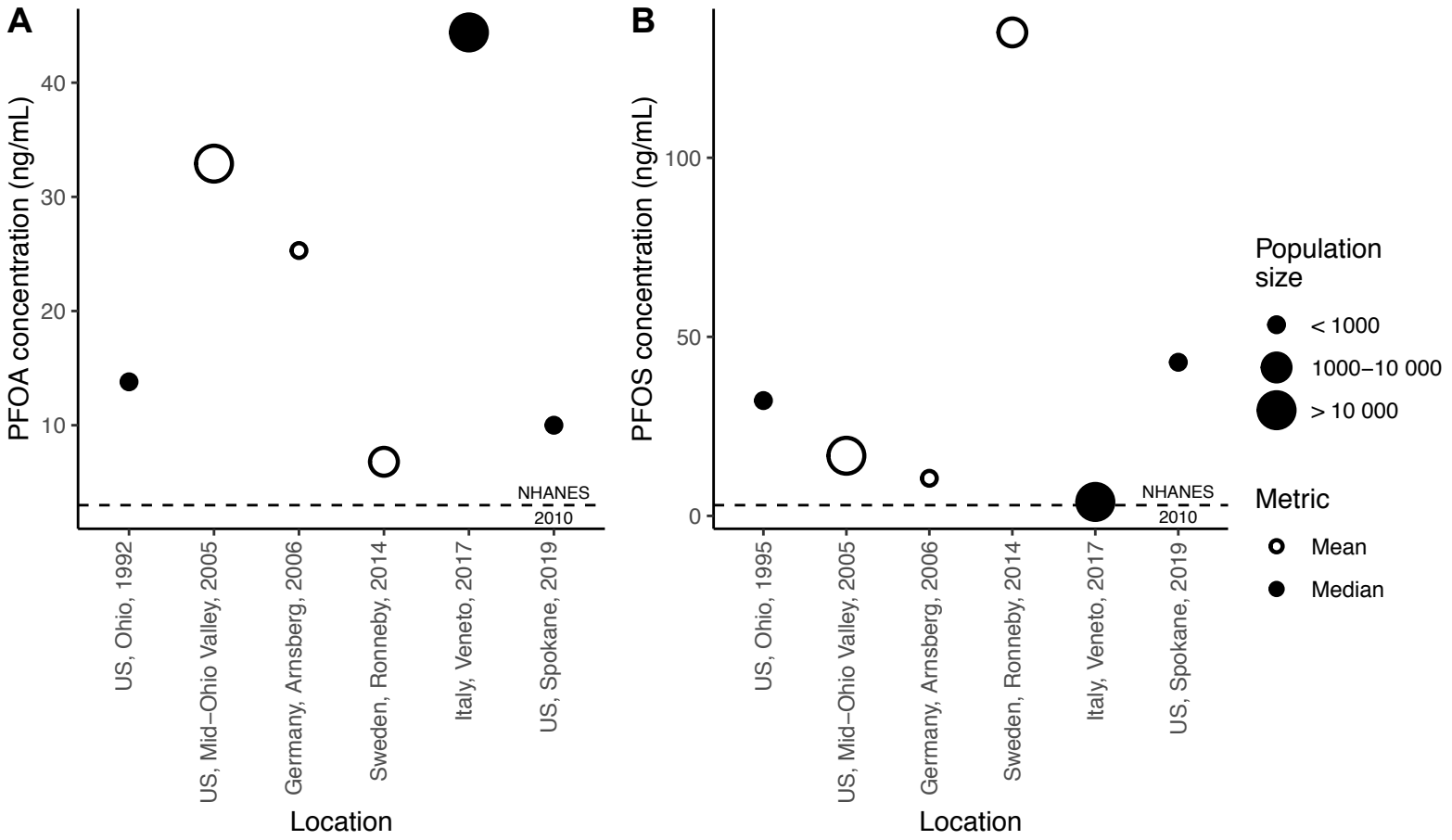
Multiple PFAS with long half-lives and slow rates of excretion, such as PFOA and PFOS, have been monitored in serum samples. Serum concentrations tend to be correlated with each other; for example, logarithmic concentrations showed a significant Pearson correlation coefficient of 0.66 between PFOA and PFOS in the NHANES data (Calafat et al., 2007). Correlation coefficients for circulating PFOA and PFOS levels were similar in several general populations in the cancer studies reviewed in Section 1.6.1, but there was large variability, with values ranging from < 0.15 to > 0.7 (see Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636). There were also significant correlations with other widespread PFAS with long half-lives, notably perfluorononanoic acid (PFNA) and perfluorohexanesulfonic acid (PFHxS). [The Working Group noted that these correlations may reflect a correlation in exposure or a correlation between different PFAS in individual rates of uptake and excretion.]

(c) Biomonitoring data for populations living at contaminated sites

Several large communities have experienced high exposure to PFAS because of environmental contamination, related mainly to the use fire-fighting foams containing PFAS (e.g. airports, military facilities), certain industrial facilities where PFAS are produced or used and emitted to the environment, and sites related to PFAS-containing waste (Salvatore et al., 2022). This has led to higher blood concentrations of PFOA and PFOS in some of these communities compared with the general population (see Fig. 1.8).

In the USA, high serum concentrations of PFOA were measured in samples collected in 2005–2006 from 69 030 residents living near a PTFE-production facility in West Virginia, USA (the C8 Health Project); the overall geometric mean was 32.9 μg/L, and the arithmetic mean was 82.9 μg/L. Exposures in that community varied substantially across six water districts; the mean serum concentration of PFOA was 16 μg/L in the two water districts with the lowest concentrations of PFOA in water, and 228 μg/L in the water district with the highest concentrations (Frisbee et al., 2009).

Fig. 1.8 PFOA (A) and PFOS (B) concentrations reported in blood samples from the general population in areas reported to be polluted with PFAS



NHANES, National Health and Nutrition Examination Survey; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; US, United States.

The dotted line shows the respective concentration measured in the NHANES population in 2010 (NHANES, 2023). For the individual study populations, see ATSDR (2023), Pitter et al. (2020), Ingelido et al. (2010), Hölzer et al. (2008), Frisbee et al. (2009), Xu et al. (2021b), and Herrick et al. (2017).

Also in the USA, as early as the 1970s, the Fairchild Air Force Base located in the City of Airway Heights in Spokane County, Washington, used AFFF containing PFAS during firefighter training. Over time, PFAS from the AFFF entered the ground, moved into the groundwater to off-site locations, and affected nearby municipal wells. In samples from 2019, geometric mean PFOA and PFOS serum concentrations of 9.72 μg/L and 42.4 μg/L, respectively, were reported for community residents (ATSDR, 2023).

In China, a lake adjacent to a fluorochemical-production factory was contaminated with PFAS, and serum concentrations of several PFAS were assessed in fishermen and their families who were exposed primarily via eating locally caught fish (Zhou et al., 2014). Among family members of fishery employees, extremely high PFOS levels were found, with a median concentration of linear PFOS of 2720 ng/mL, branched PFOS of 620 ng/mL, and sum of PFOS of 3540 ng/mL. PFOA concentrations were slightly elevated, with a median of 11.7 ng/mL.

At the end of 2013, drinking-water from one of the two municipal waterworks in Ronneby, Blekinge County, Sweden, was found to be contaminated by firefighting foams used at a nearby military airfield. Drinking-water containing high levels of PFOS and PFHxS, and to a lesser extent PFOA, had been distributed to approximately one third of Ronneby households (total population, approximately 30 000) since the mid-1980s (Xu et al., 2021b). Blood samples and demographic data were collected from 3297 Ronneby residents and 226 individuals from a reference group. The population geometric means for serum PFOA and PFOS concentrations were 6.8 and 135 μg/L for all Ronneby residents, i.e. 35 and 4.5 times, respectively, as high as for the reference group (Xu et al., 2021b).

In spring 2013, groundwater of part of the Veneto region in north-eastern Italy was found to be contaminated with mostly PFOA and to a smaller degree with PFOS and other PFAS from a factory that had been manufacturing a variety of PFAS since the 1960s. A population of 140 000 was potentially affected, and a population-based screening programme including measurement of serum PFAS was offered by the regional health service to residents who were exposed to PFAS via contaminated drinking-water (Ingelido et al., 2018). Among 18 122 subjects aged 14–39 years living in the Veneto region, the median concentration of PFOA was elevated, at 44 μg/L (Pitter et al., 2020), whereas the median concentration of PFOS, 3.9 μg/L, was close to levels reported for the Italian general population (Ingelido et al., 2010).

A study of 641 residents of Arnsberg, Germany, in 2006 reported geometric mean PFOA serum concentrations of 22.1, 23.4, and 25.3 μg/L in children, mothers, and men, respectively, because of surface water contamination from upstream agricultural use of soil conditioner mingled with industrial waste (Hölzer et al., 2008). PFOA levels of children and adults living in Arnsberg were 4.5–8.3 times as high as those of the reference population used in the study and living in non-contaminated sites (Hölzer et al., 2008).

(d) Other biological matrices used in biomonitoring

Although serum samples are most commonly used in biomonitoring campaigns, PFOA and PFOS have also been measured in other biological matrices, such as breast milk and urine. [The Working Group noted that these biological matrices could also be used in biomonitoring, particularly in biomonitoring campaigns performed in highly contaminated sites.]

PFOA and PFOS have been detected in breast milk, which is a significant route of exposure to infants through breastfeeding. [The Working Group noted that concentrations in breast milk are much lower than in serum; however, the large volume of breast milk ingested by infants on a

body-weight basis results in considerable exposure.] In a study of 109 paired maternal serum and breast milk samples in a population with high PFAS exposure in Sweden, breast milk concentrations were 0.03 ng/mL for PFOA and 0.130 ng/mL for PFOS (Blomberg et al., 2023). The transfer efficiency or ratio of breast milk to serum concentration was 2.16% for PFOA and 1.02% for PFOS (Blomberg et al., 2023). In a summary of 23 studies, all except 4 reported concentrations in breast milk that were above the LOQ in > 50% of samples; however, LOQs varied between studies (Fromme et al., 2022). Median values above the LOQ for PFOA were 7.2, 26, and 138 ng/L for three studies in Spain (Serrano et al., 2021; Motas Guzmàn et al., 2016; and Beser et al., 2019, respectively), and median values were 139, 121 and 35 ng/L in three studies in China (Awad et al., 2020; Liu et al., 2010, 2011). Median values for PFOA in two studies in the USA were 14 and 36 ng/L (Tao et al., 2008b; Zheng et al., 2021). In a study of a contaminated site in Germany, PFOA could be quantified in all breast milk samples, with a mean value of 199 ng/L (range, 33–854 ng/L) (Fromme et al., 2022). PFOS was observed in only 3 out of 13 samples, at levels of 33 ng/L, 35 ng/L, and 61 ng/L.

PFOA and PFOS can be detected in urine, although concentrations in urine are much lower than in serum. In a study of 104 paired samples in a population with high PFAS exposure in Sweden, the median ratio of urinary to serum level was 0.23% for PFOA and 0.07% for linear PFOS and ranged from 0.02% to 0.07% for branched PFOS. Median urinary concentrations for the three sampling rounds carried out were between 0.017 and 0.025 ng/mL for PFOA and between 0.050 and 0.075 ng/mL for PFOS (Li et al., 2022c). In general population campaigns, values in urine samples are mostly below the LOD. In the NHANES 2013–2014 round, urine levels were above the LOD (0.1 ng/mL) for < 0.1% of the population, even though serum levels were above the LOD for almost 100% of participants (Calafat et al., 2019).

[The Working Group noted that PFOA and PFOS have been measured in other biospecimens, such as nails, hair, and semen, but these have rarely been used to assess exposure for epidemiological studies.]

1.5 Regulations and guidelines

Regulations, guidelines, and guidance for PFOA and PFOS have been established by international, national, and local governing bodies, as well as nongovernmental organizations (e.g. standards, non-profit, and professional organizations). The aim is to reduce human exposure and environmental contamination via approaches covering production, use, and disposal; occupational exposures; food and consumer products; environmental media; and biomonitoring. Unless otherwise stated, numerical standards and guidelines for PFOA and PFOS are generally based on non-cancer effects.

Internationally, PFOS and PFOA and their salts derivatives are recognized as persistent organic pollutants and were included in the Stockholm Convention on 2009 and 2019, respectively. PFOS is listed under Annex B (Restriction) (measures must be taken to restrict production and use), whereas PFOA is listed under Annex A (Elimination) (measures must be taken to eliminate production and use) (UNEP, 2023).

Various regions and countries have also specific regulations in place to prevent the use of PFAS such as PFOA and PFOS (OECD, 2023b). More detailed information on the actions being developed and on regulations in place in each country or region can be found in the supplementary material (Annex 2, Actions and regulations for the elimination of PFAS worldwide, available from: https://publications.iarc.who.int/636).

Table 1.19 Occupational exposure thresholds for PFOA, APFO, and PFOS, by country

Country	PFOA (mg/m³)		APFO (mg/m³)		PFOS and its salts (mg/m³)	
	8-hour	Short-term	8-hour	Short-term	8-hour	Short-term
ACGIH			0.01[b]			
Australia			0.1			
Belgium			0.01[f]			
Canada – Ontario			0.01			
Canada – Quebec			0.01[b]			
Denmark			0.01[b]	0.02[b,c]		
Germany (AGS)					0.01[a,b]	0.08[a,b,c]
Germany (DFG)	0.005[a,b]	0.04[a,b,c]			0.01[a,b]	0.08[a,b,c]
Ireland			0.01			
Japan (JSOH)	0.005[d]					
New Zealand			0.1			
Singapore			0.01			
Spain			0.01[b]			
Sweden					900	1400[c]
Switzerland	0.005[e]	0.04[e]			0.01[e]	0.08[e]

ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Ausschuss für Gefahrstoffe (Hazardous Substances Committee); APFO, ammonium perfluorooctanoate; DFG, Deutsche Forschungsgemeinschaft (German Research Foundation); JSOH, Japan Society for Occupational Health; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.
[a] Inhalable fraction.
[b] Skin.
[c] 15-minute average.
[d] Not applicable to women of child-bearing potential.
[e] Inhalable aerosol.
[f] Skin, mucous membranes, and eyes.
From IFA (2022).

1.5.1 Occupational limits

Occupational exposure limits for air concentrations are available for PFOA, APFO, and PFOS (Table 1.19). Germany and Switzerland have identical 8-hour TWAs and short-term exposure limits (STELs): TWA for inhalable PFOA, 0.005 mg/m³ (STEL, 0.04 mg/m³) and TWA for inhalable PFOS, 0.01 mg/m³ (STEL, 0.08 mg/m³). Japan also uses the value of 0.05 mg/m³ as the 8-hour TWA for PFAS; however, Sweden's 8-hour TWA for PFOS is 900 mg/m³ (and the STEL is 1400 mg/m³). APFO is assigned an 8-hour TWA of 0.01 mg/m³ in Belgium, Canada (Ontario and Quebec), Denmark, Ireland, Singapore, and Spain, (IFA, 2022). The same value is adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 2023). Australia and New Zealand set their 8-hour TWA at 0.1 mg/m³, and Denmark has a STEL of 0.02 mg/m³. Belgium, Denmark, Germany, Quebec, Spain, and the ACGIH all assign a skin notation to their guidance, indicating that dermal protection is needed to prevent skin absorption (IFA, 2022).

1.5.2 Consumer products and food

See Table 1.20.

Numerous countries have set recommended limits for exposure to PFAS in consumer products and food. Food Standards Australia New Zealand (FSANZ) and the National Health and Medical Research Council (NHMRC) of Australia set a tolerable daily intake (TDI) for PFOA of 160 ng/kg bw and a combined intake

Table 1.20 Examples of consumer products in which the presence or use of PFOA and PFOS is restricted

Consumer product	Country or region	Reference
Food packaging	USA, European Union, Japan	US FDA (2022b) OECD (2023a)
Children's products	Some states in the USA	ITRC (2023a) ITRC (2023b)
Carpets, textiles, rugs, and fabric treatments, furniture	European Union, some states in the USA	ITRC (2023a) ITRC (2023b) MNPCA (2023); Maine DEP (2023)
Cookware	Some states in the USA	MNPCA (2023)
Cosmetics and other personal products	Some states in the USA	MNPCA (2023)
Firefighting foams	Canada, European Union, Australia, some states in the USA	ECHA (2023) ECCC (2017) ITRC (2023b)

PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; USA, United States of America.

of PFOS and PFHxS of 20 ng/kg bw (Australian Government, 2017). In the USA, the Agency for Toxic Substances and Disease Registry (ATSDR) developed intermediate-duration oral minimal risk levels of 3 ng/kg per day for PFOA and 2 ng/kg per day for PFOS. The ATSDR minimal risk levels are estimates of the daily intake below which harm to human health is not anticipated to occur and are often used as screening levels for environmental media (e.g. water) (ATSDR, 2021).

In 2008, the European Food Safety Authority`s Panel on Contaminants in the Food Chain (CONTAM) established TDIs of 150 ng/kg bw per day for PFOS and 1500 ng/kg bw per day for PFOA. In 2020, the same agency established a new safety threshold for PFOA, PFOS, and two other PFAS (PFHxS and PFNA), a group tolerable weekly intake (TWI) of 4.4 ng/kg bw per week.

1.5.3 Environmental guidelines

National and local jurisdictions have established regulations and guidelines on acceptable concentrations of PFOA and PFOS in drinking-water and other environmental compartments. [The Working Group noted that these guidelines are evolving on the basis of current science and regulatory processes.] Many of these regulations, particularly those pertaining to drinking-water, have been updated in recent years and are closely tracked by organizations such as the Interstate Technology and Regulatory Council (ITRC). More information on water and soil regulations is available online in tables that are maintained by the ITRC (ITRC, 2023c).

Table 1.21 presents a non-exhaustive list of some regulations for different environmental compartments.

Canada additionally has guidelines for PFOS in surface water, aquatic life, fish tissue, and wildlife diet, as part of the Federal Environmental Quality Guidelines (ECCC, 2023). In the USA, several states have implemented PFAS limits for a variety of environmental media. PFOA and PFOS in drinking-water, surface water, groundwater, and sediment or soil (residential, industrial or commercial, and construction site) are regulated in various combinations in up to 20 states. A few states additionally have testing requirements or allowable concentrations for PFOA and PFOS in biosolids and wastewater. Consumption advisories or limits on concentrations of PFOS and, to a lesser extent, PFOA in fish as well as in shellfish, deer, turkey, beef, and milk exist in numerous states for different consumption patterns and

Table 1.21 Examples of guidelines in place for environmental compartments

Environmental compartment	Country or region	Limit established; year	Reference
Drinking-water	New Zealand	PFOA, 560 ng/L; PFOS, 70 ng/L; 2017	Australian Government (2017)
Drinking-water	Canada	PFOA, 200 ng/L; PFOS, 600 ng/L; 2018	Health Canada (2018a, b)
Drinking-water	European Union	500 ng/L for total PFAS; 100 ng/L for the sum of 20 PFAS, including PFOA and PFOS; 2020	EU (2020)
Drinking-water	Denmark	2 ng/L for the total of PFOA, PFOS, PFNA, and PFHxS; 2021	Danish Environmental Protection Agency (2023)
Drinking-water	UK	10–100 ng/L for PFOS or PFOA; 2021	DWI (2021)
Drinking-water	USA	PFOA, 0.004 ng/L; PFOS, 0.02 ng/L; 2022 (Interim Health Advisory)	Office of the Federal Register (2022)
Recreational water	New Zealand	PFOA, 10 000 ng/L; PFOS, 2000 ng/L; 2017	Australian Government (2017)
Ambient water	Canada (British Columbia)	PFOA, 200 ng/L; PFOS, 600 ng/L; 2020	BC MECCS (2020)
Groundwater	European Union	4.4 ng/L (sum of 24 PFAS, including PFOA and PFOS); 2022	European Commission (2022)
Soil	Canada	PFOS, 0.01 mg/kg dry weight; 2021 PFOA soil screening values are 0.70, 1.05, and 9.94 mg/kg soil, for agricultural/residential, commercial, and industrial land use; 2019	CCME (2021) Health Canada (2019)
Ambient air	USA	PFOS, PFOA, and APFO concentrations ranging from 0.006 to 0.082 µg/m^3, 0.007 to 0.07 µg/m^3, and 0.024 to 0.05 µg/m^3, respectively; varies by regulation	ITRC (2023a, b)

APFO, ammonium perfluorooctanoate; PFAS, per- and polyfluoroalkyl substances; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFHxS, perfluorohexanesulfonic acid; PFOS, perfluorooctanesulfonic acid; UK, United Kingdom; USA, United States of America.

populations (ECOS, 2023; ITRC, 2023a, b). [The Working Group noted that this is a dynamic area and new regulations with lower proposed regulatory thresholds are being established.]

1.5.4 Guidance and biomonitoring reference values

Health-based threshold guidance values for biomonitoring are available in Germany and the USA. In 2016, the Human Biomonitoring Commission (HBM Commission) of the German Environment Agency (UBA) established concentrations below which no adverse health effects are expected to occur (HBM-I values), according to current knowledge and assessment, of 2 ng/mL for PFOA and 5 ng/mL for PFOS in blood serum or plasma (Hölzer et al., 2021). In 2019, concentrations above which there is an increased risk of adverse health effects (HBM-II values) were established of 5 ng/mL and 10 ng/mL for PFOA and PFOS, respectively, in blood plasma in women of childbearing age, and of 10 ng/mL and 20 ng/mL for PFOA and PFOS, respectively, in blood plasma of all other populations (Schümann et al., 2021). In its report of 2022, the US National Academies of Sciences, Engineering, and Medicine (NASEM) identified two threshold values for the sum of seven PFAS in serum or plasma, including PFOA and PFOS, to guide clinical care and exposure reduction efforts: 2 ng/mL and 20 ng/mL. NASEM recommended that clinicians provide the usual standard of care at concentrations of < 2 ng/mL; encourage exposure reduction and screen for certain medical conditions at concentrations of

2 to < 20 ng/mL; and encourage exposure reduction and screen for additional medical conditions at concentrations of ≥ 20 ng/mL (NASEM, 2022).

1.6 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

1.6.1 Quality of exposure assessment in key cancer epidemiology studies

(a) Exposure assessment methods

The exposure assessment methods employed in 12 case–control studies and 30 cohort studies, including 18 nested case–control studies, were reviewed and are described below by study design. Details on each of the studies are summarized in Table S1.22 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636).

These studies employed primarily one of two methods of exposure assessment for PFOA and PFOS: biological measurement of PFOA and PFOS in the blood (whole blood, serum, or plasma) or job (residential history) exposure matrices to estimate historical exposures. The biological matrix for the analysis of PFOA and PFOS was blood in two studies, plasma in five studies, and serum in the other studies.

An overview of chemical analysis methods used for detection and quantification of PFOA and PFOS in human biological samples is presented in Section 1.3.4. In the epidemiological cancer studies in which the exposure assessment was based on biomonitoring, targeted analytical methods were applied in all except four studies that used non-targeted methods, which do not permit quantification of concentrations but rely on semiquantitative determination of intensity level for identified PFAS (Chang et al., 2023; Chen et al., 2023; van Gerwen et al., 2023; Zhang et al., 2023).

As described in Section 1.1, several isomers exist for both PFOA and PFOS. In a few epidemiological cancer studies, isomer-specific determinations were performed that were summed for analysis (Itoh et al., 2021; Li et al., 2022a; Purdue et al., 2023; Rhee et al., 2023b; Winquist et al., 2023), but in most studies only one concentration was reported for PFOA and one for PFOS. The exception was the study by van Gerwen et al. (2023) who considered linear and branched-chain PFOS separately in their non-targeted analysis. [The Working Group noted that when one concentration value was reported for PFOA or PFOS, it was assumed that this represented the sum of branched and linear isomers, even though this was not always specified in the study.] In the studies in which non-targeted methods were used (see Section 1.3.4), compound-specific intensities, not concentrations, were reported (Chang et al., 2023; Chen et al., 2023; van Gerwen et al., 2023; Zhang et al., 2023).

(i) Case–control studies

In total, 12 relevant case–control studies were reviewed for the present monograph (Bonefeld-Jørgensen et al., 2011; Vieira et al., 2013; Hardell et al., 2014; Wielsøe et al., 2017; Lin et al., 2020b; Tsai et al., 2020; Itoh et al., 2021; Cao et al., 2022; Li et al., 2022a; Liu et al., 2022a; Velarde et al., 2022; Chen et al., 2023). In all studies except that by Vieira et al. (2013), both PFOA and PFOS were evaluated, and the exposure assessment was based on biomonitoring in the blood (serum, plasma, or whole blood).

Vieira et al. (2013) evaluated incident cancers in residents (according to address at time of cancer diagnosis) in six PFOA-contaminated water districts and 13 counties in Ohio and West Virginia, USA. PFOA concentrations in water, available for each of the six districts, varied by community. Water district information was available for all individuals, and logistic regression

analyses compared individuals in contaminated water districts with those in neighbouring water districts. For residents of Ohio, where approximately one third of the sample population lived, residential addresses were geocoded and then PFOA serum concentrations were assigned on the basis of modelled estimates (Shin et al., 2011a, b), assuming 10 years residence at that address. Exposure was then divided into four categories. However, analysis for residents of West Virginia was limited to residence by water district.

For all other studies based on general populations, blood samples were collected from participants during the same time periods for the cases and controls. For the cases in studies by Bonefeld-Jørgensen et al. (2011) and Cao et al. (2022), the timing of the blood draw relative to when treatment started was not reported, and in the study by Lin et al. (2020b), blood samples were collected 1 week after the identification of the case by pathology. In the study by Chen et al. (2023), blood spot samples were collected at birth, and diagnosis occurred on average 9.3 months after birth for unilateral retinoblastoma and 22 months after birth for bilateral retinoblastoma. For the remaining studies (Hardell et al., 2014; Wielsøe et al., 2017; Tsai et al., 2020; Itoh et al., 2021; Li et al., 2022a; Velarde et al., 2022), blood samples were collected between the time of diagnosis and the start of treatment. Controls were selected from participants in ongoing cross-sectional studies (Bonefeld-Jørgensen et al., 2011; Wielsøe et al., 2017); invited on the basis of selection from population registries (Hardell et al., 2014) or breast cancer screening programmes (Cao et al., 2022; Li et al., 2022a); in connection with medical check-ups (Itoh et al., 2021); through advertisements at the hospital and in the community (Tsai et al., 2020; Liu et al., 2022a); or invited after hospitalization due to other diagnoses or illnesses (Lin et al., 2020b). In studies by Bonefeld-Jørgensen et al. (2011), Hardell et al. (2014), Wielsøe et al. (2017), Itoh et al. (2021) and Chen et al. (2023), cases and controls were matched on age and region of residence, whereas Lin et al. (2020b) matched cases and controls on age and sex. [The Working Group noted that, given the temporal trends in PFOA and PFOS blood levels, it is important that time of blood sample collection is matched or adjusted for.]

In all studies, targeted chemical analyses were performed using LC-MS/MS, except in the study by Chen et al. (2023), in which non-targeted methods were used. Because PFOA and PFOS levels were not quantified using standard targeted methods by Chen et al. (2023), direct comparisons with the levels from other studies were not possible. Li et al. (2022a) performed separate determinations for eight PFOA isomers and nine PFOS isomers, and internal standards of linear PFOA and PFOS isomers were used. In the study by Hardell et al. (2014), only linear isomers of PFOA and PFOS were determined. In the remaining studies, one concentration for PFOA and one for PFOS were reported. In these studies, it was not stated whether only linear isomers were considered or whether other isomers were also included in the reported concentrations.

In addition to PFOA and PFOS, all studies except that by Chen et al. (2023) included at least four of the other most prominent PFAS in human blood (EFSA Panel on Contaminants in the Food Chain, 2020). Bonefeld-Jørgensen et al. (2011), Li et al. (2022a), and Wielsøe et al. (2017) assessed exposure both for single PFAS and for the sum of several PFAS. In the studies by Hardell et al. (2014), Tsai et al. (2020), Lin et al. (2020b), Liu et al. (2022a), Cao et al. (2022), and Chen et al. (2023), only single PFAS were assessed.

Bonefeld-Jørgensen et al. (2011) and Wielsøe et al. (2017) measured other carcinogens, i.e. polychlorinated biphenyls (PCBs), β-hexachlorocyclohexane, cadmium and cotinine (as a biomarker for tobacco smoke), via biomonitoring. Some studies collected information on exposure to other carcinogens, i.e. barbecuing, hair dyeing, smoking, alcohol consumption, use

of estrogen or estrogen-replacement therapy, meat consumption, via questionnaires (see Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636).

(ii) Cohort studies

This section includes cohort studies designed to study PFOA and PFOS exposure in occupational settings and contaminated communities and case–control studies nested in other general population cohort studies. Eleven cohort studies focusing on cancer incidence or mortality were reviewed by the Working Group. These included eight occupational cohort analyses (Alexander et al., 2003; Alexander and Olsen, 2007; Lundin et al., 2009; Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014; Steenland et al., 2015; Girardi and Merler, 2019), two cohort studies in highly exposed communities (Barry et al., 2013; Li et al., 2022b), and one in the general population in the USA (Wen et al., 2022). Three of the cohort analyses were conducted in the C8 study area (a fluorochemical-production plant in Parkersburg, West Virginia, USA, and the six water districts in Ohio and West Virginia in which water was contaminated by a chemical plant that used APFO in the production of PTFE) and focused on either occupational exposure to PFOA or exposure through residential consumption of drinking-water (Steenland and Woskie, 2012; Barry et al., 2013; Steenland et al., 2015). Additionally, four studies were conducted among fluorochemical-manufacturing workers at a PFOS-production site in Alabama, USA (Alexander and Olsen, 2007) and at an APFO-manufacturing site in Minnesota, USA (Alexander et al., 2003; Lundin et al., 2009; Raleigh et al., 2014). The study by Li et al. (2022b) was based in a general population that was highly exposed to PFAS, but an ecological approach using water districts was followed, rather than measurement of subject-specific PFAS exposure. The majority of these studies that evaluated specific PFAS focused on PFOA. In the general population study (Wen et al., 2022) and the community exposure study (Li et al., 2022b), exposure to both PFOA and PFOS was evaluated.

Occupational cohort studies

Six of the occupational cohort analyses focused on PFOA (Lundin et al., 2009; Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014; Steenland et al., 2015; Girardi and Merler, 2019) and two on PFOS (Alexander et al., 2003; Alexander and Olsen, 2007).

Another cohort analysis on fluoropolymer production was a mortality analysis that did not include estimates for PFOA exposure and is not discussed further in the present monograph (Leonard et al., 2008).

All of these occupational cohort analyses relied on job history to classify potential exposure to PFOA or PFOS. Occupational exposure to PFOS was evaluated in workers in a film and chemical plant in Alabama, USA, (Alexander et al., 2003; Alexander and Olsen, 2007) using an exposure matrix developed by Olsen et al. (2003) that classified workers into three categories on the basis of potential exposure to POSF (a precursor of PFOS): ever high; ever low/never high; or no exposure. No measure of cumulative exposure was included. Serum samples were analysed but were not used to develop an exposure matrix. A variety of perfluorinated amides, alcohols, acrylates, and other fluorochemical polymers were produced at the plant (e.g. PFOA was used as a by-product or emulsifier until 1988) but were not included in the exposure assessment (Olsen et al., 2003).

For PFOA, several different approaches were used in the occupational cohort studies. Two studies used a JEM created using expert opinion (Lundin et al., 2009; Consonni et al., 2013); one used air sampling measurements together with a JEM (Raleigh et al., 2014); and others used biomarkers to enhance JEMs (Steenland and

Woskie, 2012; Steenland et al., 2015; Girardi and Merler, 2019). In the study on workers at the fluorochemical-production plant in Parkersburg, West Virginia (Steenland and Woskie, 2012; Steenland et al., 2015), exposure to PFOA was assessed using a JEM and then linked to serum exposure levels in samples collected between 1979 and 2004 from workers in eight work categories (Woskie et al., 2012). Cumulative exposure was estimated in ppm-years (μg/mL serum-years). Girardi and Merler (2019) used a similar approach to estimate cumulative serum PFOA exposure among workers at a factory in Veneto, Italy. Although PFOS was also produced, at lower volumes, in this factory (an average of [33 tonnes/year] compared with [227 tonnes/year] of PFOA), exposure to PFOS was not estimated. For APFO-manufacturing workers at the Minnesota factory (Lundin et al., 2009), exposure to PFOA was estimated according to three categories: definite; probable; and no occupational exposure, based on job history. Cumulative PFOA exposure was then estimated using weights based on serum levels of workers in different areas of the manufacturing facility; lifetime exposure was estimated based on the product of the weight and the exposure days. For manufacturing workers using APFO (the ammonium salt of PFOA), air samples were collected for combinations of department/job title/work area/equipment/task (Raleigh et al., 2014). Job histories were then linked to the air samples to create a TWA of APFO exposure (μg/m^3-years), and then all jobs were summed to create an overall summary APFO air-exposure variable.

Consonni et al. (2013) evaluated mortality among workers at a plant involved in TFE synthesis and polymerization. The TFE synthesis and polymerization process uses APFO (the ammonium salt of PFOA) and, as a result, workers were commonly co-exposed to both TFE and APFO (88%, in the study by Consonni et al., 2013). A semiquantitative JEM using arbitrary units was created, and cumulative exposure was estimated.

Studies of communities with contaminated drinking-water

Cancer risk associated with the consumption of PFAS-contaminated drinking-water was evaluated in three communities: the C8 Study in Ohio and West Virginia, in the USA; Ronneby, Sweden; and the Veneto region, in Italy.

The C8 study focused on water districts where drinking-water was contaminated by PFOA, also known as "C8", from a fluorochemical-production plant (Barry et al., 2013). One cohort study of cancer incidence was conducted in this region. This study, which included both residents and workers, used the exposure assessment metric from the study by Shin et al. (2011a, b) to assign cumulative PFOA exposure to individuals on the basis of residential history, and the exposure metric from Woskie et al. (2012) to assign PFOA exposure related to occupational exposure. Exposure was modelled based on a continuous measure of cumulative PFOA exposure as well as categories of exposure.

The study in Ronneby, Sweden, by Li et al. (2022b) relied on residential history to assign water source into categories: ever high, never high, early high, late high, short high or long high PFAS exposure. Differences in exposure between these categories were supported by measurement of PFAS blood levels in the population, with the highest levels found in the late high group (Li et al., 2022b). Water from this region was contaminated with multiple PFAS, and exposures were particularly high for PFAS related to firefighting foam (PFOS and PFHxS). Exposure assessment in this analysis was not chemical-specific and used residence as a surrogate for exposure. [The Working Group recognized that it was not possible to distinguish PFOS from PFHxS because of the elevated levels of both compounds and the presence of somewhat elevated PFOA levels that correlated with

levels of PFOS and PFHxS, even though PFOA levels were much lower than those of PFOS and PFHxS.]

Another location in the world where there is extensive contamination of water with PFAS is the region of Veneto, Italy, where a factory produced PFOA between 1968 and 2014 (Girardi and Merler, 2019). [No publication has comprehensively described the exposure experience in this community. The Working Group reviewed several papers and reports to characterize PFOA and PFOS exposure in this community and included details in Annex 2, Actions and regulations for the elimination of PFAS worldwide, available from: https://publications.iarc.who.int/636.] Drinking-water contamination was discovered in 2013, and since that time extensive environmental and human biological sampling has been conducted (Ingelido et al., 2018; Pitter et al., 2020; Giglioli et al., 2023). Initially, the highly contaminated area, also known as the "red area", was composed of 21 municipalities, with 126 000 inhabitants. In 2018, nine additional municipalities were added, some of which were only partially supplied by the contaminated waterworks; the updated red area has a size of 595 km^2 and a total population of approximately 140 000.

General population cohorts including nested case–control studies

Wen et al. (2022) used NHANES exposure data from 1999 to 2014 to evaluate cancer mortality in adults in a general population sample in the USA. The NHANES is a nationally representative sampling of the population, designed to assess the health and nutritional status of adults and children in the USA. This evaluation used serum measurements of PFOA and PFOS, and other PFAS; only one serum measurement was available for each individual. Deaths were identified through linkage to the National Death Index, with a median follow-up of 81 months (range, 46–112 months). Cancer mortality risk was estimated using tertiles of exposure for PFOA and PFOS, but the majority of the analysis focused on the PFAS mixture.

In total there were 18 case–control studies nested within cohorts that used biomonitoring of PFAS in their analyses (Eriksen et al., 2009; Bonefeld-Jørgensen et al., 2014; Ghisari et al., 2017; Hurley et al., 2018; Cohn et al., 2020; Mancini et al., 2020; Shearer et al., 2021; Feng et al., 2022; Frenoy et al., 2022; Goodrich et al., 2022; Chang et al., 2023; Purdue et al., 2023; Rhee et al., 2023a, b; van Gerwen et al., 2023; Winquist et al., 2023; Zhang et al., 2023; Madrigal et al., 2024). Two studies used the E3N (Etude épidémiologique auprès de femmes de la Mutuelle générale de l'Education nationale) prospective cohort of women in the national education system in France (Mancini et al., 2020; Frenoy et al., 2022). Two studies used the Danish National Birth Cohort (Bonefeld-Jørgensen et al., 2014; Ghisari et al., 2017). One study used a cohort of retired Chinese motor-company employees (Feng et al., 2022); another was nested in a cohort of US Air Force Servicemen (Purdue et al., 2023). The others included a cohort of California teachers (Hurley et al., 2018), a Child Health and Development Studies pregnancy cohort in California (Cohn et al., 2020), a population-based national maternity cohort in Finland (Madrigal et al., 2024), and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland (Zhang et al., 2023), and the Mount Sinai Bio*Me* medical record-linked biobank in the USA (van Gerwen et al., 2023). Four studies used the US-based Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Cancer Screening Trial cohort (Shearer et al., 2021; Chang et al., 2023; Rhee et al., 2023a; Zhang et al., 2023), and two used the California- and Hawaii-based Multiethnic Cohort in the USA (Goodrich et al., 2022; Rhee et al., 2023b).

Chang et al. (2023), van Gerwen et al. (2023) and Zhang et al. (2023) used non-targeted analysis. In these studies, the analysis was conducted on quantiles of intensity measures of

the relative levels of PFOA and PFOS found in pre-diagnosis serum samples. Because PFOA and PFOS levels were not quantified using standard targeted methods, direct comparisons with the PFAS levels reported in other studies were not possible. However, the authors (Chang et al., 2023; Zhang et al., 2023) reported strong correlations of between 0.76 and 0.77 between the untargeted analysis and the standard targeted analysis.

In all studies except that by Hurley et al. (2018), blood samples were collected before case ascertainment. Hurley et al. collected samples between 9 months and 8.5 years (average, 35 months) after case diagnosis. In the other studies, the time between sample collection and case ascertainment varied (where this was reported). Zhang et al. (2023) reported that the time between sample collection and cancer diagnosis was 0–18 years (median, 9 years) for the PLCO subcohort analysed. For the study by van Gerwen et al. (2023), sample collection took place 0–1 year before diagnosis (average, 0.08 years) for 65% of cases and an average of 4 years before diagnosis for the remaining 35% of cases. For the study by Goodrich et al. (2022), the median time span between collection of blood sample and diagnosis was 7.2 years (range, 0.9–16.4 years). In the study by Ghisari et al. (2017), cases were diagnosed 11–12 years after initial blood draw, while for Eriksen et al. (2009) cases were diagnosed a median of 7 years after enrolment (and blood draw) (range, 0–12 years). Shearer et al. (2021) reported a mean of 8.8 years (range, 2–18 years) between blood draw and diagnosis, and Chang et al. (2023) reported a median of 5.6 years (range, 2–18 years) between diagnosis and blood draw. In the study by Purdue et al. (2023), the median time between blood collection and diagnosis was 5 years (range, 0–19.8 years). Rhee et al. (2023a) reported a median time between blood collection and diagnosis of 9 years (interquartile range, 5–13 years). Madrigal et al. (2024) reported that cases were diagnosed at least 3 years after delivery (samples were collected during the first trimester of pregnancy).

Both Purdue et al. (2023) and Rhee et al. (2023a) had access to multiple blood samples, which allowed them to evaluate how the rank ordering of exposure might change over time. For a subset of participants in the study by Purdue et al. (2023), a second blood sample was collected. To explore differences related to the time of collection, Purdue et al. (2023) analysed the data separately for participants with two samples and also created a combined variable based on the classification of the median level at each time point. They reported an overall Spearman coefficient of 0.6 for both PFOA and PFOS in repeat samples and an intraclass correlation coefficient (ICC) of 0.5–0.6, with stronger correlation for repeat samples taken after < 4.7 years and weaker correlation for repeat samples taken after > 4.7 years. Rhee et al. (2023a) analysed blood from 60 controls at enrolment, 1 year after enrolment, and 5 years after enrolment to assess long-term intra-individual variability in PFAS concentration. The ICC for three measures was 0.73 for of PFOA and 0.85 for PFOS; these values suggest that measurements of PFOA and PFOS were reliable over time in this study.

Eight of the studies focused on breast cancer (Bonefeld-Jørgensen et al., 2014; Ghisari et al., 2017; Hurley et al., 2018; Cohn et al., 2020; Mancini et al., 2020; Feng et al., 2022; Frenoy et al., 2022; Chang et al., 2023). Some of the studies were in birth cohorts for which blood samples were collected during pregnancy and maternal breast cancers identified subsequently (Bonefeld-Jørgensen et al., 2014; Ghisari et al., 2017). Alternatively, Cohn et al. (2020) used maternal blood collected 1–3 days postpartum to investigate breast cancer in the daughters. Chang et al. (2023), Feng et al. (2022), Frenoy et al. (2022), Mancini et al. (2020), and Hurley et al. (2018) reported on prospective studies of adult general populations. Three studies focused on people in professions related to education

(Hurley et al., 2018; Mancini et al., 2020; Frenoy et al., 2022), and one study was in a cohort in an industrial motor company (Feng et al., 2022), although occupational exposures were not its focus.

Several nested case–control studies were part of general cancer screening or prevention trials, such as the PLCO cohort (Chang et al., 2023; Rhee et al., 2023a; Zhang et al., 2023), the Cancer Prevention Study II Lifelink Cohort (Winquist et al., 2023), or the ATBC Study (Zhang et al., 2023). One study used a hospital-based biobank in the USA (van Gerwen et al., 2023), and another was a population-based national maternity cohort in Finland (Madrigal et al., 2024).

Many studies measured multiple PFAS in their samples; however, much of the outcome analysis focused on potential associations with a limited number of individual PFAS (Eriksen et al., 2009; Ghisari et al., 2017; Hurley et al., 2018; Cohn et al., 2020; Mancini et al., 2020; Shearer et al., 2021; Goodrich et al., 2022). Some authors attempted to sum a variable number of the measured PFOA or PFOS isomers, and use these summed metrics in their analysis (Bonefeld-Jørgensen et al., 2014; Feng et al., 2022), and Frenoy et al. (2022) used principal components analysis and Bayesian kernel machine regression on all the PFAS measurements. van Gerwen et al. (2023) used untargeted analysis to examine intensities of eight detectable PFAS, including linear PFOA and branched and linear PFOS, which were examined individually in their analysis.

(b) Critical review of exposure assessment in key epidemiological studies

Blood is considered a suitable matrix for exposure assessment (Vorkamp et al., 2021), and measured blood concentrations are an objective measure of exposure. In most studies in which blood measurements were used, the analytical methods used were state-of-the-art in 2023, the LOQs for PFOA and PFOS were sufficiently low to ensure high quantification frequencies, and the measurement error in the targeted chemical analyses was low (see Section 1.3.4). In some studies, the quantification method used was non-targeted and thus semiquantitative; therefore, exact concentrations were not available. However, ranking of levels is possible. Several occupational cohort studies that estimated cumulative exposures used older, less specific or precise methods, with higher LODs (Alexander et al., 2003; Steenland and Woskie, 2012). In some studies, estimation of serum levels combined state-of-the-art measurements of community exposures with older data from occupational cohort studies (Barry et al., 2013; Steenland et al., 2015).

The measured concentrations in blood represent combined exposure through all exposure pathways (see Section 1.4.3 on biomonitoring). Since PFOA and PFOS have long elimination half-lives (see Section 4.1), and repeated measures in humans show strong ICCs (Blake et al., 2018; Rhee et al., 2023a), the measured concentrations represent exposure over a relatively long period of time. These factors limit the potential for non-differential exposure misclassification, in general. Using repeated measures data from Rhee et al. (2023a) and Purdue et al. (2023), the Working Group evaluated the potential for exposure misclassification and resulting bias if just one biological sample is used; the results of this analysis demonstrated that using a single sample represented rather well the mean of repeated samples collected a median of 4–5 years apart in two cohort studies of populations with background levels (Spearman correlations of 0.87 and 0.83 for the PLCO and US Air Force Servicemen cohorts, respectively) (see Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). Repeat biomonitoring of PFOA and PFOS in the general population is described in Section 1.4.3.

It is important to be careful when comparing measured concentrations reported in the

various studies, since PFOA and PFOS isomers have been treated differently among studies. This is of particular importance for PFOS since branched isomers may comprise up to 50% of the total concentration of PFOS (Haug et al., 2009); whether or not the branched isomers are included could make a significant difference to participant exposure levels. Results from studies using untargeted methods also present limitations when comparing exposure concentrations with results from other studies.

Most studies relied on a single blood sample to classify lifetime exposure to PFOA and PFOS. In case–control studies, one blood sample was collected near the time of diagnosis. In the cohort and nested case–control studies, the time between blood collection and diagnosis ranged from 0 to 20 years, as described above. Thus, there is a possibility that measured blood levels of PFOA and PFOS do not reflect exposure at crucial windows in cancer development. However, as described above, the results of studies of repeated human serum measurements of PFOA and PFOS have shown strong correlations over time.

(i) Case–control studies

In the study by Vieira et al. (2013), exposure was assigned on the basis of address at the time of cancer diagnosis; this could result in exposure misclassification if individuals changed addresses before cancer diagnosis. However, the authors stated that the median residence time at current address was 17 years, suggesting that this issue was unlikely to be a source of exposure misclassification.

All the other case–control studies used biomonitoring for exposure assessment, and thus generally had the same strengths and limitations. While blood samples provide specific measures of PFOA and PFOS exposure, biological samples are influenced by interindividual variability. For the case–control studies, the fact that blood samples were collected at or near the time of diagnosis means that these biological markers may be influenced by the disease process. If cancer were to alter the absorption, distribution, metabolism, or excretion (ADME) of PFOA and PFOS, then the measured levels in the cases could not be compared with measured levels in the controls, thus resulting in differential exposure misclassification.

A limitation of these studies is that most did not measure other carcinogens in the blood samples, and that only limited information on exposure to other carcinogens was available from the questionnaires. In the studies by Bonefeld-Jørgensen et al. (2011) and Wielsøe et al. (2017), other substances classified by IARC in Group 1, *carcinogenic to humans* (PCBs, β-hexachlorocyclohexane, cadmium, and cotinine as a biomarker of tobacco smoking), were measured. Bonefeld-Jørgensen et al. (2011) reported high correlations between PFAS and other persistent organic pollutants ($r = 0.42–0.55$; $P < 0.05$), although no information on specific compounds was reported. A strength of the exposure assessment in this study was that correlations with biomarkers of co-exposures were assessed.

In summary, for all case–control studies (except Vieira et al., 2013), blood levels were measured and used as the exposure metric. A main strength was that the measured levels represent combined exposure through all exposure pathways. Measurement error was also thought to be low in all studies in which targeted analyses were performed, whereas the untargeted methods applied in other studies might have lower precision. A major weakness of all the case–control studies was that the blood samples for the cases were collected after the participants had been diagnosed. Thus, the measured levels may not reflect exposure at crucial windows in cancer development, and if cancer alters the ADME of PFAS, there could be differential exposure misclassification.

(ii) Cohort studies

In the majority of studies with occupational exposure and in communities with high exposure, PFOA and PFOS exposure was determined by exposure reconstruction, based either on occupational or residential history. Most studies used exposure reconstruction techniques that provided cumulative exposure estimates to rank-order individuals according to PFOA and PFOS exposure. These cumulative exposure estimates allowed for exposure–response analysis, which may strengthen the argument for causality. In several studies, cumulative serum-level estimates were developed using retrospective modelling (Steenland and Woskie, 2012; Barry et al., 2013; Steenland et al., 2015; Girardi and Merler, 2019); these studies have added strength because they included both environmental and biological measurements to support their estimates. In one study, cumulative estimates of air levels of APFO were developed that enabled workers to be ranked according to exposure, because the main source of PFOA was expected to be occupational (Raleigh et al., 2014). In other studies, cumulative categorical estimates were developed based on occupational history information (Alexander et al., 2003; Alexander and Olsen, 2007; Lundin et al., 2009; Consonni et al., 2013). One study relied solely on residence to assign a categorical exposure, although serum levels were said to validate the categories (Li et al., 2022b); this study also lacked specificity for individual PFAS, limiting its utility to the evaluation of the carcinogenicity of PFOA or PFOS individually. Many of these studies focused only on PFOA (Lundin et al., 2009; Steenland and Woskie, 2012; Barry et al., 2013; Steenland et al., 2015; Girardi and Merler, 2019); none presented isomer-specific estimates of exposures. In the study by Girardi and Merler (2019), workers may have been exposed to other PFAS, including PFOS, but these exposures were not evaluated. In one occupational cohort (Consonni et al., 2013) focusing on TFE workers, a very high correlation between cumulative weighted categorical exposures to TFE and cumulative weighted categorical exposures to APFO ($\rho = 0.72$) was reported in exposed workers, therefore, it was difficult to ascertain differences between these exposures. Another study focused on categories of POSF-exposed workers, resulting in estimates only of indirect exposure to its metabolite PFOS; however, serum levels of PFOS were used to validate the exposure estimates. Co-exposure to PFOA was likely but was not assessed (Alexander et al., 2003; Alexander and Olsen, 2007).

In all cohorts, exposure was ascertained before cancer diagnosis or cancer death. Because exposure was assigned before diagnosis and all individuals were evaluated in the same way, the potential for differential exposure misclassification was limited for both cohort studies and the resulting nested case–control studies.

All the nested case–control studies and one cohort analysis (Wen et al., 2022) relied on biomarker measurement of PFAS in serum or plasma samples, although van Gerwen et al. (2023) and Zhang et al. (2023) used an untargeted analysis method. As discussed for the case–control studies, blood is an appropriate matrix for biomonitoring of PFOA and PFOS. The use of non-targeted methods does not allow quantification of PFAS concentrations but does provide appropriate rank ordering of individuals. Most studies evaluated PFOA and PFOS separately. Frenoy et al. (2022) primarily used principal components analysis to characterize exposure to both PFOA and PFOS together with other PFAS and brominated flame retardants, which made individual PFOA or PFOS determinations challenging.

All studies except that by Hurley et al. (2018) used blood samples collected before case ascertainment, although the range of time between blood collection and case ascertainment varied widely. PFOA and PFOS have a relatively long half-life in blood, making them good measures

of long-term exposure. However, single sample exposure measurements may not reflect exposure at crucial windows in cancer disease development. All studies, except those by Purdue et al. (2023) and Rhee et al. (2023a), used a single blood sample to determine exposure status. Purdue et al. (2023) collected samples at two points in time and analysed them both separately and as a combined exposure metric; this may reduce exposure misclassification but also reduced the study power since not all participants had two samples. The results of the ICC analysis by Rhee et al. (2023a) suggested that PFOA and PFOS concentrations in blood samples remain relatively constant over time, suggesting that a single measure may correctly classify individuals. A bias analysis of these samples by the Working Group demonstrated little misclassification error when considering samples collected within an interval of 5–8 years (see Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636).

While all cohort and nested case–control studies accounted for potential co-exposures to some substances classified by IARC as *carcinogenic to humans* (Group 1), mostly by questionnaire, most studies focused solely on PFAS exposure. Many studies quantified additional PFAS in serum samples and presented risk estimates for individual and total PFAS as well. The most common co-exposures to carcinogens were smoking, alcohol consumption, and use of oral contraceptives, although information on occupation type was also collected by Eriksen et al. (2009) and Feng et al. (2022). Madrigal et al. (2024) also measured PCB congeners, organochlorine pesticides, and polybrominated diphenyl ethers (PBDEs) in serum samples. At present, little is known about the correlation between exposure to PFAS and to other substances classified by IARC as carcinogens.

1.6.2 Quality of exposure assessment in key mechanistic studies in exposed humans

(a) Exposure assessment methods

The exposure assessment methods used in the key mechanistic studies in humans are discussed below according to study design. [The Working Group did not review all mechanistic studies in exposed humans but reviewed a representative sample of studies for each type of study design.]

(i) Cross-sectional studies

The Working Group reviewed the exposure assessment methods used in 18 studies with a cross-sectional design (Knox et al., 2011; Fletcher et al., 2013; Watkins et al., 2014; Lin et al., 2016, 2020c; Lopez-Espinosa et al., 2016; Liu et al., 2018b; Pan et al., 2019; Abraham et al., 2020; Aimuzi et al., 2020; Di Nisio et al., 2020; Kvalem et al., 2020; Clarity et al., 2021; Lopez-Espinosa et al., 2021; Omoike et al., 2021; Cheng et al., 2022; Zhang et al., 2022; Wang et al., 2023). The studies were conducted in the USA and several European and several Asian countries. In all these studies, both PFOA and PFOS were evaluated, and the exposure assessment was based on biomonitoring.

In 16 of these studies, PFOA and PFOS concentrations were measured in the serum or plasma fractions of blood. These matrices are considered suitable for exposure assessment of environmental contaminants, including long-chain PFAS such as PFOA and PFOS (Calafat et al., 2019; Vorkamp et al., 2021; NASEM, 2022) and have been used as the exposure metric in most epidemiological studies of PFAS. PFOA and PFOS concentrations were measured in cord blood in one study (Liu et al., 2018b), in semen (as well as in serum) in the study by Pan et al. (2019), and in the placenta in the study by Wang et al. (2023). Relatively few studies have used semen or placenta for the assessment of exposure to PFAS.

Twelve of the 18 studies were of participants from the general population. In 6 of these 12

studies, the study populations included men who visited a fertility clinic (Pan et al., 2019), patients undergoing surgery for benign diseases or an elective reason (Cheng et al., 2022), children (Lin et al., 2016), and pregnant women (Liu et al., 2018b; Aimuzi et al., 2020; Wang et al., 2023). Another 6 of the 12 studies (Knox et al., 2011; Fletcher et al., 2013; Watkins et al., 2014; Lopez-Espinosa et al., 2016, 2021; Di Nisio et al., 2020) were of populations with elevated exposure to PFOA from contaminated drinking-water. However, exposure to PFOS in these populations was not higher than in the general population.

In all studies, PFAS were measured at the same time point as the assessment of the outcome, and in one study (Watkins et al., 2014), they were also measured 4–5 years before assessment of the outcome, but the two measures of PFAS were averaged to give a single exposure measure. In all the studies, PFOA and PFOS were analysed using LC-MS/MS.

Four studies (Fletcher et al., 2013; Di Nisio et al., 2020; Lin et al., 2020c; Cheng et al., 2022) reported only PFOA and PFOS. All the other studies also reported other PFAS. Although Knox et al. (2011) measured levels of other PFAS, they evaluated potential associations with the outcome only for PFOA and PFOS; Xie et al. (2023) reported 17 PFAS and considered the total concentration of the 17 PFAS that were evaluated.

In two studies (Omoike et al., 2021; Zhang et al., 2022), serum cotinine levels were measured as a biomarker for tobacco smoke, and in 11 studies (Knox et al., 2011; Fletcher et al., 2013; Watkins et al., 2014; Lin et al., 2016, 2020c; Pan et al., 2019; Aimuzi et al., 2020; Di Nisio et al., 2020; Lopez-Espinosa et al., 2021; Wang et al., 2023; Xie et al., 2023) information was obtained about either current or overall exposure to tobacco and/or tobacco smoke via questionnaires. In 10 studies (Knox et al., 2011; Watkins et al., 2014; Lin et al., 2016, 2020c; Pan et al., 2019; Aimuzi et al., 2020; Di Nisio et al., 2020; Lopez-Espinosa et al., 2021; Zhang et al., 2022; Xie et al., 2023), information on alcohol consumption was obtained using a questionnaire. Watkins et al. (2014) and Lopez-Espinosa et al. (2021) also obtained information on regular use of anti-inflammatory drugs over time through a questionnaire, Cheng et al. (2022) obtained information on use of hypolipidaemic drugs, and Knox et al. (2011) excluded participants who were taking hormonal medications.

In two studies, biomonitoring data were collected for contaminants other than PFAS. Abraham et al. (2020) measured PFAS in stored blood samples that were collected in the late 1990s and had previously been analysed for 2,3,7,8-substituted polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is classified as *carcinogenic to humans,* Group 1; IARC, 1997); non-dioxin-like-, mono-*ortho*-, and coplanar PCBs (classified as *carcinogenic to humans*, Group 1; IARC, 2015); 4,4′-dichlorodiphenyltrichloroethane (DDT) and its metabolites (classified as *probably carcinogenic to humans*, Group 2A; IARC, 2017); hexachlorobenzene and β-hexachlorocyclohexane (both classified as *possibly carcinogenic to humans*, Group 2B; IARC, 1987, 2001); lead (classified as *probably carcinogenic to humans*, Group 2A; IARC, 1979, 2006), cadmium (classified as *carcinogenic to humans*, Group 1; IARC, 1993, 2012), and mercury. Clarity et al. (2021), in a study of firefighters, measured urinary levels of four brominated flame retardants and metabolites of six organophosphate flame retardants for which there was potential occupational exposure.

(ii) Prospective birth cohort studies

Exposure assessment methods were reviewed for six mechanistic studies with a prospective birth cohort design (Grandjean et al., 2012; Goudarzi et al., 2017; Miura et al., 2018; Manzano-Salgado et al., 2019; Dalsager et al., 2021; Liu et al., 2022b). These studies were conducted in Denmark, the Faroe Islands (Denmark), Spain,

Japan, and the USA. All six studies included mother–child pairs with singleton births from the general population. Both PFOA and PFOS were evaluated, and the exposure assessment was based on blood biomonitoring.

In all six studies, PFOA and PFOS were analysed using LC-MS/MS in maternal blood serum or plasma collected during pregnancy. Grandjean et al. (2012) also measured PFAS in the children at age 5 years. Among the six studies, outcomes were measured in children at time points ranging from birth to age 12 years.

Miura et al. (2018) reported results only for PFOA and PFOS, whereas the other five studies also reported on other PFAS.

In some studies, information was collected on other exposures, including smoking, diet, and other environmental contaminants. Liu et al. (2022b) measured serum cotinine as a biomarker for maternal tobacco smoking. Grandjean et al. (2012), Manzano-Salgado et al. (2019), and Dalsager et al. (2021) collected information on smoking during pregnancy, and Goudarzi et al. (2017) collected information on parental smoking and environmental tobacco smoke when the children were aged 4 years. Manzano-Salgado et al. (2019) also collected information on maternal diet, including fish consumption, with a questionnaire. Miura et al. (2018) did not provide information on exposure to any other agents. Five of the studies did not obtain biomonitoring data for contaminants other than PFAS, whereas Grandjean et al. (2012) measured PCBs in the serum samples; and none of the studies evaluated or measured exposure to agents other than those mentioned above.

(iii) Longitudinal and repeated-measures studies

Exposure assessment methods were reviewed for three studies with a longitudinal or repeated measures design (Kim et al., 2016, 2020; Blake et al., 2018). In all three studies, LC-MS/MS was used to analyse serum levels of PFAS. Kim et al. (2020) measured serum levels of PFOA, PFOS, and 12 other PFAS and assessed outcomes in children from the general population of the Republic of Korea at the same three time points (ages 2, 4, and 6 years). Information on maternal smoking during pregnancy was collected. Blake et al. (2018) measured serum levels of PFOA, PFOS, and six other PFAS in a cohort of adults who were living near a river in the USA that was contaminated with PFOA and who were identified as being at high risk of elevated exposure to PFAS, particularly PFOA. The study group was a subset of residents near a uranium processing site, but this subset was unlikely to have uranium exposure above background. PFAS levels were measured at enrolment in the study and at one or two later time points for each participant, and outcomes were assessed at the same and/or different time point(s) as the collection of samples for measurement of serum levels of PFAS. In the first serum measurement, PFOA and PFOS were detected in all samples. No information on smoking or alcohol consumption was collected. Kim et al. (2016) measured levels of PFOA, PFOS, and 13 other PFAS in the serum of older adults (aged > 60 years) from the general population of the Republic of Korea who participated in a clinical trial on the effect of vitamin C on the outcomes. Serum levels of PFAS were measured at enrolment and at two additional time points over a 10-week period. Exposure to tobacco smoke (using urinary cotinine as a surrogate) and exposure to air pollutants (PM_{10}, ozone, and nitrogen oxide) were evaluated.

(iv) Study on pathology samples

Exposure assessment was reviewed for a study on PFAS levels in glioma and non-glioma brain tissue in patients (aged 2–77 years) with glioma, in China (Xie et al., 2023). The study included paired glioma and non-glioma brain tissue for 18 patients, as well as glioma or non-glioma brain tissue that did not come from the same patients, making a total of 137 glioma and 40 non-glioma

brain tissue samples. PFOA, PFOS, and 15 other PFAS were analysed using LC-MS/MS in these brain tissue samples to evaluate the potential association between PFAS levels and glioma pathological grade, as well as related biomarkers.

The MRL for PFOA and PFOS in brain tissue was 0.05 ng/g (wet weight). PFOA and PFOS were detected at concentrations above the RL in 69% and 82%, respectively, of the glioma tissue samples, and in 33% and 65%, respectively, of the non-glioma tissue samples. The areas of the brain that were sampled for the non-glioma tissue samples were not provided, and a study by Di Nisio et al. (2022) showed that PFAS levels vary widely in different parts of the brain. This study did not report on brain tissue concentrations of contaminants other than PFAS.

(b) Critical review of exposure assessment in key mechanistic studies in exposed humans

(i) Cross-sectional studies

Exposure assessment in all the cross-sectional studies was based on biomonitoring data, and the studies shared many strengths and limitations. In all of these studies, the analytical methods used were state-of-art at the time when the studies were conducted, and the LODs or LOQs for PFOA and PFOS, when provided, were sufficiently low to ensure detection or quantification of PFOA and PFOS (when present) in all or most samples.

In cross-sectional studies in general, it is not possible to determine the temporal relationship between exposure and outcome. Relying solely on measurements made at a certain point in time makes it difficult to comprehensively assess the impact of long-term exposure on health. For cross-sectional studies in general, a single measurement may not accurately reflect long-term exposure levels, because the concentration of chemicals in the human body may fluctuate with changes in the environment and lifestyle habits over time. However, measured serum or plasma concentrations of PFOA and PFOS are objective measures that integrate exposure from various sources and pathways, including contributions from metabolism of precursors to PFOA or PFOS (Section 4.1), and measurement error in the chemical analysis is low. Because PFOA and PFOS have long elimination half-lives (several years; see Section 4.1), the concentrations measured at a single time point represent past exposure over a relatively long period of time (see Section 1.4.3). For these reasons, measurement of serum or plasma PFOA and PFOS concentrations at the same time as the outcome appraisal is considered to be an acceptable method of exposure assessment for the outcomes considered in these studies, and this is also true for measurement of PFOA and PFOS in cord blood (Liu et al., 2018b). In 16 of the 18 cross-sectional studies, it was reported that PFOA and PFOS were detected at levels above the LOD or LOQ in all or almost all samples; Lin et al. (2020c) and Di Nisio et al. (2020) did not provide this information. These factors limit the potential for non-differential exposure misclassification, in general.

All studies except one collected blood samples once and assessed the outcome at the same time point (or during the same period, Zhang et al., 2022) as the serum or plasma PFAS levels. In the study by Watkins et al. (2014), serum levels of PFAS were measured at two time points – several years before and at the same time that the outcome was assessed – and the analysis was based on the mean of the two serum PFAS values.

A potential limitation of cross-sectional studies is that exposures to other agents that were not measured or evaluated may be correlated with PFOA and PFOS exposure and may also have an impact on the outcome (e.g. act as confounders or effect-modifiers). As one example, exposure to dioxins can result in immune system suppression (WHO, 2016). Different outcome(s) were evaluated in each study, and substances that are potential confounders would probably

differ according to the outcome. Thirteen studies assessed exposure to tobacco smoke with serum cotinine measurements or questionnaires, and 10 studies assessed exposure to alcohol with questionnaires. Two studies (Watkins et al., 2014 and Lopez-Espinosa et al., 2021) obtained information on regular use of anti-inflammatory drugs; one study (Cheng et al., 2022) obtained information on use of hypolipidaemic drugs; and one study (Knox et al., 2011) excluded participants who were taking hormonal medications.

Several studies measured exposures to contaminants other than PFAS. Abraham et al. (2020) measured several other POPs and heavy metals in plasma, and Grandjean et al. (2012) measured PCBs; in both studies, these other contaminants were evaluated as potential confounders of associations with PFAS. Additionally, Clarity et al. (2021) measured 10 flame retardants or their metabolites in the urine. However, exposures to other agents that may have an impact on the outcomes were not evaluated in the cross-sectional studies. This consideration may be particularly applicable in the study by Clarity et al. (2021) on firefighters and office workers. In this study, associations between the outcome and PFOA and PFOS were stronger in firefighters, who are exposed to many other contaminants in addition to PFAS (see Table S1.23, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/636) compared with office workers.

In one of the studies, Abraham et al. (2020) evaluated potential associations between serum levels of PFAS and antibody response to vaccination in children aged 1 year, including breast-fed and formula-fed children. In this study, samples were collected between 1997 and 1999, which corresponds with the period of highest PFOA and PFOS levels in the general population (see Section 1.4.3).

(ii) Prospective birth cohort studies

In the six prospective birth cohort studies, maternal serum or plasma PFAS level measured during pregnancy was used as an indicator of prenatal PFAS exposure for the children, in whom the outcomes were assessed at birth and/or at later time points. In one study (Grandjean et al., 2012), PFAS levels were also assessed in the children at age 5 years. The analytical methods used were state-of-art, and the LODs or LOQs for PFOA and PFOS, when provided, were sufficiently low to ensure detection or quantification of PFOA and PFOS in all or most samples. Because PFOA and PFOS have long elimination half-lives (several years; see Section 4.1), the concentrations measured in serum or plasma represent maternal exposure over a relatively long period of time.

Blood serum or plasma concentrations are an objective measure of exposure; the concentrations represent the combined exposure through all exposure pathways over a period of time and include contributions from the metabolism of precursors to PFOA or PFOS (see Section 1.4(d) or Section 4.1); and the measurement error in the chemical analyses is low. These factors limit the potential for non-differential exposure misclassification, in general. Five of the six studies (Goudarzi et al., 2017; Miura et al., 2018; Manzano-Salgado et al., 2019; Dalsager et al., 2021; Liu et al., 2022b) reported low LODs or LOQs for PFOA and PFOS, and the sixth study (Grandjean et al., 2012) did not provide information on the values of the LODs or LOQs. [The Working Group noted that even though not explicitly reported, data reported on tertiles of measured concentrations suggested that detection frequencies for PFOA and PFOS were high.] In the study by Manzano-Salgado et al. (2019), PFOA and PFOS were detected at concentrations above the LOD or LOQ in all or almost all samples, whereas Grandjean et al. (2012), Miura

et al. (2018), and Liu et al. (2022b) did not provide this information.

Factors such as plasma volume expansion and changes in glomerular filtration rate that occur during pregnancy may result in decreased PFAS concentrations in serum or plasma, and this effect may be greater when PFAS is measured later in pregnancy (reviewed in US EPA SAB, 2022). Maternal PFAS concentration was measured in the first trimester of pregnancy in the studies by Manzano-Salgado et al. (2019) and Dalsager et al. (2021), in the second or third trimester of pregnancy by Miura et al. (2018), in the first, second, or third trimester by Liu et al. (2022b), and in the third trimester by Grandjean et al. (2012) and Goudarzi et al. (2017). [The Working Group noted that although serum PFAS concentrations may decrease during pregnancy, this is unlikely to result in substantial exposure misclassification in studies in which blood PFAS concentrations are measured at the same time point in pregnancy in all participants. There is a higher risk of exposure misclassification in studies when serum PFAS concentrations are not measured during the same time period (e.g. trimester) in all participants.]

In two of the studies (Miura et al., 2018; Liu et al., 2022b), exposure and outcome were assessed in the same cord blood samples at birth, limiting the potential for non-differential exposure misclassification related to PFAS exposures other than from maternal fetal transfer. However, potential associations between the outcome and maternal PFAS concentrations were evaluated by Manzano-Salgado et al. (2019) at ages 1.5, 4, and 7 years, and by Dalsager et al. (2021) and Goudarzi et al. (2017) at up to age 4 years. The potential association between the outcome and maternal PFAS concentrations was evaluated by Liu et al. (2022b) at age 7 or 12 years as well as at birth, and by Grandjean et al. (2012) at ages 5 and 7 years. However, the potential impact of PFAS exposures that occurred postnatally was not considered, except by Grandjean et al. (2012), who also assessed the association between serum PFAS concentration at age 5 years with the outcome at age 7 years. [The Working Group noted that prenatal exposures are an important time window of exposure for epigenetic changes.] Health outcomes assessed in these children may be associated with postnatal PFAS exposure instead of or in addition to prenatal exposure. Breastfeeding has an impact on postnatal exposure, with the magnitude of the impact being dependent on breastfeeding duration, as well as exposure through drinking-water, diet, consumer products, and other sources. Although there may be some relationship between exposure to the mother (and associated prenatal exposure) and postnatal exposure (e.g. if the mother and child both drink the same contaminated drinking-water), maternal/prenatal and postnatal exposure are not necessarily strongly correlated. For example, Grandjean et al. (2012) reported weak correlations (Pearson coefficients of 0.19 for PFOA and 0.27 for PFOS) for maternal PFAS concentrations at week 32 of pregnancy and postnatal PFAS concentrations at age 5 years.

In these studies, exposures to other agents that were not measured in the mothers or children (see Section 1.6.2(a) above) may be correlated with PFAS exposure and may also have an impact on the outcome as confounders or effect-modifiers.

(iii) Longitudinal and repeated-measures studies

Longitudinal or repeated measures were used in three studies. The strengths of these studies include that repeated measurements provide information on the variability of biomarkers over time. Other strengths include that, in all three studies, the analytical methods used were state-of-the-art, and the LODs or LOQs for PFOA and PFOS were sufficiently low to ensure detection or quantification of PFOA and PFOS in all or almost all samples. Because PFOA and PFOS have long elimination half-lives (several years;

see Section 4.1), the concentrations measured in serum represent exposure over a relatively long period of time. Blood serum concentrations are an objective measure of exposure, the concentrations represent the combined exposure through all exposure pathways over a period of time, and the measurement error in the chemical analyses is low. These factors limit the potential for non-differential exposure misclassification, in general.

(iv) Study on pathology samples

In this study with a case–control design, Xie et al. (2023) measured concentrations of PFOA, PFOS, and 17 other PFAS in samples of glioma and non-glioma brain tissue. Although the analytical method (LC-MS/MS) was state-of-the-art, the percentage of samples in which PFOA and PFOS were detected at levels above the RL was 69% and 82%, respectively, of the glioma tissue samples, and 33% and 65%, respectively, of the non-glioma tissue samples, compared with other studies in which PFAS were detected in all or almost all samples in serum or plasma, or other matrices. [The Working Group noted that the low number of samples and low detection frequencies limited the informativeness of this study.]

In this study, paired glioma and non-glioma samples were available from only 18 patients, and the remainder of the total of 137 glioma and 40 non-glioma brain tissue samples did not come from the same patients. Additionally, the areas of the brain that were sampled for the non-glioma tissue samples were not reported. The comparisons of PFAS concentrations in glioma versus non-glioma tissue samples in this study were highly uncertain because, as previously stated, the specific part(s) of the brain that were sampled and compared were not known, and PFAS levels vary widely in different parts of the brain (Di Nisio et al., 2022). Also, comparison of PFAS levels in tumour and non-tumour brain tissues from different individuals is challenging to interpret because PFAS exposures vary widely among individuals. Finally, it is possible that PFAS accumulate more in tumour tissue than in non-tumour tissue in the brain, resulting in reverse causation.

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