17 Additional Information

The following sections will be included in the Additional Information menu item for the web-based document.

17.1 Additional Information for Media-Specific Occurrence

This section includes the tables of information that are summarized in Section 6 and included in the figures that section.
Table 17-1A and Figure 6-1A, Observed PFAS concentrations in outdoor air
Table 17-1B and Figure 6-1B, Observed PFAS concentrations in indoor air
Table 17-2 and Figure 6-2, Observed PFAS concentrations in soil and sediment
Table 17-3 and Figure 6-3, Observed PFAS concentrations in groundwater
Table 17-4 and Figure 6-4, Observed PFAS concentrations in surface water
Table 17-5 and Figure 6-5, Observed PFOS concentrations in fish

Table 17-1A. Observed PFAS concentrations in outdoor air

Location	Information	Concentrations (pg/m^3)
Japan (Kanazawa and Okinawa), Hong Kong, and Chennai, India (Ge et al. 2017)	Included sampling and analysis of ambient particles at four sites for 24 PFAS (9 PFSAs and 15 PFCAs). Ultrafine particles found to be largest contributor to mass fraction of PFCAs, while most PFOS mass was in the coarse-sized fractions. Seasonal differences in PFAS attributed largely to precipitation.	The yearly average PFAS mass concentration, between summer and fall samples, in Chennai was ∑PFAS = 21.5, in Okinawa ∑PFAS = 7, in Kanazawa ∑PFAS = 13. In Hong Kong, the concentration varied from ∑PFAS = 11.5 in the summer to 53 in the winter.
North Greenland (Bossi R. 2016)	Measured a range of neutral PFAS and other persistent organic pollutants (POPs) at a research station in North Greenland from 2008 to 2013.	Reported concentrations of PFAS (sum of particle and gaseous phase) [mean (range)]: • 6:2 FTOH: 2.82 (<0.45–16.5) • 8:2 FTOH: 4.93 (<0.45–22.4) • 10:2 FTOH: 1.59 (<0.20–9.68) • N-MeFOSA: 0.44 (<0.20–3.41) • N-EtFOSA: 0.33 (<0.22–1.93) • N-MeFOSE: 0.61 (<0.15–7.46) • N-EtFOSE: 0.50 (<0.11–5.96) Average ΣPFAS ranged from 1.82 to 32.1.
Northern South China Sea (Lai et al. 2016)	Air samples collected and analyzed for neutral PFAS onboard ship during a cruise campaign over the northern South China Sea in 2013.	Reported concentrations of PFAS [mean (range)]: • ΣFTOHs: 53 (17.8–105.8) • ΣFTCAs: mean not reported (0.1–0.4) • ΣFASAs: 1.2 (0.1–3.6) • Overall ΣPFAS: 54.5 (18.0–109.9)

Location	Information	Concentrations (pg/m^3)
Shenzhen China (Liu et al. 2015)	Air samples collected at 13 sites, including industrial areas with many industrial manufacturers, port districts, as well as less industrialized forested and tourist areas. Samples were analyzed for a range of PFCAs and PFSAs.	PFAS concentrations reported as mean ± standard deviation (SD) (range): • PFHxS: 0.31 ± 0.39 (ND–1.2) • PFOS: 3.1 ± 1.2 (ND–4.3) • PFBA: 1.9 ± 1.8 (ND–5.0) • PFPeA: 1.9 ± 1.4 (ND–4.0) • PFHxA: 1.5 ± 1.5 (ND–3.6) • PFHpA: 0.042 ± 0.10 (ND–0.30) • PFOA: 5.4 ± 3.8 (1.5–15) • PFNA: 0.49 ± 0.33 (ND–1.0) • PFDA: 0.48 ± 0.38 (ND–1.2) • PFUDA: 0.018 ± 0.064 (ND–0.22) • PFDoA: 0.20 ± 0.19 (ND–0.54) • Overall ΣPFAS: 15 ± 8.8 (3.4–34) Highest PFAS concentrations found within an industrial district downwind of other industrial cities.
Atlantic Ocean from North Atlantic to Antarctic (Wang, Xie, et al. 2015)	Measured 12 neutral PFAS (4 FTOHs, 3 FOSAs, 3 FOSEs, and 2 FTCAs) in the atmosphere across the Atlantic from the North Atlantic to the Antarctic, as well as snow from the Antarctic Peninsula.	Total ΣPFAS in air in the gas-phase mean (range): 23.5 (2.8 to 68.8). FTOHs were found to be the dominant compound representing 93% of the total ΣPFAS.
Toronto, Canada (Ahrens et al. 2012)	Collected samples from a semi-urban location while investigating an improved technique for measuring the gas-particle partitioning of PFAS using an annular diffusion denuder sampler.	Reported concentration range of gas-phase PFAS: • ΣFTOHs (most abundant PFAS in the gas phase): 39–153 • ΣFOSAs: 0.02–1.1 • ΣFOSEs: 0.33–0.79 • ΣFTCAs: 0.87–5.9 • PFBA (dominant PFCA): 4.0–22
Japan Sea to Arctic (Cai, Xie, et al. 2012)	Neutral PFAS were measured on board ship during an expedition from the Japan Sea to the Arctic Ocean in 2010.	Reported concentrations of PFAS in the gas phase(g)/particle-phase (p) [mean (range)]: • ΣFTOHs: 174 (61–358)(g)/3.6 (1–9.9)(p) • ΣFTCAs: 18 (5.2–47.9)(g)/0.3 (0.1–0.5)(p) • ΣFASAs: 1.4 (0.5–2.1)(g)/0.2 (0.1–0.24)(p) • ΣFASEs: 5.8 (1.9–15.0)(g)/1.8 (0.4–4.9)(p)
Birmingham and Harwell, United Kingdom (Goosey and Harrad 2012)	Measured atmospheric concentrations of a range of PFAS in homes, offices, and outdoor locations in Birmingham and Harwell, UK during 2008 and 2009. Outdoor sampling included two urban and one semirural locations. (PFAS reported as MeFOSA, EtFOSA, MeFOSE and EtFOSE).	Reported concentrations of PFAS in outdoor air [mean (range)]: • PFOS: 2.3 (<1.0–6.1) • PFOA: 3.5 (<1.9–20) • PFHxS: 7.0 (<1.1–30) • MeFOSA: 6.3 (<2.4–41) • EtFOSA: 89 (<5–170) • FOSA: 13 (1.8–27) • MeFOSE: 58 (3.4–130) • EtFOSE: 73 (20–120)

Location	Information	Concentrations (pg/m^3)
Vancouver, Canada (Shoeib et al. 2011)	Measured a range of ionic and neutral PFAS in indoor air, indoor dust, and clothes dryer lint in 152 homes in Vancouver, Canada in 2007–2008. The study included six outdoor air samples.	Reported concentrations of PFAS in outdoor air were [mean (range)]: • Σ FTOHs: 305 (161–906) • Σ FOSA/Es: 18 (8.1–108) • Σ PFCAs: below detection to 35
Atlantic Ocean: Gulf of Mexico to northeast coast of USA; Bermuda, and Nova Scotia (Shoeib et al. 2010)	Air sampling was performed in 2007 in Bermuda and Nova Scotia, and along a cruise track from the Gulf of Mexico to the northeast coast of the USA to assess air concentrations, particle-gas partitioning, and transport of a range of neutral PFAS.	Reported mean concentrations of dominant PFAS (gas + particle-phase): • ΣFTOHs: 11–165 • MeFOSE: 1.6–73
Atlantic Ocean, Antarctic Ocean, and Baltic Sea; and Hamburg, Germany (Dreyer et al. 2009)	Air samples were taken onboard several research vessels in the Atlantic Ocean, Antarctic Ocean, and the Baltic Sea as well as at one land-based site close to Hamburg, Germany, in 2007 and 2008 and were analyzed for a range of neutral and ionic PFAS.	Total gas-phase concentrations of ship-based samples (ΣPFAS) ranged from 4.5 in the Antarctic to 335 near source regions. Concentrations of 8:2 FTOH (typically the most dominant PFAS) were between 1.8 and 130. Concentrations of individual particle-bound precursors were usually below 1. Reported overall mean PFAS concentrations for all samples: • ΣFTOHs: 47 • ΣFTCAs: 3.6 • ΣFASAs: 7.6 • ΣFASEs: 3.8
Canadian Rocky and Purcell Mountains, Western Canada (Loewen et al. 2008)	Air and lake water samples were collected along an altitudinal transect across Western Canada during the spring and summer of 2004 and analyzed for a range of PFAS.	The reported ranges of vapor phase PFAS concentrations were estimated as: • ΣFTOHs: 0.8–27 • ΣFOSAs: 3.7–19 • ΣFOSEs: <25–88 The concentrations of FTOHs and FOSEs were found to increase with altitude.
Parkersburg, West Virginia. USA (Barton 2007)	Concurrent rain and air samples collected at nine locations at a manufacturing facility during a single precipitation event and analyzed for PFOA.	PFOA predominantly associated with particulates and detected as high as 1,100.
Atlantic Ocean from Germany to South Africa (Jahnke et al. 2007)	Air samples were collected on board a research vessel during cruise in the Atlantic Ocean from Germany to South Africa in 2005 and analyzed for a range of neutral and ionic PFAS.	Reported concentration ranges of PFAS: • 6:2 FTOH: ND–174 • 8:2 FTOH: 2–190 • 10:2 FTOH: 0.8–48 • N-EtFOSA: ND–2.2 • N-MeFOSA: 0.4–4.2 • N-MeFOSE: ND–22 • N-EtFOSE: ND–11.8
Albany, New York, USA (Kim and Kannan 2007)	Measured PFCAs, PFSAs, and FTSAs in air, rain, snow, surface runoff water, and lake water in an urban area.	Overall range of PFAS concentrations in air: • ΣPFAS (gas phase): 5.10–11.6 • ΣPFAS (particle-phase): 2.05–6.04

Location	Information	Concentrations (pg/m^3)
Okinawa, Japan, and Central Oregon, USA (Piekarz et al. 2007)	Air samples were collected and analyzed for a range of neutral PFAS from locations in Okinawa, Japan, and central Oregon, USA, between 2004 and 2006. (PFAS reported as MeFOSE and EtFOSE).	Reported PFAS concentration in the gas phase (g)/particle-phase (p): • ΣFTOHs: <0.4–32 • MeFOSE: <1–25 (g)/<1–21 (p) • EtFOSE: <1–8.7 (g)/<1–6.9 (p) • N-EtFOSA: <0.4–12 (g)/<0.4–12 (p)
Parkersburg, West Virginia USA (Barton et al. 2006)	This study included six sampling events over a 10-week period during 2003–2004. Air samples were collected along the fence line of a fluoropolymer manufacturer and analyzed for PFOA.	The measured concentration of PFOA ranged from 120,000–900,000.
Canada (Shoeib et al. 2004)	Indoor and outdoor air was collected from laboratories and homes in Canada from 2001–2003 and analyzed for several PFAS. The study included two outdoor sample locations.	Reported range of PFAS concentrations in outdoor air (gas + particle-phase): • MeFOSE: 16.0–31.7 • EtFOSE: 8.47–9.79
North American cities (Stock et al. 2004)	Air samples were collected in six North American cities (Reno, NV; Griffin, GA; Cleves, OH; Winnipeg, MB; Long Point, ON; and Toronto, ON) and analyzed for three FTOHs (6:2, 8:2, and 10:2) and three polyfluorinated sulfonamides (NEtFOSA, NEtFOSE, and NMeFOSE).	Reported PFAS concentration range: • ΣFTOHs: 11–165 • Σ(N-EtFOSA, N-EtFOSE, and N-MeFOSE): 22–403
ND = Nondetect		

Table 17-1B. Observed PFAS concentrations in indoor air

Location	Information	Concentrations (µg/kg)
Global Distribution		
Global distribution (Rankin et al. 2016)	Worldwide survey of 62 soils samples, PFOA and PFHxA detected in all samples, and PFOS detected in all but one sample; PFOS and PFOA the most frequently detected.	• ΣPFCAs: 0.029–14.3 • ΣPFSAs: ND–3.27 (only one sample was ND) Remote area (Lake Bonney, Antarctica): • PFOA = 0.048 • PFOS = 0.007

Location	Information	Concentrations (µg/kg)
Global, locations not associated with known PFAS sources (Strynar et al. 2012)	Evaluated 60 soil samples from six countries and reported global median concentrations. PFOS detected in 48% and PFOA detected in 28% of the samples. Note that concentrations < LOQ (~0.5 µg/kg) were assigned a value of LOQ/√2 for the median calculations.	Global median concentrations: • PFOA: 0.124 • PFOS: 0.472
Point Sources		
Location near industrial PFAS source (Davis et al. 2007)	Concentrations of ammonium perflurooctanoate (APFO) in two soil borings located within an impacted well field; concentrations decreased rapidly with depth.	APFO: 110–170
Fire Training/Fire Response (Houtz et al. 2013)	PFOS and PFOA in soils at an unlined fire training area.	Median concentrations: • PFOS: 2,400 • PFOA: 21
Fire Training/Fire Response (Anderson et al. 2016)	In a survey of 40 sites impacted by PFAS, the most frequently detected compounds were PFOS (99% of surface samples), PFHxS (77%), and PFOA (79%). PFOS was detected at the highest concentrations.	PFOS: • Median: 53 • Max: 9,700
Industrial Areas (Zareitalabad, Siemens, Hamer, et al. 2013)	PFOA and PFOS concentrations in soil were compiled.	Max: • PFOS: 48 • PFOA: 10
Sludge-Biosolids Application		

Location	Information	Concentrations (µg/kg)
Soil, groundwater, and tile water sampled after a single high-rate application of municipal biosolids (Gottschall et al. 2017)	Soil cores collected from 0–0.3 meters, entire interval homogenized; (values picked from concentrations plots).	PFOA: 0.4–0.8 PFOS: 0.2–0.4 PFNA: 0.1–0.22 PFDA: 0.05–0.33 PFUDA: 0.07–0.12
Municipal Biosolids (Sepulvado et al. 2011)	Six municipal biosolids and biosolids-amended surface soils. Soil concentrations decreased with depth. Values approximated from plots in supplemental information.	Biosolids: • PFOS: 80–219 • N-MeFOSAA: 63–143 • N-EtFOSAA: 42–72 • PFOA: 8–68 Biosolid amended soil <10 cm depth: • PFOS: 2,438 • PFOA: ~8–38 • PFNA: ~2–7 • PFHpA: ~2–8 • PFHxS: ~3–12
Sediment		
Lake Ontario, Yangtze & Mississippi Rivers (Qi et al. 2016; Yeung et al. 2013; Oliaei et al. 2013; Pan, Ying, Zhao, et al. 2014)	Maximum sediment concentrations of PFOA, PFOS, and other PFAAs.	10s–100s
Estuarine sediments–South Carolina (White et al. 2015)	Analysis of 11 PFAS.	Average of 3.79 (∑PFAS)
Surface sediments–China (Qi et al. 2016)	Analysis of 17 PFAS. Dominant PFAS: PFOA, PFOS, and PFUDA.	0.086–5.79 dry weight and an average of 1.15 (∑PFAS)
Surface sediments and cores–Great Lakes (Codling et al. 2018)	22 PFAS analyzed, surface sediment averaged for 3 different lakes, and dated cores used to approximate depositional trends over time.	1.5, 3.1, and 4.6 (surface sediment average for ∑PFAS 3 lakes)
ND = Nondetect LOQ = Limit of quantitation		

Table 17-2. Observed PFAS concentrations in soil and sediment

Location	Information	Concentrations (µg/kg)
Global Distribution		
Global distribution (Rankin et al. 2016)	Worldwide survey of 62 soils samples, PFOA and PFHxA detected in all samples, and PFOS detected in all but one sample; PFOS and PFOA the most frequently detected.	• ΣPFCAs: 0.029–14.3 • ΣPFSAs: ND–3.27 (only one sample was ND) Remote area (Lake Bonney, Antarctica): • PFOA = 0.048 • PFOS = 0.007
Global, locations not associated with known PFAS sources (Strynar et al. 2012)	Evaluated 60 soil samples from six countries and reported global median concentrations. PFOS detected in 48% and PFOA detected in 28% of the samples. Note that concentrations < LOQ (~0.5 µg/kg) were assigned a value of LOQ/√2 for the median calculations.	Global median concentrations: • PFOA: 0.124 • PFOS: 0.472
Point Sources		
Location near industrial PFAS source (Davis et al. 2007)	Concentrations of ammonium perflurooctanoate (APFO) in two soil borings located within an impacted well field; concentrations decreased rapidly with depth.	APFO: 110–170
Fire Training/Fire Response (Houtz et al. 2013)	PFOS and PFOA in soils at an unlined fire training area.	Median concentrations: • PFOS: 2,400 • PFOA: 21

Location	Information	Concentrations (µg/kg)
Fire Training/Fire Response (Anderson et al. 2016)	In a survey of 40 sites impacted by PFAS, the most frequently detected compounds were PFOS (99% of surface samples), PFHxS (77%), and PFOA (79%). PFOS was detected at the highest concentrations.	PFOS: • Median: 53 • Max: 9,700
Industrial Areas (Zareitalabad, Siemens, Hamer, et al. 2013)	PFOA and PFOS concentrations in soil were compiled.	Max: • PFOS: 48 • PFOA: 10
Sludge-Biosolids Application		
Soil, groundwater, and tile water sampled after a single high-rate application of municipal biosolids (Gottschall et al. 2017)	Soil cores collected from 0–0.3 meters, entire interval homogenized; (values picked from concentrations plots).	PFOA: 0.4–0.8 PFOS: 0.2–0.4 PFNA: 0.1–0.22 PFDA: 0.05–0.33 PFUDA: 0.07–0.12
Municipal Biosolids (Sepulvado et al. 2011)	Six municipal biosolids and biosolids-amended surface soils. Soil concentrations decreased with depth. Values approximated from plots in supplemental information.	Biosolids: • PFOS: 80–219 • N-MeFOSAA: 63–143 • N-EtFOSAA: 42–72 • PFOA: 8–68 Biosolid amended soil <10 cm depth: • PFOS: 2,438 • PFOA: ~8–38 • PFNA: ~2–7 • PFHpA: ~2–8 • PFHxS: ~3–12
Sediment		
Lake Ontario, Yangtze & Mississippi Rivers (Qi et al. 2016; Yeung et al. 2013; Oliaei et al. 2013; Pan, Ying, Zhao, et al. 2014)	Maximum sediment concentrations of PFOA, PFOS, and other PFAAs.	10s–100s
Estuarine sediments–South Carolina (White et al. 2015)	Analysis of 11 PFAS.	Average of 3.79 (∑PFAS)

Location	Information	Concentrations (µg/kg)
Surface sediments–China (Qi et al. 2016)	Analysis of 17 PFAS. Dominant PFAS: PFOA, PFOS, and PFUDA.	0.086–5.79 dry weight and an average of 1.15 (∑PFAS)
Surface sediments and cores–Great Lakes (Codling et al. 2018)	22 PFAS analyzed, surface sediment averaged for 3 different lakes, and dated cores used to approximate depositional trends over time.	1.5, 3.1, and 4.6 (surface sediment average for ∑PFAS 3 lakes)
ND = Nondetect LOQ = Limit of quantitation		

Table 17-3. Observed PFAS concentrations in groundwater

Location	Information	Concentrations (ng/L)
Firefighting Foam Sites		
AFFF Release Sites other than Fire Training Areas (Anderson et al. 2016)	Tested 149 groundwater samples; most commonly detected PFAAs: PFHxS (95%); PFHxA (94%), PFOA (90%), PFPeA (88%), PFBA and PFHpA (85%), PFOS (84%). The frequency of detections for PFSAs in groundwater was generally higher than those of PFCAs, which has been attributed to the use of specific AFFF formulations.	Median (maximum): • PFHxS: 870 (290,000) • PFHxA: 820 (120,000) • PFOS: 4,220 (4,300,000) • PFOA: 405 (250,000) • PFPeA: 530 (66,000) • PFBA: 180 (64,000) • PFHpA: 235 (75,000)
Fire Training/Fire Response (Moody and Field 1999; Moody et al. 2003; Houtz et al. 2013)	Studies at U.S. military installations and other AFFF release areas have documented relatively high detection frequencies of PFAAs in underlying groundwater.	Maximum: • PFOA: 6,570,000 • PFOS: 2,300,000
Landfill Impacts		
Raw and Treated Landfill Leachates (Yan et al. 2015)	5 municipal landfill sites in China were included in a study of 14 PFAAs concentrations in raw and treated leachate. Total PFAAs ranged from 7.28 to 292 µg/L in raw and 0.1 to 282 µg/L in treated. Dominant compounds included PFOA (28.8% of raw and 36.8% of treated) and PFBS (26.1% of raw and 40.8% of treated).	**Raw leachate** Range (mean contribution %): • PFOA: 281–217,000 (28.8) • PFBS: 1,600–41,600 (26.1) • PFPeA: 640–10,000 (15.9) • PFOS: 1,200–6,00 **Treated leachate** Range (mean contribution %): • PFOA: 30–206,000 (36.8) • PFBS: 20–55,300 (40.8)

Location	Information	Concentrations (ng/L)
Firefighting Foam Sites		
Landfill Leachates (Eggen, Moeder, and Arukwe 2010)	Leachates from two landfills were analyzed for different emerging pollutants, including PFAS. Landfills had clay liners and tubing system to collect the leachate. Data presented include PFAS concentrations in water and particle phases.	Water maximum: • PFHxS: 281 • PFOS: 2,920 • PFHxA: 757 • PFHpA: 277 • PFOA: 767 • PFNA: 539 Particle maximum: • PFHxS: 0.15 • PFOS: 339 • PFOA: 4.05 • PFOSA: 0.44
Landfill Leachate and Groundwater (NY DEC 2017b)	PFOA was detected in public and private drinking water in Petersburgh, NY. In the site investigation groundwater and leachate from the Petersburgh/Berlin landfill was tested.	PFOA groundwater range: • 1.4–1,600 PFOA leachate: • 4,200
Landfill Groundwater (NY DEC 2016)	The City of Newburgh, NY, identified PFAS in their water in 2016. Included in their investigation was the Town of New Windsor landfill, which had its monitoring wells tested for PFAS compounds.	Range: • PFOS: 2.59–50.3 • PFOA: 4.0–40.4 • PFHxS: 3.72–86.6 • PFHpA: 2.36–5.93 • PFBS: 8.08–23.9
Landfill Groundwater (VT DEC 2018b)	Analysis of groundwater monitoring wells around landfills in Bennington, VT, for PFOS and PFOA. Nine locations were tested in 2016.	Median (maximum): • PFOA: 18 (900) • PFOS: 4.98 (140)
Biosolids/Sludge		
Soil, Groundwater, and Tile Water Sampled after a Single High-Rate Application of Municipal Biosolids (Gottschall et al. 2017)	Shallow groundwater (2-meter depth) sampled at 2, 7, and 10 months after application. Values picked from concentrations plots. Tile water was similar except PFOA range nondetect to 23.	PFOA: 1.5–3 PFOS: nondetect–0.8 PFNA: nondetect–1.1 PFHpA: nondetect–6
Contaminated Biosolid Application Effects on Groundwater in Decatur, Alabama (Lindstrom et al. 2011)	Fluorochemical industry contaminated biosolids were applied on local agricultural fields for as much as 12 years in Decatur, Alabama. Sampling of well water near the fields showed elevated PFAS concentrations.	Range: • PFNA: 25.7 • PFOA: 149–6,410 • PFHpA: 77.2–5,220 • PFHxA: 9.7–3,970 • PFPeA: 12.2–2,330 • PFBA: 10.4–1,260 • PFOS: 12–151 • PFHxS: 12.7–087.5 • PFBS: 10.1–76.6
Industrial Sites		

Location	Information	Concentrations (ng/L)
Firefighting Foam Sites		
Industrial Use Contamination (Procopio et al. 2017)	Study by NJDEP and the NJ Brick Township Municipalities Authority on concentrations of PFAS compounds in various water sources. A plume of contamination was detected and attributed to a small manufacturer using materials containing PFOA.	Maximum: • PFOA: 70,000 • PFBA: 2,000 • PFPA: 560 • PFHxA: 3,800 • PFHpA: 4,300 • PFNA: 63 • PFDA: 560 • PFHxS: 6 • PFOS: 50
Fluorochemical Industrial Facility (Davis et al. 2007)	Environmental media (soil and water) were investigated in a PWS well field near a fluoropolymer manufacturing facility for the presence of PFOA.	Maximum: • PFOA: 78,000
Teflon Fabric Coating Facility (VT DEC 2018b)	2016 investigation of PFAS contamination in relation to a former Teflon coating factory in North Bennington, VT. Over 600 drinking water wells tested and more than 300 wells exceeded the state's PFOA/PFOS standard of 20 ppt.	Maximum: • PFOA: 4,600
Fluorochemical Industrial Facility (3M Company 2007)	Study completed at the 3M Company's Cottage Grove, Minnesota, plant. 8 groundwater monitoring wells were installed and sampled throughout the site for the presence of FCs.	Maximum: • PFOA: 619,000 • PFBA: 318,000 • PFBuS: 26,100 • PFHxS:40,000 • PFOS: 26,000
Water Supplies–Nonsite-Related		
Domestic Drinking Water Wells on Cape Cod, Massachusetts (Schaider, Ackerman, and Rudel 2016)	20 domestic drinking water wells in Cape Cod, MA, were investigated for the presence of organic wastewater compounds, including PFAS. All wells were located in areas served exclusively by onsite wastewater treatment systems.	Maximum: • PFBS: 23 • PFHxA: 2 • PFHpA: 1 • PFHxS: 41 • PFOS: 7
Survey across European Countries (Loos et al. 2010)	164 groundwater samples tested from 23 European countries. Sampling sites were not chosen to be "representative" or "contaminated," but most were from official monitoring stations also used for drinking water monitoring.	Median (maximum) [freq. %]: • PFOA: 1 (39) [65.9] • PFOS: 0 (135) [48.2] • PFHxS: 0 (19) [34.8] • PFHpA: 0 (21) [29.9] • PFDA: 0 (11) [23.8] • PFBS: 0 (25) [15.2] • PFNA: 0 (1) [15.2]
Public Drinking Water Sources across the U.S. (USEPA 2017g)	Results from finished groundwater testing by the EPA under UCMR3.	Range (freq. %): • PFBS: 90–220 (0.05) • PFHpA: 10–410 (0.64) • PFHxS: 30–1,600 (0.56) • PFNA: 22–56 (0.05) • PFOA: 20–350 (1.03) • PFOS: 40–7,000 (0.79)

Table 17-4. Observed PFAS concentrations in surface water

Location	Information	Concentrations (ng/L)
Freshwater		
Remote Areas (Filipovic (Filipovic et al. 2015) (Eriksson et al. 2013) (Stock et al. 2007) (Lescord et al. 2015)	PFOS and PFOA concentrations in the Faroe Islands and remote areas of Sweden have been measured in the 100s of picograms per liter range, while concentrations in the Canadian Arctic have been measured up to single nanogram per liter range.	Range: PFOS/PFOA ND to <10
Industrial Areas, Japan, and Tennessee River, USA (Saito et al. 2004; Hansen et al. 2002)	Concentrations of PFOS and PFOA as high as 144 ng/L and 67,000 ng/L, respectively, have been measured.	Maximums: PFOS: 144 PFOA: 67,000
Fire Training/Fire Response (Saito (Saito et al. 2004; Anderson et al. 2016)	Concentrations of PFOS and PFOA as high as 8,970 ng/L and 3,750 ng/L, respectively, have been measured in AFFF-impacted surface water.	Maximums: PFOS: 8,970 PFOA: 3,750
Municipal Wastewater Treatment Facilities (Becker, Gerstmann, and Frank 2008; Boulanger 2005; Wilkinson et al. 2017; MDH 2008))	Data presented typically for upstream, downstream, and effluent wastewater. Generally low frequency of detection upstream. Some treatment facilities show evidence for precursors with greater PFAS in effluent than influent.	PFOA: ND–220 PFOS: ND–814 PFHxS: ND–26 PFBS: ND–115 PFNA: ND–209
Public Drinking Water Sources across the US (USEPA 2017g)	Results from finished water testing with surface water source by the EPA under UCMR3.	Range: PFBS: 90–370 PFHpA: 10–60 PFHxS: 30–190 PFNA: 20–54 PFOA: 20–100 PFOS: 40–400
Marine Water		
Open Water (Benskin, Muir, et al. 2012; Cai, Yang, et al. 2012; Zhao et al. 2012)	The sum of PFAA concentrations in the mid-Northwest Altantic ranged from 0.077 to 0.19 ng/L, while PFAAs in the Northeast Atlantic ranged from 0.28 to 0.98 ng/L. The sum of PFAS in the North Atlantic ranged from 0.13 to 0.65 ng/L, and in the Greenland Sea from 0.045 to 0.28 ng/L.	Range: ∑PFAA 0.077–0.98 ∑PFAS 0.045–0.65
Coastal Areas (Benskin, Muir, et al. 2012; Cai, Yang, et al. 2012; Zhao et al. 2012)	Along the Rhode Island coast the sum of PFAAs ranged up to 5.8 ng/L. Along the coast of Antarctica the sum of PFAS ranged from 0.59 to 15.3 ng/L, and along the southern Atlantic coast of South America the sum of PFAA ranged from <0.21 to 0.54 ng/L.	Range: ∑PFAA <0.21 to 5.8 ∑PFAS 0.59–15.3
Stormwater		
Residential/Undeveloped (Xiao, Simcik, and Gulliver 2012), (Wilkinson et al. 2016) (Zhao, Zhou, et al. 2013)	PFAS concentrations measured in residential, campus, and field settings in Minnesota, China, and England, respectively.	Maximums: • PFOS: 15.5 • PFOA: 19.1 • PFHxA: 4 • PFHpA: 22.5 • PFNA: 23

Location	Information	Concentrations (ng/L)
Commercial/Heavy Traffic–Minneapolis/St. Paul, MN; Eastern and Central China cities; and England (Xiao, Simcik, and Gulliver 2012; Zhao, Zhou, et al. 2013; Wilkinson et al. 2016)	PFOS and PFOA measured in stormwater runoff from streets in areas not related to specific releases, but unidentified local or consumer sources may be responsible for higher concentrations detected.	Range: • PFOS: <LOQ–590 • PFOA: 3.5–1,160 • PFHpA: ND–6.8 • PFNA: ND–648 • PFDA: ND–10.6 • PFUnDA: ND–2.9
Industrial Areas–Minneapolis and St. Paul, MN (Xiao, Simcik, and Gulliver 2012)	PFOS measured in stormwater in an industrial area with suspected PFAS.	Range: • PFOS: 8.7–156
Airport Ditch, Likely Impacted by AFFF, Korea (Kim et al. 2014)	PFAAs measured, predominately PFHxS and PFOS.	• Total PFAAs: 6.42–804

Table 17-5. Observed PFOS concentrations in fish (μg/kg)

Location	Information	Mean (max)
Industrial (Oliaei et al. 2013; Delinsky et al. 2010)	Near PFAS production plants, individual fish tissues such as liver, blood, and muscle have been reported to have elevated PFOS.	PFOS: • Liver: (6,350) • Blood: (29,600) • Muscle: <3–100 (2,000)
AFFF Release (Moody et al. 2002) (Gewurtz et al. 2014) (Lanza et al. 2017)	PFOS in fish liver, muscle, and whole fish samples were detected following a release of AFFF during emergency or fire training activities.	PFOS: • Liver: (100) 72,900 • Muscle: (6,160) • Whole fish: ~200–2,000 (15,000)
Wastewater Treatment Plant (Becker, Gerstmann, and Frank 2010; Li et al. 2008)Schuetze (Schuetze et al. 2010)	PFOS concentrations have been detected in fish collected near the outfall of wastewater treatment plants.	PFOS: Liver: (400) Serum: (64) Muscle tissue: 7–250 (400)
Freshwater fish from New Jersey (NJDEP 2018)	PFOS concentrations in 12 species of freshwater fish from New Jersey.	PFOS: 1.4–119 (162.5)
Freshwater fish from U.S. urban rivers and the Great Lakes (Stahl et al. 2014)	PFOS concentrations in freshwater fish from U.S. urban rivers (25 species) and the Great Lakes (18 species).	PFOS: 10.7 (127)

17.2 Additional Information for Human Health Effects

This section supplements information provided in Section 7.1 on biomonitoring, exposure, toxicokinetic, toxicology, and epidemiology data for long-chain and short-chain PFAAs. The PFAS discussed here include perfluorocarboxylic acids (PFCAs) with four to fourteen carbons and perfluorosulfonic acids (PFSAs) with four or more carbons. Also covered are two fluorinated ether carboxylates (FECAs)—ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (also known as perfluoro-2-propoxypropanoic acid (PFPrOPrA); hexafluoropropylene oxide [HFPO] dimer acid), commonly known as GenX (Section 2.2.3.5); and 4,8-dioxa-3H-perfluorononanoate, commonly known as ADONA. These FECAs are replacements for PFOA as processing aids in certain fluoropolymer production. They are included because they are of current interest and health effects data are available. There is little or no publicly available health effects information for most of the many other PFAS used in commerce (Section 2.3), including precursors that can be converted to PFAAs in the environment and in the human body.

For further detail of scientific names and carbon chain length of PFAAs see Section 2.2.

17.2.1 Overview

Based on the number of studies located through searches of the National Library of Medicine's PubMed, a database containing relevant peer-reviewed publications, much of the information summarized here is recent. Additional studies may be available, particularly for those compounds with large health effects data sets, and additional information on the topics in this section can be found in databases such as PubMed and references listed in Section 7.1.

The publicly available toxicological data set is currently largest for PFOA and PFOS, with considerable data also available for PFBA, PFBS, PFHxA, PFNA, PFDA, and GenX, a few studies for PFHxS, PFUnA, PFDoA, and ADONA, and little or no data for PFPeA, PFHpA, PFTrA, PFTA, PFPeS, PFHpS, PFNS, or PFDS. Most of the mammalian studies were conducted in rodents, with a few in nonhuman primates (monkeys). The most notable toxicological effects from the mammalian studies of these PFAS, with relevant citations, are discussed in Section 17.2.5 and are summarized in Table 17-8 (provided as a separate Excel file). However, due to the large size of the toxicological data set, it is beyond the scope of this section to identify no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for these effects. The numerous reviews of potential epidemiological associations of health endpoints with PFAAs are discussed in Section 17.2.4. Many of the epidemiology studies evaluate associations of health endpoints with multiple PFAAs detected in the blood serum of the subjects. Finally, data gaps and research needs are discussed.

17.2.2 Human Biomonitoring and Sources of Exposure

Several long-chain PFAAs (from highest to lowest geometric mean [GM] serum levels, as follows: PFOS, PFOA, PFHxS, PFNA) are present in the low parts per billion (ng/ml) range in the blood serum of almost all adult residents of the United States, while other PFAS are detected in a smaller percentage of the population (CDC 2018; Olsen et al. 2017)). In contrast, short-chain PFAAs such as PFBS and PFHxA are more rapidly excreted and were infrequently detected in the blood serum of the U.S. general population (CDC 2018; Olsen et al. 2017). For example, PFBS was detected in less than 5% of serum samples in all National Health and Nutrition Examination Survey (NHANES) years except 2005–'06 (CDC 2018). Both NHANES and the blood donor studies show generally higher levels of long-chain PFAAs in males than females, with generally decreasing serum levels of long-chain PFAAs over time. NHANES 2013–'14 evaluated PFAS in children 3–11 years old (CDC 2018) and found serum levels of PFOS, PFOA, PFHxS, and PFNA generally similar to those in older adolescents and adults in the same time period. It was noted that most of the children studied were born after PFOS manufacturing was phased out in the United States in 2002 (Ye et al. 2018). Long-chain PFAA human serum levels in other industrialized countries are generally similar to the United States (Kato 2015) and may be lower in less developed nations (for example, Afghanistan) where they are less likely to be used industrially and consumer products containing them are less frequently used (Hemat et al. 2010). Testing in 2017 by the North Carolina Department of Health and Human Services (NC DHHS) did not detect HFPO-DA ("GenX") in the blood serum or urine of North Carolina residents with previous or current exposure from private wells, but did detect other PFAS (NC DHHS 2018). A North Carolina State University study of a public water system and its users included a larger list of PFAS analytes and, although no GenX was detected, they identified four newly identified PFAS in the drinking water and blood serum of most participants (Hogue 2019; Hopkins et al. 2018). A recent study of a potentially exposed population detected ADONA in only a few subjects (Fromme et al. 2017).

Human exposures can result from consumption of fish from waters contaminated with bioaccumulative PFAAs (for example, MDCH (2014)). PFSAs with more than eight fluorinated carbons (that is, PFOS and longer chain for PFSAs; PFNA and longer chain for PFCAs) are substantially more bioaccumulative than shorter chain PFAAs, with PFSAs generally more bioaccumulative than PFCAs with the same number of fluorinated carbons (Conder et al. 2008; Martin et al. 2003). When drinking water is contaminated with even relatively low levels of long-chain PFAAs, exposure from drinking water may dominate contributions from exposure sources such as food and consumer products that are prevalent in the general population. For example, (USEPA 2011a) predicted that ongoing exposure to 20 ng/L PFOA in drinking water will increase serum PFOA levels more than two-fold from the U.S. median of 2 ng/L. Elevated serum levels of long-chain PFAAs have been observed in communities with contaminated drinking water in several U.S. states, including Ohio and West Virginia (WV University 2008; Emmett et al. 2006; Steenland et al. 2009) (Hoffman et al. 2011), New Hampshire (NH DHHS 2015), Alabama (ATSDR 2013), Minnesota (MDH 2009; Landsteiner et al. 2014), New York (NYS DOH 2016a), and in other nations, including Germany (Hölzer et al. 2008) and Sweden (Li et al. 2018) (Table 17-6). ATSDR (2019b) plans to conduct exposure assessments that will include biomonitoring in eight U.S. locations impacted by PFAS in drinking water.

Understanding exposures to PFAS at different developmental phases (for example, fetus, infant) is important to ensure protection of the most sensitive subpopulations. Evidence for developmental effects from early life exposures to long-chain

PFAAs in humans is discussed in Section 17.2.4 and in animals in Section 17.2.5. PFAAs (primarily PFHpA and longer chain PFCAs; PFHxS and longer chain PFSAs) have been detected in human amniotic fluid (Stein et al. 2012; Zhang, Sun, et al. 2013), umbilical cord blood (Kato 2015; Kudo 2015), and breast milk (Liu, Li, et al. 2010; White et al. 2011; Post, Cohn, and Cooper 2012; Kato 2015) (Kudo 2015). Although the specific compounds analyzed for and/or detected vary among studies, other PFAAs that have been analyzed for in breast milk rarely exceeded the limit of quantitation (Tao, Kannan, et al. 2008; Tao, Ma, et al. 2008). Serum levels of several long-chain PFAAs were higher in breast-fed infants than in their mothers and declined slowly following weaning (Mogensen et al. 2015), and serum levels of infants who drank formula prepared with PFAS-contaminated water were higher than in older individuals using the same water source. Infants and toddlers may also receive higher exposures because of age-specific behaviors such as hand-to-mouth activity that results in greater ingestion of house dust, and more time spent on floors with treated carpets relative to older children or adults (Trudel et al. 2008; Shoeib et al. 2011).

Elevated serum levels of PFAAs, in some cases >100,000 ng/ml, have been found in industrially exposed workers (Olsen 2015). Serum concentrations of PFCAs (PFHpA and longer) were also increased in professional ski waxing technicians due to exposures to fluorinated ski waxes (Freberg et al. 2010; Nilsson et al. 2010). Higher serum levels of PFDA (Dobraca et al. 2015), PFOS, and PFHxS (Rotander et al. 2015) have been reported in firefighters relative to those in the general population.

17.2.3 Toxicokinetics

PFAAs for which data are available (PFOA, PFHpA, PFHxA, PFOS) were well absorbed orally (≥90%) in rodents (Kudo 2015). PFOA and PFNA were absorbed via inhalation as dusts or aerosols (Kinney, Chromey, and Kennedy 1989; Hinderliter, DeLorme, and Kennedy 2006). PFOA was absorbed to a limited extent from dermal exposure in studies of isolated human and rodent skin (Fasano et al. 2005) (Franko et al. 2012).

PFAAs, particularly long-chain PFCAs and PFSAs, have unique toxicokinetic properties as compared to other types of POPs. Unlike most other bioaccumulative organic compounds (for example, dioxins, PCBs), PFAAs do not have a high affinity for adipose tissue. In contrast, PFAAs are water soluble, have an affinity for proteins (which varies among compounds), and generally distribute primarily to the liver, blood serum (where they are bound to albumin and other proteins), and kidney (Bischel et al. 2011; Lau 2012, 2015; Kato 2015).

PFAAs are highly resistant to chemical reactions. As such, they are not metabolized, and this is also true for HFPO-DA (Gannon et al. 2016) and ADONA (Gordon 2011). However, PFAA precursors can be metabolized to PFAAs within the body, and reactive intermediates may be formed in these metabolic pathways (Rand and A. Mabury 2016). Some examples are the metabolism of 6:2 fluorotelomer alcohol (6:2 FTOH) to PFBA, PFPeA, PFHxA, and PFHpA (Buck 2015); 8:2 FTOH to PFOA and PFNA (Kudo 2015; Kabadi et al. 2018); and perfluorooctane sulfonamidoethanols (FOSEs), perfluorooctane sulfonamides (FOSAs), and perfluorooctane sulfonamidoacetic acids (FOSAAs) to PFOS (Gebbink, Berger, and Cousins 2015). Additionally, larger PFAS molecules such as polyfluoroalkyl phosphoric acid diesters (diPAPs) have been found in human blood serum and can be metabolized to FTOHs, which are further metabolized to PFCAs (D'Eon and Mabury 2011) (Lee and Mabury 2011).

Table 17-6. Long-chain PFAA serum levels in populations exposed through drinking water (ng/ml = µg/L = ppb)

(Means, medians, and maximums available from the cited studies are shown. AM–arithmetic mean; GM–geometric mean; 95^{th}–95^{th} percentile; — indicates that data are not available)

Location	Study Population	Attributed Source	Year	PFOA			PFOS			PFHxS		
				Mean	*Median*	*Max.*	*Mean*	*Median*	*Max.*	*Mean*	*Median*	*Max.*
C8 Study Population: WV/Ohio (WV University 2008) Includes occupationally exposed subject	n = ~69,000 <1 – >90 yrs. M-48%, F-52%	Industrial–PFOA	2005–06	83 (AM)	28	22,412	23 (AM)	20	759	—	—	—

Location	Study Population	Attributed Source	Year	PFOA			PFOS			PFHxS		
				Mean	*Median*	*Max.*	*Mean*	*Median*	*Max.*	*Mean*	*Median*	*Max.*
Arnsberg, Germany (Hölzer et al. 2008)	n=90 Children 5–6 yrs.	Industrial waste applied to agricultural land–mainly PFOA	2006	25 (AM)	—	97	5 (AM)	—	21	1 (AM)	—	13
	n=164 Mothers 23–49 yrs.			27 (AM)	—	100	6 (AM)	—	17	1 (AM)	—	6
	n=101 Men 18–69 yrs.			29 (AM)	—	78	12 (AM)	—	36	3 (AM)	—	9
East Metro, MN (MDH 2009)	n = 196 20–86 yrs. M-45%, F-55%	Industrial–multiple PFAS	2008–09	23 (AM)	16	177	48 (AM)	41	448	15 (AM)	9	316
Decatur, AL (ATSDR 2013)	n=153 “child” – >60 yrs. M-41%, F-59%	Industrial–multiple PFAS	2010	16 (GM)	—	144	40 (GM)	—	472	6 (GM)	—	59
Ronneby, Sweden (Li et al. 2018)	n = 3418 4–83 yrs. M-47%, F-53%	AFFF	2014	14 (AM)	10	92	245 (AM)	176	1,870	228 (AM)	152	1790
Portsmouth, NH (NH DHHS 2015)	n = 108 < 12 yrs.	AFFF	2015	4 (GM)	5	12	9 (GM)	9	31	6 (GM)	7	26
	n= 363 >12 yrs.			3 (GM)	—	16	8 (GM)	—	75	8 (GM)	—	75
Hoosick Falls, NY (NYS DOH 2016a)	n = 2,081 <17 – >60 yrs. M-45%, F-55%	Industrial–PFOA	Feb.–April 2016	24 (GM)	28	—	—	—	—	—	—	—
Merrimack, NH (NH DHHS 2017)	Public water system n = 217	Industrial–PFOA	2016	3.9 (AM)	—	10.1 (95^{th})	5.5 (AM)	—	15.2 (95^{th})	1.3 (AM)	—	3.2 (95^{th})
	Private wells N=219			4.4 (AM)	—	26.6 (95^{th})	5.4 (AM)	—	16.4 (95^{th})	1.3 (AM)	—	3.4 (95^{th})

Excretion of PFAAs and HFPO-DA is primarily through the urine, with a much smaller percentage, if any, eliminated in the feces. In women of childbearing age, excretion also occurs through menstruation and lactation (Harada and Koizumi 2009; Thomsen et al. 2010). Serum PFAS levels were lower in adult males undergoing venesection (ongoing blood withdrawal) for medical reasons (Lorber et al. 2015) and in firefighters who had donated blood, as compared to other firefighters (Rotander et al. 2015). The excretion rate for long-chain PFAAs varies substantially between animal species, and it is much slower in humans than in laboratory animals. Additionally, for some PFAS, the excretion rate is very different in males and females of the same rodent species, likely due to differences in the extent of secretion and reabsorption by organic anion transporter proteins (OATs) and possibly other transporter proteins in the kidney, reviewed in Lau (2012, 2015); Kudo (2015) and USEPA (2016h). Half-lives in rodents, nonhuman primates, and humans for the PFAS included in this section are shown in Table 17-7.

Table 17-7. Half-lives of PFCAs, PFSAs, and perfluoroethers in rodents, nonhuman primates, and humans

Notes: No information was located for PFPeA, PFDoA, PFTrDA, PFTeDA, PFPeS, PFNS, PFDS, ADONA; — indicates that data are not available; h–hour, d–day, y–year.

	Mouse		Rat		Nonhuman primate		Human	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
PFCAs								
PFBA	13 h[a]	2.9 h[a]	9.2 h[a]	1.8 h[a]	40 h[a]	41 h[a]	72 h[a] (O; mean)	87 h[a] (O; mean)
PFHxA	~1 h[b]		~2 h[c]	~2 h[c]	5.3 h[c]	2.4 h[c]	32 d[e] (O; GM)	—
					14–47 h[d]			
PFHpA	—-	—-	2.4 h[f]	1.2 h[f]	—-	—-	—	<50 yrs. of age-1.2 y[g] (G-U)
							All M & F >50 yrs. of age-1.5 y[g] (G-U)	
PFOA	19 d[h]	17 d[h]	4–6 d[i]	2-4 h[i]	21 d[j]	30 d[j]	3.8 y (O; mean); 2.4 y (O; GM)[k] 2.3 y[l] (DW; median) 3.3 y[m] (DW; GM) 3.4 y[n] (DW; mean)	
							15–50 yrs. of age-4.6 y[n] (DW)	15–50 yrs. of age-3.1 y[n] (DW)
PFNA	34–68 d[o,p]	26–69 d[o,p]	30 d[o,p]	1–2 d[o,p]	—-	—-		<50 yrs. of age-2.5 y[g] (G-U)
							All M & F >50 yrs. of age-12 y[g] (G-U)	
PFDA	—-	—-	24 d[q]	29 d[q]	—-	—-		<50 yrs. of age-4.5 y[g] (G-U)
							All M & F >50 yrs. of age-4.3 y[g] (G-U)	
PFUnA	—-	—-	—-	—-	—-	—-		<50 yrs. of age-4.5 y[g] (G-U)
							All M & F >50 yrs. of age-12 y[g] (G-U)	
PFSAs								
PFBS	—-	—-	3.1–4.5 h[r,s]	2.4–4.0 h[r,s]	15–95 h[r,s]	8.1–83 h[r,s]	26 d (O; GM)[s]	
PFPeS	—-	—-	—-	—-	—-	—-	—-	—-
PFHxS	29 d[t]	26 d[t]	29 d[t]	1.8 hd[t]	141 d[t]	87 d[t]	8.5 y (O; mean); 7.3 y (O, GM)[k] 5.3 y[n] (DW)	
							15–50 yrs. of age-7.4 y[n] (DW)	15–50 yrs. of age-4.7 y[n] (DW)
PFOS	40 d[u]	34 d[u]	47–67 d[u,v]	40–48 d[u,v]	132 d[u]	110 d[u]	5.4 y (O; mean); 4.8 y (O; GM)[k] 3.4 y [n] (DW; mean)	
							15–50 yrs. of age-4.6 y[n] (DW; mean)	15–50 yrs. of age-3.1 y[n] (DW; mean)
Perfluoroether (Replacement for PFOA in fluoropolymer manufacturing processes)								

	Mouse		Rat		Nonhuman primate		Human	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
GenX	21 h[w]	18 h[w]	3 h[x]	<3 h[x]	~2 h[y]	~2 h[y]	—-	—-

DW–Based on decline in serum levels after exposure to contaminated drinking water ended.
GM–Geometric mean.
G-U–Mean value; based on urinary excretion in general population, with modeled menstrual excretion for F < 50 yrs. old. More uncertain than estimates based on decline in serum levels. (Not shown for PFAS with half-lives based on serum decline).
O–based on decline in serum levels in workers or retired workers after exposure ended.

[a] Chang et al. (2008)

[b] Iwai (2011), reported in Russell, Nilsson, and Buck (2013)

[c] Chengelis et al. (2009)

[d] (Noker 2001) reported in Russell, Nilsson, and Buck (2013)

[e] Russell, Nilsson, and Buck (2013)

[f] Ohmori et al. (2003)

[g] Zhang, Beesoon, et al. (2013)

[h] Johnson and Ober (1979) Kemper and Jepson (2003)

[i] (Lau et al. 2006)

[j] Butenhoff, Kennedy, Hinderliter, et al. (2004)

[k] Olsen et al. (2007)

[l] Bartell et al. (2010)

[m] Brede et al. (2010)

[n] Li et al. (2018)

[o] Tatum-Gibbs et al. (2011)

[p] Ohmori et al. (2003)

[q] Gibbs et al. (2012)

[r] Chengelis et al. (2009)

[s] Olsen et al. (2009)

[t] Sundstrom et al. (2012)

[u] Chang et al. (2012)

[v] Butenhoff (2007)

[w] DuPont (2011a)

[x] DuPont (2011b)

[y] DuPont (2008)

As shown in Table 17-7, excretion rates in mammalian species vary among PFAS for which half-life data are available, with short-chain PFAAs and GenX generally excreted more rapidly than longer chain PFAAs. Half-lives in rodents and nonhuman primates are generally in the range of several weeks to several months for long-chain PFAAs, and about 1 hour to several days for short-chain PFAAs and GenX. However, PFOA, PFNA, and PFHxS (reviewed in Kudo (2015)) are excreted much more rapidly (hours to days) in female than male rats; this sex difference in rats also exists but is not as pronounced for PFBA, PFHxA, PFHpA, and PFBS (Kudo 2015). This difference in excretion rate is important in interpretation of rat toxicology studies of these compounds, particularly for developmental effects.

Human half-lives for PFAS are longer than in other mammalian species that have been studied, with estimates of several

years for long-chain PFAAs (PFOA, PFNA, PFOS, PFHxS); 1 year for PFHpA, and several days to 1 month for shorter chain PFAAs (PFBA, PFHxA, PFBS; Table 17-7). The estimates of human half-life shown in Table 17-7 are based on measured declines in serum PFAS levels in the same individuals over time after a source of elevated exposure, such as occupational exposure or ingestion of contaminated drinking water, ceases. Such estimates are less uncertain than population-based estimates from modeling of PFAS intake and biomonitoring data for serum PFAS levels from different sets of individuals from the general population at different time points. Half-life estimates based on urinary excretion are available for several PFAAs, including some with no serum-based half-life estimates ((Zhang, Beesoon, et al. 2013) shown as G-U in Table 17-7); these urinary estimates are less certain because they include modeled estimates of menstrual excretion in women of childbearing age and do not consider fecal excretion or blood loss other than menstruation (for example, blood donation). It should be noted that there are large inter-individual variations in human half-lives, which may arise from physiological factors (for example, differences in renal transport by OATs; (Yang, Glover, and Han 2010).

Because of the large species and sex differences in excretion rates, the internal dose resulting from a given administered dose varies widely among species and, in some cases, males and females of the same species. Therefore, interspecies (for example, animal-to-human) comparisons must account for the large interspecies half-life differences with approaches such as use of internal dose (serum level) as the dose metric, interspecies toxicokinetic extrapolation based on the ratio of half-lives in humans and animals, or use of physiologically based pharmacokinetic models.

17.2.3.1 Toxicokinetics Relevant to Developmental Exposures

Toxicokinetics relevant to developmental exposures to PFAAs are important because developmental effects are sensitive endpoints for toxicity of long-chain PFAAs in rodents, and prenatal exposure to some long-chain PFAA was associated with decreased fetal growth in some human epidemiology studies. Developmental exposures have been studied in rodents for several PFAAs, but not in nonhuman primates. PFAAs cross the placenta to reach the developing fetus in both humans and rodents (reviewed in Lau (2012) and Kudo (2015)), and are transferred to milk, resulting in exposure via lactation (Luebker, Case, et al. 2005; White et al. 2009; Kato 2015). In humans, long-chain PFAAs have been detected in cord blood (for example, (Wang et al. 2019) and amniotic fluid (Stein et al. 2012; Zhang, Sun, et al. 2013).

In humans, the greatest exposures to PFAAs in breast milk occur during the first few months of infancy because both PFAA concentrations in milk and the breast milk ingestion rate on a BW basis (ml/kg/day) are highest then; PFAA levels in milk may be lower in mothers who previously nursed other infants (Tao, Kannan, et al. 2008; Haug et al. 2011; Thomsen et al. 2010). Serum concentrations of long-chain PFAAs in breast-fed infants increase several-fold from the levels at birth during the first few months of life, followed by a decline in older infancy and early childhood (Fromme et al. 2010; Mogensen et al. 2015; Verner et al. 2016b, a) (MDH 2018b, 2019a); reviewed in NJDWQI (2015); (2017a), (2018a). Because of their higher rate of fluid consumption on a BW basis, exposures to infants who consume formula prepared with PFAS-contaminated water are also highest during the first few months of life (USEPA 2011a). Goeden, Greene, and Jacobus (2019) presented a model that predicts transplacental transfer and exposure to breast-fed and formula-fed infants for long-chain PFAAs in drinking water.

17.2.3.2 Relationship of Human Exposures to Serum Levels

Clearance factors (CL) that describe the relationship between oral exposures or dose (ng/kg/day) and steady-state serum levels (ng/L) in humans have been developed for PFOA (Lorber and Egeghy 2011; USEPA 2016d) and PFOS (USEPA 2016c):

$$\text{Dose [ng/kg/day]} \times \text{CL [L/kg/day]} = \text{serum concentration [ng/L]}.$$

These clearance factors, which indicate bioaccumulative potential, are based on average values for human PFAS half-lives and volumes of distribution (Vd);

$$\text{CL [L/kg/day]} = \text{Vd [L/kg Body Wt]} \times [\text{Ln2/half-life in days}].$$

Where Ln2 is the natural log of 2.

When combined with mean daily U.S. water ingestion rates (USEPA 2011a), the CLs can be used to predict the expected average increase in serum levels (above the “baseline” serum level from non-drinking water sources) that results from ongoing exposure to a given drinking water concentration of PFOA or PFOS (Bartell 2017; NJDWQI 2017a; Post, Gleason, and Cooper 2017). For PFOA, this average serum:drinking water ratio is greater than 100:1 (NJDWQI 2017a); this ratio is consistent with data from exposed populations and toxicokinetic modeling (Emmett et al. 2006; Hoffman et al. 2011; Bartell 2017). The CL for PFOS predicts an average serum:drinking water ratio of about 200:1 ((NJDWQI 2018a);(Post, Gleason, and Cooper 2017) (Lu and Bartell 2019), and available toxicokinetic data also support an estimated ratio of 200:1 for PFNA

(NJDWQI 2015) Lu and Bartell, 2019) and PFHxS (Lu and Bartell, 2019). It should be noted that PFAA serum:drinking water ratios vary among individuals using the same source of contaminated drinking water, due to inter-individual differences in daily water consumption rates (L/kg/day) and/or physiological differences relevant to toxicokinetics.

17.2.3.3 Isomer-Specific Toxicokinetics

Some PFAAs exist as a mixture of linear and branched isomers; the isomer profile varies depending on the manufacturing process used (telomerization yields primarily linear PFAS; electrochemical fluorination yields a mixture of linear and branched PFAS; Section 2.2.5.2. Toxicokinetics may differ among isomers of the same PFAA in rodents (Loveless et al. 2006; De Silva et al. 2009) and humans (Zhang, Beesoon, et al. 2013; Gao et al. 2015; Beesoon et al. 2011).

17.2.4 Human Epidemiology Studies

Many U.S. general population studies are based on data from NHANES, and other general population studies come from various worldwide locations. These include studies of specific subpopulations such as pregnant women, infants, children, or the elderly, as well as evaluations of associations of prenatal exposures with effects later in life. Data on communities exposed through contaminated drinking water come primarily from the C8 Health Study evaluations of approximately 70,000 Ohio and West Virginia residents exposed to PFOA in drinking water for at least 1 year at concentrations of 50 ng/L to >3,000 ng/L, including evaluations by the C8 Science Panel (Frisbee et al. 2009; C8 Science Panel 2020). This panel consisted of three prominent environmental epidemiologists charged with determining whether there are “probable links” (defined as “given the scientific evidence available, it is more likely than not that a connection exists between C8 exposure and a particular human disease among class members”) between PFOA exposures in this study group and disease. However, such health effects studies are not available from communities with drinking water contaminated with either the other PFAS discussed in this section or the complex mixtures of PFAS present in AFFF. Finally, health effects of several long-chain PFAAs, including PFOA, PFOS, and PFNA, have been studied in occupationally exposed workers (Khalil 2015). Because these workers were primarily male, relatively few women were included in these studies.

Exposure assessment in most but not all of these studies is based on blood serum levels of PFAS as an indicator of internal dose. The studies often evaluate associations between health endpoints and multiple PFAS detected in blood. Serum levels of long-chain PFAAs are indicators of long-term exposures (Section 7.1.2) that reflect individual differences in both exposure (for example, daily water consumption) and rate of excretion. Therefore, serum levels are less uncertain as indicators of exposure than external parameters such as drinking water concentration. In contrast to long-chain PFAS, there is little epidemiological information on short-chain PFAS because they are infrequently detected in blood serum due to their more rapid excretion. Exposure assessment in some of the C8 studies of communities with PFOA exposure from an industrial source is based on serum PFOA levels estimated from modeling of drinking water and air PFOA concentrations over time, rather than measured serum levels (Savitz et al. 2012; Winquist and Steenland 2014b, a; Dhingra, Lally, et al. 2016; Dhingra, Darrow, et al. 2016) Herrick (Herrick et al. 2017). Finally, exposure is based on job classification, rather than serum PFAA measurements in some occupational studies of PFOA (Gilliland and Mandel 1993; Leonard 2003; Lundin et al. 2009; Raleigh et al. 2014), PFNA (Mundt et al. 2007), and PFOS (Alexander et al. 2003; Olsen et al. 2004; Alexander and Olsen 2007; Grice et al. 2007).

As is the case for epidemiologic studies of environmental contaminants in general, the human studies of PFAAs are observational, in contrast to toxicology studies, which are experimental. Additionally, most epidemiology studies of PFAAs are cross-sectional, although some use other designs (prospective, retrospective, case-control). In cross-sectional studies, exposure and outcome are evaluated at the same point in time. Such cross-sectional studies cannot reveal whether increased exposure led to the health endpoint or vice versa, and reverse causality (for example, when a physiological change affects serum PFAS levels, rather than the serum PFAS levels causing the physiological change) has been hypothesized by some researchers as partially or totally explaining some of the associations in the epidemiological literature, including reduced birth weight and decreased kidney function. In general, publications of epidemiology studies report results in terms of associations with the endpoints of interest based on statistical analysis. When there are multiple studies of associations of an environmental contaminant such as PFAA(s) with a health endpoint, results often differ among studies. The differing results can arise from difference in the study design (for example, sex, age, ethnicity of population studied; magnitude and/or duration of exposure; method for assessment of endpoint of interest), size of population studied (may be too small to detect statistically significant associations), method used for statistical analysis, consideration of potential confounding factors, or chance. Therefore, conclusions about whether the overall body of evidence supports an association are based on scientific judgment. Such conclusions may differ among scientists who review the same body of data, and the conclusions are often phrased carefully to convey the nuances of the opinions being stated. Such observational studies are not designed to prove causality for health effects, and conclusions about evidence for causality are

therefore based on criteria, such as the Hill criteria (Lucas and McMichael 2005) related to the overall body of relevant scientific information (for example, consistency, dose-response, biological plausibility, potential for reverse causality). As is the case for associations, when conclusions about causality are presented in the scientific literature, they are often carefully worded to convey nuances and may differ among scientists reviewing the same body of data.

17.2.4.1 Noncancer Health Endpoints

This section summarizes information for various categories of noncancer health endpoints: Changes in systemic markers, Fetal growth, Immune system effects, Thyroid effects, and Other effects.

Systemic Markers

For PFOA and PFOS (Khalil 2015; USEPA 2016d, c; NJDWQI 2017a) (NJDWQI 2018a; ATSDR 2018e, draft), PFNA (NJDWQI 2015; ATSDR 2018e, draft), and PFDeA (ATSDR 2018e, draft), the cited reviews concluded that associations are generally consistent for increases in total cholesterol and/or low-density lipoproteins. Australia Government DOH (2018) concluded, based on a review of key reports and published systematic reviews, that an association of both PFOA and PFOS with small changes in cholesterol is generally observed. Additionally, the C8 Science Panel concluded that there is a "probable link" between PFOA and clinically defined high cholesterol (C8 Science Panel 2012a). Rappazzo, Coffman, and Hines (2017) concluded that the evidence for an association of prenatal or childhood exposure to PFAS with increased cholesterol is generally consistent; studies reviewed found associations with PFOA, PFOS, PFNA, and/or total PFAS. Regarding causality, NJDWQI (2017a) concluded that the evidence supports multiple criteria for a causal relationship between increased serum cholesterol and PFOA, while Australia Government DOH (2018) concluded that it cannot be established whether PFOA or PFOS causes increased cholesterol based on currently available data.

Most reviews have concluded that PFOA (Gleason, Post, and Fagliano 2015; Khalil 2015; USEPA 2016d; NJDWQI) (ATSDR 2018e, draft) and PFNA (NJDWQI 2015) are generally associated with increases in certain liver enzymes, particularly alanine aminotransferase (ALT). NJDWQI (2017a) concluded that there is some evidence to support a causal relationship between PFOA and ALT. In contrast, most evaluations of PFOS have found weaker or no evidence for associations with increased liver enzymes (Gleason et al., 2015; (Khalil 2015; NJDWQI 2018b) NJDWQI (2018a); (USEPA 2016c). However, (ATSDR 2018e, draft) concluded that "increases in serum enzymes and decreases in serum bilirubin, observed in studies of PFOA, PFOS, and PFHxS, are suggestive of liver damage." Australia Government DOH (2018) concluded that an association of PFOA and PFOS with elevated levels of the liver enzyme ALT was observed in many studies.

Various reviews have concluded that there is some evidence or limited evidence for an association of increased serum uric acid and/or hyperuricemia with exposure to PFOA, PFOS, and/or PFNA (Gleason, Post, and Fagliano 2015; Khalil 2015; NJDWQI 2015) (2017a), (2018a; Australia Government DOH 2018).

Fetal Growth

Exposure to PFOA and PFOS were associated with relatively small changes in measures of decreased fetal growth (for example, birth weight, head circumference) in most studies, while some studies did not find such an association. A systematic review and meta-analysis by Johnson et al. (2014) found that there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth in humans and provided a quantitative estimate of the decrease in birth weight per ng/ml serum PFOA. The main analysis included nine studies in which maternal or umbilical cord serum PFOA levels were measured in pregnant women. These studies met other inclusion criteria defined by the researchers; study subjects were from the general population in various locations. An additional analysis included a large study from the C8 Health Study population with exposure from contaminated drinking water in which maternal serum levels were retrospectively modeled. PFOA was associated with decreased birth weight in most of the studies from the general population but not in the study of the more highly exposed community. Inclusion of the study from the C8 Health Study population, in which serum PFOA levels during pregnancy were modeled from pre-pregnancy serum PFOA data, reduced the magnitude of decreased birth weight per ng/ml serum PFOA.

Several other reviews also evaluated the associations of PFOA and PFOS with decreased fetal growth. Bach et al. (2015) concluded that PFOA and PFOS are associated with decreased birth weight in most studies, but that associations in some studies were not statistically significant, and that the existing information is insufficient to determine whether or not there is an association. Khalil (2015) concluded that there is inconsistent evidence for association of decreased birth weight and PFAS. A later meta-analysis by (Negri et al. 2017), which included more recent studies not considered by Johnson et al. (2014), also reported a quantitative relationship between decreased birth weight and serum PFOA and PFOS levels. A recent

meta-analysis by Steenland, Barry, and Savitz (2018) considered additional studies not included in the two earlier meta-analyses, including the large studies from the C8 Health Study in which serum PFOA levels during pregnancy were modeled from pre-pregnancy serum PFOA data. Although Johnson et al. (2014) concluded that results from studies without measured serum data during pregnancy are too uncertain to include in a metanalysis, Steenland, Barry, and Savitz (2018) concluded that use of modeled or pre-pregnancy serum data may actually be preferable to serum levels measured during pregnancy because these exposure estimates would not be affected by potential reverse causality or confounding related to expansion of maternal plasma volume during pregnancy or renal glomerular filtration rate. Additionally, Steenland, Barry, and Savitz (2018) concluded that the decrease in birth weight in studies based on late pregnancy serum PFOA levels was larger than in those based on preconception or early pregnancy serum PFOA levels. They concluded that these findings are consistent with confounding or reverse causality as an explanation for the observed association of PFOA and decreased birth weight. A systematic review and modeling effort by Verner et al. (2015) found that PFOA is associated with decreased birth weight, and that a portion (less than half) of the reduction in birth weight results from confounding by associations of PFAS with decreases in both birth weight and maternal renal glomerular filtration rate (that is, reverse causality). USEPA (2016d, 2016c) concluded that PFOA and PFOS are associated with decreased fetal growth, and ATSDR (2018e) p.25, concluded that "evidence is suggestive of a link between serum PFOA and PFOS and small decreases in birth weight; the decrease in birth weight is <20 g (0.7 ounces) per 1 ng/mL increase in blood PFOA or PFOS level." Australia Government DOH (2018) concluded that PFAS exposure was often associated with generally small decreases in weight and length at birth in general population studies.

Immune System Effects

Of the several potential effects of PFAS on immune function, the discussion below focuses on associations with antibody response to vaccines, including in children, because this endpoint has been evaluated and reviewed most extensively. A systematic review by the National Toxicology Program (NTP 2016, p.1) concluded that PFOA and PFOS are "presumed to be an immune hazard to humans" based on a high level of evidence from animal studies and a moderate level of evidence from human studies for suppression of antibody response. ATSDR (2018e) concluded that "evidence is suggestive of a link between serum PFOA, PFOS, PFHxS, and PFDeA (meaning PFDA) levels and decreased antibody responses to vaccines." USEPA (2016d, 2016c) stated that there is an association between PFAS and decreased vaccine response and noted that serum concentrations of multiple PFAS are often correlated in the relevant studies. Rappazzo, Coffman, and Hines (2017) found that there is generally consistent evidence for association of PFAS with this effect in children. (NJDWQI 2017a)(2018a) concluded for PFOA that associations and decreased vaccine response are consistent among studies, and for PFOA, while decreased vaccine response was consistently observed, evidence is limited because most of the vaccine types were evaluated in only one or two studies. Pachkowski, Post, and Stern (2019) concluded that there is evidence that PFOS is associated with a decrease in some vaccine antibody responses following vaccination. Chang et al. (2016) concluded that a consistent association with vaccine response in general has not been demonstrated for PFOA and PFOS, and that some associations for specific vaccines are "striking in magnitude" but require replication in other studies. Australia Government DOH (2018) , pg.11 concluded, based on review of key reports and systematic reviews, that "the strongest evidence for a link between PFAS and clinically important immunological effects is for impaired vaccine response." They note both that the overall human evidence is weak, but that animal data suggests that "PFAS may alter immune function at concentrations found in humans with environmental and occupational exposures." (p. 11) Finally, Khalil (2015) stated that PFAS exposure has been associated with immunotoxicity, including decreased vaccine response, but that the data are inconsistent.

Thyroid Effects

Evaluations of PFAAs and thyroid disease have reached varying conclusions. Although stating that the overall database was mixed, the C8 Science Panel determined a "probable link" for PFOA and thyroid disease (C8 Science Panel 2012c). ATSDR (2018) p.25 concluded that "epidemiology studies provide suggestive evidence of a link between serum PFOA and PFOS and an increased risk of thyroid disease." USEPA (2016h) concluded that the increased risk for thyroid disease in women appears to be associated with PFOA, while there is weaker or no evidence in men. For PFOS, USEPA (2016g) concluded that there is limited support for an association of incidence or prevalence of thyroid disease with PFOS, including large studies of representative samples of the general U.S. adult population. (NJDWQI 2017a) 2018a) found limited evidence for association of PFOA and thyroid disease, while associations of PFOS with thyroid disease were not noted, and Khalil (2015) found that the data are inconsistent. Australia Government DOH (2018) concluded that "there are no consistent associations between any particular PFAS and thyroid hormones," and that there is limited evidence of an association between PFOA and thyroid disease in women but not in men. Rappazzo, Coffman, and Hines (2017) stated that conclusions about PFAS and thyroid disease in children cannot be reached with certainty due to the small number of studies and variable results. Coperchini et

al. (2017) found that hypothyroidism was the most consistent thyroid effect for PFOA, and for PFOS to a lesser extent, with women and children most susceptible. Ballesteros et al. (2017) stated that although there is a small number of studies with comparable data, there is some consistency in evidence for increased thyroid-stimulating hormone (TSH) with PFHxS and PFOS in pregnant women, and with PFNA TSH in teenage boys; associations with thyroid disease were not noted. More recently, a very large study (n = ~ 63,000) evaluated thyroid diseases in a Swedish community in which one-third of the population had previous residential exposure to very high levels of PFOS (8,000 ng/L) and PFHxS (17,000 ng/L) in drinking water. (Andersson et al. 2019). A consistent pattern of increased risk of hypothyroidism or hyperthyroidism was not found in men or women with residential exposure to the contaminated water.

Other Effects

The C8 Science Panel also found probable links for PFOA with ulcerative colitis (C8 Science Panel 2012b) and pregnancy-induced hypertension (C8 Science Panel); PIH was also associated with PFOS in the same two studies that linked it with PFOA (Stein, Savitz, and Dougan 2009; Darrow, Stein, and Steenland 2013). ATSDR (2018e) concluded that "there is suggestive epidemiological evidence for an association between serum PFOA and PFOS and [PIH] and/or pre-eclampsia."

For many other epidemiological endpoints that have been studied, generally consistent associations were not found and/or the available data are too limited to make firm conclusions.

It is notable that associations for several of the effects mentioned above (serum lipids, liver enzymes, vaccine response, birth weight) were observed even within the exposure range prevalent in the general population (without specific exposures from environmental sources), as well as at higher exposures. For several of these effects, the dose-response curves (for example, serum lipids, liver enzymes) are steepest at very low exposures with a much flatter slope approaching a plateau at relatively low serum concentrations (for example, ~40 ng/L for PFOA and cholesterol).

17.2.4.2 Carcinogenicity

Several evaluations of the epidemiological evidence for carcinogenicity are available for PFOA and PFOS, while such evaluations have not been conducted for other PFAAs. The C8 Science Panel (2012d) found a "probable link" of PFOA with testicular and kidney cancer based on an increased incidence of these cancers in the Ohio and West Virginia communities with drinking water exposure as well as data from other human and animal studies. Although some other occupational studies of PFOA, such as Raleigh et al. (2014), did not find increased incidence of these tumors, increased kidney cancer was reported in workers exposed to PFOA in the West Virginia industrial facility (Steenland and Woskie 2012). In consideration of these findings, IARC (2016) classified PFOA as "possibly carcinogenic to humans" (Group 2B) based on limited evidence that PFOA causes testicular and renal cancer, and limited evidence in experimental animals. Based on reviews of key reports and systematic reviews, the Australia Government DOH (2018), p.70 concluded that "the evidence on cancer risk is limited;" that it is possible that PFOA is associated with an increased risk of kidney and testicular cancer; and that the evidence does not support PFAS being a major contributor to cancer burden in workers or exposed community populations. As discussed in Section 9.1.3.2, PFOA, PFOS, and GenX chemicals were described as having suggestive evidence for human carcinogenicity by USEPA (2016d, 2016c, 2018g) and (NJDWQI 2017a – PFOA) (NJDWQI 2018a – PFOS) based primarily on animal data.

In contrast to PFOA, studies of cancer incidence in large populations with exposure to PFOS-contaminated drinking water are not available. Arrieta-Cortes et al. (2017) concluded that while associations with cancer were not observed in the available occupational and general population studies of PFOS, such associations cannot be ruled out because problems with the studies may have precluded detection of associations if they were present. They therefore concluded that there is "inadequate evidence of carcinogenicity" based on the human data. Chang et al. (2014) stated that "many positive associations with PFOA exposure were detected in community settings" but were not confirmed in studies of workers with much higher exposures, although increases in certain cancers in some occupational studies are noted within the paper. They concluded that a causal association between PFOA or PFOS and human cancer is not supported by the currently available epidemiological evidence.

17.2.5 Animal Toxicology Studies

Many scientific considerations and decision points are involved in developing human health toxicity factors from animal toxicology data. In the hazard identification component of the toxicity factor development, the toxicological endpoint selected as the basis for the reference dose should be determined to be well established (that is, supported by multiple studies), related to an adverse health outcome, and relevant to humans based on mode of action considerations. Peroxisome proliferator-activated receptor-α (PPAR-α) is a nuclear receptor found in many human and animal tissues that is involved with numerous physiological processes (Corton (Corton, Anderson, and Stauber 2000; Michalik et al. 2006). The role

of PPAR-α in the effects caused by PFAS and the human relevance of effects in rodents that are mediated by PPAR-α have been a focus of research on the mode of action for the toxicological effects of PFAAs (Lau 2012; Post, Gleason, and Cooper 2017). In the dose-response evaluation portion of toxicity factor development, the selected endpoint must provide the data needed to determine a point of departure (that is, benchmark dose [BMD], NOAEL, or LOAEL). To appropriately account for the large differences in PFAA half-lives among species, and among sexes of the same species in some cases, dose-response evaluation for long-chain PFAAs is most appropriately based on internal dose, as indicated by serum level, rather than external (administered) dose. Finally, in development of RfDs, uncertainty factors appropriate to the specific study and endpoint are selected and applied to the point of departure to account for factors such as sensitive human subpopulations, interspecies differences, shorter-than-chronic exposure duration, extrapolation from a NOAEL to a LOAEL, and potentially more sensitive toxicological effects (Section 8.3 and the ITRC tables posted as an Excel file of the basis for PFOA and PFOS values).

Toxicological effects that have been reported as statistically significant in mammalian laboratory animal studies for each PFAS, with relevant citations, are presented in Table 17-8 (provided as a separate Excel file). The sections following the table present general discussions of systemic, reproductive and developmental, and carcinogenic effects of these PFAS.

17.2.5.1 Systemic Effects

All of the PFAS included in Table 17-8 (provided as a separate Excel file) for which data are available caused increased liver weight in the rodent and nonhuman primate species studied. For most of these PFAS, increased liver weight was accompanied by hepatocellular hypertrophy. Developmental (in utero or lactational) exposures to some PFAAs caused increased liver weight in rodent offspring. Many PFCAs, as well as PFOS and GenX, caused additional hepatic effects that are more severe in nature such as hepatocellular necrosis and/or vacuolation in rodents and nonhuman primates, or hepatic lipid accumulation in rodents. For PFOA (Butenhoff et al. 2012; NJDWQI 2017a)) and PFOS (Butenhoff et al. 2012; NJDWQI 2018a), these hepatic effects increased in severity with longer duration of exposure and may represent a progression to neoplastic changes, including hepatic adenomas. Additional effects reported for some PFAS include bile duct toxicity in rodents and increased serum levels of liver enzymes in rodents and/or nonhuman primates.

Some PFAAs and FECAs caused decreased serum cholesterol in rodents and/or nonhuman primates. The increased cholesterol in humans associated with much lower exposures to some PFAS may be attributable to interspecies differences, such as differences in activity of relevant receptors involved with cholesterol metabolism. However, these contrasting observations in rodents and humans may also arise from differences in the fat content of a typical low-fat laboratory diet and the higher fat diet in the humans who were studied (Tan et al. 2013; Rebholz et al. 2016), or to dose-related differences in this response, because the doses in the toxicology studies are much higher than human exposure levels.

Some long-chain PFAAs caused immune system toxicity (Table 17-8, provided as a separate Excel file). Decreased antibody response to antigens has been identified as a sensitive endpoint for PFOS toxicity (Lilienthal et al. 2017; MDH 2019a; ATSDR 2018e, draft) (NJDWQI 2018a) (Pachkowski, Post, and Stern 2019).

The majority of PFAS covered herein have not been tested for neurobehavioral effects. Of those PFAAs that have been evaluated in rodents, exposure-related effects were not observed for PFBA and PFHxA, while exposure of adult rodents to PFOS and PFDA caused effects including changes in learning, memory, activity, and habituation or other effects indicative of cognitive defects. Additionally, developmental exposures to PFOA, PFOS, and PFHxS caused persistent neurobehavioral effects in mice.

17.2.5.2 Reproductive and Developmental

Reproductive effects in males and females and developmental effects of several PFAS have been evaluated in rodents (Table 17-8, provided as a separate Excel file), but these effects have not been studied in nonhuman primates. In addition to the considerations common to developmental toxicity studies in general, the much faster excretion of several PFAS in female rats than in males must be considered when interpreting results of the rat reproductive and developmental studies.

Dosing of pregnant females with PFAAs results in gestational exposure to the fetus and also to the offspring during lactation. Cross-fostering studies of PFOA (White et al. 2009) and PFOS (Luebker, Case, et al. 2005) in which dosed dams fostered pups from control dams and vice versa showed that effects can result from exposures during either gestation or lactation.

Although malformations have been reported in a few rodent studies of PFOA and PFOS, effects such as full litter resorptions, decreased litter or number of live pups at birth, decreased survival of neonates, and decreased fetal and neonatal weight have been more frequently and consistently found. These developmental effects may result from toxicity to the placenta, as

has been observed for PFOA (Suh et al. 2011) and PFOS (Lee et al. 2015). With PFOS at relatively high doses, neonatal mice and rats appeared normal at birth but died within a few hours; the genesis of this phenomenon is not understood (multiple studies reviewed in NJDWQI (2018a)).

Decreased growth of offspring and/or delays in reaching developmental milestones was observed for several PFAS in rodent studies (Table 17-8, provided as a separate Excel file). For PFBS (Feng et al. 2017) and PFNA (Das et al. 2015), BW decrements persisted until adulthood. PFOA caused delays in ossification of bones and eruption of teeth (Lau et al. 2006; Yahia et al. 2010). Developmental markers such as eye opening and/or reaching sexual maturity were also delayed by some PFAAs, while noting that sexual maturity was conversely accelerated in male mice by PFOA (Lau et al. 2006). Persistent neurobehavioral effects in mice resulted from developmental exposures to several long-chain PFAS.

Certain developmental effects of some PFAAs persisted into adulthood. These include decreased size of uterus and ovaries, accompanied by decreased number of follicles and corpora lutea, and changes in reproductive and thyroid hormone levels in female mouse offspring exposed to PFBS (Feng et al. 2017). Developmental exposures of mice to PFOA caused persistent delays in mammary gland development (White et al. 2009) and persistent liver toxicity (Quist et al. 2015) at doses lower than those that caused other systemic and developmental effects; these endpoints have not been evaluated for other PFAS.

17.2.5.3 Chronic Toxicity and Tumorigenicity

PFAAs have generally not been found to be mutagenic or genotoxic (Lau 2015).

Of the PFAS included in Table 17-8 (provided as a separate Excel file), chronic studies that evaluated carcinogenicity and other effects of long-term exposure have been conducted in rats only for PFHxA, PFOA (two studies; one in males only), PFOS, and GenX. PFHxA did not increase the incidence of tumors in either sex of rats. PFOA increased the incidence of benign tumors, including testicular Leydig cell adenomas in both studies, and hepatic adenomas and pancreatic acinar cell adenomas in the study that included only males. In the chronic PFOS study, benign tumors were increased, including hepatic adenomas in females, and thyroid follicular cell adenomas in males only in the high dose “recovery group” (dosed for the first year only and evaluated at the end of the 2-year study). GenX increased the incidence of both hepatocellular adenomas and carcinomas in females, and the incidence of combined pancreatic acinar cell adenomas and carcinomas and testicular Leydig cell adenomas in males.

IARC (2016) classified PFOA as “possibly carcinogenic to humans” (Group 2B) based on limited evidence that PFOA causes testicular and renal cancer, and limited evidence in experimental animals. Based on the USEPA (2005a) Guidelines for Carcinogen Risk Assessment, USEPA (2016d, 2016c, 2018k) and NJDWQI (2017–PFOA, 2018–PFOS) described PFOA, PFOS, and GenX as having suggestive evidence for human carcinogenicity. For PFOA, USEPA (2016d) and ATSDR (2018e) concluded that the hepatic tumors are unlikely to be relevant to humans, while human relevance was not discounted for the testicular and pancreatic tumors. For PFOS, USEPA (2016g)and NJDWQI (2018a) not discount human relevance of the hepatic tumors. USEPA (2005a) and NJDWQI (2017b) developed cancer slope (potency) factors for PFOA based on the incidence of testicular Leydig cell tumors in rats. USEPA (2016h) noted that, while the mode of action for these tumors is not known, a nonlinear mode of action is likely because PFOA is metabolically inert.

17.2.6 Data Gaps and Research Needs

Although many studies relevant to health effects of PFAAs have become available in the last few years, important data gaps remain for most of the PFAAs and FECAs discussed here, as well as for many additional PFAS used in commerce or found in AFFF.

Human half-lives and other toxicokinetic data are not available for some PFAS found in drinking water and other environmental media. This information is critical for adequately assessing the bioaccumulative potential and relevant routes of exposure (for example, placental and breast milk transfer), and for extrapolation of animal toxicity information to humans.

Available data suggest that reactive intermediates can form in the metabolic pathways that convert PFAA precursors to PFAAs within the body. Additional information on the formation and potential toxicity of these reactive intermediates is needed.

Although the C8 Health Study provides a large body of epidemiological data from communities with exposure to PFOA in drinking water, such data are not available from communities with drinking water contaminated with PFOS, other PFAAs, or the complex PFAS mixtures found in AFFF. Health studies in communities exposed to PFAS from AFFF use at nearby military sites were funded in the 2018 federal budget (Walton 2018), and these studies could provide such information.

Additional toxicology data are needed for some PFAAs found in environmental media, including drinking water. For example, there are very limited toxicology data for PFHpA, and no information was located for PFPeA. Additionally, although humans are exposed to multiple PFAS, very little toxicological data are available for mixtures of PFAS. Multigeneration studies are important for assessment of reproductive and developmental effects, and they are available for only a few PFAS. PFHxS is a PFAA with a long human half-life that has been found in human serum and in drinking water impacted by both industrial discharges and AFFF. Although developmental effects of PFHxS are of concern, there are currently no multigenerational developmental studies for PFHxS. Available information from rodent studies suggests that developmental exposures to some long-chain PFAS (PFOA, PFOS, PFHxS) cause permanent neurobehavioral effects, but these data are limited. Additional studies are needed on neurobehavioral effects of PFAS, particularly from early life exposure.

Studies that provide data on chronic effects, including carcinogenicity, are available for only four PFAS (PFHxA, PFOA, PFOS, GenX), and such studies are needed for PFHxS, PFNA, ADONA, and other PFAS to which humans may be exposed. All of the chronic studies were conducted in rats, and chronic studies in a second species such as mice would provide valuable information, particularly for those PFAS that are rapidly excreted in female rats.

The mode(s) of action for the toxicological effects of PFAAs are not fully understood and continue to be the focus of ongoing research. Although not the focus of this section, data on bioavailability of PFAS from environmental media other than drinking water (for example, soil) are limited, and such information can be useful in assessing exposures at contaminated sites.

Challenges related to the use of toxicity information from surrogates for PFAS for which no toxicity data are available are discussed in Section 9.1.1.2. There is a need to develop approaches for addressing groups and mixtures of PFAS, such as the relative potency approach described by Zeilmaker et al. (2018).

Finally, OECD (2018) identified 4,730 PFAS-related CAS numbers, including compounds with many different structures, including some that have not been used commercially. The majority of these PFAS, including those in commercial use, have very limited or no toxicity data (Wang, Cousins, et al. 2015; Wang, DeWitt, et al. 2017), indicating a critical data gap in health effects information for PFAS. Approaches currently under development at EPA and the National Toxicology Program (NTP) may prove useful for screening of a large number of PFAS with rapid assays that evaluate parameters related to toxicokinetics and toxicity (USEPA 2018k). Additional information is found on the EPA CompTox website (USEPA 2020; Williams et al. 2018) and from the NTP Rapid Evaluation and Assessment of Chemical Toxicity (REACT) Program (DeVito 2018).

If this effort is successful, the results could be used, along with data on human exposure, for prioritization of PFAS for more detailed toxicological studies (USEPA 2018k).

17.3 Additional Information for Risk Assessment

17.3.1 Human Health Exposure Assessment

Figure 9-5 illustrates predominant exposure pathways. In the following sections information is presented for exposures by environmental medium. Information about site risk assessment is in Section 9.

17.3.1.1 Soil

Soil exposure scenarios are possible at a site. Some of the PFAAs, such as PFOA and PFOS, are mobile and persistent in soil. As indicated in Section 5, PFAS distribution in soils is complex, reflecting several site-specific factors and individual PFAS-specific factors.

Sorption and retardation generally increase with increasing perfluoroalkyl tail length, and functional groups contribute to the degree to which a PFAS has the affinity to leach from soil to groundwater. A detailed discussion of the fate of PFAS in soil is provided in Section 5. If PFAS are retained in soil, they are available for contact by receptors, resulting in soil exposures.

PFAS are not well absorbed through the skin (ATSDR 2015; USEPA 2016g, h). Therefore, dermal contact is not expected to be an important exposure route for the general public compared to other exposure pathways. However, dermal contact may pose a risk for people with high-level occupational exposures to PFAS.

17.3.1.2 Potable Water

Potable water can be a major exposure pathway. When drinking water exposures are occurring, the drinking water pathway

typically represents the dominant exposure in comparison to other exposure pathways (for example, via food), even when PFAS concentrations in drinking water are relatively low (Post, Gleason, and Cooper 2017; Bartell 2017). PFAS levels in young children (up to the age of 6) are higher than in adolescents and adults consuming the same drinking water source, as discussed and cited in Section 7.1.2. This is most likely due to the higher levels of water ingestion per unit of body mass at these ages. Even if bottled water is supplied for drinking water purposes, potential exposures may occur to PFAS in potable water if it is used for non-drinking water purposes (for example, showering, bathing, hand washing dishes). Although the dermal absorption potential from water is low and in most cases is expected to be insignificant, exposure may occur. In addition, if PFAS is present in potable water used for food preparation (in commercial or residential settings), PFAS will be transferred to foods, resulting in dietary exposures.

17.3.1.3 Groundwater

The same potential exposure pathways described above for potable water apply to groundwater when used as a potable source. In addition, construction workers may contact PFAS in shallow groundwater (if within the depth of construction activities), although dermal absorption potential from water is low. If PFAS-impacted groundwater is used as irrigation water for crops, homegrown produce, or animal watering, PFAS in groundwater may be transferred to biota (plants or animals), resulting in dietary exposures.

As indicated in Section 6.3, due to the mobility and persistence of PFAA in soil and groundwater, PFAAs are expected to form larger plumes than other contaminants in the same hydrogeological setting. However, sorption and partitioning might restrict leaching rates from the vadose zone and reduce the advection-driven transport velocity of PFAS in groundwater, depending on specific properties of the PFAS. These processes might limit plume development and discharge to surface water and might also provide time for transformation of PFAA precursors. Groundwater geochemistry might dictate the extent of transformation because nearly all microbial processes identified to date are aerobic (Liu and Mejia Avendaño 2013).

17.3.1.4 Surface Water

Surface water exposure scenarios are possible because surface water may become impacted with PFAS by surface runoff or groundwater discharge. Surface water exposures can occur through drinking water or by consuming aquatic biota from contaminated water bodies. Much of the PFAAs reaching surface water tend to remain in solution, although there is likely to be partitioning to sediment and uptake to biota. Once in surface water, PFAAs can contaminate groundwater through groundwater recharge (Liu et al. 2016; ATSDR 2008).

Biofilms on surface water are known to accumulate PFAS (Munoz et al. 2018), as do other organic-/protein-rich particles in aquatic systems (Ahrens and Bundshuh 2014). Therefore, surface water films that contain these matrices are very likely significant repositories (and potential sources of exposure) of long-chain PFAS.

17.3.1.5 Sediment

Sediment exposure scenarios are possible because surface water may become impacted with PFAS by surface runoff or groundwater discharge, and there is likely to be partitioning to sediment and uptake to biota. However, when reaching marine waters, the solubility of anionic PFAAs decreases and sorption increases, which likely results in a salting-out effect that scavenges some PFAAs, especially long-chain PFAAs, to the sediments of estuarine environments (Hong et al. 2013).

17.3.1.6 Air

Inhalation exposure scenarios are possible for PFAS. Dusts containing PFAS may be generated from a site where PFAS are present in soil. In addition, some PFAS (for example, FTOHs and some perfluoroalkyl sulfonamides) have higher volatilities and tend to partition into air from other media (ITRC 2018a). Certain PFAS are found in ambient air, with elevated concentrations observed or expected in urban areas nearest to emission sources, such as manufacturing facilities, wastewater treatment plants, fire training facilities, and landfills (Barton et al. 2006; Ahrens et al. 2011; Liu et al. 2015).

17.3.1.7 Diet

PFAS exposures may occur from food consumption scenarios (specifically, ingesting aquatic and terrestrial plants and animals). Crops may be impacted by PFAS if irrigated with contaminated groundwater or surface water; if impacted by soil, runoff, or atmospheric deposition; or where biosolids have been applied to soil. In addition, because some PFAS biomagnify in food webs, ingestion of contaminated biota, especially fish and animals that eat fish (for example, bears), may be a major exposure route (ATSDR 2018c) (ATSDR 2015; USEPA 2016g, h). Recreationally caught fish from areas with PFAS contamination may be a specific source of elevated exposures to PFAS such as PFOS that bioaccumulate in fish. PFAS

exposures may also occur from food packaging materials containing PFAS (see Section 17.3.1.8, Consumer Products).

Breast Milk and Infant Formula

Consumption of breast milk and infant formula are potential exposure scenarios for infants. A mother's breast milk may be impacted through exposure to PFAS-contaminated media, and infants may ingest formula prepared with PFAS-contaminated water (Fromme et al. 2010) (Mogensen et al. 2015). Higher exposures to infants are of concern because infants are sensitive subpopulations for developmental effects of PFAS, including PFOA and PFOS }(USEPA 2016g, h), as discussed in Section 7.1. Infant exposure through breast milk or formula prepared with contaminated water is higher than older adults (for example, the mother) using the same water source. The USEPA Exposure Factors Handbook (USEPA 2011a) provides detailed information on breast milk consumption rates and the higher water consumption rate of infants.

17.3.1.8 Consumer Products

Typically, exposure scenarios associated with consumer products are not included in human health risk assessments (HHRAs) for contaminated sites. However, the HHRA should acknowledge that analytical results for environmental media (including indoor air and dust) may reflect impacts from consumer products (for example, carpets and upholstered furnishings) containing PFAS that have degraded, released fibers, or volatilized.

17.3.2 Other Considerations When Calculating Exposure Point Concentrations

Other contaminants present at the site can affect the movement of PFAS, which are not easily accounted for in fate and transport models. For example, petroleum hydrocarbon co-contaminants, particularly light nonaqueous phase liquids (LNAPLs), may affect the fate and transport of AFFF-derived PFAS (Guelfo and Higgins 2013; Lipson, Raine, and Webb 2013; McKenzie et al. 2016). As discussed in detail in Section 5 and Section 10.4.1, the movement of PFAS in environmental media depends on both site-specific media properties and properties of the specific PFAS. Leaching potential is a function of both media properties (for example, pH, redox conditions) and PFAS structural properties (for example, chain length) (Gellrich, Brunn, and Stahl 2013; Gellrich, Stahl, and Knepper 2012).

It is critically important to collect site-specific soil partitioning and soil-to-groundwater pathway data for PFAS sites. Existing models and standard methods are not able to accurately predict or calculate soil-to-groundwater movement of PFAS, and therefore site-specific empirical data are necessary.

As discussed in detail in Section 5.4, the composition of PFAS can change in media. Studies have reported both biotic and abiotic transformations of some polyfluorinated substances (precursors), which may form PFAAs (Buck et al. 2011). Precursors that are ingested can be transformed in the body to PFAAs (USEPA 2016g, h). However, PFAAs likely do not degrade or otherwise transform under ambient environmental conditions. PFAS composition may change in surface water because of biotic and abiotic degradation of PFAA precursors. These complex transformations are not incorporated in current fate and transport models.

17.3.3 Information about Selecting Bioaccumulation and Bioconcentration Factors

As indicated in Section 5.5 (PFAS Uptake into Aquatic Organisms) and Section 6.5.3 (Fish), certain PFAS can bioaccumulate in the food web. PFAS occur widely in biota through bioaccumulation processes. PFAAs, particularly PFOS, are typically the dominant PFAS detected in biota (Houde et al. 2011). Figure 17-1 illustrates bioaccumulation from sediment and surface water.

Section 5.5.2 provides a detailed discussion of factors affecting the bioaccumulation potential of PFAS.

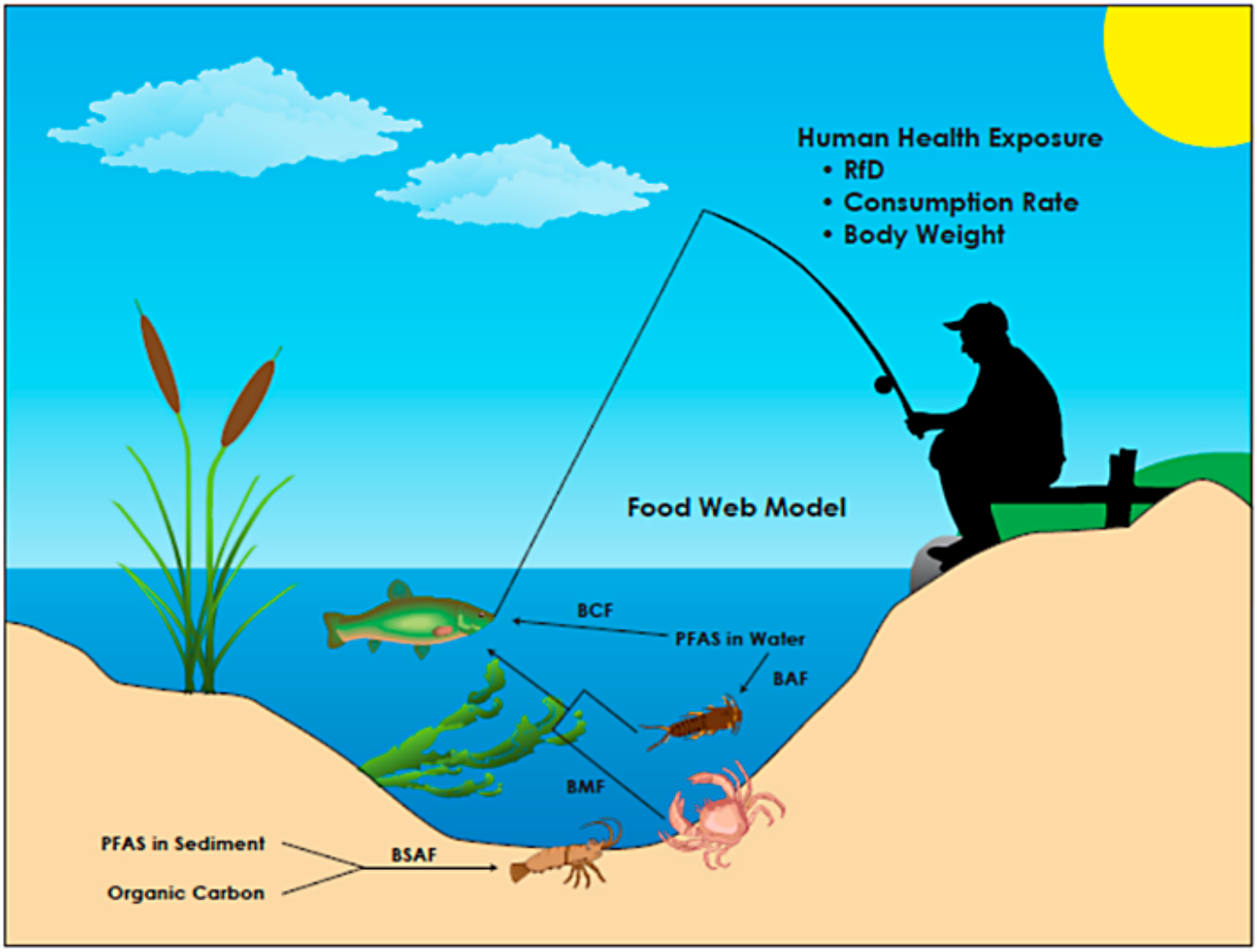

Figure 17-1. Bioaccumulation of PFAS from sediment and surface water. (BAF–bioaccumulation factor; BCF–bioconcentration factor; BSAF–biota-sediment accumulation factor; RfD–reference dose. *(Source: J. Conder, Geosyntec. Used with permission.)*

Section 6.5.3 (Fish) provides a detailed discussion of bioaccumulation of PFAS in fish. Accumulation of PFAS in fish has been documented, particularly for PFOS, longer chain PFCAs (with eight or more fluorinated carbons), and perfluorodecane sulfonate (PFDS) (Houde et al. 2011; Martin et al. 2013; Conder et al. 2008). In fish, PFOS tends to partition to the tissue of highest protein density, including the liver, blood serum, and kidney (Falk et al. 2015; Ng and Hungerbühler 2013). PFOS BAFs in field-based studies are presented in Table 5-2 (provided as a separate Excel file).

Trophic level biomagnification in food webs (Figure 17-1) can occur for some PFAS (Franklin (Franklin 2016; Fang et al. 2014) as discussed in further detail in Section 5.5.3.

Sections 5.6 and 6.5.1 discuss partitioning of PFAS to plants. Plant uptake and bioaccumulation

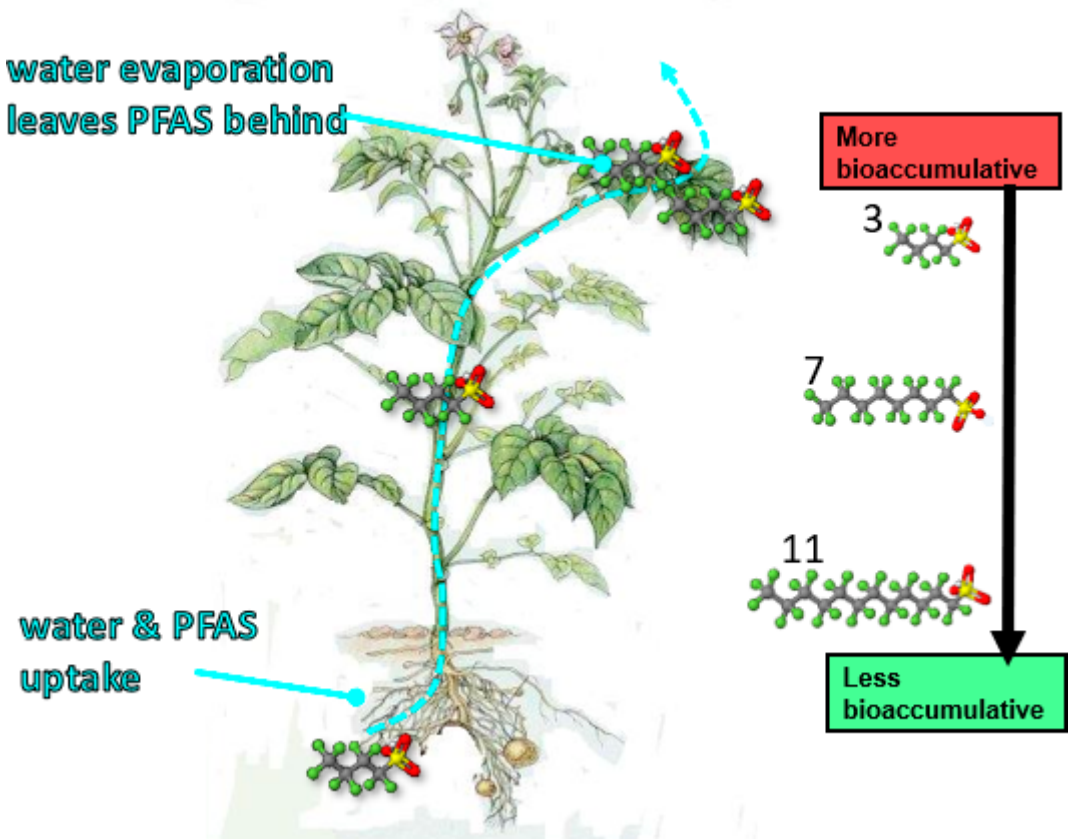

Figure 17-2. Bioaccumulation of PFAS in plants.
Source: J. Conder, Geosyntec. Used with permission.

and partitioning within the plant appear to depend on PFAS chemical structure and the plant species. Figure 17-2 illustrates bioaccumulation of PFAS in plants. Most studies report partitioning of PFAAs within plants, with longer chain PFAAs, especially PFSAs, partitioning to the roots and more soluble, shorter chain PFAAs, especially PFCAs, partitioning to other parts of the plant (Lechner and Knapp 2011; Stahl et al. 2009) Blaine (Blaine et al. 2013; Blaine, Rich, Sedlacko, Hundal, et al. 2014; Yoo et al. 2011; Scher et al. 2018; Gobelius, Lewis, and Ahrens 2017). Table 5-2 (provided as a separate Excel file) contains BCFs and BAFs for 14 different PFAS for a variety of plant species. In general, most plant BCFs and BAFs fall between a range of 0.1 and 10.

As indicated in Section 4.2.8 (Octanol/Water Partition Coefficient (K_{ow})) and Section 5.5.2 (Bioaccumulation), it is difficult to measure K_{ow} for PFAS due to their complex chemistry, and because many PFAS have both lipophobic and hydrophobic properties. Therefore, BAFs rely on calculations from empirical data instead of modeling (Haukås et al. 2007).

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⇑ Return to Top

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