Chapter 13
Epidemiological Findings

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Abstract Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are man-made compounds which have been extensively used over the past 60 years. They are detectable globally in humans and animals. Among several PFAS compounds, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) have been most examined in epidemiological studies. In the United States PFOS is found at the highest levels in human serum, followed by PFOA. Median human serum levels are dropping for most PFAS in the US since phase out of production, but they are still being used in manufacturing a variety of products. PFHxS has a much longer elimination half-life [geometric mean: GM (GM: 7.3 years)] than PFOS (GM: 4.8 years) or PFOA (GM: 3.5 years).

Serum PFOA concentration has been linked with increased serum lipids, and uric acid levels in occupational cohorts, a highly exposed community population, and general population studies. PFAS exposure has also been associated with adverse effects on thyroid homeostasis, liver enzymes, osteoarthritis, non-malignant kidney disease, and immunotoxicity, in some studies but the associations are inconsistent. Data are sparse but largely negative for Type 2 diabetes neurodegenerative disease,

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children's cognition, adult CVD and stroke, immune function, liver disease, and obesity. Despite a large body of literature, and some positive findings regarding low birth weight, the data are overall inconsistent regarding reproductive/developmental outcomes in relation to PFAS.

In conclusion current epidemiologic evidence suggests that there is an association between PFOA and six health outcomes: high cholesterol, ulcerative colitis, thyroid disease, testicular cancer, kidney cancer, and pregnancy-induced hypertension, although some of the findings come from only one large longitudinal study of a high exposed population, and have not been replicated elsewhere. Data remains limited for health effects of other PFAS. Longitudinal studies in populations with exposure above general background levels are needed to corroborate these results and increase our understanding of PFAS exposure and health outcomes.

Keywords Perfluoroalkyl • Polyfluoroalkyl substances (PFAS) • Perfluorooctanoic acid (PFOA) • Perfluorooctane sulfonic acid (PFOS) • Perfluorohexane sulfonate (PFHxS) • Perfluorononanoic acid (PFNA) • Epidemiology

13.1 Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are man-made chemicals. PFAS were widely used over the past 60 years because of their heat stable, non-flammable properties. They are detectable globally in human, animal and aquatic environments. PFAS can bioaccumulate and biomagnify through food chain. Among several of the PFAS compounds, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) have been addressed in epidemiological studies.

Over the past decade, the National Health and Nutrition Examination Survey (NHANES) data in the US have shown that PFOS was the dominant PFAS in human blood, followed by PFOA (Kato et al. 2011). PFHxS has a much longer elimination half-life [geometric mean: GM (GM: 7.3 years)] than PFOS (GM: 4.8 years) or PFOA (GM: 3.5 years) (Olsen et al. 2007). As described in NHANES 1999–2008 data PFOS, PFOA, PFNA, and PFHxS were detected in >95 % of participants. Since 1999–2000, PFOS concentration in US general population exhibited a significant decreasing trend due to discontinued PFOS industrial production, but PFNA concentration showed an upward trend. PFOA levels in 1999–2000 were significantly higher that other surveys, but stabilized during 2003–2008. PFHxS concentrations exhibited a downward trend from 1999 to 2006, but increased in 2007–2008 (Kato et al. 2011).

Epidemiologic studies examining PFAS exposure on human health have been conducted at three 'exposure levels': (1) occupational cohorts such as workers who were

mostly exposed at the source of contamination, (2) highly exposed communities to PFAS through water, soil, and/or air contamination, and (3) general populations such as NHANES participants exposed to PFAS at background exposure level.

Occupational studies in workers employed at the PFAS chemical plants (Olsen et al. 2003; Lundin et al. 2009) comprised of medical surveillance cross sectional studies (reviewed in Costa et al. 2009) and a few longitudinal studies (Sakr et al. 2007b; Leonard et al. 2008; Shin et al. 2011). Costa et al. summarized health outcomes of 30 years (1978–2007) of medical surveillance in PFOA exposed workers. Workers aged 20–63 years had medical examination annually including blood tests for serum chemistry and serum PFOA (Costa et al. 2009). The monitoring data and its link with workers' mortality and health effect have been published in a number of epidemiological studies (Lundin et al. 2009; Costa et al. 2009; Sakr et al. 2007b; Leonard et al. 2008; Shin et al. 2011).

The most comprehensive epidemiological data linking PFOA exposure and health outcomes has been reported from Mid-Ohio Valley communities which is ongoing. The C8 Science Panel carried out exposure and health studies in residents potentially affected by the releases of PFOA (or C8) emitted since the 1950s from the Washington Works plant in Parkersburg, West Virginia. Exposures to the community started in 1951 and peaked in the early 1990s, due to contamination of drinking water by PFOA emissions (Winquist et al. 2013; Simpson et al. 2013). In 2005–2006, as part of the settlement of a class action lawsuit, a community survey called the C8 Health Project was conducted. In this survey, approximately 69,030 people who lived in one of six contaminated water districts in West Virginia and Ohio between 1951 and 2004 were surveyed and information regarding demographics, residential history, medical history, and health-related behaviors was collected. These participants were grouped into two cohorts based on their occupational exposure (worker cohort, n = 6,000) at the chemical plant or residential exposure (community cohort, n = 40, 000) to drinking water contaminated with PFOA. The summarized evidence and technical conclusion of these studies are publicly available in the form of non-peer reviewed Probable Link reports (www.c8sciencepanel.org).

In this chapter, we will review evidence between PFAS exposure and risk of adverse human health outcomes, each outcome has a separate section and epidemiological evidence is presented in separate studies segment as cross sectional or longitudinal studies (where available) and within each section occupational or population studies are discussed. Association between PFAS and cancer is not discussed as it is addressed in a separate chapter of this book.

13.2 Lipids

Epidemiologic studies have shown that environmental PFAS exposure may have an important role in elevating serum lipid (hypercholesterolemia), although findings have not been uniform (Frisbee et al. 2010; Sakr et al. 2007a, b; Lin et al.

2009, 2013; Olsen and Zobel 2007; Emmett et al. 2006; Steenland et al. 2009; Nelson et al. 2010).

Cross-sectional The inconsistent positive relationships between environmental PFAS exposure, in particular PFOA, and lipid and lipoproteins levels were reported in many cross-sectional studies even though the magnitudes of effect varied by studies. In occupational cohorts, positive associations have been observed between PFOA and total cholesterol (Sakr et al. 2007a, b), low-density lipoprotein cholesterol (LDL-C) (Lin et al. 2013) and triglycerides (Olsen and Zobel 2007). Two epidemiologic studies conducted on a highly exposed community yielded dissimilar results, with Emmett et al. reporting no association (n = 371) (Emmett et al. 2006), and Steenland et al. reporting a positive association between PFOA and total cholesterol, LDL-C and triglycerides (n = 46,294) (Steenland et al. 2009).

Studies on general populations report more positive associations between PFAS concentrations in blood and lipids than in studies on occupational cohorts or highly exposed communities. Using the data from NHANES 2003–2004, Nelson et al. reported positive associations between PFOA and PFOS exposure and total cholesterol and non high density lipoprotein cholesterol (HDL-C) in a general population sample of adults (Nelson et al. 2010). A Canadian study did not show significant evidence to support the association of cholesterol outcomes with PFOS and PFOA exposure. However, several significant positive associations with the PFHxS and cholesterol outcomes were noted (Fisher et al. 2013). In this study using cross-sectional data in adults from the Canadian Health Measures Survey (2007–2009), the associations between plasma levels of PFOA, PFOS and PFHxS and cholesterol were assessed. Evidence of significant positive associations between PFHxS, with total cholesterol, LDL-C, TC/HDL-C and non-HDL-C as well as elevated odds of hypercholesterolemia was noted (Fisher et al. 2013). A Danish cross-sectional study of middle aged adults described significant positive associations between both PFOS and PFOA and total cholesterol (Eriksen et al. 2013).

A previous study in children and adolescents had reported positive associations between PFAS and abnormal lipid levels in the C8 community cohort (Frisbee et al. 2010). In a study of adolescents (age <18 years) from NHANES 1999–2008, Geiger et al. (2014) identified positive relationships of exposure to PFOA and PFOS with high total cholesterol and LDL-C levels (Geiger et al. 2014). Compared to children in quartile 1 (reference), the adjusted odds ratios (ORs) and 95 % confidence interval (CI) for high total cholesterol among children in quartile 4 was 1.16 (1.05–2.12) for PFOA and 1.53 (1.11–1.64) for PFOS. PFOA and PFOS were not significantly associated with abnormal HDL-C and triglyceride levels.

Longitudinal Longitudinal studies on health effects PFAS on lipids are scarce. A C8 short term follow-up study on C8 community cohort (n = 560) without taking any lipid lowering medications showed interesting results between relationships between changes in PFAS and change in lipids (Fitz-Simon et al. 2013). While large decrease (~50 %) in serum PFOA and PFOS levels over a 4.4 follow-up year was noted, mean increase in LDL-C (1.8 % increase) and other lipids was minimal. Interestingly,

authors found that greater decreases in PFOA and in PFOS were associated with greater decreases in LDL-C levels, 3.6 % (1.5–5.7 %) for PFOA reduction in 50 % and 5.0 % (2.5–7.4 %) for PFOS reduction in 50 %, respectively. This tendency was significant but less prominent in the relationship between the decrease in total cholesterol and PFOA (e.g., predicted 1.7 % decrease per halving PFOA). This result renders some support that PFOA and PFOS may cause the reversible elevation of lipids, especially LDL-C.

In longitudinal analyses of worker and community cohorts (n = 32,254), the C8 Science Panel found a 'probable link' between incidence of hypercholesterolemia (n = 9,909) and PFOA (Winquist and Steenland 2014a). In a principal retrospective analysis, hazard ratios (HR) of hypercholesterolemia, defined as subjects taking medications, were significantly higher in estimated cumulative PFOA exposure quintiles from 2 to 5 compared to quintile 1. Participants in C8 Health Project in upper quintile groups of cumulative exposure had between 1.17 and 1.24 times higher hazards of having hypercholesterolemia compared with participants in the lowest quintile (Winquist and Steenland 2014a). However, a short-term follow-up (164 days) study of workers (n = 179) who involved in the demolition projects of 3M plants in Minnesota (medical surveillance study) showed no association between changes in serum PFOA concentrations and changes in TC levels (Olsen et al. 2012). Only significant positive associations noted in this study were between changes in PFOA and changes in TC/HDL-C in a sub-sample with low baseline PFOA levels (<15 ng/ml) (Olsen et al. 2012).

Conclusion Many epidemiologic studies on health effects of PFAS were cross-sectional in nature, which preclude conclusions about causality. Reverse causality is also possible: higher lipid levels may cause the increase in PFAS levels measured in blood samples. Alternatively, possible unknown confounders cause changes in both PFAS levels and lipid levels. Further, caution must be taken to interpret results for studies on general population with relatively low homogenous exposure, which may not correspond with those from occupational cohorts and from highly-exposed communities. However, despite these caveats, epidemiologic evidence, in particular from the longitudinal analysis of C8 Health Project, suggests that there is an association between PFOA and PFOS and adverse lipid profiles, and further that high PFOA exposure may increase the risk of incident hypercholesterolemia in adults.

13.3 Uric Acid

Uric acid is a metabolite of purine breakdown and is a renal function biomarker. Elevated uric acid is associated with risk of hypertension, diabetes mellitus (Bandaru and Shankar 2011), cardiovascular disease, and kidney disease (Cain et al. 2010) (reviewed in (Geiger et al. 2013)).

Cross Sectional In a cross sectional analysis of the same occupational cohort Costa et al. (2009) described mean uric acid levels of 6.29 μg/mL for 34 currently exposed

workers, versus 5.73 μg/mL for 34 matched non-exposed workers (p = 0.04) (reviewed in (Steenland et al. 2010a)). In a cross-sectional community study of C8 adult population Steenland et al. (2010b) reported a positive association between PFOA, PFOS and uric acid among 54,951 highly-exposed community residents (Steenland et al. 2010b). For PFOA, the OR of hyperuricemia increased modestly with increasing serum concentration of PFOA. A less steep trend for PFOS was observed (Steenland et al. 2010b). When PFOS and PFOA were included in the model together PFOA was a more significant predictor than PFOS. However cross sectional study design and possibility of reverse causality, prohibit inference of cause effect relationship.

In a cross sectional NHAAES survey 1999–2006 of the US general population (n = 3,883) a positive relationship between serum levels of PFOS and PFOA and serum uric acid was documented. This demonstrates that even at low PFAS exposure levels observed in the US general population, PFAS are associated with hyperuricemia (Shankar et al. 2011b). Additionally, evidence regarding a positive association between PFAS and hyperuricemia in children is emerging. As described in a cross-sectional NHNAES 1999–2008 survey a positive association between serum PFOA and PFOS levels and hyperuricemia (≥6 mg/dL) was seen in 1, 772 US children (Geiger et al. 2013).

Longitudinal In a longitudinal study of occupationally exposed workers (n = 56), Costa et al. (2009) found a positive association between uric acid and PFOA by using repeated measures of both PFOA and uric acid over a 7-year follow up.

Conclusion Limited evidence supports an association between hyperuricemia and PFAS, although the only data are available come from cross-sectional studies, which cannot provide evidence of causality.

13.4 Kidney Disease

Kidneys are an important target organ for PFAS; PFAS are stored and excreted there.

Cross-sectional Previous studies of occupational cohorts or communities highly exposed to PFOA did not find an association between serum PFOA concentrations and blood urea nitrogen or serum creatinine, markers of kidney damage, (Costa et al. 2009; Emmett et al. 2006). Cross-sectional NHANES1999-2008 data showed positive relationship between serum levels of PFOS and PFOA and chronic kidney disease (CKD) in 4,587 adults (Shankar et al. 2011a). Because of the cross-sectional nature of NHANES survey authors could not conclude if high levels of PFOA and PFOS in serum preceded CKD or *vice versa*. In another cross sectional study association between estimated renal glomerular filtration rate (eGFR), a marker of kidney function, and serum PFASs in 9,660 children 1 to <18 years of age was studied (Watkins et al. 2013). The concurrent and historical serum PFOA concentrations were predicted

using an environmental exposure, and pharmacokinetic model utilizing residential history. It was hypothesized that predicted serum PFOA levels would be less prone to reverse causation than measured levels. Measured serum levels of PFOA, PFOS, PFNA, and PFHxS were associated with decreased eGFR (Watkins et al. 2013). However modeled serum PFOA was not associated with decreased eGFR.

Longitudinal In longitudinal unpublished analyses of the highly exposed mid-Ohio valley population, the C8 Science Panel found no 'probable link' between medically confirmed kidney disease (n = 50, 308) and PFOA (C8 Science Panel 2012c). In longitudinal mortality study of 6,027 highly exposed workers, Steenland and Woskie (2012) reported a higher kidney disease related mortality in PFOA workers compared to other workers in the plant; exposure response trend was also significant (Woskie et al. 2012).

Conclusion Evidence linking chronic kidney disease to PFAS exposure is limited and inconsistent. The observed cross-sectional positive association between eGFR and serum PFOA in C8 populations may be a consequence rather than a cause of decreased renal function. Longitudinal are sparse and inconsistent.

13.5 Heart Disease and Hypertension

Experimental studies have revealed that PFAS exposure is related to oxidative stress (Liu et al. 2007) and endothelial dysfunction (Qian et al. 2010), which are regarded subclinical antecedents to cardiovascular pathology. Although health effects of PFAS were inconsistent at different exposure levels, PFOA, PFOS and/or PFNA have been positively linked to total cholesterol and LDL-C levels (Starling et al. 2014; Winquist and Steenland 2014a), hyperuricemia (Steenland et al. 2010b; Shankar et al. 2011b; Geiger et al. 2013), altered glucose homeostasis (Lin et al. 2009; Lind et al. 2014), which are putative CVD risk factors. These results provide some epidemiologic evidence that PFAS exposure may play a role in the development of coronary heart disease (CHD).

Cross-sectional There are two conflicting reports on PFOA exposure and CHD prevalence on U.S. general population (Melzer et al. 2010; Shankar et al. 2012). Among 3,974 adults aged over 20 years in the NHANES 1999–2000 and 2003–2006, weighted CHD prevalence was 5.8 % (n = 321, unweighted). Across quartile groups using sex-specific cutoff s for PFOA and PFOS concentration, there were no significant increases in odds of reporting CHD in this study. Among 1,216 adults aged over 40 years (NHANES 1999–2003), however, Shankar et al. (2012) reported that the exposure to PFOA was positively associated with risk of self-reported CVD including CHD, heart attack, or stroke, and objectively measured peripheral artery disease (PAD). Reported weighted prevalence of CVD and PAD was 13.0 % and 4.5 %, respectively. Compared with participants in quartile 1 in serum PFOA levels (<2.9 ng/ml for women and <3.0 ng/ml for men), participants

in quartile 4 (>5.6 ng/ml for women and >6.1 ng/ml for men) had 2.01 times (95 % CI; 1.12–3.60) higher odds of reporting CVD and 1.78 (1.03–3.08) time higher odds of having PAD. Authors also reported that the adjusted OR in quartile 4 was 2.24 (1.02–4.94) for reporting specifically CHD compared to the quartile 1 (p-trend = 0.007) (Shankar et al. 2012).

There were two cross-sectional studies on general population examining the PFOA on hypertension or blood pressure levels (Geiger et al. 2014; Min et al. 2012). A cross-sectional study reported an association between PFOA exposure and hypertension in 2,934 US adults from 2003–2004 and 2005–2006 NHANES (Min et al. 2012). In the adjusted analysis on participants in quartiles for PFOA levels, odds of having hypertension was significant increased (p for tend =0.001):1.21 (0.86–1.70) for quartile 2, 1.60 (1.15–2.22) for quartile 3, and 1.71 (1.23–2.36) for quartile 4. Using NHANES data from 1999–2000 and 2003–2008, Geiger et al. (2014) reported no association between PFOA and PFOS exposure and hypertension in 1,655 children aged 18 years old in general US population (Geiger et al. 2014). Weighted hypertension prevalence was 23.4 % in this study.

Longitudinal Mortality studies on occupational cohorts reported no significant positive associations between PFOA exposure and CHD (Leonard et al. 2008; Lundin et al. 2009; Sakr et al. 2009; Steenland and Woskie 2012). Based on an occupational cohort (n = 3,922) at 3M plant in Cottage Grove, Minnesota exposed to PFOA, Lundin et al. reported no significant SMR (standardized mortality ratio) trend across three groups according to job category for PFOA exposure levels. SMRs (95 % CI) for non-exposed workers (n = 1,792) was 0.7 (0.6–0.9, 92 deaths), for probably exposed workers (n = 1,688) was 0.8 (0.7–1.0, 93 deaths), and for definitely exposed (n = 512) workers was 0.8 (0.5–1.4, 16 deaths). The CHD SMRs were generally lower than that of the general population in MN. CHD specific mortality rate ratios by characterizing the workers by job classification or cumulative exposure years yielded no significant association (Lundin et al. 2009). Based on data collected on 6,027 workers at DuPont plant in West Virginia, Leonard et al. reported no significant increase in ischemic heart disease (IHD) mortality of workers in comparison with U.S. population, the West Virginia and 8-state DuPont employee population (Leonard et al. 2008). Again, Sakr et al. reported there was no dose-response relationship between the cumulative exposure of serum PFOA and CHD mortality based on the same cohort (n = 4,747) with 239 reported IHD deaths (Sakr et al. 2009). C8 Scientific Panel conducted another study on this occupational cohort (i.e., C8 worker cohort) at DuPont plant (Steenland and Woskie 2012). Among 5,791 workers, cumulative serum PFOA based on eight job category was estimated (Woskie et al. 2012) and cause-specific mortality was documented. There was no significant increase in SMRs (287 deaths) compared with that of US general population [SMR (95 % CI) 0.68, (0.60–0.77)] or other DuPont workers [0.97 (0.86–1.09)] in the analysis using a no-lag. The results were similar in the analysis using 10-year lag (Steenland and Woskie 2012).

In longitudinal analyses of worker and community cohorts (n = 32,254), a recent report found no association between medically confirmed CAD such as heart attack

or angina or self-reported medicated hypertension and PFOA (Winquist and Steenland 2014a). In the primary retrospective for hypertension (n = 11,798) and CAD (n = 2,468), there were no significant trends in increase in HRs for either for hypertension and CAD in higher quintiles of cumulative exposure serum PFOA compared to quintile 1. Reported HRs (95 % CI) for CAD by increasing quintile were 1.00 (referent), 1.26 (1.10–1.45), 1.17 (1.02–1.35), 0.99 (0.86–1.14), and 1.07 (0.93–1.23) (Winquist and Steenland 2014a). Prospective analyses on data collected between 2005/2006 and 2008/2011 also showed no significant positive association between CAD and PFOA exposure.

Conclusion Mortality studies on occupational cohorts and a longitudinal study on C8 cohorts did not provide significant evidence to associate PFOA exposure with CHD and hypertension while cross-sectional studies on general population demonstrated inconsistent results.

13.6 Cerebrovascular Disease

Given positive association between PFAS and blood pressure or uric acid, researchers have examined the relationship between particularly PFOA exposure and cerebrovascular disease.

Cross-sectional Previous studies reporting association between strokes and PFOA is limited to two mortality studies among occupational cohorts (Leonard et al. 2008; Lundin et al. 2009). Leonard et al. (2008) found a deficit of deaths from cerebrovascular disease in workers (35 deaths) at DuPont plant vs. the general US population (estimated deaths = 57.9). The SMR was 0.86 (95 % CI, 0.60–1.20). Based on data on 3,993 workers at 3M plant, Lundin et al. (2009) r that SMRs were 1.6 (95 % CI: 0.5–3.7, 5 deaths) in definitely exposed workers, 0.7 (95 % CI: 0.4–1.1; 17 deaths) in probably exposed workers, and 0.5 (95 % CI: 0.3–0.8; 13 deaths) in non-exposed workers. There was no significant hazard in cerebrovascular disease mortality across workers in PFOA exposure categorized by job classification or cumulative exposure years (Lundin et al. 2009). Stroke mortality in C8 worker cohort reported by Steenland and Woskie showed modestly lower stroke mortality than the US population or other DuPont employee (Steenland and Woskie 2012). Stroke mortality may not be the best endpoint for evaluating stroke because fatality attributed to stroke is low.

There is lack of information associating PFOA with cerebrovascular disease in highly exposed communities or in general population. Shankar et al. reported the positive association between prevalence of stroke and serum levels of PFOA among general adult population from NHANES 1999–2003. In a model adjusting for age, sex, race/ethnicity, education level, alcohol intake, BMI, hypertension, DM, and serum total cholesterol levels, participants in increasing quartiles showed higher odds of reporting stroke (p-trend = 0.02); 1.00 (reference), 4.39 (1.44–13.37), 3.94 (1.48–10.50), and 4.26 (1.84–9.89) (Shankar et al. 2012).

Longitudinal No significant association between PFOA and self-reported stroke incidence (n = 1,596) has been identified from a longitudinal study on combined C8 worker and community cohorts (n = 32,354) (Simpson et al. 2013). In retrospective analysis on medical-record validated incident stroke (n = 825), the HRs of stroke in the higher quintiles was 1.39 (95 % CI: 1.11–1.76), 1.36 (1.08–1.71), 1.45 (1.15–1.82), and 1.13 (0.90–1.44) compared with the lowest quintile of cumulative PFOA exposure. Linear relationship between cumulative PFOA exposures with incident stroke was not significant.

Conclusion There is lack of data suggesting any significant positive association between PFAS exposure, specifically PFOA exposure, and incident and prevalent stroke.

13.7 Diabetes

While experimental studies suggested that PFASs are not directly linked to the pathways associated with dysglycemia, some human studies have reported positive association between PFASs and diabetes, but not all. Diabetes related outcomes examined in epidemiologic studies are T2DM mortality, self-reported or medical record-verified T2DM and glucose homeostasis related biomarkers such as fasting insulin and glucose, and homeostasis model assessment of insulin resistance (HOMA-IR).

Cross-sectional In a study on highly exposed C8 community cohort (n = 54,468), C8 scientific panel reported of no significant association between PFOA and prevalence of T2DM (MacNeil et al. 2009). Authors reported that 7.8 % prevalence of DM in C8 communities, which was comparable to that of Ohio and West Virginia at the time of survey (2005). In multivariable analyses on medical record-validated T2DM cases (n = 3,539) or validated T2DM case (n = 1,055) who resided in communities more than 10 years prior to diagnosis, there were non-significant decreasing trends in odds of having T2DM across serum PFOA decile groups compared with the lowest decile group. In addition, authors found no difference or pattern in fasting glucose levels across PFOA deciles among non-diabetics (MacNeil et al. 2009).

However, studies on general populations reported mixed yet confusing results between PFAS and diabetes related outcomes. Serum PFHS, PFNA, PFOA, and PFOS were examined in relation to glucose homeostasis and indicators of metabolic syndrome from 474 adolescents and 969 adults in the general population analyzed from NHANES 1999–2004 (Lin et al. 2009). In adolescents, elevated serum PFNA concentrations were related with higher blood glucose concentrations, but were significantly associated with lower odds of having metabolic syndrome (OR, 0.37 (0.21–0.64)). In adults, elevated serum PFOA concentrations were significantly related with higher HOMA calculated beta-cell function, which suggests favorable beta-cell function. Serum PFOS concentrations showed positive association with insulin, HOMA-IR, and beta-cell function (Lin et al. 2009). A study on Swedish

elderly men and women (n = 1,016, aged 70 years) reported the positive but non-linear association between plasma PFNA concentration and prevalent T2DM self-reported or defined by glucose levels >126 mg/dl (7 mmol/L) (Lind et al. 2014). The pattern of relationship was similar between PFOA and T2DM (P = 0.01) while the other five PFASs examined were not related to T2DM. Any of seven PFASs examined in this study was not related to HOMA-IR (Lind et al. 2014). In a Canadian Health Measures Survey (2007–2009) of the general population (n = 2,700) the association between plasma levels of PFOA, PFOS and PFHxS, metabolic syndrome, and glucose homeostasis was examined in adults. Regardless of PFASs examined, there was no significant relation between any PFAS and any glucose homeostasis biomarkers and metabolic syndrome (Fisher et al. 2013).

Longitudinal In an occupational cohort (n = 3,993) at a 3M plant in Cottage Grove, MN, Lundin et al. reported that DM -specific SMRs was 2.0 (95 % CI: 1.2–3.2) among 'probably exposed' workers with 18 DM related death (Lundin et al. 2009). However, there was no reported death due to DM among 'definitely exposed' workers. Similar results were reported in studies on C8 worker cohort reported (Leonard et al. 2008; Steenland and Woskie 2012). C8 worker cohort (n = 5,791) had about a twofold (95 %: 1.35, 2.61, 38 deaths) excess of DM mortality compared to other non-exposed DuPont plant workers (Steenland and Woskie 2012). However, in comparison with US referent group, DM mortality rate in C8 workers was not significantly elevated (SMR, 1.06, 95 % CI, 0.75–1.46).

C8 Health Project reports are only available longitudinal study on the incidence of T2DM in adults (Karnes et al. 2014; MacNeil et al. 2009). In an analysis of combined C8 worker and community cohorts (n = 32,254), estimated cumulative retrospective PFOA exposure between 1951 or birth years of participants and 2011 was not associated with incidence of T2DM (n = 4,129). The adjusted HRs (95 % CI) by quintile of cumulative PFOA were 1.0 (reference), 0.91 (0.76–1.08), 1.18 (0.99–1.40), 0.96 (0.81–1.15), 1.04 (0.87–1.24), 1.11 (0.93–1.32), 1.06 (0.89–1.26), 1.00 (0.85–1.19), 1.03 (0.86–1.23), and 1.01 (0.84–1.20) (Karnes et al. 2014).

Conclusion There is little evidence of a significant positive relationship between PFOA and T2DM incidence or prevalence among highly exposed community sample or in the general population (Karnes et al. 2014; MacNeil et al. 2009; Fisher et al. 2013; Nelson et al. 2010; Lin et al. 2011) despite findings of increased diabetes mortality risk in occupational settings (Lundin et al. 2009; Steenland and Woskie 2012; Leonard et al. 2008). Considering that DM mortality examined may not be a good outcome because adult onset T2DM itself is not likely a fatal disease, it appears unlikely that there is an association between PFAS, in particular PFOA, and T2DM.

13.8 Liver Function and Liver Disease

PFOS and PFOA are known to be hepatotoxic in rodents (Lau et al. 2007). Most epidemiologic studies have examined the effects of PFASs on blood liver function enzymes; direct bilirubin, γ-glutamyl transpeptidase (GGT), aspartate

aminotransferase (AST), alanine aminotransferase (ALT) (Costa et al. 2009; Emmett et al. 2006; Gallo et al. 2012; Lin et al. 2010; Fei et al. 2012; Olsen and Zobel 2007; Sakr et al. 2007b; Yamaguchi et al. 2013).

Cross-sectional Increased GGT, AST, and ALT levels associated with increase in PFOA exposure were reported in several occupational cohort studies (Olsen and Zobel 2007; Sakr et al. 2007a) but not in all (Costa et al. 2009; Olsen et al. 2003). In a cross-sectional study on workers (n = 1,025), AST, ALT, and total bilirubin levels were not significantly associated with the level of PFOA, but GGT was positively associated with PFOA ($p = 0.02$) (Sakr et al. 2007a).

An early study on highly exposed community reported no significant relationship between PFOA and various biomarkers for liver function or history of liver disease (Emmett et al. 2006). This study was conducted on a selected group of volunteers (n = 371) residing in Little Hocking Water Association District nearby DuPont plant. Based on C8 community cohort (n = 47,092), however, Gallo et al. reported significantly positive cross-sectional associations between serum PFOA and PFOS concentrations and markers of liver function (ALT, GGT and direct bilirubin). The PFOS and PFOA exposures were related to increased ALT. One unit increase in log-transformed PFOA and PFOS concentrations was positively associated with significant increase in log-transformed ALT [β (95 % CI): 0.022 (0.018–0.025) for PFOA, 0.020 (0.014–0.026) for PFOS] in multiple regression analyses. However, no consistent association between PFOA and GGT or total bilirubin was noted (Gallo et al. 2012).

In a study of 2,216 adults enrolled in the NHANES 1999–2004, significant trends ($p < 0.05$) for increasing ALT and log-transformed GGT concentrations across quartiles of PFOA were described (Lin et al. 2010). There were significant differences in total bilirubin levels across PFNA quartiles ($p = 0.014$). In adjusted analyses, one unit increase in log-transformed PFOA levels was positively associated with increases in ALT [β (95 % CI), 1.86 (0.62), $p = 0.006$] and log-GGT [β (95 % CI), 0.08 (0.03), $p = 0.019$] concentrations. Borderline positive association was also observed between serum PFNA and total bilirubin levels [0.48 (0.25), $p = 0.053$] (Lin et al. 2010). A recent Japanese study in 307 men and 301 women (aged 16–76 years) reported cross sectional association between serum PFOS and PFOA and hepatic enzymes (GGT, ALT, AST) and omega-3 polyunsaturated fatty acids (DHA and EPA). Serum levels of ALT, AST, DHA and EPA showed significant positive correlations with PFOS and PFOA in blood (Yamaguchi et al. 2013).

Longitudinal In longitudinal unpublished analyses of the highly exposed C8 community cohort, the C8 Science Panel found no 'probable link' between estimated cumulative PFOA levels and medically confirmed non-malignant liver disease (n = 647) in 2008–2010 survey (C8 Science Panel 2012c). C8 Science Panel reported that HRs of liver disease was 1.0, 1.19, 1.08, 1.04, and 0.95 by increasing estimated cumulative PFOA exposure quintiles (p-trend = 0.32).

Conclusion A number of epidemiological studies in occupational settings and the general population reported positive associations of serum levels of PFOA with

biomarkers for liver function, although results are inconsistent. However, studies on the prevalence or incidence of liver diseases including hepatitis or non-alcoholic or alcoholic fatty liver disease have been negative, although they are few in number (C8 Science Panel 2012a).

13.9 Immune Function

Certain PFAS are considered immunotoxic as documented in some epidemiological studies (Grandjean et al. 2012; Okada et al. 2012; Looker et al. 2014) and numerous animal studies (Smits and Nain 2013; Taylor et al. 2005; Dewitt et al. 2008, 2009).

Cross-sectional In a recent cross sectional study of 411 C8 Health Panel participants elevated PFOA serum concentrations were associated with a weakened antibody response (Looker et al. 2014). However, no evidence for an association between self-reported colds or influenza and PFOA, and PFOS serum concentrations was noted. In a cross-sectional analysis in Faroese children aged 5 and 7, elevated exposures to PFAS were related to reduced humoral immunity after routine childhood immunizations (Grandjean et al. 2012).

Asthma is an immune response in the bronchial airways, and hence might be affected by PFAS induced alterations in immune function, although few epidemiologic studies have explored the link. Therefore evidence is inconsistent, as yet, and prospective studies are needed. A recent cross-sectional Taiwanese study described positive associations between PFAS serum concentrations with asthma, asthma severity, and immunological markers in children (Dong et al. 2013). A total of 231 asthmatic children and 225 non-asthmatic controls were recruited. Structured questionnaires and interviews were conducted. Serum concentrations of 11 PFAS and immunological markers were measured. Adjusted odds ratios for asthma among those with the highest versus lowest quartile of PFAS exposure ranged from 1.81 for the perfluorododecanoic acid (PFDoA) to 4.05 for PFOA. PFOS, PFOA, and subsets of the other PFCs were positively associated with immunological markers, and asthma severity scores among asthmatics. This study suggests an association between PFC exposure and juvenile asthma. Another cross-sectional analysis in participants 12–19 years of age from NHANES 1999–2000 and 2003–2008 documented positive relationship between PFOA and with self-reported lifetime asthma, recent wheezing, and current asthma. PFOS exposure had an inverse relationship with both asthma and wheezing. PFNA and PFHxS were unrelated to any outcome (Humblet et al. 2014).

Longitudinal In a Japanese prospective cohort study, Okada et al. (2012) investigated association between PFOS and PFOA maternal exposure from 2002 to 2005 and infant allergies and infectious diseases during the first 18 months of life (Okada et al. 2012). Concentrations of PFOS and PFOA in maternal serum and concentrations of IgE in umbilical cord serum at birth were measured. Development of infant allergies and infectious diseases was determined from self-administered questionnaires at

18 months of age. Although cord blood IgE level decreased significantly with high maternal PFOA levels among female infants, no relationship was found between maternal PFOS and PFOA levels, and allergies and infections at 18 months age.

In a prospective Norwegian study pre-natal exposure to PFAS was associated with immunosuppression in early childhood. In this analysis pregnant women were recruited during 2007–2008. Three annual questionnaire-based follow-ups were performed. Blood samples were collected from the mothers at the time of delivery and from the children at the age of 3 years. Pre-natal exposure to PFOA PFOS, PFNA, and PFHxS were determined in maternal blood in a subgroup. Main outcome measures were anti-vaccine antibody levels, common infectious diseases and allergy- and asthma-related health outcomes in the children up to the age of 3 years. In the children at age 3 years, an inverse association was noted between the level of anti-rubella antibodies and four PFAS concentration in serum. Furthermore, there was a positive association between the maternal concentrations of PFOA and PFNA and the incidence of common cold in children, and between PFOA and PFHxS and the number of episodes of gastroenteritis. No associations were found between maternal PFAS concentrations and the allergy- and asthma-related health outcomes investigated (Granum et al. 2013).

Conclusion Based on the current epidemiologic studies there is no evidence of any increased risk of non-infectious lung disease (Asthma and Chronic Obstructive Pulmonary Disease – COPD).

13.10 Autoimmune Disease

Longitudinal Steenland et al. (2013) reported that PFOA was linked with ulcerative colitis, an autoimmune disease in C8 cohort. In 2008–2011 past disease history was obtained in 32,254 C8 participants from 1952 onwards (or at birth if born after 1952). Any self-reported autoimmune disease (ulcerative colitis, lupus, juvenile diabetes, rheumatoid arthritis, multiple sclerosis, Crohn's disease) was validated through medical records. Cumulative exposure to PFOA was estimated from plant emissions, residential and work history, and exposure modeling during follow-up. The incidence of ulcerative colitis was significantly increased in higher quartiles of PFOA exposure (p-trend < 0.0001). Additional analysis of 29 prospective ulcerative colitis cases diagnosed after the 2005–2006 baseline survey suggested a positive non-monotonic association with PFOA exposure and incidence of ulcerative colitis. However, no association with any other autoimmune diseases was observed.

Conclusion On the basis of existing epidemiological data a probable link between exposure to PFOA and ulcerative colitis may exist. No probable link between PFOA and any of the other autoimmune diseases (rheumatoid arthritis, lupus, type1 diabetes, Crohn's disease, or multiple sclerosis) has been found based on existing data (C8 Science Panel 2012b).

13.11 Osteoarthritis and Bone Mineral Density

Cross-sectional In a large cross sectional study (2005–2006) Innes et al. assessed association between PFOA, PFOS and self-reported physician diagnosed osteoarthritis (OA) in 49,432 adult C8 Health Project participants (Innes et al. 2011). In adjusted analysis, a significant positive association between OA and PFOA serum levels was observed. In contrast, a significant inverse association with PFOS and OA was seen. Because of the cross sectional nature of the study it could not be ascertained whether PFAS exposure preceded OA.

In another cross sectional study Uhl et al. (2013) investigated the association between PFOA and PFOS exposures and self-reported OA in US general population aged 20–84 years using NHANES 2003–2008 data (Uhl et al. 2013). Compared to participants in the lowest quartile, those in the highest exposure quartile had elevated odds of OA. In gender stratified analysis, OA was associated with PFOA only in women. Further, a borderline association between OA and PFOS was noted only in women (Uhl et al. 2013). In a separate cross sectional analysis of NHANES data from 2005 to 2008, serum PFOS concentration was associated with decreased total lumbar spine bone mineral density in pre-menopausal women (Lin et al. 2014). However no association among PFOA and PFOS concentration and self-reported fracture was noted.

Longitudinal In longitudinal unpublished analyses of the C8 Health Project no 'probable link' was reported between PFOA, and either self-reported OA (n = 6,641), or the subset of cases reporting taking OA medication (n = 2,268) (C8 Science Panel 2012d).

Conclusion Data are limited to three studies, which are inconsistent. Two cross-sectional studies reported a positive association between PFOA and osteoarthritis, while the single large longitudinal study did not.

13.12 Thyroid Function

Numerous occupational and population cross-sectional studies report inconsistent relationships between PFAS exposure and thyroid function ranging from null (Bloom et al. 2010; Emmett et al. 2006) to modest changes (Olsen et al. 2003; Olsen and Zobel 2007). There are no longitudinal studies of thyroid function.

Cross Sectional In occupational settings 506 male workers who manufactured or used PFOA at three facilities, no statistically significant associations between PFOA and thyroid stimulating hormone (TSH) or thyroxine (T4) was reported. A negative association was observed for free T4 and a positive association for triiodothyronine (T3) (Olsen and Zobel 2007). In another cross sectional occupational study, PFOA or PFOS exposure assessed in quartiles showed no significant association with T3,

T4, or TSH (Olsen et al. 2003). However linear regression analysis showed positive association between PFOA concentration and T3 levels. In a longitudinal follow-up of a subset of participants, no association was observed between PFOA and thyroid hormones (Olsen et al. 2003).

A cross sectional analysis of C8 Health Project showed that PFOA and PFOS were associated with significant elevations in serum T4 and a significant reduction in T3 uptake (Knox et al. 2011a). In the same community, positive associations between PFOS, PFNA exposure with total T4, and of PFOA with hypothyroidism were observed in children (Lopez-Espinosa et al. 2012). In another cross sectional Taiwanese study in adolescents, and young adults that assessed 12 PFASs, serum PFNA was positively associated with serum free T4. The association was more significant in male participants aged between 20 and 30, active smokers or in those with higher BMI (Lin et al. 2013).

A cross-sectional study of U.S. general population using NHANES data from 2007 to 2010 examined the association between serum PFASs and thyroid function in 1,181 participants (aged >20 years). Elevated serum concentrations of PFOA and PFHxS were associated with total T3, total T4, and free T4 (Wen et al. 2013). In another cross sectional analysis of NHANES data from 2007 to 2008, Jain (2013) described association of six PFAS compounds including PFOS, PFOA, perfluorodecanoic acid, PFHxS, 2-(N-methyl-perfluorooctane sulfonamide acetic acid), and PFNA with thyroid hormones and thyroglobulin (Jain 2013). Elevated serum PFOA was associated with raised TSH, total T3. A positive association between PFHxS and total T4 was noted. No association between any of the six PFAS and thyroid hormones was observed.

PFAS exposure during pregnancy and effect on thyroid hormone homeostasis in pregnant women and fetuses has been addressed in a few cross sectional studies. In a cross sectional population based Norwegian study PFAS exposure during pregnancy and its effect on maternal thyroid function and their offspring was described. A total of 903 pregnant women were enrolled from 2003 to 2004. During the 18th week of gestation serum concentrations of 13 PFASs and TSH were measured. Pregnant women with higher PFOS had higher TSH levels. After adjustment, with each 1 ng/mL increase in PFOS concentration, there was a small rise in TSH. The odds ratio of having an abnormally high TSH, however, was not increased, and other PFASs were unrelated to TSH. It was concluded that PFOS was associated with slight increase in TSH in pregnant women that may be of no clinical significance (Wang et al. 2013).

In a separate cross sectional Taiwanese study serum concentrations of nine PFASs and four thyroid hormones were measured in 285 pregnant women (third trimester) along with cord serum thyroid hormones in 116 neonates (Wang et al. 2014). PFHxS concentrations were positively associated with maternal TSH levels. Pregnant women with elevated PFNA, perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) had lower free T4 and total T4 levels. Also, maternal PFNA, PFUnDA, and PFDoDA levels were associated with lower cord T3 and total T4 levels, and maternal perfluorodecanoic acid was associated with lower cord total T3 (Wang et al. 2014).

Conclusion Data are mainly limited to cross-sectional studies, and results are mixed.

13.13 Thyroid Disease

Most of the epidemiological research evaluation PFAS and thyroid disease is cross sectional and primarily comprises of general population studies.

Cross-sectional In cross sectional NHANES 1999–2006 data among 3,974 adults from the U.S. general population, men and women with elevated PFOA were more likely to report current treated thyroid disease. Similar association with PFOS exposure was reported only in men (Melzer et al. 2010). A cross sectional study in Canadian pregnant women in community evaluated link between four FFAS and thyroid hormones and thyroid peroxidase antibody (TPOAb, a marker of autoimmune hypothyroidism (Hashimoto's disease)) during the second trimester (Webster et al. 2014). PFASs had positive association with TSH and weak negative relationship with free T4 in the subset of pregnant women with high TPOAb. A cross sectional study in 10,725 children from C8 communities identified a link between hypothyroidism and elevated PFOA and elevated thyroid hormones with increase in PFOS and PFNA exposures (Lopez-Espinosa et al. 2012).

Longitudinal In a cohort study among participants of C8 Health Project, Winquist and Steenland (2014b) found that elevated PFOA exposure was associated with thyroid disease. Participants provided health information during 2008–2011. Retrospective exposure to PFOA was estimated for each participant starting at birth or in 1952, whichever came later. A total of 2,109 cases of thyroid disease on thyroid medication were identified after medical record review. PFOA was associated with increased risk of hyperthyroidism and hypothyroidism in women, and with hypothyroidism in men (Winquist and Steenland 2014b).

Conclusion Cross-sectional studies of thyroid disease and PFAS have had mixed results. Current evidence in a single longitudinal study reports a positive association between PFOA and thyroid diseases.

13.14 Neurological and Neurodegenerative Disorders

Cross-sectional A C8 Health Project analysis assessed the cross-sectional association between PFOA, PFOS, PFHxS, PFNA and self-reported memory impairment in 21,024 adults aged 50 years and over. Results indicated that as serum PFOS and PFOA increased, memory impairment decreased. Modest associations between PFNA and PFHxS were seen (Gallo et al. 2013). A cross-sectional study on the general population also suggested that there may be a protective association between

exposure to PFAS and cognition in older adults aged 60–85 years, particularly in diabetics. Power et al. examined the association between four PFASs exposure (PFOS, PFOS, PFHxS, PFNA), and self-reported memory problems in the NHANES 1999–2000 and 2003–2008 surveys (Power et al. 2013). In adjusted analyses, a protective association between PFASs and self-reported cognitive impairment was seen, which was more marked in diabetic older adults (Power et al. 2013).

Longitudinal In longitudinal unpublished of combined C8 worker and community cohorts, the C8 Science Panel found no 'probable link' between medically validated Parkinson's disease (n = 138) and PFOA (C8 Science Panel 2012e). C8 Science Panel reported non-significant relationship between cumulative PFOA exposure and risk of Parkinson's disease (p-trend = 0.61). Compared with participants in the lowest quartile, reported HRs was 1.0, 0.8 and 1.0 in increasing quartiles.

Conclusion A few cross-sectional studies on highly exposed community and general population suggested that higher blood PFAS (PFOS and PFOA) concentrations were favorably linked to memory function. A single longitudinal study found no link between PFAS and Parkinson's disease. Overall, the data are too sparse to assess the association between PFAS and development of cognitive impairment or neurodegenerative diseases.

13.15 Cognitive and Behavioral Disorders in Children

Epidemiologic evidence on PFOA exposure and child development is limited with varied exposure timing and levels, and measures of outcomes. Health outcomes studied in relation to PFAS exposures included cognitive and behavioral development milestones, performance testing, and attention deficit hyperactivity disorder (ADHD).

Cross-sectional Data based on highly exposed C8 community cohort, Stein and Savitz (2011) reported positive association between PFHxS level and ADHD (Stein and Savitz 2011). However, there was no significant association between any of four PFAS examined (PFOA, PFOS, PFHxS and PFNA) and parental reports of children' learning problems. Analysis was completed on data from 10,546 non-Hispanic white children 5–18 years of age. The prevalence rate of ADHD was 12.4 % (n = 1,303), and learning problem was 12.1 % (n = 1,281). In age and sex adjusted analyses, an inverted J-shaped association between PFOA and ADHD was noted. The prevalence of ADHD plus medication (5.1 %) was increased across PFHxS quartiles, with adjusted ORs of 1.00 (reference), 1.44 (95 % CI: 1.09–1.90) for quartile 2, 1.55 (1.19–2.04) for quartile 3 and 1.59 (1.21–2.08) for quartile 4 (Stein and Savitz 2011).

In a study of 571 children 12–15 years of age using the data from NHANES 1999–2000 and 2003–2004 data, elevated PFOA concentration was related to

parent-reported ADHD (Hoffman et al. 2010). One unit (ug/l) increase in PFOA was associated with 1.12 times increase in odds of having parentally reported ADHD (95 % CI, 1.01–1.23). The magnitudes of relationship between PFOS and PFHxS and ADHD were similar to that of PFOA. In a small study (n = 83) of children at background exposure levels, higher levels of five PFAS were associated with impulsivity in children (Gump et al. 2011).

Longitudinal Another analysis on the C8 community cohort did not find a relationship between PFOA exposure in 320 children and their performance on neuropsychological tests (Stein et al. 2013). Children enrolled in 2005–2006 had serum measures of PFOA, estimated in utero PFOA exposure, and prospective evaluation of neuropsychological tests 3–4 years later at ages 6–12 years. These tests included Intelligence Quotient (IQ), reading and math skills, language, memory and learning, visual-spatial processing, and attention. In multivariate analysis, children in the highest quartile as compared with the referent quartile of estimated in utero PFOA showed improved Full Scale IQ (beta 4.6, 95 % CI: 0.7–8.5) and decreases in ADHD (Stein et al. 2013). A recent study on children from C8 community cohort (n = 321) supplements the current evidence by providing a prospective assessment of childhood PFOA levels and mother and teacher report of child behavior measured using Behavior Rating Inventory of Executive Function scale assessed 3–4 years later (Stein et al. 2014a). Stein et al. reported that PFOA exposure were associated with behavioral problems in sex-specific manner. Survey results from mother's reports (n = 313) on behavioral problems suggested inverse associations between PFOA exposure and behavioral problem among boys but positive associations among girls (Stein et al. 2014a). Compared with boys in the lowest quartile, for example, boys in the highest quartile of PFOA exposure levels had about 6.39 lower score (95 % CI; −11.14, −1.35). A study of general population at background exposure level, prenatal PFOA and PFOS levels were measured in the Danish National Birth Cohort, and those were examined in relation to mothers report on behavioral (n = 787) and motor coordination (n = 526) outcomes (Fei and Olsen 2011). In this study, either prenatal PFOS or PFOA levels were not related to child's developmental milestones through age 7 (Fei and Olsen 2011; Fei et al. 2008).

Conclusion There are limited data on the associations between PFAS and adverse childhood behavioral and cognitive development. The data which do exist to not suggest any marked negative effects.

13.16 Reproductive and Developmental Outcomes

There have been a large number of epidemiologic studies of reproductive and developmental outcomes. These outcomes include decreased sperm count, longer time to pregnancy, birth defects, miscarriage and still birth, lower birth weight and birth size of neonates.

Cross-sectional Previous population studies in men had indicated a negative association between PFAS exposure and semen quality (Joensen et al. 2009) as seen in a cross-sectional study of 105 Danish men (median age, 19 years) in 2003 (reviewed in Steenland et al. 2010a, b). Men with high serum PFOS and PFOA had lower sperm count and fewer morphologically normal sperm than men with low PFOS, PFOA. In a recent cross sectional Danish population study of 247 men conducted during 2008–2009 PFOS levels were negatively associated with testosterone (T), calculated free testosterone (FT), free androgen index (FAI) (Joensen et al. 2014). However other cross sectional studies from European populations (Specht et al. 2012) and in the US (Raymer et al. 2012) have reported no consistent evidence that PFAS exposure affects semen quality or reproductive hormones in men. PFAS exposure in C8 Health Project was associated with delayed puberty in boys (cross sectional) (Lopez-Espinosa et al. 2011).

In a cross-sectional study in European women, PFOA exposure was associated with longer menstrual cycles (Lyngso et al. 2014). A total of 1,623 pregnant women were enrolled during antenatal care visits (2002–2004). Serum PFOA, and PFOS were assessed and retrospective information on menstrual cycle characteristics was obtained. Women with elevated PFOA had statistically significant longer cycles; a weaker association was also seen with PFOS.

Longitudinal PFAS exposure has been associated with infertility and subfecundity in women (reviewed in Steenland et al. 2010a, b). Fei et al. (2009) assessed time to pregnancy in 1,240 women from the Danish National Birth Cohort recruited from 1996 to 2002 (Fei et al. 2009). Plasma levels of PFOS and PFOA were measured during pregnancy. Higher maternal serum PFOS and PFOA were associated with longer time to pregnancy. Elevated PFOA and PFOS exposure was associated with infertility. A later study by Whitworth et al. (2012) reported that elevated PFOA and PFOS serum concentration was linked with subfecundity (ascertained as time to conceive >12 months) in multiparous Norwegian pregnant women enrolled in 2003–2004, no association was seen in nulliparous women (Whitworth et al. 2012).

Elevated exposure to PFAS in women has been associated with later menarche and earlier menopause. In a cross sectional analysis, PFOS and PFOA were related with delayed puberty in 3,076 boys and 2,931 girls aged 8–18 years in 2005–2006 survey of C8 communities (Lopez-Espinosa et al. 2011). Emerging evidence from prospective epidemiological studies suggest that prenatal exposure to PFAS has long-term effects on female reproductive function. From a Danish population-based cohort established in 1988–1989, levels of PFASs in maternal serum from 30th gestational week were used as a measure of prenatal exposure collected in mothers. The daughters were enrolled 20 years later and their reproductive history regarding age of menarche, menstrual cycle length, and levels of reproductive hormones were obtained. Daughters with elevated PFOA in utero exposure had a 5 months later age of menarche (Kristensen et al. 2013).

In the US, two studies have reported earlier menopause with higher exposure to PFAS (Knox et al. 2011b; Taylor et al. 2014). In 25,957 women aged 18–65 years enrolled from the C8 Health Project, serum estradiol levels and onset of menopause

were assessed (Knox et al. 2011b). The odds of menopause were significantly elevated with increased PFOA and PFOS exposure. In a cross sectional study among the US general population using NHANES 1999–2010 data, a positive association between PFAS exposure and earlier menopause was reported (Strongest for PFHxS) (Taylor et al. 2014). In this study, women with elevated PFOA, PFNA, and PFHxS were 36 %, 47 %, and 70 % more likely to have experienced menopause, respectively. Premenopausal women had the lowest levels of all four PFCs, whereas women who had undergone hysterectomy had the highest levels. PFHxS was most strongly associated with rate of hysterectomy. Women with elevated PFHxS were 3.5 times more likely to have had a hysterectomy. PFOA, PFNA, and PFOS were also significantly associated with having had a hysterectomy. However due to cross-sectional nature of the study, it was difficult to distinguish if raised PFAS led to earlier menopause or vice versa (reverse causality).

Association between PFAS exposure and preterm births has been investigated (reviewed in Darrow et al. 2014). In previous studies (Stein et al. 2009; Savitz et al. 2012a) no association between retrospective PFOA exposure and miscarriage risk was found. In a recent prospective study only limited evidence of association with PFOS was noted (Darrow et al. 2014).

PFAS exposure and major birth defects have been described in epidemiological studies (reviewed by Stein et al. 2014a, b). An earlier study from the C8 Health Project reported increased odds of birth defects with higher PFOA exposure (Stein et al. 2009). Another report from the same area described weak association with cardiac birth defects (Savitz et al. 2012b). A third study did not find any significant association between PFOA and birth defects (Nolan et al. 2010). The most recent study reports modest association of PFOA exposure with brain birth defects based on 13 cases (Stein et al. 2014b).

An association between PFOA exposure and pregnancy-induced hypertension (or pre-eclampsia) has been reported in C8 communities in two studies (Darrow et al. 2013; Savitz et al. 2012a), but not in one other (Savitz et al. 2012b). Overall this evidence was such that the C8 Science Panel decided that PFOA was more probably than not linked to pregnancy-induced hypertension (C8 Science Panel 2011).

Lower birth weight indicates insufficient fetal growth during pregnancy and is associated with future health problems. Both PFOA and PFOS can cross human placental barrier (Midasch et al. 2007); toxicological studies have reported evidence of LBW in animals at higher exposure levels than noted in human populations with background exposure (Lau et al. 2007).

Existing epidemiologic studies examining PFAS exposure and birth weight measured on a continuous scale in the general population provide inconsistent evidence of associations (Apelberg et al. 2007; Fei et al. 2007; Hamm et al. 2010; Washino et al. 2009). Two studies reported clear evidence of decreased mean birth weight in relation to increased PFOA (Apelberg et al. 2007; Fei et al. 2007). Smaller decrements were reported in two other (Hamm et al. 2010; Washino et al. 2009). One study (Fei et al. 2007) reported a reduction of 10.6 g per ng/ml increase in PFOA. Three smaller studies reported no association between PFOA and birth

weight (So et al. 2006; Monroy et al. 2008; Inoue et al. 2004). A large study (17,000 pregnancies) in C8 population, using estimated past exposure based on a well validated model which correlated well with recent measured PFOA, found no evidence of an association of PFOA with birth weight (Savitz et al. 2012b). Similarly a smaller study in the same population (1,600 births) found no association (Nolan et al. 2009). On the other hand, a recent meta-analysis of nine low-exposure general population studies, found a significant reduction of birth weight with higher PFOA (Johnson et al. 2014). The findings of no association in a population which much greater exposure contrasts (Savitz et al. 2012b) vs. an association in the meta-analysis of very low exposed general population (Johnson et al. 2014), are clearly contradictory. There could be a number of explanations. Effects are sometimes seen with low exposure contrasts which are less apparent using high exposure contrasts. Alternatively, an artificial association could be seen in general population studies due to increased maternal blood volume with more fetal growth, and decreased serum PFOA with increased blood volume.

Three other studies that examined PFOA exposure (dichotomous) with odds of low birth weight (LBW) (<2,500 g) rather than birth weight on a continuous scale reported no evidence of an association. In a general population study of the Danish National Birth Cohort, the authors reported no consistent association of either PFOA or PFOA with LBW (Fei et al. 2007). Two large studies in C8 population, using estimated past exposure based on a well validated model, found no evidence of an association of PFOA with LBW (Savitz et al. 2012a, b).

Conclusion Human population studies have reported inconsistent associations between PFAS exposure and reproductive and developmental outcomes. These outcomes include decreased sperm count, longer time to pregnancy, birth defects, miscarriage and still birth, pre-term birth lower birth weight and birth size of neonates. None of these outcomes show consistent associations with any PFAS, and when positive associations have been reported, their magnitude has been small. Two out of three studies have reported a positive association between pregnancy-induced hypertension and PFOA, but data remain sparse. One meta-analysis of nine studies reported a significant association of lower birth weight with more PFOA at low general population levels, but is contradicted two other studies with much greater exposure contrasts, and not supported by three studies showing no association of PFOA with LBW.

13.17 Overweight and Obesity in Offspring

Epidemiological findings support developmental (pre-natal or early life) effects of low-dose exposures to PFAS. In a recent Danish prospective study, low dose pre-natal exposure to PFOA had an obesogenic effect in female offspring at 20 years of age (Halldorsson et al. 2012). Pregnant women (n = 665) were enrolled in 1988–1989 and PFOA was measured in serum at 30 weeks of pregnancy. Body mass index

(BMI) and waist circumference in offspring were recorded at follow-up (n = 665), and biomarkers of adiposity were measured in 422 participants. Pre-natal PFOA exposure showed a positive relationship with BMI and waist circumference only in female offspring 20 years of age (Halldorsson et al. 2012). It has been hypothesized that early life PFAS exposure may alter weight controlling hormones, possibly by activating peroxisome proliferator-activated receptor alpha (PPAR-α). PPAR-α, is a hormone receptor that plays a role in energy homeostasis. Another mechanism hypothesized mechanism is that PFOA may stimulate steroid hormone production in ovaries and thereby women may be more susceptible to the effects than men (White et al. 2011).

Longitudinal In a retrospective study, Barry et al. (2014) reported no association between PFOA exposure during the first 3 years of age and BMI measured later in adulthood among C8 Health Project participants (Barry et al. 2014). Data for height and weight of 8,764 adults aged 20–40 years were collected between 2008 and 2011. Using exposure modeling, annual retrospective early life PFOA serum concentrations were estimated for each participant based on residential history, and proximity to plant emissions. Elevated PFOA exposure in early life (up to 3 years of age) was not associated with overweight and obesity risk in adult hood.

Conclusion Data are sparse and contradictory regarding whether early life exposure to PFAS is associated with later obesity.

13.18 Conclusion

Serum PFOA has been linked relatively consistently with increased serum lipids, and uric acid levels in occupational, a highly exposed community population and general population studies. The largest body of evidence is for serum lipids. Furthermore, a large cohort study found a positive association with hypercholesterolemia and PFOA. A positive association has been described between PFOS serum levels and total cholesterol, triglycerides, and uric acid in the general population. In contrast, occupational studies did not indicate consistent associations between PFOS and cholesterol and/or triglycerides in either cross-sectional surveys or in a longitudinal analysis.

A large cohort study found a strong positive relationship between cumulative PFOA exposure and ulcerative colitis, an auto-immune disease. There was no other association between PFOA and other auto-immune diseases. One large cohort study of a highly exposed population did find a positive association between PFOA and thyroid disease.

Although the relationship between PFAS and cancer has not been addressed in this chapter, current data are also sparse, and largely restricted to PFOA. Occupational mortality studies have found isolated increases in some cancers based on small numbers, including one study with a significant elevation of kidney cancer (Steenland and Woskie 2012; Vieira et al. 2013). One large population cohort study

found a non-significant elevation of prostate and pancreatic cancer (Eriksen et al. 2009). One large cohort study and one ecologic study in a highly PFOA-exposed population in the mid-Ohio valley found positive associations with testicular cancer and kidney cancer (Barry et al. 2013). Testicular tumors were of a prior interest because they have been found in animal studies (Biegel et al. 2001; Lau et al. 2007). Overall, an association between PFOA and testicular and kidney cancer seems plausible, with limited data.

PFAS exposure has also been associated in some studies with adverse effects on thyroid homeostasis, liver enzymes, osteoarthritis, non-malignant kidney disease, and immunotoxicity, but the data are inconsistent. Data are sparse but largely negative for T2DM, neurodegenerative disease, children's cognition, adult CVD and stroke, immune function, liver disease, and obesity. Despite a large body of literature, and some positive findings regarding low birth weight, the data are overall inconsistent regarding reproductive/developmental outcomes. Two of three longitudinal studies found a positive association between PFOA and pregnancy-induced hypertension, but data remain sparse.

Epidemiologic evidence available at present is derived from occupational cohorts, highly exposed community cohorts, or general population studies. There are a number of limitations to the evidence. Interpretation of results from general population studies with low exposures may not match with those from occupational cohorts and with those from highly-exposed communities.

PFAS studies are often cross-sectional in nature, and cannot be used to determine causality. Further, cross sectional studies may report subclinical endpoints (blood chemistry) which may not have clinical significance because of a small magnitude of effect. These studies may suffer from reverse causality where it cannot be distinguished, for example, if increase in PFAS decreases glomerular function, or *vice versa* (Watkins et al. 2013). Alternatively, a third parameter that changes overtime may change both PFAS and glomerular function. Furthermore, interpretation of cross-sectional studies of disease endpoints in the general population has often been hindered by the lack of validation of outcomes (i.e., self-reported stroke). There are only a limited number of prospective studies exploring PFAS and human health outcomes in selected populations, which limits generalizability.

In summary, epidemiologic evidence suggest that there is an association between PFOA and six health outcomes: diagnosed high cholesterol, ulcerative colitis, thyroid disease, testicular cancer, kidney cancer, and pregnancy-induced hypertension. Data remains limited for other PFAS. To validate these results and increase our understanding of PFAS exposure, longitudinal studies in populations with exposures above general population background levels are needed. However, there are limited numbers of such populations.

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