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Differences in Exposure to Perfluorocarbons and Renal and Liver Function among Foreign-Born U.S. Residents

Reynolds A. Morrison
Georgia State University

DIFFERENCES IN EXPOSURE TO PERFLUOROCARBONS AND RENAL AND LIVER FUNCTION AMONG FOREIGN-BORN U.S. RESIDENTS

By

REYNOLDS ARTHUR MORRISON

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Reynolds A. Morrison

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REYNOLDS ARTHUR MORRISON

Committee:

Ike Okosun, MS, MPH, PhD (Chair)

Christina H. Fuller, ScD, MS

Dora Il'yasova, MS, MSPH, PhD

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ABSTRACT

Polyfluorochemicals (PFCs) are industrial compounds that tend to bioaccumulate in humans and may be associated with impaired renal and liver function. Differences in background exposure to PFCs in the general population exist worldwide, which suggest that populations with lower exposure concentrations, such as foreign-born U.S. residents, may have lower risk for adverse health effects associated with PFCs. Using data from the 2007-2012 waves of US National Health and Nutritional Examination Survey (NHANES) this study investigated differences in serum concentrations of perfluorooctanoic acid, (PFOA), perfluoroctane sulfonic acid (PFOS), perfluorohexane sufonic acid (PFHxS) and perfluorononanoic acid (PFNA) among native-born and foreign-born U.S. residents; and examined the association between these chemicals and estimated glomerular filtration rate (eGFR), Alanine aminotransferase (ALT), γ-glutamylytransferase (GGT) and total bilirubin among foreign-born U.S. residents, and on stratifying by length of residence (LOR). Additionally, the association between joint exposures to multiple PFCs and renal and liver function was examined.

The results showed that least square geometric mean concentrations of PFOA and PFHxS were higher, and least square mean of eGFR was lower among native-born when compared to foreign-born residents. As LOR increased, mean and median concentrations of PFOS and PFHxS significantly increased, and mean eGFR decreased. LogPFOA, logPFHxS, and logPFNA concentrations were significantly associated with increased odds of having low eGFR. The associations remained significant among individuals who had been resident for 10-19 years, and 20+ years. Differences in the mean and median concentrations of ALT, GGT, and Total bilirubin between foreign-born and native-born residents, and by LOR were inconclusive. Similarly, significant associations between the selected PFCs and liver function indicators were

not conclusive. Increasing quartiles of a combined PFOS/PFHxS exposure variable was associated with increased odds of low eGFR, and elevated total bilirubin.

Findings from this study suggest that differences in exposure to PFCs exist among native-and foreign-born U.S. residents. Also, increasing serum concentrations of some PFCs with increasing LOR may be associated with increased risk for decreased renal function. Longitudinal studies among new U.S. residents can help determine whether exposure to low background concentrations of the selected PFCs may be associated with any negative health effects over time. There are currently no studies on the combined effect of exposure to multiple PFCs. The findings of this study can serve as the basis for future studies on the association between combined exposures and adverse health outcomes.

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LIST OF ABBREVIATIONS

ACS	American Chemical Society
ALT	Alanine aminotransferase
APFO	ammonium perfluorooctanoate
APFO	Ammonium perfluorooctanoate
AST	Aminotransferase
ASTSWMO	Association of State and Territorial Solid Waste Management Officials
BMI	Body mass index
CAR	Constitutive androstane receptor
CDC	Centers for Disease Control and Prevention
CI	Confidence intervals
CKD	Chronic kidney disease
CVD	Cardiovascular disease
ECA	European Chemical Agency
ECF	Electro-Chemical Fluorination
EFSA	European Food Safety Authority
eGFR	Estimated glomerular filtration rate
ER-alpha	Estrogen receptor
ETS	Environmental tobacco smoke
FEV1	Forced expiratory volume at 1s
FTOHs	Fluorotelomer alcohols
FVC	Forced vital capacity
FXR	Farnesoid X receptor
GGT	γ-glutamylytransferase
GLM	General linear modeling

HNF4a	Hepatocyte nuclear factor 4 alpha
IQR	Interquartile range
LOR	Length of residence
LSGM	Least square geometric means
LSM	Least Square Means
NCBI	National Center for Biotechnology Information
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
PAPs	Polyfluoroalkyl phosphoric Acid
PCA	Principal component analysis
PFCs	Perfluorocarbons
PFHxS	Perfluorohexane sulfonic acid
PFIs	Polyfluorinated iodides
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluoroctane sulfonic acid
POPs	Persistent Organic Pollutants
POSF	Perfluorooctanesulfonyl fluoride
PPAR	Peroxisome proliferator-activated receptor
PPARG	Peroxisome proliferator-activated receptor gamma
PPARα	Peroxisome proliferator- activated receptor-alpha
PXR	Pregnane X receptor
SE	Standard error

TCB	Total chemical burden
TCE	Trichloroethylene
TDI	Tolerable Daily Intake
TSH	Thyroid stimulating hormone
UNEP	United Nations Environment Program
USDHHS	United States Department of Health and Human Services
USEPA	United States Environmental Protection Agency
VOCs	Volatile organic compounds

Chapter I: Introduction and Statement of Purpose

Background

Perfluorocarbons (PFCs) are organic compounds that consist of fully fluorinated carbon chains, between four to twelve carbons long, with either a carboxylic acid, sulfonic acid, or alcohol end chain group (C. Lau, 2012). For instance, perfluorooctanoic acid (PFOA) is an 8-carbon chain with a carboxylic acid end group (Figure 1); perfluoroctane sulfonic acid (PFOS) is an 8-carbon chain with a sulfonic acid end group (Figure 2); perfluorohexane sulfonic acid (PFHxS) is a 6-carbon chain with a sulfonic acid end group (Figure 3); and perfluorononanoic acid (PFNA) is 9-carbons long with a carboxylic acid end group (Figure 4) (De Silva & Mabury, 2004); The strong carbon-fluorine bonds make PFCs extremely stable and resistant to thermal and chemical degradation (European Food Safety Authority (EFSA), 2008; Olsen et al., 2007; United States Environmental Protection Agency (USEPA), 2009). They are non-flammable, non-volatile, non-oxidized even with strong acids or bases, stable in extremely elevated temperatures, and highly resistant to biodegradation (C. Lau, 2012; USEPA, 2009). Due to these properties, PFCs are useful for many industrial applications, including water repellant coating for carpets, textiles, leather, and food packing materials; as well as cleaning agents in cosmetics and fire-fighting foams (Fromme, Tittlemier, Völkel, Wilhelm, & Twardella, 2009; Hekster, Laane, & de Voogt, 2003; Organization for Economic Cooperation and Development (OECD), 2002). However, these properties also make them persistent compounds which are bioaccumulative and toxic to both humans and the environment. Hence, they are included in the Stockholm Convention on Persistent Organic Pollutants (POPs) (OECD, 2002).

Between 1970 and 2002, cumulative global production of PFC chemicals stood at nearly 100,000 metric tons (Paul, Jones, & Sweetman, 2009). It is estimated that since production of

PFCs began in the 1950s, up to 45,300 metric tons of PFCSs have been released into the environment, of which more than 95% have been released directly into aquatic environments (Ahrens, Yeung, Taniyasu, Lam, & Yamashita, 2011; Paul et al., 2009). Due to the concerns about their toxic effects on humans and the environment, a voluntary phase-out of the production of PFCs, in particular PFOS, started in the year 2000 (American Chemical Society (ACS), 2010). By 2003, PFOS production in the United States had ceased (USEPA, 2009), with a goal of reducing emissions by 95% by 2010 and eliminating emissions completely by 2015 (ACS, 2010). However, existing stocks and products already in the United States before rules stopping PFOS manufacture took effect in 2002, can still be used without any restrictions (USEPA, 2009, 2016a). Most developed countries have followed suit, but production of PFOS-related chemicals has continued on a smaller extent since 2003 in other countries (Houde, De Silva, Muir, & Letcher, 2011; Lim, Wang, Huang, Deng, & Yu, 2011). For instance, with the phase-out of Perfluorooctane sulfonic acid(PFOS) manufacturing in the United States by 3M, the principal producer, large-scale production has continued in China (Lim et al., 2011). Annual production of PFOS in China increased from less than 50 tons in 2004, to 200 tons in 2006, of which nearly 50% was designated for export (Lim et al., 2011; Liu et al., 2017). And in the U.S., limited quantities of PFOS can still be imported (USEPA, 2009). Due to these factors, and the persistence of PFCs, populations worldwide are bound to be exposed to background levels of these chemicals for the conceivable future.

In recent years, PFCs have become a focus of public health concern due to their ubiquitous presence in the environment. Environmental contamination occurs in all aspects of the chemical's life cycle including production, supply chain, product use, and disposal (L.S. Haug, Huber, Becher, & Thomsen, 2011; Houde et al., 2011; Kudo & Kawashima, 2003; Liu et

al., 2017). PFCSs are generally water-soluble and as a result are often detected in drinking water (L.S. Haug et al., 2011; Post, Cohn, & Cooper, 2012; Tittlemier et al., 2007). PFCSs have also been detected in measurable background levels in animal and human tissue and serum samples on nearly every continent including some remote locations (Hanssen, Röllin, Odland, Moe, & Sandanger, 2010; Kannan, Corsolini, Falandysz, Fillmann, & Kumar, 2004). The most common PFCs detected in environmental and human samples are PFOS, PFOA, PFNA, and PFHxS (Kannan et al., 2004; Paul et al., 2009; Steenland, Tinker, Frisbee, Ducatman, & Vaccarino, 2009). Other PFCs detected in human tissue samples include perfluorooctane sulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH), 2-(N-ethylperfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH or PFOSAA), perfluoroheptanoic acid (PFHpA), perfluorodecanoic acid (PFDeA or PFDA), perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDoA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), and perfluorobutanesulfonic acid (PFBS) (USEPA, 2009).

Studies in experimental animals indicate that PFCs adversely affect liver, kidney, and immune system function. Laboratory studies of rats show that exposure to PFCs is associated with renal hypertrophy and histopathologic changes indicative of renal microvascular disease (Cui, Zhou, Liao, Fu, & Jiang, 2009). Similar studies in other rodents and primates show that PFC toxicity impairs liver function (Post et al., 2012; Rosen et al., 2010; Wolf, Zehr, Schmid, Lau, & Abbott, 2010). In humans, PFCs are associated with various diseases and metabolic abnormalities including chronic kidney disease (Shankar A., Xiao J., & Ducatman A., 2011), elevated cholesterol levels (J.W. Nelson, E. E. Hatch, & T.F. Webster, 2010; Sakr, Leonard, Kreckmann, Slade, & Cullen, 2007; Steenland et al., 2009), insulin resistance and metabolic

syndrome (Lin, Chen, Lin, & Lin, 2009), and liver dysfunction (Gleason, Post, & Fagliano, 2015). The study of PFC concentrations in human blood serum is relatively new. As such there is little information on exposure limits in various countries. Wilhelm et al., (2009) suggested the following reference values for internal contamination with some PFCs in Germany: for PFOA 10μg/L for the general population; and for PFOS, 10 μg/L for children of school age, 15 μg/L for adult women, and 25 μg/L for men (Wilhelm, Angerer, Fromme, & Holzer, 2009). The European Food Safety Authority (EFSA), based on their assessment of PFC contamination in various food sources, also suggested a Tolerable Daily Intake (TDI) of 150 ng/kg b.w. per day for PFOS, and 1.5 μg/kg b.w. per day for PFOA (European Food Safety Authority (EFSA), 2008).

Studies suggest blood serum concentrations of PFCs among various populations differ worldwide. The EFSA found that the mean blood serum concentrations of various European populations were between 4 to 20 μg/L for PFOA; and 4 μg/L to 55 μg/L for PFOS (EFSA, 2008). Kannan et al.,(2004) studied PFC concentrations in nine different countries world-wide, namely the United States, Colombia, Brazil, Italy, Belgium, Poland, India, Malaysia, and Korea (Kannan et al., 2004). They found that mean PFOS concentrations were highest in serum samples from the United States and Poland (greater than 30 ng/mL), followed by mean concentrations in Japan, Korea, Malaysia, Belgium, and Brazil (between 10 and 25 ng/mL), Italy and Colombia (between 4 and 10 ng/mL), with India having the lowest concentration (1 ng/mL) (Kannan et al., 2004). They also found that median concentrations of PFOA in Polish and Korean serum samples were 21 and 28ng/mL respectively, approximately two times greater than median concentrations for samples from the United States. Finally, median concentrations of PFHxS in samples from the United States, Korea, and Japan were in the range of 1.5-3 ng/mL higher than concentrations found in other countries (Kannan et al., 2004). Fromme *et al.,* (2007)

also found that concentrations of PFOS, PFOA, AND PFHxS measured in blood samples from Germany were lower than that measured in a related study in the USA and Canada (Fromme et al., 2007). Another study also concluded that serum PFOS, PFOA and PFHxS concentrations of the US population are higher than that of residents of Europe, Asia, or Australia (Fromme et al., 2009). A pilot study conducted in South Africa found concentrations of 1.6 μg/L PFOS, 1.3 μg/L PFOA, and 0.5 μg/L PFHxS in maternal blood, with the highest PFC concentrations observed among subjects who lived in urban and semi-urban areas, which were associated with the highest quality of living (Hanssen et al., 2010). On the other hand Kärrman et al.,(2006) found no significant differences in mean PFC concentrations among urban and rural residents in Australia (Kärrman et al., 2006).

Considering that level of exposure to PFCs may be an important risk factor for adverse health effects, country of residence may be a key factor in examining the association between blood serum PFC concentrations and adverse health effects. Differences in levels of exposure to PFCs may translate into a difference in risk for associated diseases and health disorders. However, to the best of our knowledge, no studies have examined this phenomenon. In 2010, about 40 million foreign-born individuals (representing 13 percent of the total population) resided in the United States (Grieco et al., 2012)**.** Foreign-born individuals are a unique population that can be assessed to examine whether PFC serum concentrations increase with increasing years of residence in the United States, and whether that will be associated with increased risk for adverse health effects, including renal and liver dysfunction.

Additionally, PFCs are typically detected as a mixture of two or three compounds in the environment and biological samples (Grandjean et al., 2012; Granum et al., 2013; Stein, McGovern, Pajak, Maglione, & Wolff, 2016). Even though individual PFCs have subtle

structural differences that affect their uptake and binding with human and animal tissue, and in turn result in different toxicity profiles (Post et al., 2012; Rosen et al., 2010), little is known about the adverse health effects of simultaneous exposure to these chemicals (Rappazzo, Coffman, & Hines, 2017). Most studies have examined the effects of exposure to these chemicals on an individual basis and not their combined or interactive effects on health outcomes. By examining their combined effects, instead of one chemical at a time, it may be possible to identify any associations between simultaneous exposure to PFCs and adverse health effects more accurately. This will provide insight into understanding the biological mechanisms of pollutant toxicity to guide public health interventions.

Study Purpose

The overall aim of this study is to evaluate the association between long-term background exposures to selected PFCs and renal and liver function. This study aims to fill the gaps in the understanding of how differences in exposure patterns to PFCs are associated with (1) Measures of renal function (as indicated by estimated glomerular filtration rate (eGFR); and (2) measures of liver function (as indicated by markers of liver toxicity; Alanine aminotransferase (ALT), γ-glutamylytransferase (GGT) and total bilirubin). The study will answer the following research questions, using data available from the National Health and Nutritional Examination Survey (Centers for Disease Control, 2010).

Research Questions

1. Do PFC serum concentrations significantly differ between native- and foreign-born U.S. residents?

Among foreign-born U.S. residents:

2. Do PFC serum concentrations increase with increasing length of residence in the U.S?
3. Are there significant associations between PFC serum concentrations and kidney function [as measured by estimated glomerular filtration rate (eGFR)]?
    a. Does length of residence in the U.S have a significant moderating impact on the association between selected PFCs and kidney function?
4. Are there significant associations between PFC serum concentrations and liver function [as measured by Alanine aminotransferase (ALT), γ-glutamylytransferase (GGT) and total bilirubin]?
    a. Does length of residence in the U.S have a significant moderating impact on any observed associations PFC serum concentrations and liver function indicators?
5. Considering that background exposure to the selected PFCs occurs concurrently, what is the association between the joint exposures of multiple PFCs and either kidney and or liver function?

Chapter II: Literature Review

Toxicology of PFCs

Sources of Exposure: PFCs are released into the environment through degradation of precursors and throughout the life cycle of products made with PFCs (Lindstrom et al., 2011a). Manufacturing facilities, waste treatment plants, military bases, and landfills can also be point sources for PFCs in the soil (Filipovic, Woldegiorgis, Norström, et al., 2015; Xiao, Simcik, Halbach, & Gulliver, 2015), and outdoor air (Ahrens, Shoeib, et al., 2011). Soil contamination can also occur from the application of PFC-contaminated biosolids as an amendment to soils as fertilizers (Lindstrom, Strynar, & Libelo, 2011; USEPA, 2011; Washington, Yoo, Ellington, Jenkins, & Libelo, 2010; Yoo, Washington, Ellington, Jenkins, & Neill, 2010). Because of the use of PFCs in manufacturing carpets, upholstered furniture, and other textiles, PFCs have been detected in dust from indoor spaces. Exposure to PFCs and their precursors can occur through inhalation of contaminated air (Fraser et al., 2013; L. S. Haug et al., 2010; Langer, Dreyer, & Ebinghaus, 2010; Shoeib, Harner, & Vlahos, 2006), and through ingestion of dust and dirt particles containing PFCs. Dermal exposure can also occur through skin contact with products that have been treated with PFCs or its precursor compounds (Goosey E, 2011; Haug L.S., Huber S., Schlabach M., Becher G., & Thomsen C., 2011). This is of particular concern in children because exposure can occur if children touch PFC-treated products and put their hands in their mouth, or if an infant sucks on such products (Stahl, Mattern, & Brunn, 2011). However, despite their ubiquitous presence in the environment, the predominant route of exposure to PFCs occurs through the ingestion of contaminated food and/or drinking water (Stahl et al., 2011; Tittlemier et al., 2007; Trudel D. et al., 2008). One study to estimated that Canadians ingest on average

250ng of PFOA and PFOS daily. (Tittlemier et al., 2007). In a similar study in Germany, Fromme at al., (2007) estimated that study subjects were exposed to 1.8 ng/kg/BW and 3.9 ng/kg/BW of PFOS and PFOA respectively on a daily basis (Fromme H. et al., 2007).

Uptake and Distribution: Laboratory studies show that PFCs are well-absorbed and assimilated following oral and inhalation exposure, and to a lesser extent following dermal exposure. In studies of male rats, ninety-five percent of radioactively labeled PFOS dose (4.3 mg/kg BW) and 93% of labeled PFOA dose (11 mg/kg BW) were resorbed within twenty-four hours (Gibson & Johnson, 1979). Kennedy et al.,(1986) found that mean blood concentration of ammonium perfluorooctanoate (APFO) in male rats was 108 mg/L after 10 inhalations of 84 mg/m^3 of APFO (Kennedy, Hall, Brittelli, Barnes, & Chen, 1986). PFOS and PFOA are weakly lipophilic, water soluble, and bind preferentially to proteins (Stahl et al., 2011). They usually bind with albumin (Han, Snow, Kemper, & Jepson, 2003; Völkel et al., 2007), or β-lipoproteins and fatty acid binding proteins in the liver (L-FABP) (Lübker, Hansen, Bass, Butenhoff, & Seacat, 2002). As such, they are usually detected as accumulated in the liver, blood serum, and kidneys, although small concentrations can be detected in other tissues (Stahl et al., 2011).

Elimination: PFOA and PFOS are not metabolized in mammals and can only be eliminated through excretion once they have been absorbed into the body (Kudo & Kawashima, 2003). They are eliminated slowly in humans and can persist for several years. Harada et al.,(2005) determined renal clearance values of 0.012 mL/kg/day for men and 0.019 mL/kg/day for women for PFOS excreted in urine (Harada et al., 2005). In the same study, PFOA clearance was 0.033 mL/kg/day for men and 0.0027 mL/kg/day for women (Harada et al., 2005). Due to this low renal clearance of PFOA and PFOS, they have a long half-life when compared with other similar chemicals (Stahl et al., 2011). In studies carried out among occupationally exposed workers,

PFCs had a relatively long half-life with a mean time of 5.4 years for PFOS, 3.8 years for PFOA, and 8.5 years for PFHxS (Olsen et al., 2007). In a study conducted in Germany among community residents who had been exposed to PFC-contaminated drinking water, plasma PFOA concentrations were 4.5 to 8.3 times concentrations of residents in unaffected neighboring towns. On follow-up one year later, geometric mean PFOA concentrations had decreased by an average of 10% for men, 17% for women, and 20% for children (Hölzer et al., 2009).

Perfluorooctanoic acid (PFOA)

Chemical and Physical Properties: Perfluorooctanoic acid (PFOA) is a completely fluorinated 8-carbon organic synthetic acid that has a carboxylic acid end group and exists as both linear and branched isomers (Naile, Garrison, Avants, & Washington, 2016) (Figure 1). It is one of the most common PFCs and has been identified as an environmental pollutant (Danish Environmental Protection Agency, 2013). It has liquid repellant properties which makes it a suitable raw material for water-resistant consumer products such as paper plates and cups (Vierke, Staude, Biegel-Engler, Drost, & Schulte, 2012). PFOA forms aqueous micelles which attract positively charged surfaces (USEPA, 2016). Due to its strong bonds, it is stable in environmental media and resists breakdown by environmental degradation processes such as biodegradation, photolysis, and hydrolysis both in the natural environment and under laboratory conditions (National Center for Biotechnology Information (NCBI), 2018; USEPA, 2016b; Vierke et al., 2012; Winquist & Steenland, 2014). The breakdown process ends once PFOA is formed, whether synthetically or as the byproduct of production or breakdown of other compounds. As a result, PFOA persists throughout the environment, in the air, soil sediments and water systems (Koskela et al., 2016), and in blood and tissue samples of animals and humans (USEPA, 2016b; Vierke et al., 2012; Winquist & Steenland, 2014).

Use and Manufacturing: PFOA can be produced through an industrial process or is the byproduct of degradation of other synthetic organic products (Koskela et al., 2016; Vierke et al., 2012). It can be produced from the breakdown of an ammonium salt, ammonium perfluorooctanoate (APFO), which is used as an emulsifier during polymerization in fluoropolymer production (C. Lau, Anitole, Hodes, et al., 2007). APFO is not consumed during the polymerization process, and disassociates to create a PFOA anion which is then ionized in water to form the acid (USEPA, 2016b). Under certain environmental conditions, other PFCs can also degrade to create PFOA (Vierke et al., 2012). This is usually observed when a minimum of seven perfluorinated carbon atoms which are connected to various functional groups in a carbon chain undergo a breakdown reaction. Examples of such PFCs include fluorotelomer alcohols (FTOHs), polyfluoroalkyl phosphoric Acid (PAPs), and polyfluorinated iodides (PFIs) (Vierke et al., 2012).

Another common way is to manufacture PFOA is by telomerization, which is the reaction of tetrafluoroethylene and fluorine-bearing chemicals to produce fluorinated intermediates to PFOA and perfluorinated iodides (PFIs). The telomerization process results in the production of linear-chained PFOA molecules (Vierke et al., 2012). PFOA is also produced by Electro-Chemical Fluorination (ECF), which involves the passage of electric current through a solution of hydrogen fluoride and organic feedstock to produce carbon-hydrogen molecules that are both linear and branched isomers. The carbon-hydrogen bonds are then replaced with carbon-fluorine bonds to create PFOA (USEPA, 2016b). Other sources of PFOA include the atmospheric degradation or transformation of PFOA precursors such as fluorotelomer alcohols, olefins, and perfluoroalkyl sulfonamide substances (Wallington et al., 2006).

The use of PFOA in industrial products started in the 1940s (Association of State and Territorial Solid Waste Management Officials (Association of State and Territorial Solid Waste Mangement Officials (ASTSWMO), 2015). PFOA is used to produce fluoropolymers (USEPA, 2016b; Winquist & Steenland, 2014). It's heat-, water- and stain-resistant properties make it valuable as a surfactant in many industrial and consumer products. For example, it is applied to Teflon-based products because it helps prevent Teflon from boiling. It serves as an emulsifier for fluoropolymers which act as surface protectants in carpets, fabrics, cookware, outdoor apparel, clothing, paper plates, paper, cardboard packaging, electrical wire casings, ski wax, paints, photographic film additives, the textile finishing industry, cleaning agents, tile, stone, leather, and fire-fighting foams (Renner, 2001; USEPA, 2016b; Vierke et al., 2012). Therefore, products like Teflon, Gore-Tex, Stainmaster, and Scotchgard are likely to contain PFOA (Danish EPA, 2013). The presence of PFOA in the environment is the result of contamination from manufacturing and industrial plants (Association of State and Territorial Solid Waste Mangement Officials (ASTSWMO), 2015; Lindstrom et al., 2011), as well as its ubiquitous use in commercial and household products. PFOA is detected around the globe under various environmental conditions (Kannan et al., 2004; Sinclair, Mayack, Roblee, Yamashita, & Kannan, 2006).

Toxicokinetics: Once absorbed into the body, PFOA is distributed by binding with plasma proteins (Cui et al., 2009; C. Lau, Anitole, C., et al., 2007). Postmortem studies found PFOA in human tissue, including the lung, kidney, and bone (USEPA, 2016b). PFOA is not lipophilic and does not metabolize, and it is not necessarily genotoxic to the human body (Steenland et al., 2009). Laboratory studies conducted in rodents show PFOA is detectable in plasma within a half hour after nasal exposure (Cui et al., 2009; Gibson & Johnson, 1979; Hinderliter, DeLorme, &

Kennedy, 2006). When ingested, it can take up to 2 to 10 hours to be absorbed in rats (Hinderliter, Han, Kennedy, & Butenhoff, 2006; Karrman et al., 2007). Fasting causes PFOA absorption at higher rates (Karrman et al., 2007; Sibinski L.J., 1987). Differences in absorption rates are detectable by sex, where female rats absorb PFOA faster (1 hour) compared to male rats (10 hours) when ingested (S. C. Chang et al., 2008). Franko et al., (2012) found that 24% of a single dose of PFOA is absorbed by the human skin after 24 hours, with the rate of dermal absorption being dependent on skin ph (Franko, Meade, Frasch, Barbero, & Anderson, 2012). PFOA can also enter the placenta and traces are found in breast milk (USEPA, 2016b). Laboratory research in rats, showed that breast milk contained 10 times less PFOA than the maternal blood plasma concentrations (Hinderliter, Han, et al., 2006). However, the PFOA concentrations found in the milk equaled the amount of PFOA concentrations found in the blood plasma of the nursing rat (Hinderliter, Han, et al., 2006).

In the body, PFOA is transported to the blood, kidney, lungs, skin, pancreas, spleen, thymus, heart, testes, epididymal fat, fat pads, brain, muscle, bones, and bone marrow (S. C. Chang et al., 2008; Koskela et al., 2016). Higher concentrations are found in in the liver and plasma (Houde et al., 2011; Kudo & Kawashima, 2003) compared to other areas of the body. The plasma aids to absorb PFOA and its travel into the soft tissue (Kerstner-Wood, Coward, & Gorman, 2003). PFOA has hepatotoxic effects that negatively impact the behavior and kinetics of enzymatic reactions (USEPA, 2016b; Yan et al., 2015). Exposure to PFOA leads to the activation of the receptor protein, Peroxisome proliferator-activated receptor alpha (PPAR-alpha), in the liver (Yan et al., 2015). Proliferation of PPAR-alpha agitates nuclear receptors Peroxisome proliferator-activated receptor (PPAR), Constitutive androstane receptor (CAR), Farnesoid X receptor (FXR), and Pregnane X receptor (PXR) to produce negative effects on

human liver carcinoma cells (HepG2). The primary function of the nuclear receptors is to detect the presence of foreign toxic substances, and then increase the cellular response of proteins involved in the process of detoxification and clearance of such substances (Fiorucci, Zampella, & Distrutti, 2012; Kliewer, Goodwin, & Willson, 2002; Ueda et al., 2002).

In the body, PFOA is not metabolized and does not undergo further processes until it is cleared through urine and feces (Butenhoff, Chang, Ehresman, & York, 2009; Conder, Hoke, De Wolf, Russell, & Buck, 2008; Harada et al., 2005). This process is slow and can take between 2 to 4 years in humans, once exposure ceases (Harada et al., 2005; Olsen et al., 2007). Differences in the rate of renal clearance are detected between species and sex (Kudo & Kawashima, 2003). Rats clear PFOA through renal cavities at an average rate of 1.35 mL/hr/kg and bronchial tract at a rate of 0.12 mL/hr/kg (Conder et al., 2008). Renal elimination of PFOA from the system showed gender variances in adult rats (Worley & Fisher, 2015). In humans, hormonal differences among males and females affect the function of organic anion transporters that manage absorption and clearance of PFOA in the body (Worley & Fisher, 2015). In laboratory studies, female rats cleared PFOA through urine, while males cleared the PFOA in both urine and bile. When rats were given PFOA through IV, females cleared nearly the full dose within 24 hours, compared to the 20% cleared by males within the same time, which suggested that female rats excreted PFOA 44 times faster than males (USEPA, 2005).

Human Health Effects: The vast majority of the global population have detectable levels of PFOA in their system, usually at very low levels, an average of 5 parts per billion (Steenland, Fletcher, & Savitz, 2010). Approximately 98% of the U.S population have detectable traces of PFOA in their urine (Steenland et al., 2010). Available studies suggest that at high exposure concentrations, PFOA can produce negative health outcomes in humans (Naile et al., 2016; Post

et al., 2012). Yet there is no consensus on the health effects of continuous background exposure to these chemicals (Post et al., 2012). Various studies have examined the association between PFOA exposure and various health outcomes among factory workers, who have historically high exposures, and the general population. Numerous studies have documented a positive association between PFOA and high cholesterol in occupational settings (Costa, Sartori, & Consonni, 2009; Olsen, Burris, Burlew, & Mandel, 2000; Olsen & Zobel, 2007; Sakr et al., 2007; Steenland, Zhao, & Winquist, 2015) and in high exposure communities (Fitz-Simon et al., 2013; Frisbee et al., 2010; Steenland et al., 2009; Winquist & Steenland, 2014). The results remained significant even after controlling for cholesterol lowering medications (Steenland et al., 2015; Winquist & Steenland, 2014). In the occupational studies, the mean serum levels ranged between 0.4 - > 12 μg/mL, while in the general population studies, the mean serum levels ranged between 0.002–0.007 μg/ml (Eriksen et al., 2013; Fisher, Arbuckle, Wade, & Haines, 2013; Geiger et al., 2014; Starling et al., 2014).

PFOA is also associated with adverse fertility, pregnancy, and birth outcomes. It has been linked to tumors and neonatal death in rats (Steenland et al., 2010). PFOA is found in the umbilical cord blood, placenta, and amniotic fluid of pregnant individuals (USEPA, 2016b), and has been linked with pregnancy-induced hypertension and preeclampsia (Darrow et al., 2016; USEPA, 2016b). Additionally, infants are exposed to PFOA in the breast milk of exposed mothers (USEPA, 2016b; Völkel et al., 2007). Johnson et al (2014) conducted a meta-analysis of available studies and found that a 1-ng/mL increase in maternal or cord serum PFOA levels was associated with a 0.1 (95% CI: –0.1, –0.02) cm decrease in birth length, a 0.01 (95% CI: –0.03, 0.01) decrease in ponderal index, a 0.03 (95% CI: –0.1, 0.01) cm decrease in head circumference, and a mean birth weight reduction of –18.9 g (95% CI: –29.8, –7.9) (Starling et

al., 2014). Wu et al., (2012) surveyed a Chinese district near an electronic recycling facility to examine the relationship between PFOA and neonatal health. Participants included the district's pregnant residents and facility employees who had higher levels of PFOA than the control group. They found that higher concentrations of PFOA in pregnant mothers resulted in shorter gestational age, and lower weight, length, and Apgar scores at birth (Wu et al., 2012). Lam et al., (2015), also found that high concentration of PFOA during gestation is associated with reduced neonatal development and growth outcomes (Lam et al., 2014). On the other hand, in studies of a community with high exposures to PFOA, the researchers did not observe any associations between PFOA and either birth weight among term births or the risk of low birth weight among all (singleton) births (Darrow, Stein, & Steenland, 2013; Nolan, Nolan, Shofer, Rodway, & Emmett, 2009; Savitz, Stein, Bartell, et al., 2012; Savitz, Stein, Elston, et al., 2012). Also, while studies suggest an association between increase in PFOA levels and decreases in female fertility (Fei, McLaughlin, Lipworth, & Olsen, 2009; Velez, Arbuckle, & Fraser, 2015), comparable results have not been demonstrated in males (Joensen et al., 2009).

Studies also suggest that PFOA negatively impacts metabolism, homeostasis, and cellular differentiation (Naile et al., 2016). PFOA is toxic to the liver, endocrine and immune system (Steenland et al., 2010) and alters cyclins that regulate cell control (Buhrke et al., 2015). Studies indicate that increasing concentrations of PFOA were associated with significant increase in total bilirubin, which is an important indicator of liver function (Costa et al., 2009; Olsen & Zobel, 2007; Sakr et al., 2007). On the other hand, the C8 Health Project observed a U-shaped exposure-response pattern for serum bilirubin among the residents of a community with high PFOA exposure, which was similar to the inverse associations observed in occupational exposed cohorts (Gallo et al., 2012). Darrow et al., (2015) also found that PFOA was associated with

hepatocellular damage and increase in serum levels of alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and total bilirubin levels. However, other studies have suggested that the association between PFOA and AST, ALT, and GGT might be moderated by the presence of covariates such as BMI, use of lipid lowering medications, and triglycerides in the models (Costa et al., 2009; Olsen et al., 2000; Olsen, Church, et al., 2003; Olsen & Zobel, 2007; Sakr et al., 2007).

Buhrke et al., (2015) found that PFOA negatively affects signaling pathways for various receptor proteins including PPAR-alpha, estrogen receptor (ER-alpha), peroxisome proliferator-activated receptor gamma (PPARG), and hepatocyte nuclear factor 4 alpha (HNF4a) (Buhrke et al., 2015). Steenland, et al., (2013) found significant positive associations in the relationship between PFOA and ulcerative colitis in exposed individuals (Steenland, Zhao, Winquist, & Parks, 2013). Tubular resorption of PFOA in the kidney allows PFOA to travel and exit the body. As a result, exposure to high PFOA concentrations can negatively affect kidney function (USEPA, 2016b). Numerous studies have demonstrated that increasing concentrations of PFOA are associated with increased concentration of uric acid in the urine of exposed individuals (Shankar A. et al., 2011; Steenland et al., 2010). Other studies among workers exposed to high PFOA concentrations shows that increasing PFOA serum concentrations were associated with reduced kidney function as measured by estimated glomerular filtration (eGFR) rates (Costa et al., 2009; USEPA, 2016b). Some studies demonstrate a relationship between PFOA and some types of cancer such as prostate, kidney, and testicular cancer (Barry, Winquist, & Steenland, 2013; V. M. Vieira et al., 2013). Steenland et al., (2012) found that exposure to high concentrations of PFOA was associated with ovarian cancer (Steenland & Woskie, 2012). Ma et al., (2015) found that PFOA stimulates cell migration, and invasion in endometrial cancer by promoting the down-regulation

of the tumor suppressor gene, E-cadherin (Ma et al., 2016). On the other hand, studies of occupational cohorts did not find an increased risk of kidney or testicular cancer (Raleigh et al., 2014; Steenland & Woskie, 2012). Additionally, studies conducted among populations exposed to background PFOA concentration levels did not find any significant associations between increasing concentrations and colorectal, breast, prostate, bladder, or liver cancer (Bonefeld-Jørgensen, Long, Fredslund, Bossi, & Olsen, 2014; Hardell et al., 2014; Innes, Wimsatt, Frisbee, & Ducatman, 2014).

Perfluorooctane sulfonic acid (PFOS)

Chemical and Physical Properties: Perfluorooctane sulfonic acid (PFOS) is an 8-carbon organic compound with a sulfonate end chain group (Figure 2). It is a strong acid that is generally present in solution as a Perfluorooctane sulfonic acid anion with a mixture of linear (70%) and branched chain isomers (30%) (Beesoon & Martin, 2015; De Silva & Mabury, 2004). It is a very stable compound that has a low vapor pressure and is solid at room temperature (USEPA, 2016a). PFOS resists breakdown by natural degradation processes and can be transported for long distances through advection, dispersion, and sorption to particulate matter (USEPA, 2016a). It can be detected in ambient air and in water bodies all over the world, even in remote locations like the Arctic (Ahrens, Yeung, et al., 2011; Lindstrom et al., 2011).

Use and Manufacturing: PFOS is produced commercially from perfluorooctanesulfonyl fluoride (POSF), an intermediate used to synthesize other fluorochemicals, and by the environmental degradation of other POSF-derived fluorochemicals. Due to its water- and lipid-resistant properties, PFOS was used as a waterproofing or stain-resistant agent in carpets, leathers, textiles, upholstering, and paper packaging (Renner, 2001; USEPA, 2016a). It is also

used in the production of firefighting foam, and aviation fluid due to its heat resistant properties (USEPA, 2016a).

With the cessation of PFOS production in the United States, the concentration of PFOS in humans and wildlife have decreased, even though significant concentrations can be measured in animal tissue and environmental samples worldwide (USEPA, 2016a). Efforts are ongoing to develop replacement products for PFOS and other PFCs that do have similar range of toxicity, and bioaccumulation issues, but suitable replacement products have not been developed (USEPA, 2016a). As a result, some PFOS-related chemicals continue to be used until alternatives can be found, such as in aviation fluid, photo microlithography, and film processing (USEPA, 2016a). Additionally, existing stocks and products already in the United States before rules stopping PFOS manufacture took effect in 2002, can still be used without any restrictions (USEPA, 2009, 2016a).

Toxicokinetics: PFOS is absorbed from the gastrointestinal tract and distributed to the tissues and organs (Cui et al., 2009; Curran et al., 2008), with high concentrations found in the liver, kidneys, and lungs (Perez et al., 2013). It binds with serum proteins such as albumin (Weiss et al., 2009), immunoglobulins and transferrin (Kerstner-Wood et al., 2003) and displaces other chemicals that normally occupy the binding sites (Beesoon & Martin, 2015). PFOS also binds with receptors (e.g. peroxisome proliferator- activated receptor-alpha [PPARα]), transport proteins (e.g., transthyretin [TTR]), fatty acid binding proteins, and enzymes (Lübker et al., 2002; Weiss et al., 2009; Wolf et al., 2010). This causes a change in the conformation of the serum proteins and affect their affinity for endogenous compounds they normally transport (Beesoon & Martin, 2015; Kerstner-Wood et al., 2003).

A portion of PFOS absorbed in the body is excreted in bile (S. C. Chang et al., 2008; Harada et al., 2005). Thus, the concentration of PFOS in fecal matter include both unabsorbed material and that discharged with bile (S. C. Chang et al., 2008; Harada et al., 2005). Studies suggest that PFOS is transferred to the fetus during pregnancy (S. C. Chang et al., 2008; Lübker et al., 2002), as well as through breastmilk during lactation (Bjerregaard-Olesen et al., 2017; Hanssen et al., 2010). The arithmetic mean half-life in humans for occupationally exposed workers was 5.4 years (95% CI=3.9, 6.9) (Olsen et al., 2007).

Human Health Effects: Laboratory studies of rats shows that PFOS exposure leads to increases in liver weight, liver hypertrophy, and a decrease in serum cholesterol and triglyceride levels (Elcombe et al., 2012; Seacat et al., 2003). Exposure to PFOS also led to decreased body weight and lipid metabolism defects (F. Wang, Liu, Jin, Wang, & Ma, 2015). Additionally, increasing PFOS exposure levels were associated with decrease in glomerular filtration rates, as well as reduced serum thyroid hormone levels (S. C. Chang et al., 2008). PFOS exposure also appears to have negative reproductive effects in rats such as decreased sperm count and reduced birth weight and size (C. Lau, Anitole, C., et al., 2007).

In humans, increases in PFOS serum concentrations are associated with increases in total cholesterol level (Olsen et al., 2000; Olsen & Zobel, 2007), as well as hypercholesterolemia (defined as cholesterol > 240 mg/dL) (Fisher et al., 2013; Steenland et al., 2009). PFOS also has a significant positive association with increased serum ALT values (Gallo et al., 2012; Lin et al., 2009). However, Gallo et al., (2012) did not find significant associations between PFOS and increased serum cholesterol. Shankar et al., (2011) found a significantly positive association between increasing concentrations of PFOS and chronic kidney disease (as defined as an eGFR of < 60 mL/min/1.73 m^2) (Shankar A. et al., 2011). Watkins et al., (2013) found that for every

unit increase in PFOS concentration, eGFR decreased by 1.10 mL/min/1.73 m2 (95% CI: −1.66 to −0.53) (Watkins et al., 2013). Other studies have also found a significant positive association between PFOS and increase in uric acid concentrations (Steenland et al., 2010).

PFOS is also associated with adverse pregnancy and birth outcomes among exposed individuals. Numerous studies found that increases in maternal serum/cord PFOS concentrations were associated with birth weight deficits (Darrow et al., 2013; Savitz, Stein, Elston, et al., 2012; USEPA, 2016a). Although a few of these studies showed some suggestion of dose-response relationships across different fetal growth measures (Fei et al., 2009; Maisonet et al., 2012), study limitations, including the potential for exposure misclassification, likely precluded the ability to adequately examine the exposure-response pattern. Other studies did not find significant associations between exposure to PFOS and negative birth outcomes (Fei et al., 2009; Hamm, Cherry, Chan, Martin, & Burstyn, 2010).

Studies have shown an association between increasing PFOS serum concentrations and gestational diabetes (X. Wang et al., 2017), pre-eclampsia (Stein et al., 2016) and pregnancy-induced hypertension (Darrow et al., 2013). PFOS exposure may also be associated with measures of fertility such as morphologically abnormal sperm and poor semen quality (Joensen et al., 2009), increased odds of infertility (Jorgensen et al., 2014). However, other studies did not find significant relationships between PFOS exposure and semen quality (Joensen et al., 2009; Vested et al., 2013).

Some studies have evaluated that association between PFOS and immune function. Studies in children found that the antibody response (as measured by antibody titer) in children (up to 7 years) after vaccination with one or more vaccines was decreased in relation to increasing

prenatal serum PFOS levels (Grandjean et al., 2012; Granum et al., 2013). A study using NHANES data also found decreased rubella and mumps antibody concentrations in relation to serum PFOS concentration among 12–19-year-old children, especially among seropositive children (Stein et al., 2016). In adults, no associations were observed between PFOS exposure and antibody response to influenza vaccine (Looker et al., 2014).

A few studies have examined the association between PFOS and cancer risk. Alexander et al., (2003) found an increased risk of bladder cancer mortality with increasing PFOS exposure levels in a cohort of occupational exposed workers (Alexander, Olsen, Burris, Mandel, & Mandel, 2003). On the other hand, a subsequent study to examine cancer incidence did not find any significant associations with PFOS exposure (Alexander & Olsen, 2007). Eriksen et al., (2009) also did not find any significant associations between elevated bladder cancer risk and increasing PFOS concentrations in a Danish cohort (Eriksen et al., 2009).

Perfluorohexane sulfonic acid (PFHxS)

Chemical and Physical Properties: Perfluorohexane sulfonic acid (PFHxS) is 6 carbons in length with a sulfonate end chain group (Figure 3) (European Chemical Agency, 2017). Samples of PFHxS are found, both in the environment and in organisms, as an aqueous mixture of perfluorohexanesulfonic acid (PFHxS), and its conjugate base perfluorohexanesulfonate (PFHxS-) (European Chemical Agency, 2017). This gives PFHxS both hydrophobic and hydrophilic properties and it forms multiple layers in an octanol-water mixture (Conder et al., 2008; European Chemical Agency, 2017). Just like other PFCs, PFHxS resists chemical, thermal and biological degradation due to their strong carbon-fluorine bonds (Baran, 2001; Braunig et al., 2017; Taniyasu, Yamashita, Yamazaki, Petrick, & Kannan, 2013). For instance, PFHxS resists

degradation by photolysis at high altitudes (Taniyasu et al., 2013). It is frequently found in soil and water near fire-fighting training, manufacturing plants and waste disposal sites areas following the historical use of PFHxS-containing foams, showing that it is persistent and does not undergo any abiotic or biotic degradation (Braunig et al., 2017; Filipovic, Woldegiorgis, Norstrom, et al., 2015)**.** PFHxS, along with PFOS and PFOA is the most frequently detected PFC in the general population in several countries, with a detection rate of greater than 98% (Bjerregaard-Olesen et al., 2017; Calafat, Wong, Kuklenyik, Reidy, & Needham, 2007). It is also present in umbilical cord blood samples and breast milk (Gutzkow et al., 2012; Karrman et al., 2007). PFHxS, can undergo long-range environmental transport (Llorca et al., 2012; Lohmann, Breivik, Dachs, & Muir, 2007)**,** and is transported over long geographical distances to remote areas by ocean currents and through the air (Llorca et al., 2012; Lohmann et al., 2007; Routti et al., 2017). As a result, PFHxS can be detected in the environmental and serum samples from remote areas (Llorca et al., 2012; Lohmann et al., 2007; Routti et al., 2017).

Toxicokinetics: PFHxS is absorbed after oral and inhalation exposure, and to a lesser extent after dermal exposure (Stahl et al., 2011). Studies suggest that more than 50% of PFHxS is absorbed after oral exposure (Stahl et al., 2011), and it biomagnifies as we move up the food chain (Haukas, Berger, Hop, Gulliksen, & Gabrielsen, 2007; Houde et al., 2006; Riget, Bossi, Sonne, Vorkamp, & Dietz, 2013). PFHxS tends to accumulate in the liver, blood, lung, and kidney (European Chemical Agency, 2017; Olsen, Hansen, Stevenson, Burris, & Mandel, 2003; Perez et al., 2013). Pérez et al., (2013) conducted a study on the presence of PFCs in human organ/tissues and found that PFHxS was most frequently detected in the lung (32%), but the highest median concentrations were found in the kidney (18 μg/kg wwt.,) followed by the lung (5.7 μg/kg wwt.).

Compared to other PFCs, PFHxS has the highest half-life ever reported. Olsen et al., (2007) estimated the elimination half-life of PFHxS, PFOS and PFOA in the serum samples of 26 retired among a cohort of occupationally exposed fluorochemical production workers from a 3M plant in Decatur, USA over a 5-year period. They found that mean/geometric mean elimination half-lives for PFHxS, PFOS and PFOA were 8.5 years (95% CI 6.4 - 10.6)/7.3 years (95% CI 5.8 - 9.2)/ (range: 2.2 y – 27 years), 5.4 years (95% CI 3.9 - 6.9)/4.8 years (95% CI 4.0 - 5.8)/ (range: 2.4 – 21.7 years), and 3.8 years (95% CI 3.1 - 4.4)/3.5 years (95% CI 3.0 - 4.1)/ (range: 1.5 – 9.1 years), respectively.

In another study conducted among Chinese adults, the researchers examined the rate of elimination of a number of perfluorinated compounds (PFCs), including PFHxS. They found that PFOS was excreted more efficiently than PFHxS, and major branched isomers were more efficiently excreted than the corresponding linear isomers of PFOS and PFOA. Furthermore, they found that that urine is an important pathway of excretion of perfluoroalkyl substances even though other routes of excretion likely contribute to the overall elimination. The estimated arithmetic mean (range) elimination half-lives for the female / male groups for PFHxS, PFOS and PFOA were 7.7 (2.3 - 13) / 3.5 (1.6 – 18.2) years, 6.2 (3.2 – 10) / 2.7 (1.6 – 12.1) years and 2.1 (0.19 – 5.2) / 2.6 (0.06 - 14) years, respectively (Zhang, Beesoon, Zhu, & Martin, 2013).

Human Health Effects: Numerous studies suggest an association between PFHxS and adverse health outcomes such as elevated serum cholesterol, and other lipids (Fisher et al., 2013; Steenland et al., 2009), and endocrine (Jain, 2013; Long, Ghisari, & Bonefeld-Jorgensen, 2013; Weiss et al., 2009; Wen, Lin, Su, Chen, & Lin, 2013) and immune system disrupting effects (Grandjean et al., 2012; Granum et al., 2013).

Studies suggest that PFHxS exposure has immunotoxic effects in children. Granum et al.,(2013) studied the association between PFHxS maternal serum levels and decreased immune response in children. They found that increasing quartiles of PFHxS were associated with decreased serum levels of anti-rubella antibodies and increased number of episodes of gastroenteritis at age 3 (Granum et al., 2013). Grandjean et al., (2012) observed decreased immune response after tetanus vaccination at 7 years of age (Grandjean et al., 2012). Also, higher exposure concentrations of PFHxS was associated with an increased incidence of asthma among exposed children (Dong et al., 2013; Zhu et al., 2016). Dong et al., (2013) found an increased risk of being diagnosed with asthma for increasing quartile concentrations of PFHxS (OR: Q1 vs. Q4= 3.83, 95% CI 2.11–6.93) among children aged 10–15 years, after controlling for sex, age, BMI, parental education, environmental tobacco smoke exposure, and month of survey. On the other hand, Humblet et al., (2014) did not find an increased risk of self-reported asthma for increasing serum concentrations of PFOA, PFHxS, or PFNA among a nationally representative sample of U.S. children aged 12–19 years in the NHANES (Humblet, Diaz-Ramirez, Balmes, Pinney, & Hiatt, 2014).

Laboratory studies in rodents show that PFHxS exposure has adverse effects on the liver and nuclear receptors that regulate metabolism, and is associated with increasing serum levels of cholesterol, and other lipids (Bijland et al., 2011; Butenhoff et al., 2009; Das et al., 2017). Butenhoff et al., (2009) found that rats exposed to 10 mg/kg/d of PFHxS developed hepatocellular hypertrophy (56% increase in liver weight) after 42 days of exposure, as well as thyroid organ toxicity (Butenhoff et al., 2009). Other studies suggested that exposure to PFHxS has adverse effects on thyroid hormones in Arctic birds (Nost et al., 2012) and polar bears (Bourgeon et al., 2017). Oral exposure to PFHxS affects rodent behavior and levels of brain

neuroproteins after at a critical period in brain development (Lee & Viberg, 2013). Other studies of rodents exposed to PFHxS did not find any negative treatment-related effects in the respiratory tract, heart, or gastrointestinal tract (Butenhoff et al., 2009; Hoberman & York, 2003).

Studies have also found significant associations between PFCs and biomarkers of renal and liver function. Lin et al., (2010) found that increasing serum concentrations of PFHxS was associated with increasing serum total bilirubin levels. Other studies found significant associations between serum lipid concentrations and PFHxS concentrations (Fisher et al., 2013; J.W. Nelson, E.E. Hatch, & T.F. Webster, 2010). Watkins et al., (2013), and Emmett et al., (2006a) examined the association between biomarkers of renal function and elevated levels of PFOA in the water supply of a community living near a DuPont facility in West Virginia (Emmett et al., 2006; Watkins et al., 2013). Watkins et al., (2013) found that increasing PFOA, PFOS, PFNA, and PFHxS serum levels were associated with decreasing estimated glomerular filtration rates. They suggested that the association between serum perfluoroalkyl levels and estimated glomerular filtration rates may be a result of reverse causation because PFOA levels were not significantly associated with eGFR 3 or 10 years before commencement of the study (Watkins et al., 2013). On the other hand, Emmett et al., (2006a) did not find significant associations between blood urea nitrogen (BUN) or serum creatinine levels and serum PFOA levels.

Studies have also found conflicting results on the association between background exposure levels of PFCs and reproductive hormones in men. Raymer et al., (2012) found significant associations between PFOA levels and free testosterone and LH levels, but not with other reproductive hormones. They did not find any significant associations between serum PFOS levels and the reproductive hormones (Raymer et al., 2012). Joensen et al., (2013) found that

increasing concentrations of PFOS was associated with decreasing concentrations of testosterone, free testosterone, and free androgen index levels (Joensen et al., 2013). On the other hand, other studies did not find significant associations between PFOA, PFOS, or PFHxS testosterone levels (Joensen et al., 2009; Specht et al., 2012).

Perfluorononanoic acid (PFNA)

Chemical and Physical Properties: Perfluorononanoic acid (PFNA) is nine-carbons in length, with a carboxylate end chain group (Figure 4) (De Silva & Mabury, 2004). Samples of PFNA can be found as mixture of multiple linear, iso-branched, and multiple branched isomers (De Silva & Mabury, 2004). The branched isomers are more common near industrial sites and the linear isomer more common in remote areas (De Silva & Mabury, 2004). PFNA can be formed from the biodegradation of Fluorotelomer alcohols (FTOH) in the environment (Henderson & Smith, 2007). It can also be produced directly under laboratory conditions during the oxidation of linear fluorotelomer olefin mixtures or the carboxylation of PFOA (Organization for Economic Cooperation and Development (OECD), 2002).

Use and Manufacturing: Production of PFNA in the United States was stopped in 2000 due to concerns about their persistence in the environment. Although the levels in the PFNA in the environment and in humans are lower than those of PFOS or PFOA, the concentration of PFNA in the general population has increased over the years (Calafat, Kuklenyik, et al., 2007). It is very stable due to the strength of its carbon-fluorine bonds, and resists breakdown by oxidation in the environment (Prevedouros, Cousins, Buck, & Korzeniowski, 2006). PFNA is used as a surfactant in many household and industrial products.

Toxicokinetics: The toxicity of PFNA is not as well-studied as PFOA, PFOS, or PFHxS. In available laboratory studies, exposure of rodents to PFNA resulted in adverse reproductive and developmental effects such as increased neonatal death, delayed eye opening and delayed puberty (Das et al., 2015); increased oxidative stress and apoptotic signaling in spleen cells (Fang, Gao, Xue, Zhang, & Wang, 2012); and increased apoptosis in the testes (Feng, Shi, Fang, Xu, & Dai, 2009).

Current PFC Health Advisories

Currently in the United States, there are no federal regulations or nationally recommended ambient water quality standards for PFOA and PFOS (USEPA, 2016a, 2016b). However, both national and international agencies have identified PFCs as potentially harmful substances due to their persistent, bioaccumulative, and toxic characteristics. The US EPA, and ATSDR and other national and international agencies have taken steps to set exposure limits, and maximum levels in drinking water and food items that would require reporting to the appropriate agency (USEPA, 2016a, 2016b). In 2009, the U.S. Environmental Protection Agency (USEPA) produced a provisional health advisory (HA) 0.4 ng/mL for PFOA, and 0.2 ng/mL for PFOS in drinking water (USEPA, 2009). These recommended levels reflect the amount of PFOA and PFOS that could cause adverse health effects in the short term (weeks to months) (USEPA, 2016a, 2016b).

The EPA is in the process of developing lifetime exposure limits for exposure to PFOS and PFOA (USEPA, 2016a, 2016b). Also, the EPA has established drinking water monitoring requirements of 0.02 ng/mL, 0.04 ng/mL, 0.03 ng/mL, and 0.02 ng/mL for PFOA, PFOS, PFHxS, and PFNA respectively . The ATSDR has also derived an intermediate-duration oral maximum residue level (MRL) of $2x10^{-5}$ mg/kg/day (Butenhoff et al., 2009) and $3x10^{-5}$

mg/kg/day (Seacat et al., 2003) for oral exposure to PFOA and PFOS respectively. Several international agencies have established guideline values for PFOA and PFOS (Appendix 1).

Background concentrations of PFCs in the General Population in various countries

Numerous studies have shown that significant geographic differences in mean serum PFC concentrations exist worldwide. Kannan et al., (2004) studied PFC concentrations in nine different countries world-wide, namely the United States, Colombia, Brazil, Italy, Belgium, Poland, India, Malaysia, and Korea. They found that mean PFOS concentrations were highest in serum samples from the United States and Poland (greater than 30 ng/mL), followed by mean concentrations from Japan, Korea, Malaysia, Belgium, and Brazil (between 10 and 25 ng/mL), Italy and Colombia (between 4 and 10 ng/mL), with India having the lowest concentration (1 ng/mL). They also found that median concentrations of PFOA in Polish and Korean serum samples were 21 and 28ng/mL respectively, approximately two times greater than median concentrations for samples from the United States. Finally, median concentrations of PFHxS in samples from the United States, Korea, and Japan were in the range of 1.5-3 ng/mL higher than concentrations found in other countries (Kannan et al., 2004).

Fromme et al., (2007) also found that concentrations of PFOS, PFOA, AND PFHxS measured in blood samples from Germany were lower than that measured in a related study in the USA and Canada (Fromme et al., 2007). Another study also concluded that serum PFOS, PFOA and PFHxS concentrations of the US population are higher than that of residents of Europe, Asia, or Australia (Fromme et al., 2009). A pilot study conducted in South Africa found concentrations of 1.6 ng/mL PFOS, 1.3 ng/mL PFOA, and 0.5 ng/mL PFHxS in maternal blood, with the highest PFC concentrations observed among subjects who lived in urban and semi-urban areas, which were associated with the highest quality of living (Hanssen et al., 2010). On the other hand,

Kärrman et al., (2006) found no significant differences in mean PFC concentrations among urban and rural residents in Australia (Kärrman et al., 2006).

Kärrman et al., (2006) examined concentrations of PFOA, PFOS, and PFHxS in blood samples (N=66) of participants who were resident in ten counties in the southern half and one county in the northern half of Sweden. The median (range) of PFOA, PFOS, and PFHxS were 2.5 ng/mL (1.9 - 3.3), 17.1 ng/mL (13 - 23), 1.5 ng/mL (0.4 - 28.4), respectively. The sample was not considered representative of the adult Swedish population because it was skewed in both age and gender distribution and had poor geographical distribution. Ericson et al., (2007) examined the concentrations of 13 PFCs in whole-blood samples from residents in Catalonia, Spain (n=48). They determined any significant differences in serum concentrations based on gender and age. The reported median concentration (range) of PFOA, PFOS, and PFHxS 1.65 ng/mL (0.79 - 3.13), 7.60 ng/mL (0.76 - 16.17) and 2.92 ng/mL (0.65 - 19.96) respectively. PFHxS serum concentrations were significantly higher among the younger age group (25 ± 5 years) when compared to the older age group (55 ± 5 years). Additionally, PFHxS and PFOA serum concentrations were significantly higher ($p < 0.05$) among men than women (Ericson et al., 2007).

Hölzer et al., (2008) examined the concentrations of 6 PFCs in PFC-contaminated drinking water, and blood samples of residents of Arnsberg, Germany, and compared the concentrations to two reference areas, Siegen and Brilon. The exposed community, and reference communities were similar in terms of age, height, body weight and sex distribution. The geometric mean blood concentration of PFHxS, PFOS, and PFOA in blood plasma (ng/mL) was higher among males in Arnsberg was than males in Brilon (2.5 vs. 2.2; 10.5 vs. 9.7; and 25.3 vs. 5.8,

respectively); children in Arnsberg than children in Siegen (1.2 vs. 0.8; 4.9 vs. 4.6, and 22.1 vs. 4.8., respectively), and females in Arnsberg than females in Siegen (1.1 vs. 0.6; 5.8 vs. 5.2; and 23.4 vs. 2.8., respectively). The differences in serum concentrations between Arnsberg and the respective reference communities was significant for all groups for PFHxS and PFOA and was significant between females for PFOS ($p<0.05$). In addition, concentrations of PFHxS, PFOS, and PFOA significantly increased for increasing age of participants (Hölzer et al., 2008). Holzer et al., (2008) also found that blood concentrations of PFHxS was significantly associated with consumption of drinking water ($p = 0.066$), male sex, age, and study area (all $p<0.01$); PFOS was significantly associated with age, male sex, region, and consumption of locally caught fish (all $p<0.01$) and inversely with BMI ($p=0.02$) (Hölzer et al., 2009).

Several studies have used the U.S. NHANES to examine the distribution of PFC serum concentrations among a representative sample of U.S. residents, and their association with various health outcomes. Lin et al., (2009) examined the association between PFCs and metabolic syndrome among 474 adolescents (12 – 20 years) and 969 adults (> 20 years) using the 1999-2000 and 2003-2004 NHANES. The arithmetic mean ± SE (ng/mL) among adolescents and adults were respectively 0.95 ± 0.10 and 0.60 ± 0.04 for PFHxS; 3.11 ± 0.05 and 1.51 ± 0.05 for PFOS; and 3.19 ± 0.04 and 1.48 ± 0.04 for PFOA (Lin et al., 2009). Hoffman et al., (2010) found that median (ng/mL) PFHxS, PFOS and PFOA serum concentrations in the 1999-2000 and 2003-2004 NHANES were respectively 2.2, 22.6 and 4.4 respectively among children 12-15 years of age (n = 571) (Hoffman, Webster, Weisskopf, Weinberg, & Vieira, 2010). Nelson et al., (2010) also found that median (ng/mL) concentrations of PFHxS, PFOS and PFOA were 1.8, 21.0, and 3.9, respectively among NHANES participants 12 years and older in the 2003-2004 survey year (J.W. Nelson et al., 2010).

Fromme et al., (2010) monitored the concentration of several perfluorinated compounds in a cohort of pregnant women over a nearly 2-year period (December 2007 -October 2009) in Munich, Germany. They measured concentrations in samples of maternal blood during pregnancy and six months after delivery (n = 47), in umbilical cord blood and in the blood of infants six and nineteen months after birth and in monthly breast milk samples. They found that the median maternal blood concentrations (ng/mL) during pregnancy, at delivery and six months after delivery for PFHxS, PFOS and PFOA were 0.5/0.5/0.3, 3.2/3.2/2.9, and 2.4/1.9/1.5, respectively. The median concentrations (ng/mL) in cord blood serum, in the blood of infants six and nineteen months of age for PFHxS, PFOS and PFOA were 0.2/0.6/0.6 ng/mL, 1.0/3.0/1.9 ng/mL, and 1.4/6.9/4.6 ng/mL, respectively. PFHxS was only detected in 6 out of 201 (Range <0.02-0.3 ng/mL); PFOS was detected in 145 out of 201 [median (range) 0.04 (<0.3 - 0.11) ng/mL]; and PFOA was detected in 4 out of 201 (Range <0.15 - 0.25 ng/mL) breast milk samples (Fromme et al., 2009).

In a study of a cohort of pregnant Canadian women, the arithmetic mean concentrations (ng/mL) of PFHxS, PFOS and PFOA were 2.1, 9.0 and 2.1 respectively (Hamm et al., 2010).

Jönsson et al., (2010) randomly selected a sample of 50 Swedish military conscripts (~18 years) and found that their median (range) (ng/mL) serum concentrations of PFHxS, PFOS and PFOA were 0.78 (0.38 - 2.5), 6.9 (3.7 - 19), and 1.9 (1.2 - 3.3), respectively (Jönsson et al., 2010).

Hölzer et al., (2011) measured the levels of several PFCS in fish, drinking water and the blood plasma of anglers at Lake Möhne, Germany. PFHxS concentration levels were below the level of detection in the fish, while PFOA was detected in about 20% in of the fish and PFOS was detected in every fish that was caught. The concentration levels of PFHxS, PFOS and PFOA in anglers ranged from 0.4 – 17 ng/mL (LOD = 0.1 ng/mL), 1.1 – 650 ng/mL and 2.1 – 170 ng/mL,

respectively. PFHxS were not detected in any tap water. The range of PFOS and PFOA concentration in the tap water was 0.011- 0.059 ng/mL and 0.020 - 0.047 ng/mL respectively. Hölzer et al., (2011) found that among the anglers, serum concentrations of PFHxS and PFOS had a significant positive association with age and the consumption of fish ($p < 0.01$); and concentrations of PFOA were significantly positively associated with age and concentration of PFOA in tap water ($p < 0.01$) (Hölzer et al., 2009).

Kim et al., (2011) examined the concentrations of PFCs in the blood, fetal cord serum, and breast milk of pregnant Korean women. The median concentrations (IQR) (ng/mL) of PFHxS, PFOS and PFOA in blood serum, fetal cord serum and breast milk were 0.55 (0.46 -0.85), 0.34 (0.27-0.51) and <0.05, respectively. The concentrations (ng/mL) in blood serum, fetal cord serum and breast milk were 2.93 (2.08-4.36), 1.26 (0.81-1.82), 0.06 (0.00-0.10) for PFOS and 1.46 (1.15-1.91), 1.15 (0.95-1.86) and 0.05 (0.03-0.07), for PFOA respectively (Kim et al., 2011). Stein & Stavitz (2011) examined the cross-sectional association between serum PFCS concentrations and parent or self-report of doctor-diagnosed Attention Deficit Hyperactivity Disorder (ADHD) in children (5-18 years; n = 10456) living in the Mid-Ohio Valley in the U.S., a community exposed to PFOA through contaminated drinking water. The arithmetic mean ± SD (ng/mL) serum concentrations of PFHxS, PFOS and PFOA were 9.3 ± 13.7, 22.9 ± 12.5 and 66.3 ± 106.1, respectively (Stein & Savitz, 2011).

Ji et al., (2012) examined the association between PFC blood serum concentrations and total thyroxine (T4) and thyroid stimulating hormone (TSH) levels in the general population in South Korea (n =633, > 12). The median concentrations (IQR) (ng/mL) of PFHxS, PFOS and PFOA were 1.51 (0.92 – 2.34), 7.0 (5.58 – 12.10) and 2.74 (2.04 – 3.64) respectively (Ji et al., 2012).

Toft et al., (2012) examined any associations between PFC exposure and male semen quality among 588 men from Greenland (n =196), Poland (n = 189) and Ukraine (n = 203). The highest levels of exposure (median, 33rd – 66th percentile (ng/mL)) were among the Greenlandic men than among men in Poland and Ukraine for PFHxS [2.2 (1.9-2.7), 1.2 (1.0 - 1.3), and 0.3 (0.3 - 0.4) respectively]; PFOS [44.7 (38.8 - 56.1), 18.5 (15.4 - 21.2), and 7.6 (6.0 - 8.5) respectively]; PFOA [4.5 (4.2 - 5.2), 4.8 (4.2 - 5.6), and 1.3(1.0 - 1.6) respectively]; and PFNA [(1.7 (1.3 - 2.4), 1.2 (1.0 - 1.3), and 1.0 (0.8 - 1.2) respectively] (Toft et al., 2012).

Another study in Sweden examined the association between blood serum concentrations of several PFCs and diet and personal characteristics of adults (18 - 80 years, n=270) living in 21 counties in Sweden. They found that median (5th -95th percentile, ng/mL) serum concentration of PFHxS, PFOS, PFOA, and PFNA among the participants was 1.95 (0.73 - 10.29), 11.20 (3.89 - 25.41), 2.25 (0.76 - 5.01), 0.80 (0.35 – 1.66), respectively (Bjermo et al., 2013). They found that higher education was significantly associated with higher concentrations of PFHxS ($p = 0.02$) and PFOS ($p = 0.004$), but not of PFOA ($p= 0.009$). They also found that serum concentrations of the PFCs were higher among men than women after adjustments for age and education. However, after including total full breastfeeding time as a covariate in the regression analysis, no sex difference remained except for PFOS. They found significant regional differences in serum concentrations of all PFCs, except for PFNA, after adjusting for age, sex, and education level. Stockholm/Uppsala areas had twofold higher median concentrations of PFHxS as compared to Umeå, and Lund had 60 - 70% higher concentrations of median PFOS and PFOA as compared to Umeå. They indicated that the higher median concentrations of PFHxS in the Stockholm/Uppsala areas may have been due to the contamination of the communities' water sources with PFHxS (Bjermo et al., 2013).

Brantsæter et al., (2013) examined factors associated with serum concentrations of PFOA, PFOS, PFHxS, and PFNA in pregnant women (n = 485) in Norway. The median (IQR) plasma level (in ng/ml) was 12.8 (10.1–16.6 ng/ml) for PFOS; 2.11 (1.54–2.93) for PFOA; 0.60 (0.43–0.86) for PFHxS; and 0.39 (0.28–0.51) for PFNA (Brantsaeter et al., 2013). They also found parous women had 46%, 70%, 19%, and 62% lower concentrations of PFOS, PFOA, PFHxS, and PFNA, respectively when compared to nulliparous women. Additionally, increasing duration of breastfeeding, as well as increasing time since last pregnancy, was associated with decreasing levels of all PFCs (Brantsaeter et al., 2013). Zhou et al., (2014) performed a comprehensive exposure assessment of several PFCS in fishery employees from Tangxun Lake, located in Hubei Province, China which is the site of several small-scale fluorochemical manufacturers and users in China. They collected blood and urine samples from fishery employees (n =39; male = 38), their family members (n=7, male=1) and a background-exposed reference group (n=9, male=5). They found that levels of all PFCs in the fishery employees and their family members was significantly higher (2 to 3 orders of magnitude) than that of the reference group. The median (ng/mL) blood serum concentrations of PFCs in fishery employees/family members/reference group were10400/3540/18.7 for PFOS, and 542/150/1.22 for PFHxS, and 41/11.7/2.88 ng/mL for PFOA, respectively. They observed that increasing time of employment at the fishery was associated with an increase in serum PFC. After examining various exposure pathways, they concluded that contaminated fish from Tangxun Lake was the primary source of PFAS exposure to fishery employees (Zhou et al., 2014).

Geographical Location as a Health Determinant

Generally speaking, an individual's residence history is an important predictor of his/her current health status (Boscoe, 2011). Two factors which influence the association between residence history and current health status are socioeconomic factors, and the physical environment. Socioeconomic factors such as income, employment, and education, have a direct impact on the prevalence of chronic and psychosocial conditions ranging from heart disease, stroke, diabetes and cancer to obesity, depression, and teenage pregnancy (Jelleyman & Spencer, 2008; Power et al., 2005). The physical environment determines specific chemical exposures from air, soil, or water and can contribute to diseases such cancer, and birth defects. Most of the time, the quality of the socioeconomic environment and the physical environment are correlated (Boscoe, 2011).

Research participants' residential history is commonly used in studies that estimate lifetime exposure to environmental chemicals that have varying levels of exposure due to geographic location and other community-level characteristics (Boscoe, 2011; Ryan, Brokamp, Fan, & Rao, 2015). This becomes even more relevant in longitudinal studies where participants can change their residence during the course of the study. However, studies also indicate that residential mobility can be a source of exposure misclassification, since other factors such as indoor sources, and personal activities can affect exposure (Boscoe, 2011; Ryan et al., 2015; Van Ryswyk et al., 2014). While some studies found that the inclusion of residential mobility as a factor increased the strength of association between health outcomes and environmental pollutants (Andersen et al., 2012; Gan et al., 2010), others found little or no change after inclusion of address history in their analysis (Canfield, Ramadhani, Langlois, & Waller, 2006; Chen, Bell, Caton, Druschel, & Lin, 2010). In urban areas, a relatively minor change in distance from one residence to the next can be associated with substantial changes in exposure levels

depending on proximity to the source of exposure, or terrain (Heckel & LeMasters, 2011). Therefore, studies that seek to examine the effect of environmental chemicals among large populations, such as general population sample of U.S. residents, can use geographic location as a proxy for exposure.

Several studies have examined the association between residential history and various health outcomes. Several studies have been conducted in the Cape Cod region of Massachusetts, U.S.A. due to concerns about elevated cancer incidence in the region which may have been associated with air and water pollution from the Massachusetts Military Reservation (MMR), pesticide applications to cranberry bogs, particulate air pollution from a large electric power plant, and tetrachloroethylene-contaminated drinking water from vinyl-lined asbestos cement distribution pipes (McKelvey, Brody, Aschengrau, & Swartz, 2004; V. Vieira, Webster, Weinberg, & Aschengrau, 2009; V. M. Vieira, Webster, Weinberg, & Aschengrau, 2008). In various studies, increasing duration of residence was associated with an increased risk for breast cancer in the region (Brody et al., 2004; McKelvey et al., 2004). McKelvey et al., (2004) found that breast cancer risk was elevated among women who had lived on Cape Cod for 5 or more years with a peak occurring in the 25 to less than 30-year category (AOR= 1.72; 95% CL, 1.12, 2.64) (McKelvey et al., 2004).

Vieira et al., (2005, 2008, 2009) in a series of case-control studies using spatial-temporal analysis, evaluated the association between residential location and breast, lung and colorectal, bladder, kidney, and pancreatic cancer in the Upper Cod region using data from population-based cancer registries. Their cases and controls were selected from residents of that region with complete residential histories. They found evidence for spatial clustering of breast cancer (2005) in the region, and evidence of spatial and temporal elevated risk for breast (2008), kidney, and

bladder (2009) cancer. For instance, a large area of residence near the MMR and increased duration of residence was associated with a statistically significant elevated risk for breast cancer near the MMR (V. M. Vieira et al., 2008).

In another study, Ziegler et al., (1993) examined the association between migration and breast cancer risk in Asian-American women. They found that risk for breast cancer was 60% higher among Asian-American women born in the West than those born in the East. Also, Asian-American women with three or four grandparents born in the West had a 50% higher risk for cancer than those with all grandparents born in the East. Among the Asian-American women born in the East, those who had lived for a decade or longer in the United States had an 80% higher risk than more recent migrants, and those who lived in urban areas had a 30% higher risk than migrants from rural areas (Ziegler et al., 1993).

Length of Residence as a Health Determinant

In numerous studies among immigrants, length of residence in the United States has been shown to be associated with adverse health outcomes such as cardiovascular disease and other metabolic diseases (Kershaw et al., 2016; Koya & Egede, 2007; Salinas, Abdelbary, Rentfro, Fisher-Hoch, & McCormick, 2014). Salinas et al., (2014) examined the association between immigrant status, length of residence in the United States, age, and CVD markers in a cohort of Mexican American adults living in Brownsville, Texas. They found that long-term immigrants were significantly more likely to report having high cholesterol (OR=1.9, p=0.004), and had on average lower diastolic blood pressure (beta=-1.40, p=0.04) than short-term immigrants to. Also, U.S. born participants had on average significantly higher systolic blood pressure (beta=3.45,

p=0.003), lower average levels of total cholesterol (beta=-4.19, p=0.03), and average LDL cholesterol (beta=-3.77, p=0.03) than short-term immigrants.

Kershaw et al., (2016) on the other hand examined the association between nativity and length of residence in the US, a commonly used proxy for acculturation, with indicators of low cardiovascular disease risk (not currently smoking; no diabetes; untreated total cholesterol <200mg/dL; untreated blood pressure <120/<80; body mass index <25 kg/m2; and no major ECG abnormalities) among a sample of Hispanics/Latinos resident in the United States. They found that women living in the US for less than 10 years had a lower risk for CVD than US-born women after adjusting for sociodemographic characteristics, diet, physical activity, and self-reported experiences of ethnic discrimination (OR=1.96, 95% CI= 1.37, 2.80). However, length of residence was largely unrelated to CVD risk in Hispanic men.

In another study, Koya & Egede (2007) examined the association between length of residence and cardiovascular disease risk factors among a national sample of U.S. immigrants. They found that compared to those who had been resident in the U.S. for <10 years, those had been resident for ≥15 years were more likely to be obese (OR 1.31, 95% CI 1.03–1.65), have hyperlipidemia (OR 1.59, 95% CI 1.14–2.22), and be smokers (OR 1.39, 95% CI 1.04–1.85), but were less likely to live a sedentary lifestyle (OR 0.63, 95% CI 0.47– 0.84). They also found no association between length of residence and being diagnosed with diabetes or hypertension.

Environmental Chemical Mixtures

Several studies have demonstrated that children and adults are exposed to background concentrations of various environmental chemical mixtures and that there is the possibility of synergism between low doses of mixtures of chemicals, which may result in different toxic

effects than that attributed to the individual chemicals (Carpenter, Arcaro, & Spink, 2002; Claus Henn, Coull, & Wright, 2014; Hertzberg & Teuschler, 2002). However, little is known about any adverse health outcomes associated with exposure to complex mixtures (Claus Henn et al., 2014; Rappazzo et al., 2017). An analysis of the effect of exposure to these complex chemicals instead of one chemical at a time can help to accurately predict adverse health outcomes and design appropriate health interventions. In studies that have examined chemical mixtures, various statistical techniques such as principal component analysis, global scores, Bayesian model averaging, Hierarchical regression etc. have been used to generate summary variables from the multiple individual pollutants (Billionnet, Gay, Kirchner, Leynaert, & Annesi-Maesano, 2011; Taylor et al., 2016).

Some studies have examined the effects of exposure to environmental chemical mixtures on renal and liver metabolism and function. Tsai et al., (2017) examined the association between exposure to chromium, lead, and cadmium and renal function in a sample of 360 Taiwanese adults aged 18 years and older. They found that a doubling of urinary chromium or lead serum concentrations was associated with a 6.61 mL/min/1.73 m^2 (95% CI= -9.71, -3.51) decrease in eGFR after adjusting for age, sex, body mass index, hypertension, diabetes, cigarette smoking, sodium intake, education, urinary volume, and other metals. Also, for participants in the highest tertile of cadmium exposure, eGFR decreased by 12.68 mL/min/1.73 m^2 (95% CI= -20.44, -4.93) and 11.22 mL/min/1.73 m^2 (95% CI= -17.01, -5.44), as urinary chromium or lead levels doubled, respectively. They concluded that there was a significant and independent association between chromium exposure and decreased renal function., and that co-exposure to lead and cadmium was potentially associated with additional decline in glomerular filtration rate in their sample (Tsai et al., 2017).

Chang et al., (2013) examined the association between mixed exposure to lead and organic solvents and liver function indicators among 593 occupationally-exposed male workers. They divided the sample into five groups: a lead-exposed group, an organic solvent-exposed group exposed to trichloroethylene (TCE co-exposed solvent group), an organic solvent-exposed group not exposed to trichloroethylene (TCE non-exposed solvent group), a lead and organic solvent-exposed group (mixed exposure group), and a non-exposed group (control group). They compared geometric means of liver function indices among the groups and found that mean ALT and aspartate aminotransferase (AST) concentrations were higher in the mixed group, when compared to the other exposure groups. After using general linear modeling (GLM) to control for the effect of age, work duration, BMI, smoking, and alcohol intake, the same results were obtained except for no significant difference in ALT levels between mixed exposure group and the TCE co-exposed solvent group (W. J. Chang, Joe, Park, Jeong, & Lee, 2013).

Other studies have examined the effect of air pollution mixtures on respiratory outcomes. Arif et al., (2007) examined the association between exposure to volatile organic compounds (VOCs) and physician-diagnosed asthma among a cross-section of U.S. adults. They used exploratory factor analysis to group the VOCs into factors which were included as indicator variables. Based on a loading value greater than 0.4, they selected two factors represented by ‘‘aromatic compounds’’ and ‘‘chlorinated hydrocarbons’’. They found that the odds of physician-diagnosed asthma were significantly higher among those exposed to aromatic compounds when compared to those who are not exposed (aOR = 1.63, 95% CI: 1.17–2.27). Among those who did not have physician-diagnosed asthma, there was significantly increased odds of one to two wheezing attacks for exposure to aromatic compounds (aOR = 1.68, 95% CI: 1.08–2.61)., and chlorinated hydrocarbons (aOR = 1.50, 95% CI: 1.01–2.23) (Arif & Shah, 2007).

Qian et al., (2004) examined the association between multiple pathways of exposure to pollution from household coal combustion and environmental tobacco smoke (ETS), and respiratory health, using factor analysis, among a cross-section of 7058 children in China. They identified five factors: heating coal smoke, cooking coal smoke, socioeconomic status, ventilation, and environmental tobacco smoke (ETS) and parental asthma. They found that exposure to heating coal smoke was associated with increased odds of reporting cough with phlegm (OR= 1.29, 95% CI= 1.11 – 1.50), wheeze (OR= 1.22, 95% CI=1.02–1.45), and asthma (OR= 1.52, 95% CI=1.06–2.15). Cooking coal smoke was not associated with any of the outcomes. The odds of reporting a persistent cough and bronchitis was lower among individuals in lower socioeconomic groups. Also, increase in household ventilation was associated with a decrease in reports of persistent cough, persistent phlegm, cough with phlegm, bronchitis, and wheeze. Finally, they found that increasing exposure to ETS and the presence of parental asthma were associated with increased odds of reporting persistent cough, persistent phlegm, cough with phlegm, bronchitis, wheeze, and asthma (Qian, Zhang, Korn, Wei, & Chapman, 2004).

Sherriff et al., (2005) examined the association between prenatal exposure to multiple chemical agents and the onset of wheezing in young children. They derived a score, called Total chemical burden (TCB), that was sum of the scores assigned to frequency of use of 15 different chemical-based products, such as disinfectant, bleach, carpet cleaner, window cleaner, and dry cleaner fluid. They found increased odds of persistent wheezing during early childhood for participants with the top decile of TCB scores when compared to those in bottom decile scores (OR= 2.30, 95% CI=1.20–4.39) but no significant associations were found with transient early wheeze or late-onset wheeze (Sherriff, Farrow, Golding, & Henderson, 2005).

Billionnet et al., (2011) examined the individual and combined effects of exposures to twenty VOCs on asthma and rhinitis on among a representative sample of the adult French population. They measured the concentrations of the VOCs in the indoor environments of 567 households. Also, 1012 eligible individuals living in 490 households completed a health questionnaire that measured their respiratory health. Each VOC was categorized as a 0 if less than the 3rd quartile value, and 1 if greater. To account for the multi-exposure to pollutants and correlations between the VOCs, they generated a global score that represented the sum of the categorized VOCs, such that the global score is the number of air pollutants in the indoor environment with elevated concentrations (> 3rd quartile). They then used generalized estimating equation (GEE) to examine the association between various health indicators and each VOC and global VOC score. They found that increasing global VOC score was associated with increased odds of diagnosis of asthma in the past year (aOR=1.07; 95% CI= 1.00–1.13) and rhinitis (aOR=1.04; 95% CI= 1.00–1.08). Significant positive associations were also found between aromatic and aliphatic hydrocarbons and asthma (aOR=1.12, 95% CI= 1.01–1.24; and aOR=1.41, 95% CI=1.03–1.93, respectively). Finally, they found significant positive associations between halogenated hydrocarbons and rhinitis (aOR 1.28; 95% CI= 1.07–1.54) (Billionnet et al., 2011).

In another study, Qian et al., (2007) examined the association between diverse sources of household combustion pollution sources and respiratory health among a sample of 2360 Chinese fathers and 463 children. They hypothesized that exposure to the pollution sources and their factors was positively associated with the prevalence of respiratory conditions in the men, and negatively associated with the children's lung function, as measured by forced vital capacity (FVC), and forced expiratory volume at 1s (FEV1). Using a factor analysis, they generated five different uncorrelated factors among the men (Heating coal smoke, Cooking coal smoke,

Ventilation, Socioeconomic status, and Any home cigarette smoker) and three different factors among the children (Cooking coal smoke, Heating coal smoke, and Ventilation). Among the adults, they found that heating coal smoke was associated with an increased prevalence of persistent cough, persistent phlegm, and wheeze; and cooking coal smoke was associated with increased prevalence of physician-diagnosed of asthma. They also observed decreasing pulmonary function with increase in exposure to cooking coal smoke among the children (Qian et al., 2007).

Studies that have examined the effects of multiple PFCs found that the associations between an individual PFC and a health outcome is usually complicated by correlations among the different PFCs, and similar associations between the health outcome and some of the multiple PFCs (Grandjean et al., 2012; Granum et al., 2013; Stein et al., 2016), which complicates the conclusions of these studies. However, available studies have yet to address the combined effect of exposure to multiple PFCs and any adverse health outcomes.

The Foreign-born U.S. Population

The U.S. Census Bureau describes foreign-born U.S. residents as individuals who are not U.S. citizens at birth; as compared to native-born residents who are born in the United States, Puerto Rico, or a U.S. Island area, or are born abroad to at least one U.S. citizen parent (Grieco et al., 2012). Nearly 53 percent of the foreign-born were born in Latin America, 28 percent in Asia, 12 percent in Europe, 4 percent in Africa, 2 percent in Northern America, and less than 1 percent in Oceania. Individuals born in Mexico are the largest foreign-born population, comprising 55 percent (11.7 million) of Latin American-, and 29 percent of the total foreign-born population (Grieco et al., 2012).

Immigrant populations often tend to have increased risk for inadequate access to health care due to political and social marginalization (Derose, Escarce, & Lurie, 2007). However, despite these disparities, they tend to have better health and lower mortality rates (Singh & Miller, 2004; Singh & Siahpush, 2002). This has been referred to as the immigrant health paradox (Scribner, 1996; Speciale & Regidor, 2011). This may be because migration is selective of healthier individuals (Marmot, Adelstein, & Bulusu, 1984; Norman, Boyle, & Rees, 2005), and immigrants are less likely to engage in risky behaviors and more likely to engage in healthy behaviors (Borrell, Castor, Conway, & Terry, 2006; Scribner, 1996). However, with increasing length of stay in the U.S., immigrants are more likely to adopt U.S. norms and behaviors which may nullify their health advantages and lead to a decline in health status (Abraido-Lanza, Chao, & Florez, 2005). Most studies have examined the association between increasing length of residence in the U.S. and increased odds of obesity, chronic conditions and other cardiovascular risk factors among immigrants (Goel, McCarthy, Phillips, & Wee, 2004; Kaplan, Huguet, Newsom, & McFarland, 2004; Koya & Egede, 2007). It is unknown whether any studies have examined the association between length of residence and blood serum concentrations of PFCs.

Summary

PFCs are widely occurring environmental chemicals that are persistent, bioaccumulative and toxic to both animals and humans. Numerous studies have shown differences in exposure to background concentrations of these chemicals among populations in several countries worldwide. PFCs are associated with adverse health outcomes including renal and liver dysfunction. However, no studies have established exposure limits for background concentrations of PFCs in the environment. The development of such exposure limits will be dependent on biomonitoring studies among populations over a period of time. Foreign-born U.S.

residents are potentially a population that may have historically low exposure concentrations to PFCs when compared to native-born U.S. residents. They therefore present a unique population to determine if increasing length of residence in the U.S. will be associated with increasing serum concentrations of selected PFCs. If there is a significant increase in the serum concentrations, then further analysis can be performed to determine if the association between the selected PFCs and renal and liver function indicators will be different among this population when stratified by length of years of residence.

Additionally, even though PFCs occur as mixtures of multiple chemicals in the environment and blood and serum samples, the health effects of the complex mixtures are largely unknown (Rappazzo et al., 2017). Further analysis will be carried out to determine the combined effects of exposure to the selected PFCs and renal and liver function indicators. Finding from this study can help inform future designs of more rigorous studies, such as longitudinal studies, among this population.

Chapter III: Methods

Data Source

Data from the 2007 – 2012 waves of the US National Health and Nutritional Examination Survey (NHANES) were used for this study. The NHANES is a stratified multistage probability sample of the Civilian non-institutionalized U.S. population (Centers for Disease Control, 2010). For each survey year, a random 1/3 subsample of participants 12 years or older were selected for the measurement of blood serum PFC concentrations (Centers for Disease Control, 2010). Multiple waves of NHANES data were selected and used for this study to increase the study sample size. PFCs selected for this study were PFOA, PFOS, PFHxS, and PFNA because they are the ones most often included in most epidemiological studies. Similar to other studies that have been conducted among the NHANES subsample (Taylor, Hoffman, Thayer, & Daniels, 2014; Webster et al., 2016), only 20 years and older participants assayed for the selected PFCs were eligible for this study. A complete description of the NHANES survey methodology is described elsewhere (National Center for Health Statistics, 2018).

Independent Variables

The main independent variables of interest were the PFCs (PFOA, PFOS, PFHxS and PFNA), place of birth, and length of residence in the U.S. (Categorized as <10, 10 – 19, and 20+ years). The PFC concentrations were natural-log transformed to approximate normal distributions before statistical analysis. Mean (SE), median, and quartile values were used to describe serum PFC concentrations.

Covariates: Potential covariates were selected a priori based on evidence from other studies (Gleason et al., 2015; Lin et al., 2009; Steenland et al., 2009). These covariates include age, sex,

race/ethnicity, body mass index (BMI), smoking status, heavy alcohol use, level of education, and impaired glucose tolerance and hypertension. Individuals were classified as smokers if they had serum cotinine levels > 1.78 ng/mL for men and > 4.47 ng/mL for women (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009; Caraballo, Giovino, Pechacek, & Mowery, 2001). BMI was calculated as weight in kilograms divided by height in meters squared (National Heart Lung and Blood Institute, 1998). Heavy alcohol use was defined as consumption of 5 or more drinks on at least one day over the past 12months (Ward, Clarke, Nugent, & Schiller, 2016). Impaired glucose tolerance was defined as having a fasting blood glucose level greater than or equal to 100mg/dl, or currently on prescribed medication to lower blood sugar (American Diabetes Association, 2014). Hypertension was defined as currently taking prescribed medication for high blood pressure or having a systolic blood pressure at 140mmHg or higher, or a diastolic blood pressure at 90 mmHg or higher (American Heart Association, 2018).

Outcome Variables

Renal Function: Serum creatinine measurements obtained in the NHANES were used to measure kidney function. Estimated glomerular filtration rate (eGFR; measured in mL/min/1.73m^2) was calculated from serum creatinine values by using the 4-variable Modification of Diet in Renal Disease study equation: eGFR=175 * (serum creatinine in mg/dL)$^{-1.1543}$ * (age in years)$^{-0.2033}$ *(0.742 if female)*(1.21 if black) (Levey et al., 2006). The eGFR values were then categorized based on the National Kidney Foundation cut-off values for CKD: GFR ≥ 90 (Normal) and GFR<90 (Low) (National Kidney Foundation, 2002). Weighted means with 95% confident intervals (CIs) were calculated for eGFR values.

Liver Function: Three markers of liver injury available from the NHANES were used for this study: alanine aminotransferase (ALT), γ-glutamyltransferase (GGT) and Total bilirubin. Total bilirubin is mostly derived from the metabolism of hemoglobin and increases are usually indicative of dysfunction of the liver, bile ducts, or gall bladder. ALT is present in liver parenchymal cells and is elevated during acute liver damage. Elevation of GGT levels is an early sign of cholestatic disorders, where flow of bile from the liver is slowed or impeded (Rosalki & Mcintyre, 1999). Each biomarker of liver function was dichotomized by creating threshold values for high concentrations using cut-off values from previously published studies: 45 IU/L in males and 34 IU/L in females for ALT (Schumann et al., 2002a), 55 IU/L in males and 38 IU/L in females for GGT (Schumann et al., 2002b), and 0.3 mg/dL in both sexes for total bilirubin (McPherson & Pincus, 2017). The cutoff values reflect the reference ranges beyond which the concentrations of the liver function indicators would be considered abnormally high and could prompt additional investigation in a clinical setting (Darrow et al., 2016). The continuous measures of liver biomarkers were natural log-transformed and their weighted means with 95% confident intervals (CIs) were calculated.

Statistical Analysis:

Research Question 1 and 2: Demographic characteristics of the study sample were described using frequencies. Multiple linear regression analysis was used to calculate the least square geometric means (LSGM) of the log-transformed PFC concentrations by place of birth, and length of residence, controlling for gender, race, age, educational level, and smoking status. Similarly, multiple regression was used to calculate the Least Square Means (LSM) of eGFR by place of birth, and by length of residence, controlling for education level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis. Gender, age and race were

not included in calculating differences in LSM of eGFR because their impact on eGFR had already been accounted for in the Modification of Diet in Renal Disease study equation (Levey et al., 2006) .

Research Question 3a. & 3b: In assessing the associations between individual PFCs and eGFR, multivariable logistic regression models were used to estimate the odds of having low eGFR for every unit increase in log-PFC serum concentrations. In Model 1, the crude association between serum PFCs and eGFR were determined, and in Model 2 the association was determined controlling for smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level. The regression analyses were carried out both for the overall sample of foreign-born residents, and then stratified by length of residence to examine any significant differences by length of residence.

Research Question 4a. & 4b: Multiple linear regression was used to calculate the Least Square Means (LSM) of liver function biomarkers by place of birth, and by length of residence, controlling for race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis. Logistic regression models were used to determine the odds of having elevated ALT, GGT, or total bilirubin for every unit increase in log-PFC serum concentrations. In Model 1, the crude association between serum PFCs and the liver function biomarkers were determined, and in Model 2 the association was determined controlling for race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level. The regression analyses were carried out both for the overall sample of foreign-born residents, and then stratified by length of residence to examine any significant differences by length of residence.

Research Question 5: Correlation analysis was used to examine the association between individual PFCs and the outcome variables. Principal component analysis (PCA) was then used to generate linear combinations of the PFC serum concentrations using the SAS software principal components procedure (version 9.4; SAS Institute, Inc, Cary, NC). Principal components with observed eigenvalues greater than 1.0 were further evaluated. The larger the absolute value of a loading for a variable to a principal component, the greater the contribution of that variable to that principal component. Variables that had loadings of 0.40 or greater were considered as making a reasonable contribution to the principal component. In PCA, the second principal component is independent of the first principal component and the third is independent of the first two principal components (Hu et al., 2018; Navarro Silvera et al., 2011). Therefore, labeling of the principal components was done based upon interpretation of the data.

After a varimax rotation, which typically makes the principal component more interpretable, principal component scores were generated using the SAS Proc Factor command (O'Rourke & Hatcher, 2013). These scores represent the weighted sums of the exposure variables, where the weights are equal to the principal component loading (O'Rourke & Hatcher, 2013). The scores were then categorized into quartiles and multivariate unconditional logistic regression analyses was used to examine the association between the component scores and the dichotomized eGFR, and liver function biomarkers by calculating odds ratios (OR) and corresponding 95% confidence intervals (CI). In model 1, the association between a principal component and eGFR, ALT, GGT, and total bilirubin was mutually adjusted for all other principal components from the factor-loading matrix. In model 2, all other covariates of interest were additionally included. All tests of significance were two-sided, with a pvalue of 0.05 considered statistically significant.

Chapter IV: Results

Demographic Characteristics of Study Sample: The demographic characteristics of the study participants are outlined in Table 1. The general sample consisted of 5167 adults aged 20 or more years (3678 native and 1485 foreign-born). Males comprised 2521 (48.1%) of the general sample, 1786 (47.7%) of the native-born and 732 (49.6%) of the foreign-born participants. Approximately 69% of general sample were non-Hispanic white, 10% were non-Hispanic black, 8% were Mexican American and 13% were 'Other' race. Most the participants were aged between 20 – 39 years (36.5%) or 40 – 59 years (39.4%). Among the foreign-born residents, 384 (33.6%), 373 (26.8), and 661 (39.7) had been U.S. residents for <10 years, 10 – 19 and 20+ years, respectively.

Associations between PFCs and Renal Function: Foreign-born residents had lower mean and median concentrations for all the examined PFCs when compared to native-born residents (Table 2). The median (ng/ml) PFOA, PFOS, PFHxS, and PFNA serum concentrations of native and foreign-born residents were respectively; PFOA (3.35 vs. 2.46), PFOS (10.29 vs. 8.19), PFHxS (2.53 vs. 1.81), and PFNA (1.43 vs. 1.40). Similarly, among the foreign-born residents, mean and median concentrations of all the PFCs increased as length of residence in the U.S. increased. The mean serum concentrations (ng/ml) of PFCs for foreign-born individuals who had been resident in the US for 10, 11-19 and 20 or more years were respectively 2.64, 2.84 and 3.46 for PFOA; 2.64, 2.84 and 3.46 for PFOS; 1.15, 1.59 and 2.52 for PFHxS; and 1.25, 1.45 and 1.47 for PFNA (Table 2). The log-transformed PFCs were moderately to strongly positively correlated (Range, r = 0.47 – 0.70) (Table 3).

The least square geometric mean (LSGM) concentrations of PFCs were compared by place of birth and length of residence. As shown in Table 4, adjusted LSGM concentrations of

PFOA and PFHxS were significantly higher among native-born than foreign-born residents ($p < .05$). Among foreign-born residents, adjusted LSGM concentrations of PFOS and PFHxS were significantly higher among individuals who were resident in the U.S. for 20+ years when compared to those resident for <10 years; and adjusted LSGM concentrations of PFHxS among those resident for 10– 19years was significantly higher than among those resident for <10 years. There were no statistically significant differences in PFOA and PFNA concentrations by length of residence in the U.S. (Table 4).

Mean eGFR was higher among the foreign-born participants when compared to native-born participants. However, mean eGFR decreased as the length of years of residence among foreign-born participants increased (Table 5). After adjusting for educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis, LSM of eGFR was significantly higher among foreign-born residents when compared to native-born residents ($p<0.001$). Similarly, LSM of eGFR among foreign-born residents who had been resident for <10 years was significantly higher than the LSM eGFR among those who had been resident for 20+ years ($p=0.002$). There was no significant difference in eGFR between foreign-born individuals who had been resident for <10 years vs. 10-19 years and 10-19 vs. 20+ years (Table 5).

Results showing the odds of low eGFR with increasing serum concentrations of PFCs are presented in Table 6. After adjusting for all covariates, a unit increase in logPFOA serum concentrations was associated with a twofold increased odd of having low eGFR (OR=2.04; 95% CI=1.26 – 3.28), a unit increase in logPFHxS serum concentrations was associated with a 40% increased odds of having low eGFR (OR=1.40; 95% CI =1.09 – 1.79), and a unit increase in logPFOS serum concentrations was associated with an 88% increased odds of having low eGFR

(OR=1.88; 95% CI =1.48 – 2.39). On stratifying by length of residence, logPFOA serum concentrations were significantly associated with low eGFR among individuals who had been resident for 10-19 years (OR=2.96; 95% CI=1.37 – 6.39), and 20+ years (OR=3.59; 95% CI=1.45 – 8.90), logPFHxS serum concentrations were significantly associated with low eGFR among individuals who had been resident for 20+ years (OR=2.38; 95% CI=1.53 – 3.70), and logPFNA serum concentrations were significantly associated with low eGFR among individuals who had been resident for 10–19 years (OR=6.04; 95% CI=2.59 – 14.11). Except for logPFNA, there was an increasing trend in the odds ratio estimates with increase in length of residence, though not all the associations were significant (Table 6).

Association between PFCs and Liver Function Indicators: The mean ALT serum measurements among native-born and foreign-born residents were respectively 25.52 (IU/L) and 26.78 (IU/L). After adjusting for age, race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis, least-square mean (LSM) ALT measurements were significantly higher among foreign-born residents when compared to native-born residents (31.12 vs. 28.24, p=0.02) (Table 7). The mean serum concentrations (IU/L) of ALT for foreign-born individuals who had been resident in the US for 10, 11-19 and 20 or more years were respectively 26.80, 28.06 and 25.76. The LSM concentration of ALT were significantly higher among individuals who had been resident in the U.S. for 10-19 years when compared to that of those who had been resident for 20+ years (34.94 vs. 32.06, p=0.04). No significant differences in serum concentrations of GGT were observed among native-born and foreign-born individuals. However, LSM of GGT among foreign-born residents who had been resident for 10-19 years (42.75) was significantly higher than that among both those who had been resident for <10 years (36.48, p=0.01), and 20+ years (37.50, p=0.003) (Table 8). Mean

total bilirubin measurements among native-born and foreign-born residents were respectively 0.76 and 0.74 mg/dl. LSM of total bilirubin concentrations were significantly higher among native-born than foreign-born residents (0.75 vs. 0.72 mg/dl, p=0.03). There was no significant difference in total bilirubin measurements by length of years of residence among foreign-born individuals (Table 9).

The odds of elevated liver function biomarkers with increasing serum concentrations of PFCs are presented in Tables 10-12. There were no significant associations between the selected PFCs and ALT in the total sample of foreign-born residents. On stratifying by length of residence, significant associations were observed among individuals who had been resident for 20 years or more. Among this subsample of foreign-born individuals, a unit increase in logPFOA serum concentrations was associated with a 49% increased odds of having elevated ALT (OR=1.49; 95% CI=1.00 – 2.22), a unit increase in logPFOS serum concentrations was associated with a 37% increased odds of having elevated ALT (OR=1.37; 95% CI =1.02 – 1.82), and a unit increase in logPFHxS serum concentrations was associated with a 65% increased odds of having elevated ALT (OR=1.65; 95% CI =1.28 – 2.14) (Table 10). After controlling for all covariates, there were no significant associations between the selected PFCs and GGT in the total sample but on stratifying by length of residence, individuals who had been resident for 20+ years had a 98% increased odds of having elevated GGT for a unit increase in logPFOA serum concentrations (OR=1.98; 95% CI =1.07 – 3.69) (Table 11).

After controlling for all covariates in the total sample of foreign-born residents, a unit increase in logPFOS serum concentrations was associated with a 69% increased odds of having elevated total bilirubin (OR=1.69; 95% CI =1.12 – 2.53), a unit increase in logPFHxS serum concentrations was associated with a 60% increased odds of having elevated total bilirubin

(OR=1.60; 95% CI =1.11 – 2.30), and a unit increase in logPFNA serum concentrations was associated with an 81% increased odds of having elevated total bilirubin (OR=1.81; 95% CI =1.05 – 3.13) (Table 12). After stratifying by length of residence, logPFOS serum concentrations were significantly associated with elevated total bilirubin among individuals who had been resident for 10-19 years (OR=2.31; 95% CI=1.13 – 4.72), logPFHxS serum concentrations were significantly associated with elevated total bilirubin among individuals who had been resident for 10-19 years (OR=2.01; 95% CI=1.08 – 3.72), and logPFNA serum concentrations were significantly associated with elevated total bilirubin among individuals who had been resident for 10–19 years (OR=3.02; 95% CI=1.20 – 7.65) (Table 12).

Association between Combined Exposure to PFCs and Renal and Liver Function: Principal component loadings for each of the PFCs are shown in Table 13. The principal axis method was used to extract the components, and this was followed by a varimax rotation. Three components were retained in the analysis, which together accounted for 94.9% of the total variance. In interpreting the rotated factor pattern, an item was said to load on a given component if the factor loading was .40 or greater for that component. The first pattern loaded heavily on PFOS and PFHxS and was therefore termed PFOS/PFHxS pattern. In contrast, the second principal component, termed a PFOS/PFNA pattern, loaded heavily on PFOS and PFNA. The third principal component was distinguished from the others as it loaded most heavily on only PFOA. After controlling for principal components factors, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level, significant direct associations were found between increasing quartiles of the PFOS/PFHxS components and low eGFR (OR: Q2 vs. Q1= 1.38, 95% CI: 1.04 - 1.83; Q3 vs. Q1= 1.53, 95% CI: 1.16 - 2.01; Q4 vs. Q1= 2.41, 95% CI: 1.82 – 3.19) (Table 14). There was a significant

positive association between the PFOA principal component and ALT concentrations (OR: Q4 vs. Q1= 1.28, 95% CI: 1.00 - 1.64), but the association was not significant after adjusting for covariates (Table 15). None of the principal component factors were significantly associated with elevated GGT (Table 16). There was a significant association between the PFOA principal component and elevated total bilirubin in the crude model (OR: Q4 vs. Q1= 1.80, 95% CI: 1.25 – 2.58), but not in the adjusted model (Table 17). After adjusting for all covariates, significant direct associations were found between elevated total bilirubin and increasing quartiles of the PFOS/PFHxS component (OR: Q2 vs. Q1= 2.33, 95% CI: 1.17 – 4.64; Q3 vs. Q1= 2.47, 95% CI: 1.24 – 4.92; Q4 vs. Q1= 2.82, 95% CI: 1.42 – 5.16) (Table 17).

Chapter V: Discussion, Conclusions and Recommendations

Discussion

Associations between PFCs and Renal Function: Results from this study showed that foreign-born residents had lower mean and median concentrations for all the examined PFCs when compared to native-born residents. Among the foreign-born residents, mean and median concentrations of PFOS and PFHxS increased as length of residence in the U.S. increased. Additionally, among the foreign-born the serum concentrations of PFOS and PFHxS increase as the number of years of residence increase. Internal exposure to PFCs is usually measured based on concentrations in plasma, serum or whole blood (Fromme et al., 2009). Because PFCs, such as PFOS and PFOA, are very persistent chemicals that do not undergo metabolism, serum PFC concentrations are indicative of cumulative exposure overs several years (Yusa, Ye, & Calafat, 2012), and body burdens may increase with increasing age (Fromme et al., 2009). Several studies have also shown that that serum concentrations, such as PFOA and PFOS, are higher in males than females (Calafat, Kuklenyik, et al., 2007; Fromme H. et al., 2007; Harada et al., 2004; Kärrman et al., 2006). However, other studies did not find significant sex-related differences in PFOA and PFOS concentrations (Kannan et al., 2004; Olsen, Church, et al., 2003; Olsen, Hansen, et al., 2003). In our analyses, we controlled for age and sex when we examined the differences in PFC serum concentrations. Thus, the results suggest that foreign-born U.S residents have, on average, lower serum concentrations of PFCs when compared to native-born residents, and that the exposure concentrations increase with increasing years of residence in the U.S. among the foreign-born. Available studies have mostly demonstrated that serum concentrations of PFCs differed between samples taken in different countries (Fromme et al., 2007; Fromme et al., 2009; Kannan et al., 2004), and not among various population subgroups in

the same country. Several factors can be suggested as contributing to the observed differences in PFC serum concentrations. Mean and median concentrations of PFCs seem to be higher in North American populations than in European, Asian, and Australian populations, with most concentrations highest in U.S. samples (Fromme et al., 2009). Studies also show that average PFC concentrations in outdoor air tend to be higher in urban communities when compared to rural communities (Fromme et al., 2009; Jahnke, Ahrens, Ebinghaus, & Temme, 2007; Martin et al., 2002). Thus, exposure to PFCs is likely to be higher in more urbanized and industrialized societies than in rural societies. This is supported by studies that show that urban populations have higher serum concentrations of PFCs than rural populations (Fu, Wang, Wang, Fu, & Lu, 2014; Hanssen et al., 2010). Immigrants are also more likely to engage in high risk occupations, and live is socioeconomically deprived communities with an increased exposure to environmental chemicals (Eamranond & Hu, 2008). Subsequently, with time they may develop increased levels of environmental chemicals after arrival to the U.S (Eamranond & Hu, 2008).

Mean eGFR was higher among the foreign-born participants when compared to native-born participants, and eGFR was significantly higher among foreign-born residents who had been resident for <10 years when compared to those who had been resident for 20+ years. Except for logPFNA, there was an increasing trend in the odds ratio estimates with increase in length of residence, though not all the associations were significant. Studies have shown that increasing age is associated with decreasing kidney function (Denic, Glassock, & Rule, 2016; Weinstein & Anderson, 2010). Considering that increasing length of residence will be associated with increasing age, the inclusion of age in the eGFR estimates accounted for its effect. Other covariates that were included in the analysis were smoking and heavy alcohol use, as well as diagnosis of diabetes and hypertension. Other clinical conditions that may be associated with

increasing age and decreased renal function were not included in the analysis. Future studies can examine this relationship by including more potential covariates in the analysis

After adjusting for all covariates, a unit increase in log-PFOA, log-PFHxS, and log-PFNA concentrations were associated with increased odds of having low eGFR. This finding is consistent with previous studies that found that increasing serum concentrations of both PFOA and PFOS were inversely associated with eGFR levels (Watkins, Josson et al., 2013), and positively associated with CKD (Shankar, Xiao et al., 2011). Watson et al., (2013), also found that increased serum PFNA levels were significantly associated with decreased eGFR.

On stratifying by length of residence, logPFOA serum concentration was significantly associated with low eGFR among individuals who had been resident for 10-19 years, and 20+ years, logPFHxS serum concentration was significantly associated with low eGFR among individuals who had been resident for 20+ years, and logPFNA serum concentration was significantly associated with low eGFR among individuals who had been resident for 10–19 years. Previous studies show that length of residence is an important proxy for determining risk for some chronic diseases (Kershaw et al.,2016, Abraido-Lanza, Chao et al., 2005, Koya and Egede 2007, Voeks, McClure et al., 2008, Howard, Woolson et al., 2010). For example, among immigrants in the United States, longer duration of residence was found to be associated with increased odds of obesity and hyperlipidemia (Koya and Egede 2007). Similarly, compared to other parts of the United States, lifetime residence in the Southeastern region of the U.S. is associated with a higher prevalence of diabetes (Voeks, McClure et al., 2008), and hypertension (Howard, Woolson et al., 2010); two important risk factors for kidney dysfunction. The results suggest that increasing length of residence in the US, which can be an indicator for exposure to background concentrations of PFCs in the general population, may be associated with increasing

serum concentrations of some PFCs, and may mediate the association between the PFCs and renal function. Length of residence is therefore an important factor to consider in studies that examine the association between PFCs and associated health outcomes.

Association between PFCs and Liver Function Indicators: The results showed that after adjusting for age, race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis, when comparing foreign-born and native-born U.S. residents, least-square mean (LSM) ALT measurements were significantly higher among foreign-born residents, no significant differences in serum concentrations of GGT were observed, and LSM of total bilirubin concentrations were significantly higher among native-born residents. Among foreign-born residents LSM concentration of ALT were significantly higher among individuals who had been resident in the U.S. for 10-19 years when compared to that of those who had been resident for 20+ years, LSM of GGT of those who had been resident for 10-19 years was significantly higher than those who had been resident for <10 years, and 20+ years, and there was no significant difference in total bilirubin measurements by length of years of residence. Total bilirubin, ALT, and GGT are useful biomarkers of liver function, with an increase beyond certain thresholds classified as indicative of liver damage (Johnston, 1999). The results were inconclusive on whether differences in liver function biomarkers are significantly different between native- and foreign-born U.S. residents.

Also, there were no significant associations between the selected PFCs and ALT in the total sample of foreign-born residents. Among individuals who had been resident for 20 years or more, a unit increase in logPFOA serum concentrations was associated with an increased odds of having elevated ALT, and elevated GGT; unit increases in logPFOS and logPFHxS serum concentrations were associated with an increased odds of having elevated ALT. On the other

hand, increases in logPFOS, logPFHxS, and logPFNA serum concentrations were associated with increased odds of having elevated total bilirubin in the total sample of foreign-born residents. After stratifying by length of residence, logPFOS, logPFHxS, and logPFNA serum concentrations were significantly associated with elevated total bilirubin among individuals who had been resident for 10-19 years. Available studies on the association between PFCs are inconclusive, with some suggesting that increasing concentrations of PFOA were associated with significant increase in total bilirubin (Costa et al., 2009; Olsen & Zobel, 2007; Sakr et al., 2007), while others observed a U-shaped exposure-response pattern (Gallo et al., 2012). Other studies have observed associations between PFOA and ALT, GGT, and hepatocellular damage (Darrow et al., 2015). The results suggest that some of the PFCs may have a significant association with the liver function indicators, even though the findings are not conclusive after stratifying by length of residence.

The lack of significance in the associations between some PFCs and the liver function indicators could be due to a variety of reasons. Bilirubin is produced from the breakdown of hemoglobin within the reticuloendothelial system and can be elevated due to other factors such as over production of bilirubin, acute hepatitis, decreased hepatic uptake, viral hepatitis, or ischemic liver injury (Gowda et al., 2009). Also, the are studies that suggest that ALT and GGT can be elevated due to other nonspecific liver injuries, and may remain at normal levels in cases of chronic liver cell damage (Gowda et al., 2009). Future studies can examine the associations between PFCs and liver function using other indicators, or a summary index such as the Aspartate amino transferase: Alanine amino transferase (AST/ALT) ratio (Giannini et al., 2003; Gowda et al., 2009).

Association between Combined Exposure to PFCs and Renal and Liver Function: After controlling for all covariates, increasing quartile concentration of the PFOS/PFHxS principal component was associated with increased odds of low eGFR, and elevated total bilirubin. Also, increasing quartiles of the PFOA principal component were associated with elevated ALT and elevated total bilirubin concentrations in the crude model. However, the relationship was not significant after adjusting for all covariates. There are currently no available studies on the effects of simultaneous exposure to multiple PFCs and adverse health outcomes. Nevertheless, the findings of this study suggest that PFOS and PFHxS may have additive/synergistic effects on renal and liver function. Future studies, such as longitudinal studies, can examine this effect.

Limitations: This study is subject to a few limitations. The NHANES is a cross-sectional study, which does not eliminate the possibility of reverse causality. Hence the significant associations between the selected PFCs and low eGFR observed may not indicate a causal relationship. It may be argued that the increasing serum PFC concentrations may in fact be causing or be the result of decreased kidney function or some combination of the two. A more robust study design, such as a longitudinal study with a larger sample size may be more effective at identifying significant associations between increasing PFC concentrations and risk of kidney or liver dysfunction.

This study did not examine the age and sex distributions of the foreign-born and native-born residents. There may be the possibility of misclassification bias due to differences in the age and sex distributions between the two groups. Future studies can look at variation between these groups.

Another limitation is the designation of 'Foreign-born' respondents. While respondents can accurately indicate their place of birth, the question does not measure residential history. It is possible that the foreign-born residents live in more urban locations when compared to some native-born residents. Also, foreign-born residents may not have necessarily spent all their lives residing in their country of origin before moving to the U.S. Considering that residential history plays a significant role in level of exposure, participants' historical exposures will have an important impact on their levels of exposure to PFCs. Therefore, this is likely to introduce some measure of bias into the study since just one question is used to determine place of birth, and length of exposure is designated by length of residence in the US. However, the findings show that exposure levels may still be different based on length of residence among this representative sample of foreign-born and native-born U.S. residents.

Also, we are unable to identify the country of birth of respondents. Differences observed among foreign-born individuals based on length-of-residence may be impacted by participants' exposure history from their country of birth. Future studies can examine differences in PFC serum concentrations among foreign-born individuals from specific countries.

Also, past studies on the impact of PFCs on renal and liver function have mostly been carried out among occupationally exposed cohorts and in communities exposed to historically elevated levels. In such situations, it may be possible to elucidate the associations exposures to the high concentrations and adverse health outcomes. Studies that focus on the effects of low dose background exposures to PFCs in the general population may not observe significant findings. Additionally, liver and renal dysfunction can occur due to the presence of many other factors such as heavy alcohol use, use of some medications, and some preexisting health issues. Therefore, if the general population is exposed to low dose concentrations of these chemicals,

liver and renal dysfunction can occur through the additive or interaction effects of these factors, some of which were not accounted for in the analysis.

This study operated on the premise that foreign-born US residents who were recent migrants were more likely to have lower exposures when compared to longer term foreign-born residents. Studies have shown that the health status of newly arrived immigrants can vary over a very short period, such as within 5 years (Jasso, Massey, Rosenzweig, & Smith, 2004). Thus, the use of duration of US in a cross-sectional data such as the NHANES, may introduce classification bias such that individuals with relatively shorter years of residence in the US may be considered to have potentially lower PFC serum concentrations, and vice versa. Future studies among immigrants can use multiple cross-sections or longitudinal data that will make it possible to follow immigrant cohorts over a period of time after their arrival in the United States. In addition, studies can compare the exposure characteristics of immigrants with that of populations in their countries of origin. This will provide more information on differences in exposure characteristics between immigrant subgroups. Finally, this study did not examine whether differences in residential segregation patterns were associated any differences in PFC-exposure characteristics among the native-born and foreign-born U.S. residents. Future studies can examine this phenomenon

Conclusions and Recommendations

In a representative sample of US adults, being native-born was associated with significantly higher serum concentrations of PFOA and PFHxS when compared to foreign-born residents. This association appeared to be independent of age, gender, race, age, educational level, and smoking status. Mean eGFR among foreign-born residents was higher than that of native-born residents. Among foreign-born residents, increased length of stay in the U.S. was associated with

increased serum concentrations of PFOS and PFHxS and decreasing eGFR. Also, increasing serum concentrations of PFOA, PFHxS, and PFNA were significantly associated with increased odds of low eGFR among foreign-born U.S. residents. The association between some PFCs and eGFR was significant among foreign-born individuals with longer duration of residence (10-19years, 20+ years) but not among those who had been resident for a shorter period (<10years). Future studies can use trend analyses to examine the increases observed in PFC serum concentrations and decline in eGFR concentrations with increase in length of residence among the foreign-born participants.

Differences in the mean and median concentrations of liver function indicators (ALT, GGT, Total bilirubin) was inconclusive among foreign-born and native-born residents. Among the foreign-born residents, uniform increase or decrease in serum concentrations of liver function indicators were not observed. Similarly, significant associations between the selected PFCs and liver function indicators were not conclusive. Further studies can examine this relationship. Increasing quartiles of a combined PFOS/PFHxS exposure variable was associated with increased odds of low eGFR, and elevated total bilirubin. There are currently no studies on the combined effect of exposure to multiple PFCs. The findings of this study can serve as the basis for future more rigorous studies.

Though the production of some PFCs has ceased in the United States, they are persistent environmental chemicals that are likely to have significant health and environmental effects in the coming years. Thus, there is the need for ongoing monitoring and research on this group of chemicals. Foreign-born individuals are a unique population to examine the increase in PFC serum concentrations over time and associated health outcomes. Also, this study has demonstrated that there is the need to examine the effects of simultaneous exposure to multiple

PFCs. Further studies can examine differences in risk for PFC-associated negative health outcomes between foreign-born and native-born individuals, as well as among populations with low levels of exposure to PFCs, with emphasis placed on PFC serum concentration increases over time.

TABLES

Table 1: Demographic Characteristics of Study Population

Variable	N (Weighted %)					
	General Sample (N= 5167)	Place of Birth				
		Native-born	Foreign-born	Length of Residence (years) Among the Foreign-born		
Place of Birth				<10	10 – 19	20+
Native-born	3678 (82.3)					
Foreign-born	1485 (17.7)			384 (33.6)	373 (26.8)	661 (39.7)
Missing	4				67	
Sex						
Male	2521 (48.1)	1786 (47.7)	732 (49.6)	180 (48.1)	178 (49.3)	342 (51.0)
Female	2646 (51.9)	1892 (52.3)	753 (50.4)	204 (51.9)	195 (50.7)	319 (49.0)
Race						
Non-Hispanic White	2318 (69.2)	2202 (80.3)	116 (17.4)	28 (16.8)	27 (14.3)	60 (21.6)
Non-Hispanic Black	1031 (10.4)	915 (11.2)	116 (6.7)	25 (5.5)	34 (7.9)	56 (7.4)
Mexican American	801 (7.9)	300 (3.7)	500 (27.0)	115 (23.3)	125 (30.7)	223 (25.0)
Other	1017 (12.6)	261 (4.8)	753 (48.9)	216 (54.3)	187 (47.0)	322 (45.9)
Age (years)						
20 – 39	1729 (36.5)	1236 (35.2)	493 (42.7)	231 (66.8)	165 (50.5)	65 (15.0)
40 – 59	1713 (39.4)	1142 (39.4)	493 (39.7)	109 (27.6)	142 (39.2)	298 (51.3)
60+	1725 (24.0)	1300 (25.4)	423 (17.6)	44 (5.6)	66 (10.3)	298 (33.6)
Education Level						
< High School Diploma	1241 (17.2)	708 (14.1)	532 (32.8)	118 (29.2)	140 (36.1)	256 (31.8)
High School Diploma	1006 (21.3)	811 (22.5)	195 (15.2)	58 (17.1)	51 (17.3)	82 (12.5)
> High School	2385 (61.5)	1854 (63.4)	531 (52.1)	154 (53.7)	130 (46.6)	237 (55.8)
Smoking Status						
Current Smoker	1379 (26.5)	1149 (28.8)	230 (16.0)	67 (19.0)	52 (13.1)	93 (14.5)
Heavy alcohol use						
Yes	852 (41.4)	652 (42.3)	200 (36.4)	64 (45.1)	53 (42.3)	73 (24.6)

Table 2. Blood Concentrations of PFOA, PFOS, PFHxS and PFNA in Overall Sample and Stratified by Place of Birth, And Length of Residence

Concentrations in ng/mL	General Sample	By Place of Birth		Length of Residence (Years)		
		Native-born	Foreign-born	<10	10 – <20	20+
PFOA						
Mean (SE)	3.76 (0.08)	3.91 (0.09)	3.04 (0.12)	2.64 (0.24)	2.84 (0.10)	3.46 (0.13)
Median	3.14	3.35	2.46	2.09	2.28	2.89
Q1	0.07 – 2.01	0.07 – 2.14	0.07 – 1.60	0.10 – 1.40	0.07 – 1.49	0.07 – 2.04
Q2	2.02 – 3.15	2.15 – 3.36	1.61 – 2.47	1.41 – 2.10	1.50 – 2.29	2.05 – 2.90
Q3	3.16 – 4.80	3.37 – 5.00	2.48 – 3.80	2.11 – 3.20	2.30 – 3.61	2.91 – 4.40
Q4	4.81 – 24.00	5.01 – 24.00	3.81 – 23.90	3.21 – 16.20	3.62 – 19.00	4.41 – 23.90
PFOS						
Mean (SE)	13.41 (0.54)	13.63 (0.63)	12.42 (0.80)	8.86 (0.67)	11.82 (0.93)	16.00 (1.34)
Median	10.01	10.29	8.19	5.60	7.90	10.59
Q1	0.14 – 5.85	0.14 – 6.29	0.14 – 4.40	0.14 – 2.90	0.14 – 4.10	0.14 – 6.30
Q2	5.86 – 10.10	6.30 – 10.30	4.41 – 8.20	2.91 – 6.00	4.11 – 7.91	6.31 – 10.60
Q3	10.11 – 16.40	10.31 – 16.80	8.21 – 14.60	6.01 – 11.30	7.92 – 14.90	10.61 – 17.00
Q4	16.41 – 281.00	16.81 – 276.00	14.61 – 281.00	11.31 – 92.10	14.91 – 83.60	17.01 – 281.00
PFHxS						
Mean (SE)	2.41 (0.10)	2.53 (0.11)	1.81 (0.08)	1.15 (0.06)	1.59 (0.09)	2.51 (0.15)
Median	1.60	1.70	1.19	0.80	1.11	1.79
Q1	0.07 – 0.92	0.07 – 1.00	0.07 – 4.40	0.07 – 0.40	0.07 – 0.69	0.07 – 0.90
Q2	0.93 – 1.60	1.01 – 1.71	4.41 – 8.20	0.41 – 0.80	0.70 – 1.12	0.91 – 1.80
Q3	1.61 – 2.80	1.72 – 3.00	8.21 – 14.60	0.81 – 1.40	1.13 – 1.70	1.81 – 3.00
Q4	2.81 – 81.60	3.01 – 47.80	14.61 – 81.60	1.41 – 12.80	1.71 – 14.30	3.01 – 81.60
PFNA						
Mean (SE)	1.43 (0.06)	1.43 (0.08)	1.40 (0.06)	1.25 (0.09)	1.45 (0.09)	1.47 (0.09)
Median	1.14	1.14	1.06	0.10	1.05	1.14
Q1	0.05 – 0.75	0.06 – 0.79	0.06 – 0.70	0.06 – 0.57	0.08 – 0.66	0.06 – 0.75
Q2	0.76 – 1.15	0.80 – 1.15	0.71 – 1.06	0.58 – 0.98	0.67 – 1.07	0.76 – 1.15
Q3	1.16 – 1.64	1.16 – 1.64	1.07 – 1.72	0.99 – 1.56	1.07 – 1.80	1.16 – 1.72
Q4	1.65 – 80.77	1.64 – 80.77	1.72 – 12.05	1.57 – 6.48	1.80 – 10.91	1.73 – 12.05

Table 3. Correlation Matrix of Selected PFCs

	PFOA	PFOS	PFHxS	PFNA
PFOA				
PFOS	0.70			
PFHxS	0.66	0.71		
PFNA	0.67	0.69	0.47	

Table 4. Least square geometric mean (LSGM) concentrations of PFOA, PFNA, and PFHxS by country of birth and length of residence

	Least Square Geometric Mean* (95% CI)			
	PFOA	PFOS	PFHxS	PFNA
By Place of Birth				
Native-born	2.99 (2.83 – 3.17)*	9.90 (9.16 – 10.69)	1.57 (1.45 – 1.70)*	1.18 (1.09 – 1.28)
Foreign-born	2.50 (2.32 – 2.70)	8.62 (7.75 – 9.58)	1.28 (1.18 – 1.38)	1.10 (1.01 – 1.21)
By Length of Residence (Years)				
<10	2.34 (2.00 – 2.73)	7.19 (6.08 – 8.51)*	0.91 (0.80 – 1.03)*	1.04 (0.90 – 1.21)
10 – 19	2.59 (2.30 – 2.93)	9.47 (7.99 – 11.22)	1.22 (1.07 – 1.39)*	1.23 (1.07 – 1.42)
20+	2.88 (2.60 – 3.20)	10.04 (8.85 – 11.39)*	1.56 (1.36 – 1.78)*	1.16 (1.05 – 1.27)

*Controlling for education level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis. Gender, age and race already accounted for in the Modification of Diet in Renal Disease study equation (Levey et al., 2006).

*Significant at α=0.05

Table 5. Mean and Least Square Mean (LSM) eGFR by Place of Birth, and Length of Residence

Variable	General Sample Mean (95% CI)	LSM* (95% CI)	Difference in LSM	
			Estimate (95% CI)	pvalue
General Sample	89.87 (88.83 – 90.90)			
By Place of Birth				
Native-born (NB)	87.79 (86.59 – 89.00)	91.41 (83.69 – 99.14)		
Foreign-born (FB)	99.55 (97.27 – 101.83)	107.15 (91.67 – 122.62)		
NB vs. FB			-15.73 (-25.49, -5.98)	0.002*
By Length of Residence (Years)				
<10	106.94 (103.79 – 110.09)	136.54 (126.28 – 146.80)		
10 – 19	103.74 (100.56 – 106.93)	129.22 (116.41 – 142.03)		
≥ 20	90.16 (86.63 – 93.70)	126.00 (114.98 – 137.01)		
<10 vs. (10-19)			7.32 (-0.08, 14.72)	0.05
<10 vs. ≥ 20			10.55 (6.34 – 14.75)	<0.001*
(10-19) vs. ≥ 20			3.22 (-1.95,8.39)	0.21

*Controlling for education level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis. Gender, age and race already accounted for in the Modification of Diet in Renal Disease study equation (Levey et al., 2006)

*Significant at α=0.05

Table 6. Odds Ratios (OR) of having low eGFR for a unit increase in PFOA, PFOS, PFHxS, and PFNA Concentrations

	OR (95% CI)			
	PFOA	PFOS	PFHxS	PFNA
		Model 1[a]		
All foreign-born	1.85 (1.46 – 2.34)*	1.49 (1.28 – 1.75)*	1.69 (1.42 – 2.00)*	1.54 (1.23 – 1.92)*
		By Length of Residence (Years)		
<10	1.55 (0.98 – 2.44)	1.16 (0.89 – 1.50)	1.30 (0.91 – 1.87)	1.30 (0.88 – 1.93)
10 – 19	1.48 (0.86 – 2.53)	1.52 (1.02 – 2.28)*	1.36 (0.94- 1.97)	2.13 (1.24 – 3.66)*
≥ 20	1.71 (1.21 – 2.42)*	1.34 (1.10 – 1.64)*	1.64 (1.31 – 2.06)*	1.25 (0.89 – 1.74)
		Model 2[b]		
All foreign-born	2.04 (1.26 – 3.28)*	1.40 (1.09 – 1.79)*	1.88 (1.48 – 2.39)*	1.44 (0.89 – 2.33)
		By Length of Residence (Years)		
<10	1.21 (0.56 – 2.63)	0.94 (0.69 – 1.28)	1.27 (0.70 – 2.31)	1.68 (0.76 – 3.71)
10 – 19	2.96 (1.37 – 6.39)*	1.19 (0.69 – 2.04)	1.59 (0.96 – 2.64)	6.04 (2.59 – 14.11)*
20 +	3.59 (1.45 – 8.90)*	1.11 (0.90 – 1.36)	2.38 (1.53 – 3.70)*	0.83 (0.44 – 1.60)

[a]Model 1: Crude model *Significant at α=0.05

[b]Model 2: Controlling for smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 7. Mean and Least Square Mean (LSM) of Alanine aminotransferase (ALT) (IU/L) by Place of Birth, and Length of Residence

Variable	General Sample Mean (95% CI)	LSM* (95% CI)	Difference in LSM	
			Estimate (95% CI)	pvalue
General Sample	25.74 (25.22 - 26.26)			
By Place of Birth				
Native-born (NB)	25.52 (24.89 - 26.14)	28.24 (26.13 – 30.35)		
Foreign-born (FB)	26.78 (25.78 – 27.79)	31.12 (28.45 – 33.80)		
NB vs. FB			-2.88 (-5.29 - -0.47)	0.02*
By Length of Residence (Years)				
<10	26.80 (24.30 - 29.31)	32.93 (30.33 - 35.53)		
10 – 19	28.06 (25.54 - 30.58)	34.94 (31.20 - 38.69)		
≥ 20	25.76 (24.66 – 26.86)	32.06 (30.07 - 34.05)		
<10 vs. (10-19)			-2.01 (-6.40 – 2.37)	0.36
<10 vs. ≥ 20			0.87 (-2.25 – 4.00)	0.33
(10-19) vs. ≥ 20			2.88 (0.07 – 5.69)	0.04*

*Controlling for age, race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis.

*Significant at α=0.05

Table 8. Mean and Least Square Mean (LSM) of Gamma glutamyl transferase (GGT) (IU/L) by Place of Birth, and Length of Residence

Variable	General Sample Mean (95% CI)	LSM* (95% CI)	Difference in LSM	
			Estimate (95% CI)	pvalue
General Sample	28.05 (26.18 – 29.91)			
By Place of Birth				
Native-born (NB)	28.33 (26.01 – 30.64)	35.30 (32.09 – 38.52)		
Foreign-born (FB)	26.70 (24.93 – 28.47)	35.66 (32.23 – 39.09)		
NB vs. FB			-0.36 (-2.94 – 2.23)	0.78
By Length of Residence (Years)				
<10	24.56 (20.95 – 28.17)	36.48 (32.48 – 40.47)		
10 – 19	29.77 (26.63 – 32.91)	42.75 (32.48 – 40.47)		
≥ 20	26.45 (24.42 – 28.49)	37.50 (33.39 – 41.60)		
<10 vs. (10-19)			-6.27 (-10.99 - -1.55)	0.01*
<10 vs. ≥ 20			-1.02 (-4.55 – 2.52)	0.56
(10-19) vs. ≥ 20			5.25 (1.86 – 8.65)	0.003*

*Controlling for age, race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis.

Table 9. Mean and Least Square Mean (LSM) of Total Bilirubin (mg/dL) by Place of Birth, and Length of Residence

Variable	General Sample Mean (95% CI)	LSM* (95% CI)	Difference in LSM	
			Estimate (95% CI)	pvalue
General Sample	0.76 (0.74 – 0.77)			
By Place of Birth				
Native-born (NB)	0.76 (0.74 – 0.78)	0.75 (0.73 – 0.77)		
Foreign-born (FB)	0.74 (0.72 – 0.76)	0.72 (0.70 – 0.74)		
NB vs. FB			0.03 (0.003 – 0.05)	0.03*
By Length of Residence (Years)				
<10	0.75 (0.71 – 0.78)	0.73 (0.68 – 0.78)		
10 – 19	0.73 (0.70 – 0.77)	0.74 (0.69 – 0.78)		
≥ 20	0.74 (0.71 – 0.77)	0.73 (0.70 – 0.76)		
<10 vs. (10-19)			-0.01 (-0.06 – 0.05)	0.76
<10 vs. ≥ 20			-0.004 (-0.05 – 0.04)	0.87
(10-19) vs. ≥ 20			0.005 (-0.04 – 0.05)	0.82

*Controlling for age, race/ethnicity, educational level, smoking status, heavy alcohol use, impaired glucose tolerance, and hypertension diagnosis.

*Significant at α=0.05

Table 10. Odds Ratios (OR) of having elevated ALT for a unit increase in PFOA, PFOS, PFHxS, and PFNA Concentrations

	OR (95% CI)			
	PFOA	PFOS	PFHxS	PFNA
	Model 1 [a]			
All foreign-born	0.93 (0.70- 1.24)	1.07 (0.82 - 1.39)	1.07 (0.85 -1.34)	0.86 (0.62 -1.18)
By Length of Residence (Years)				
<10	1.07 (0.58 – 1.97)	1.10 (0.69 - 1.73)	1.17 (0.75 - 1.83)	0.96 (0.51 - 1.82)
10 – 19	0.79 (0.53 - 1.18)	0.81 (0.58 - 1.13)	1.02 (0.68 – 1.53)	0.82 (0.53 - 1.28)
≥ 20	1.00 (0.70 - 1.43)	1.07 (0.82 - 1.39)	1.19 (0.94 - 1.52)	0.80 (0.58 - 1.10)
	Model 2 [b]			
All foreign-born	1.03 (0.70 -1.50)	1.05 (0.77 – 1.45)	1.21 (0.88 – 1.65)	0.87 (0.58 -1.30)
By Length of Residence (Years)				
<10	1.14 (0.49- 2.67)	1.11 (0.59 – 2.10)	1.14 (0.66 - 1.98)	0.87 (0.38 - 1.95)
10 – 19	0.80 (0.49 - 1.31)	0.82 (0.55 - 1.20)	0.99 (0.63 - 1.56)	0.83 (0.50 - 1.40)
20 +	1.49 (1.00 - 2.22)*	1.37 (1.02 - 1.82)*	1.65 (1.28 - 2.14)*	1.01 (0.67 - 1.52)

[a]Model 1: Crude model *Significant at α=0.05

[b]Model 2: Controlling for race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 11. Odds Ratios (OR) of having elevated GGT for a unit increase in PFOA, PFOS, PFHxS, and PFNA Concentrations

	OR (95% CI)			
	PFOA	PFOS	PFHxS	PFNA
	Model 1[a]			
All foreign-born	1.46 (1.09 - 1.95)*	1.31 (1.05 - 1.65)*	1.22 (0.99 - 1.51)	1.40 (1.01 - 1.92)*
By Length of Residence (Years)				
<10	1.24 (0.73 - 2.11)	1.15 (0.85 - 1.54)	1.24 (0.84 - 1.84)	0.98 (0.64 -1.49)
10 – 19	1.17 (0.69 - 2.00)	1.24 (0.80 - 1.91)	1.00 (0.63 - 1.59)	1.35 (0.73 -2.48)
≥ 20	1.91 (1.04 – 3.51)*	1.36 (0.94 - 1.97)	1.27 (0.93 - 1.74)	1.57 (0.85 - 2.90)
	Model 2[b]			
All foreign-born	1.24 (0.87 - 1.76)	1.24 (0.95 - 1.62)	1.10 (0.87 - 1.41)	1.24 (0.84 - 1.83)
By Length of Residence (Years)				
<10	0.96 (0.53 - 1.78)	0.97 (0.71 - 1.33)	1.06 (0.65 - 1.74)	0.74 (0.49 - 1.10)
10 – 19	0.84 (0.49 - 1.42)	1.03 (0.65 - 1.63)	0.81 (0.48 - 1.37)	1.02 (0.55 -1.88)
20 +	1.98 (1.07 - 3.69)*	1.37 (0.93 -2.03)	1.35 (0.98 - 1.87)	1.44 (0.78 - 2.68)

[a]Model 1: Crude model *Significant at α=0.05

[b]Model 2: Controlling for race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 12. Odds Ratios (OR) of having elevated Total Bilirubin for a unit increase in PFOA, PFOS, PFHxS, and PFNA Concentrations

	OR (95% CI)			
	PFOA	PFOS	PFHxS	PFNA
	Model 1[a]			
All foreign-born	1.39 (0.83 - 2.32)	1.43 (0.98 -2.09)	1.43 (1.03 -1.97)*	1.57 (0.85 - 2.91)
By Length of Residence (Years)				
<10	1.02 (0.33 - 3.15)	1.25 (0.57 - 2.75)	1.25 (0.63 - 2.47)	1.06 (0.39 - 2.91)
10 – 19	1.57 (0.88 -2.80)	1.79 (1.11 - 2.89)	1.66 (1.04 - 2.66)	2.13 (1.44 - 3.17)*
≥ 20	1.82 (0.93 - 3.54)	1.33 (0.81 - 2.20)	1.44 (1.00 - 2.07)	1.97 (0.67 - 5.81)
	Model 2[b]			
All foreign-born	1.63 (0.94 - 2.83)	1.69 (1.12 -2.53)*	1.60 (1.11 -2.30)*	1.81 (1.05 -3.13)*
By Length of Residence (Years)				
<10	0.96 (0.29 - 3.20)	1.26 (0.55 - 2.90)	1.29 (0.62 - 2.66)	0.99 (0.38 - 2.57)
10 – 19	1.70 (0.86 - 3.40)	2.31 (1.13 - 4.72)*	2.01 (1.08 - 3.72)*	3.02 (1.20 - 7.65)*
20 +	2.11 (0.96 - 4.64)	1.34 (0.76 -2.37)	1.50 (0.86 - 2.63)	1.59 (0.79 - 3.19)

[a]Model 1: Crude model *Significant at α=0.05

[b]Model 2: Controlling for race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 13: Assessment of the factor loading matrix of PFC serum concentration principal components

Variables	PFOS/ PFHxS	PFOS/ PFNA	PFOA
PFOA	0.38	0.38	0.83*
PFOS	0.68*	0.64*	0.20
PFHxS	0.90*	0.16	0.34
PFNA	0.18	0.90*	0.33

* Items with factor loadings 0.4 or greater are retained for that component

Table 14: Crude and Adjusted Logistic Regression of PFC Serum concentration principal components and risk of low eGFR

	OR (95% CI)		
	PFOS/ PFHxS	PFOS/ PFNA	PFOA
	Model 1 [a]		
Quartile			
1	Ref.	Ref.	Ref.
2	1.64 (1.40 -1.91) *	1.03 (0.88 - 1.21)	1.27 (1.09 - 1.49)
3	1.85 (1.58 - 2.16) *	1.12 (0.96 - 1.32)	1.25 (1.06 - 1.46)
4	2.89 (2.46 - 3.40) *	1.33 (1.13 - 1.55)	1.27 (1.08 - 1.49)
	Model 2 [b]		
Quartile			
1	Ref.	Ref.	Ref.
2	1.38 (1.04 - 1.83)*	0.91 (0.68 - 1.20)	1.24 (0.90 - 1.71)
3	1.53 (1.16 - 2.01)*	0.91 (0.69 - 1.20)	0.96 (0.71 - 1.30)
4	2.41 (1.82 - 3.19)*	1.14 (0.86 - 1.50)	1.22 (0.90 - 1.65)

[a] Mutually adjusted for all other principal components factors *Significant at α=0.05

[b] Adjusted for all principal components factors, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 15: Crude and Adjusted Logistic Regression of PFC Serum concentration principal components and risk of elevated ALT

	OR (95% CI)		
	PFOS/ PFHxS	PFOS/ PFNA	PFOA
	Model 1 [a]		
Quartile			
1	Ref.	Ref.	Ref.
2	1.12 (0.88 - 1.44)	1.02 (0.80 - 1.32)	0.78 (0.59 - 1.02)
3	1.02 (0.80 - 1.31)	0.81 (0.63 - 1.06)	1.10 (0.85 - 1.42)
4	0.75 (0.58 - 0.98)	0.92 (0.71 - 1.19)	1.28 (1.00 - 1.64)*
Model 2 [b]			
1	Ref.	Ref.	Ref.
2	1.36 (0.85 - 2.18)	0.91 (0.57 - 1.46)	0.54 (0.32 - 0.93)
3	1.55 (0.96 - 2.50)	0.94 (0.59 - 1.50)	0.69 (0.43 - 1.12)
4	1.34 (0.82 - 2.18)	1.36 (0.86 - 2.16)	0.88 (0.56 - 1.42)

[a] Mutually adjusted for all other principal components factors *Significant at α=0.05

[b] Adjusted for all principal components factors, race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 16: Crude and Adjusted Logistic Regression of PFC Serum concentration principal components and risk of elevated GGT

	OR (95% CI)		
	PFOS/ PFHxS	PFOS/ PFNA	PFOA
	Model 1 [a]		
Quartile			
1	Ref.	Ref.	Ref.
2	1.13 (0.89 - 1.43)	0.87 (0.68 - 1.13)	1.26 (0.98 - 1.61)
3	1.00 (0.78 - 1.27)	1.06 (0.83 - 1.36)	1.27 (0.99 - 1.63)
4	0.83 (0.64 - 1.07)	1.20 (0.95 - 1.53)	1.22 (0.95 - 1.57)
	Model 2 [b]		
Quartile			
1	Ref.	Ref.	Ref.
2	0.99 (0.65 - 1.52)	0.72 (0.47 - 1.12)	1.23 (0.77 - 1.98)
3	1.09 (0.72 - 1.67)	0.93 (0.62 - 1.42)	1.01 (0.64 - 1.60)
4	0.76 (0.49 - 1.18)	0.93 (0.61 - 1.41)	1.25 (0.80 - 1.95)

[a] Mutually adjusted for all other principal components factors *Significant at α=0.05

[b] Adjusted for all principal components factors, race, age, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

Table 17: Crude and Adjusted Logistic Regression of PFC Serum concentration principal components and risk of elevated Total Bilirubin

	OR (95% CI)		
	PFOS/ PFHxS	PFOS/ PFNA	PFOA
	Model 1 [a]		
Quartile			
1	Ref	Ref	Ref
2	1.35 (0.91 – 2.00)	0.85 (0.59 - 1.22)	1.22 (0.83 - 1.80)
3	1.56 (1.06 - 2.29) *	0.98 (0.69 - 1.40)	1.38 (0.95 - 2.01)
4	1.99 (1.37 - 2.88) *	1.19 (0.84 - 1.68)	1.80 (1.25 - 2.58) *
	Model 2 [b]		
Quartile			
1	Ref	Ref	Ref
2	2.33 (1.17 - 4.64) *	0.99 (0.56 - 1.75)	1.00 (0.50 - 2.00)
3	2.47 (1.24 - 4.92) *	1.20 (0.69 - 2.08)	1.20 (0.63 - 2.29)
4	2.82 (1.42 - 5.61) *	1.18 (0.66 - 2.10)	1.44 (0.76 - 2.72)

[a] Mutually adjusted for all other principal components factors *Significant at α=0.05

[b] Adjusted for all principal components factors, smoking status, BMI, heavy alcohol use, impaired glucose tolerance, hypertension status, total cholesterol level, and education level

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APPENDICES

Appendix 1. International Guideline Health-based Values for PFOA and PFOS *

Country/Agency	**Guideline Value (µg/ L)**		**Source**
	PFOA	PFOS	
German Ministry of Health	0.3	0.3	German Ministry of Health (2006)
United Kingdom (UK) Drinking Water Inspectorate	5.0	1.0	UK Drinking Water Inspectorate (2009)
Danish Ministry of the Environment	0.3	0.1	Danish Ministry of the Environment (2015)
Dutch National Institute for Public Health and the Environment	-	0.09	RIVM (2010)
Swedish National Food Agency		0.09	Livsmedelsverket (2014), cited in Danish Ministry of the Environment (2015)

* Cited in (USEPA, 2016a, 2016b)

Appendix 1: Molecular Structures of PFOA, PFOS, PFHxS, and PFNA

Figure 1: Molecular structure of Perfluorooctanoic acid (PFOA)

Figure 2: Molecular structure of perfluorooctane sulfonic acid (PFOS)

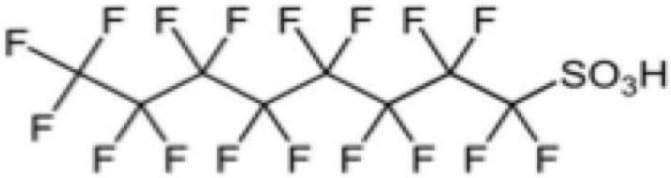

Figure 3: Molecular structure of perfluorohexane sulfonic acid (PFHxS)

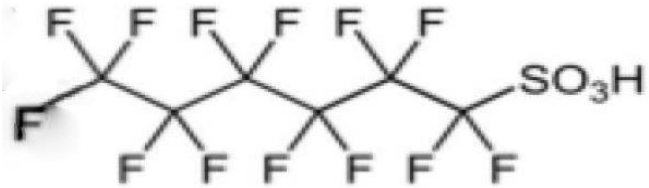

Figure 4: Molecular structure of perfluorononoic acid (PFNA)