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Perfluoroalkyl Substances Exposure and Cancer in NHANES 2011-2016 U.S. Population

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Abstract

Background: Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are persistent synthetic compounds that may have associated health risks.

Purpose: To explore the association between four common detectable serum PFASs perfluorooctanoic acid (PFOA), perfluorooctyl sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) and cancer risk in United States (U.S.) adults.

Methods: Data from 4,497 participants from the 2011–2016 National Health and Nutrition Examination Survey (NHANES) were analyzed. Gender stratified adjusted logistic regression analysis was conducted to determine association between serum PFASs tertiles and risk of cancer.

Results: Median (IQR) PFASs were significantly higher in men compared to women, and among individual with cancer than healthy participants ($p < .05$ for both). In unadjusted analysis, a significantly high risk of cancer was noted in males in high PFOS tertile compared to low group the unadjusted odds of cancer in males were 115% (OR 2.15; 95% CI 1.502, 3.078; $p < .001$) elevated in high PFOS tertile compared to referent. In unadjusted analysis, a significantly elevated risk of cancer was noted in females for PFOA, PFOS, PFHxS high tertile as well as medium tertile compared to low group. The unadjusted odds of cancer in females were 132%, $p < .001$, 157%, $p < .001$, 235%; $p < .001$ elevated in women in high PFOA, PFOS, PFHxS tertile, respectively compared to low group. In adjusted models no significant association between PFAS serum levels and cancer was observed in men or women.

Conclusion: In U.S. adults, serum PFASs levels were not significantly associated with cancer.

Keywords: perfluoroalkyl substances, NHANES, public health, cancer

The relationship of perfluoroalkyl and polyfluoroalkyl substances and cancer risk: 2011 – 2016 NHANES Data

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) represents a family of manmade chemicals that contain a carbon and fluorine backbone. They are part of a larger universe of organic and inorganic substances that contain at least 1 Fluorine atom, with vastly different physical, chemical, and biologic properties called 'fluorinated substances' (Buck et al., 2011). There are hundreds of PFAS compounds with a varying functional group or groups which can include other elements such as oxygen, hydrogen, or sulfur. Originally fabricated in 1950, PFAS compounds have been used extensively in commercial and industrial applications: textiles, stain and soil repellents, and aqueous film-forming foams used frequently in fire-fighting (Buck et al., 2011).

Over the past half of a century, the ubiquitous use of these compounds and their subsequent discharge into the environment has led to the detection of these compounds at all ecological levels, including human beings (Hu et al., 2016). However, despite the United States (U.S.) and global interventions on PFAS production, reduction, and elimination, these long-lasting compounds are now ubiquitous in our environment which makes understanding their impact paramount (Mueller & Yingling, 2017).

Research Question

What impact do PFAS's (perfluoroalkyl and polyfluoroalkyl substances) exposure have on the risk of cancer among the adult population (≥ 20 years) in the U.S.? Since PFASs have been shown to increase risk of cancer in animal models and limited human studies (Barry, Winquist, & Steenland, 2013), we hypothesize that there will be an association between

detectable PFASs levels in serum and the presence of cancer in adults aged 20 years and greater within the U.S.

Literature Review

Human Exposure to PFAS

During production and use, PFAS can migrate into the soil, water, and air. Most PFAS (including PFOA and PFOS) do not breakdown, so they remain in the environment. Because of their widespread use and their persistence in the environment, PFAS are found in the blood of people and animals all over the world and are present at low levels in a variety of food products and in the environment. Some PFAS can build up in people and animals with repeated exposure over time (Mueller & Yingling, 2017).

Health Effects of PFAS

Many researchers have targeted the potential relationship of PFAS to multiple health effects. These include, but are not limited to, PFAS affecting growth, learning, and behavior of infants and older children, lowering a woman's chance of getting pregnant, interfering with the body's natural hormones, increase cholesterol levels, affecting the immune system, and increase the risk of cancer (Lefebvre et al., 2008).

PFAS and Cancer Risk

Overall, there have been a limited number of studies focused on the potential relationship of PFAS to cancer risk. Animal studies in rats have shown a statistically significant ($p \leq 0.05$) increased incidence of Leydig cell tumors and adenomas of the testes, liver, and pancreas and hyperplasia when fed 300 ppm ammonium perfluorooctanoate (PFOA or also referred to as C8 in the literature) (Butenhoff, Kennedy, Chang, & Olsen, 2012). Thomford (2002) demonstrated increased incidence ($p \leq 0.05$) of hepatocellular adenomas in male rats fed high dose PFOS (20

ppm) for two years compared to controls. In addition, female rats in the same study showed also demonstrated a dose related increase in hepatocellular adenomas but also had a non-dose related increase in mammary gland adenomas (0.5 ppm). Other polyfluorinated compounds have also shown animal carcinogenicity such as 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propionic acid, ammonium salt (CAS 62037-80-3) which showed increases in liver adenomas in rats (Anand, 2013). The increase in liver associated lesions is not surprising given that the liver is the main target organ for PFAS compounds. It is thought that one mechanism of action for this is the proliferation of peroxisomes and increased liver mitogenesis that was associated with PFOA (Biegel, Hurtt, Frame, O'Conner, & Cook, 2001). PFOA mechanism of action on the Leydig cell tumors was thought to be related to PFOA inhibiting testosterone biosynthesis and increases in serum estradiol levels via induction of hepatic aromatase activity (Liu, Hurtt, Cook, & Biegel, 1996). And likewise, pancreatic acinar cell proliferation is also thought to be related to secondary PFOA liver effects.

Human studies are limited in nature and the majority are occupational cohort studies. Human data for cancer from two occupational cohorts are limited to mortality and are based on small numbers. One of the two cohorts showed increased kidney cancer (Leonard, Kreckmann, Sakr, & Symons, 2008), and the other showed positive exposure–response trends for pancreatic and prostate cancer that were not statistically significant (Lundin, Alexander, Olsen, & Church, 2009). In a prospective Danish cohort study, plasma concentrations of background PFOA exposures were not associated with prostate, bladder, pancreatic, or liver cancer (Eriksen et al., 2009). A case-control study of Greenland Inuit women found a positive but not statistically significant association between PFOA exposure and breast cancer (Bonefeld-Jorgensen et al.,

2011). The positive associations were generally not consistent among cancer sites between studies, and for the remaining cancer sites reported, no associations were observed.

Methods

Data Source and Study Sample

Data for three survey cycles from 2011-2012, 2013-2014, and 2015-2016 were obtained from the freely available National Health and Nutrition Examination Survey (NHANES), which is a population-based survey. NHANES collects individual, laboratory and physical examination information about noninstitutionalized U.S. individuals every two years. The survey's goal is to collect a representative sample of the U.S. population. All survey operations manuals, brochures and consent documents for the dataset are publicly available on the NHANES website as part of the Centers for Disease Control and Prevention (CDC).

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. This process is broken down to three steps: a doorstep screener with a brief interview for exclusion criteria, and in-depth confidential home interview, and a health examination performed in the Mobile Examination Center (MEC**)** that contains high-tech medical equipment and allows for in depth laboratory analysis. From the 2011-2016 NHANES combined dataset, individuals with data available for the four PFASs in question were included in the studied population.

PFAS Concentration Measured via Serum Analysis

The CDC sponsored NHANES website provides in depth protocol for each of the laboratory measure collected in the MEC. Online solid phase extraction coupled to high performance liquid chromatography-turboionspray ionization-tandem mass spectrometry (online

SPE-HPLC-TIS-MS/MS) is used for the quantitative detection of PFAS (Kuklenyik, Needham, & Calafat, 2005). The lower limit of detection (LLOD) for each PFAS was 0.10 ng/mL. If a sample had analytic results below the LLOD, an imputed value was placed in the database for that sample by the NHANES study designers. Given the skewed distribution serum PFAS among participants included in the study, each of the four serum PFASs were split in into equal tertiles: low, medium, and high based on gender specific cutoff points.

Confounders

Socioeconomic and sociodemographic information (i.e., age, race/ethnicity, gender, and income) were collected by trained interviewers using the in-home NHANES Family Questionnaire via the Computer-Assisted Personal interview (CAPI) system. Race/Ethnicity was reported as Hispanic, non-Hispanic White, non-Hispanic Black, and other multi-racial (referent category). Race and income were recoded from the NHANES data set to form three categories: non-Hispanic White (NHW), non-Hispanic Black (NHB), and others. Income was recoded into low ($0 to, 24,999/year), medium (25,000 to 54,999/year, and high categories ($55,000+/year).

Statistical Analysis

Data analyses were performed Statistical Package for the Social Science (SPSS) version 26.0 (IBM Corp, Released 2019). Descriptive statistics for continuous variables such as age and PFAS included measures of centrality (mean or median) and dispersion (standard deviation or interquartile range) overall and by gender, and by presence of cancer. Frequency distributions were computed for categorical variables (race, income).

Across gender statistical significance for continuous variables were tested using Student's 2-tailed *t*-test for normally distributed variables (age) and the Mann-Whitney U test for non-

normal (non-parametric variables) (PFASs). For categorical variables (race and income), difference were computed with the Chi-square test.

To determine independent association between PFAS serum levels and cancer, logistic regression analysis was performed. Exposure was categorized as gender specific PFAS tertiles (low, medium, and high). The low category was used as the referent to compare with medium and high categories. In the first logistic regression model (unadjusted) only cancer outcome and PFAS exposure as tertiles was entered (each PFAS was modeled separately) which compared the odd of cancer in individual who had medium or high serum PFAS exposure compared to the referent or low category. The second model was adjusted for age and the third model was adjusted for age, income, and race. The odds ratio (OR) and 95% confidence interval (CI) of risk of cancer per exposure level to the four PFASs were reported with the two tailed *p*-value used at an $\alpha = 0.05$ significance level.

Results

Descriptive Statistics

The descriptive statistics of the overall study population and by gender are included in Table 1. The *p*-value represents comparison between gender. The average age was 49.03 and did not differ significantly between genders. Overall, the predominant income bracket was annual household income of $55,000. Income distribution was statistically different between genders. The ethnicity groups overall showed a predominance of the “other” category and were not significantly different among genders. Each of the PFAS selected for this study were significantly higher among males; however, cancer rates between genders were not significantly different.

Table 1

Descriptive Characteristics of NHANES 2011-2016 Participants, Overall and by Gender

	Overall	Male	Females	*p*-value*
Age (years), mean ± SD	49.03±17.63	49.09±17.64	48.97±17.62	*0.806*
Annual Household Income, n (%)				*0.019*
< $25, 000	1,347(30.0)	601(28.0)	746(31.8)	
$25,000 to 54,999	1,368 (30.4)	664 (30.9)	704 (30.0)	
> 55,000	1,782 (39.6)	883(41.1)	899 (38.3)	
Ethnicity, n (%)				*0.772*
NHW	1,723 (38.3)	836(38.9)	887(37.8)	
NHB	1,020 (22.7)	481(22.4)	539(22.9)	
Others	1,754(39.0)	851(38.7)	923(39.3)	
PFASs (ng/mL) median, IQR				
PFOA	1.90 (1.26-2.80)	2.17(1.54-3.07)	1.57(0.970-2.49)	<0.001
PFOS	6.00 (3.40-10.2)	7.63(4.82-12.2)	4.59(2.50-8.20)	<0.001
PFHxS	1.30 (0.70-2.23)	1.72(1.10-2.70)	0.93(0.50-1.64)	<0.001
PFNA	0.74 (0.50-1.14)	0.80(0.55-0.80)	0.70(0.40-1.02)	<0.001
Cancer, n (%)	407(9.1)	201(9.4)	206(8.8)	0.493

The descriptive statistics were also analyzed by cancer diagnosis (Table 2). Mean age was significantly higher in individuals with cancer compared to those who did not have cancer (about 18 years; $p < .001$). Ethnicity, gender distribution was significantly different between the cancer diagnosis group and the no-cancer diagnosis grouping, while income was not. Among those with cancer NHW ethnicity was predominant (65%), whereas only 15% NHB had cancer. Median serum PFAS was significantly higher in those with cancer compared with individuals without cancer ($p < .05$ for all).

Table 2

Descriptive Characteristics of NHANES 2011-2016 Participants, by Cancer Diagnosis

	Cancer	No-cancer	*p*-value*
Age (years), mean ±SD	65.66 (13.06)	47.37(17.16)	<.001
Gender			.471
Male	201(49.4)	1947(47.6)	
Female	206(50.6)	2143(52.4)	
Annual Household Income, n (%)			.793
Low	124(30.5)	1223(29.9)	
Medium	128(31.4)	1240(30.3)	
High	155(38.1)	1627(39.8)	
Ethnicity, n (%)			<.001
NHW	265(65.1)	1458(35.6)	
NHB	61(15.0)	959(23.4)	
Others	81(19.9)	1673(40.9)	
PFASs (ng/mL) Median, IQR			
PFOA	2.17(1.59)	1.87(1.59)	<.001
PFOS	7.80(8.27)	5.800(6.69)	<.001
PFHxS	1.60(1.52)	1.30(1.50)	<.001
PFNA	0.80(.71)	0.720(.62)	0.010

Table 3 shows the unadjusted odds ratios of cancer with exposure to PFAS by gender. Among males, out of the four PFAS analyzed, only PFOS was associated with cancer diagnosis. Compared to the referent low PFOS group, males who had “high” serum PFOS demonstrated a 115% significant elevated risk of cancer (odd ratio of 2.15, CI: 1.502, 3.078). In contrast, among females except PFNA, all PFAS showed a dose dependent elevated risk of cancer.

Table 3

Unadjusted Odds Ratio (95% Confidence Interval) of Cancer with Exposure to PFASs in NHANES 2011-2016 Participants, by Gender

	Male		Females	
	OR(95% CI)	*p*-value*	OR (95% CI)	*p*-value*
PFOA				
Low	Referent		Referent	
Medium	1.105 (0.765, 1.595)	0.595	1.825 (1.222, 2.726)	.003
High	1.339 (0.940, 1.908)	0.106	2.317 (1.563, 3.435)	<.0001
PFOS				
Low	Referent		Referent	
Medium	1.144 (0.768, 1.702)	.508	1.597 (1.071, 2.383)	.022
High	2.150 (1.502, 3.078)	<.0001	2.569 (1.764, 3.743)	<.0001
PFHxS				
Low	Referent		Referent	
Medium	1.270 (0.881, 1.831)	.200	2.192 (1.437, 3.344)	<.0001
High	1.371 (0.956, 1.965)	.086	3.350 (2.242, 5.006)	<.0001
PFNA				
Low	Referent		Referent	
Medium	1.355 (0.960, 1.913)	.084	1.110 (0.775, 1.589)	.569
High	1.422 (0.951, 2.126)	.086	1.384 (0.980, 1.955)	.065

Age adjusted odds ratios and multivariable logistic regression (Tables 4 and 5) did not show any significant association between PFAS and cancer neither in males or females.

Table 4

Age Adjusted Odds Ratio (95% Confidence Interval) of Cancer with Exposure to PFASs in NHANES 2011-2016 Participants, by Gender

		Male		Females	
PFAS		Unadjusted OR(95% CI)	*p*-value*	MV adjusted OR(95% CI)	*p*-value*
PFOA					
	Low	Referent		Referent	
	Medium	1.016(0.689, 1.499)	.935	1.229(0.808, 1.868)	.335
	High	1.038(0.706, 1.527)	.849	1.092(0.715, 1.668)	.683
PFOS					
	Low	Referent		Referent	
	Medium	0.804(0.519, 1.245)	.327	1.018(0.668, 1.552)	.933
	High	0.848(0.566, 1.270)	.424	1.039(0.683, 1.581)	.858
PFHxS					
	Low	Referent		Referent	
	Medium	1.031(0.689, 1.542)	.883	1.462(0.942, 2.269)	.090
	High	0.952(0.641, 1.414)	.807	1.409(0.904, 2.195)	.130
PFNA					
	Low	Referent		Referent	
	Medium	0.937(0.639, 1.373)	.738	0.789(0.541, 1.150)	.217
	High	0.874(0.563, 1.357)	.548	0.562(0.527, 1.101)	.148

Table 5

Multivariable Adjusted Odds Ratio (95% Confidence Interval) of Cancer with Exposure to PFASs in NHANES 2011-2016 Participants, by Gender

		Male		Females	
PFAS		Unadjusted		MV adjusted	
		OR(95% CI)	*p*-value*	OR(95% CI)	*p*-value*
PFOA					
	Low	Referent		Referent	
	Medium	0.843(0.552, 1.289)	.431	1.134(0.742, 1.733)	.561
	High	0.748(0.496, 1.127)	.165	1.004(0.652, 1.545)	.986
PFOS					
	Low	Referent		Referent	
	Medium	0.797(0.506, 1.256)	.328	0.985(0.645, 1.505)	.945
	High	0.792(0.517, 1.214)	.285	1.103(0.720, 1.688)	.652
PFHxS					
	Low	Referent		Referent	
	Medium	0.916(0.602, 1.396)	.684	1.431(0.920, 2.226)	.112
	High	0.806(0.531, 1.222)	.309	1.340(0.858, 2.090)	.198
PFNA					
	Low	Referent		Referent	
	Medium	0.847(0.566, 1.267)	.419	0.799(0.546, 1.168)	.247
	High	0.950(0.597, 1.512)	.828	0.837(0.547, 1.221)	.356

In secondary analysis, selected gender specific cancers were also analyzed including breast and prostate cancer. The odds breast cancer in unadjusted analysis (Table 6) was significantly elevated in women who had high PFOS exposure as well in women with medium and high PFHxS exposure. However, adjusted OR for breast cancer were not significantly elevated. Unadjusted OR for prostate cancer in the high exposure category was significant for PFOS, PFHxS, and PFNA; however, the odds ratios were not significant in multivariable logistic regression (Table 7).

Table 6

Unadjusted Odds Ratio (95% Confidence Interval) of Breast Cancer with Exposure to PFASs in NHANES 2011-2016 Female Participants

	Female Breast Cancer			
PFAS	Unadjusted		MV adjusted	
	OR(95% CI)	*p*-value*	OR(95% CI)	*p*-value*
PFOA				
Low	Referent		Referent	
Medium	1.915(0.866,4.232)	.108	1.149(0.509, 2.597)	.738
High	2.166(0.985, 4.760)	.054	0.833(0.362, 1.914)	.666
PFOS				
Low	Referent		Referent	
Medium	1.350(0.616, 2.957)	.454	0.732(0.323, 1.657)	.454
High	2.255(1.097,4.636)	.027	0.718(0.234, 1.594)	.416
PFHxS				
Low	Referent		Referent	
Medium	3.262(1.296, 8.213)	.012	1.905(0.739, 4.910)	.182
High	4.332(1.767, 10.620)	.001	1.463(0.560, 3.823)	.437
PFNA				
Low	Referent		Referent	
Medium	0.881(0.435, 1.783)	.724	0.588(0.285, 1.210)	.149
High	1.172(0.605, 2.269)	.639	0.561(0.279, 1.127)	.104

Table 7

Unadjusted Odds Ratio (95% Confidence Interval) of Prostate Cancer with Exposure to PFASs in NHANES 2011-2016 Male Participants

	Male Prostate Cancer			
PFAS	Unadjusted OR(95% CI)	*p*-value*	MV adjusted OR(95% CI)	*p*-value*
PFOA				
Low	Referent			
Medium	1.045(0.549, 1.991)	.893	0.894(0.453, 1.766)	.747
High	1.563(0.865, 2.825)	.139	1.098(0.587, 2.053)	.771
PFOS				
Low	Referent		Referent	
Medium	1.273(0.608, 2.667)	.522	0.865(0.400, 1.870)	.712
High	3.063(1.614, 5.813)	.001	1.071(0.539, 2.126)	.845
PFHxS				
Low	Referent		Referent	
Medium	1.550(0.798, 3.013)	.198	1.185(0.592, 2.373)	.632
High	2.062(1.096, 3.879)	.025	1.296(0.666, 2.521)	.445
PFNA				
Low	Referent		Referent	
Medium	1.616(0.828, 3.154)	.159	0.960(0.475, 1.941)	.910
High	3.276(1.666, 6.442)	.001	1.840(0.898, 3.769)	.096

Discussion

In this this analysis of selected NHANES participants, the unadjusted models showed a significant association between PFHxS and cancer in males and a significant relationship of PFOA, PFOS, and PFHxS with cancer in females. However, the age adjusted and multivariate models did not show a statistically significant relationship. In addition, selected cancers for males (prostate cancer) and females (breast cancer) also showed a significant unadjusted association with PFAS levels, this was not the case with multivariate analyses.

Previous animal studies have a shown a dose related association of PFAS compounds to testicular cancer, liver and pancreatic adenomas, mammary tissue adenomas, and prostate cancer. There is some evidence of PFAS and linkage with risk of cancer in human studies (Vieira, et al., 2012). In addition, there have been reported marked intergender differences in the elimination of

PFOA in rats and substantial differences in the half-life of PFOA in rats, monkeys, and humans; the potential to estimate risks to humans from animal doses is uncertain (Centers for Disease Control & Prevention [CDC], 2009). The CDC (2009) also commented that PFOS levels appear to be two to threefold higher in the US than other comparable countries such as Brazil, Poland, Belgium, and Japan.

Carcinogenicity of PFASs remains unclear. Of the 5000 or so PFASs currently used, only PFOA has been categorized as "2B possible human carcinogen" by the World Health Organization's International Agency for Research on Cancer (IARC) (https://monographs.iarc.fr/wp-content/uploads/2018/06/mono110-01.pdf). This categorization is based on "limited" evidence for testicular and renal cancer from studies in human and experimental animals. The US Environmental Protection Agency has also classified PFOA's carcinogenic potential as "likely to be carcinogenic" in 2016 (Donohue, Duke, & Wambaugh, 2016).

Mechanistic data for PFOA shows that it is not metabolized in humans and is fully reabsorbed after filtration in the kidneys leading to much longer retention in the body when compared with all other tested animals. Therefore, the body burden of PFOA experienced by humans is much greater than in animal models.

The proposed mechanism of carcinogenicity for PFOA is thought to be due to induction of oxidative stress, hepatotoxity, and liver injury. Other mechanisms that could play a role in carcinogenesis include tumor induction, endocrine disruption, developmental toxicity, and, immune-toxicity.

In laboratory animals the liver is a well-known target for PFOA toxicity. The molecular mechanisms for PFOA-induced hepatotoxicity and carcinogenicity in the liver include PPARα

activation, involvement of other molecular pathways such as estrogen receptor and cytotoxicity. Other possible pathways are hypothesized to be via modulation of inflammatory pathways. Studies in human cells, rodents, and fish, have documented perturbation of molecular pathways involving reproductive hormones and hormone receptors, such as activation of estrogen receptor.

A recent nested case-control study conducted in French postmenopausal women (non-occupational exposure) suggests a dose-response relationship between PFOS serum concentrations and the risk of hormone receptor-positive breast cancer (Mancini et al., 2019).

Our study did show positive cancer relationships between several PFAS, and these appeared to be more robust in the female population. The median respective PFAS levels between males and females were significantly different (males greater than females), suggesting that there may be a gender association in humans, possibly due to occupational exposure, gender differences in physiologic elimination, or diet related. Given that the females, despite having lower PFAS levels in general, had more frequent positive associations with cancer might suggest that they are more sensitive to PFAS. This would be a possible area of additional research.

Strengths

The study had several strengths. Data from NHAHES represents a state of the art biomonitoring of US population. It includes detailed sociodemographic information, dietary and health related questions that are helpful in epidemiologic studies in general population to monitor common environmental exposures and health outcomes. Their methods of data collection have been repeatedly tested and are a subject to continuous process improvement. In this study, race and socioeconomic status were included in the model. To our current knowledge, this is the first analysis to explore link between PFAS isomers and cancer in NHANES data.

Weaknesses

The study did have several weaknesses. A cross-sectional study does not allow assessment of causations between PFAS and cancer. In addition, the multivariate analysis could have included BMI (given the potential endocrine disruptive properties of PFAS) and smoking, (a significant carcinogen) to adjust for other potential cancer risk factors. Multiple specific cancer types have been associated with both animal and human models with PFAS exposure; however, those specific cancer types in this analysis dis not have a robust sample size. Given the unadjusted result with the specific cancer types, especially in the female analysis, this would likely be an area for further research.

Conclusion

According to the results of our study, PFAS levels were did not show a statistically significant association with cancer in the multivariable regression model. Although the study did utilize an extended dataset over multiple survey cycles, it would likely benefit from a larger number of participants.

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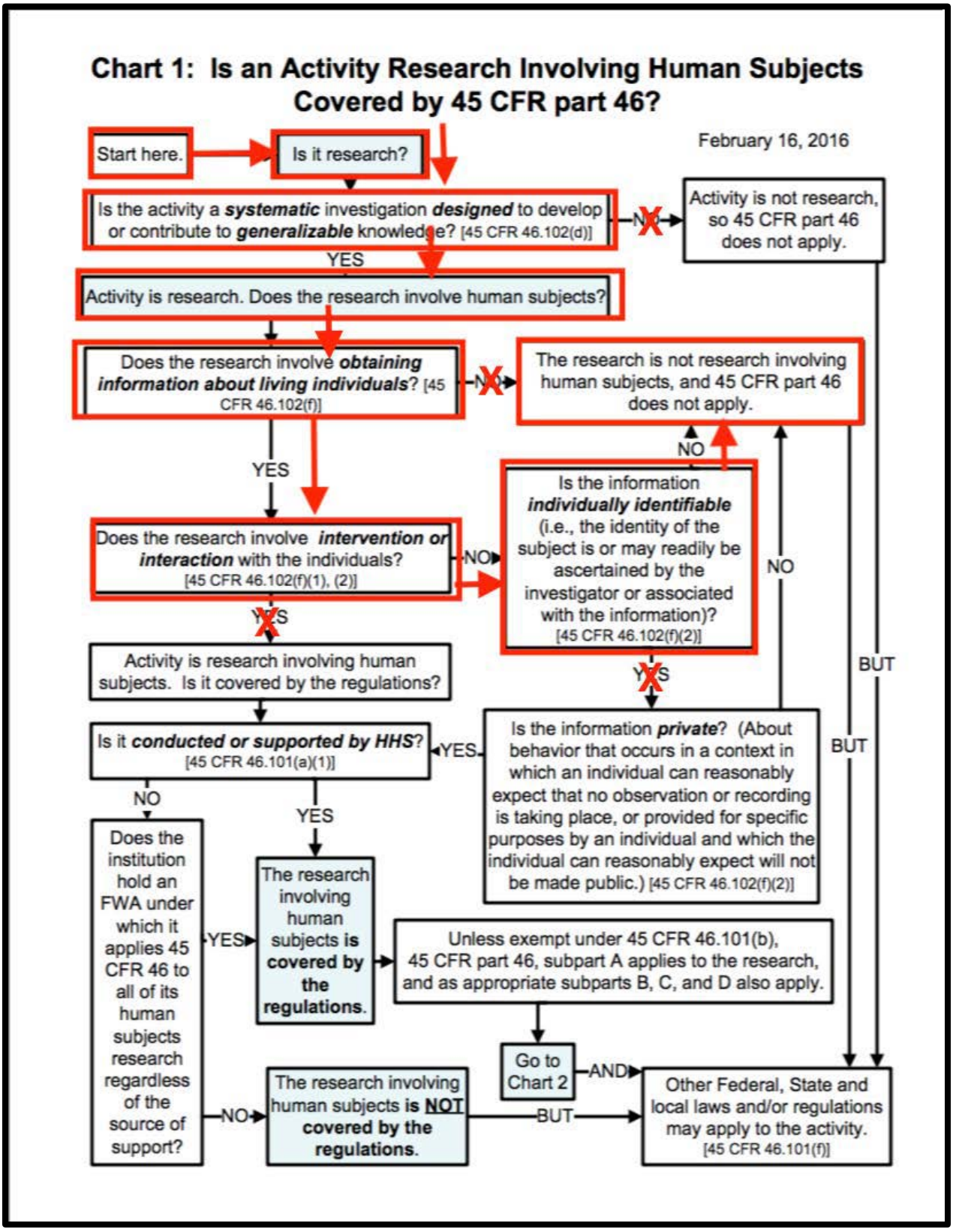
Appendix A: Human Subjects Regulations Decision Chart



Appendix B: Capstone Competency Synthesis

Foundational Competencies

Evidence-based Approaches to Public Health
1. Select quantitative and qualitative data collection methods appropriate for a given public health context
2. Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate
3. Interpret results of data analysis for public health research, policy or practice

Concentration Competencies

Population Health
1. Demonstrate application of an advanced quantitative or qualitative research methodology
2. Demonstrate the ability to contextualize and integrate knowledge of specific population health issues.