Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances (PFAS): A multi-site cross-sectional study

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1. PROJECT OVERVIEW

1.1 Summary

1.1.1 Literature Review

Per- and polyfluoroalkyl substances (PFAS) are a family of chemicals used in industrial applications and consumer products. A number of PFAS chemicals including perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexane sulfonate (PFHxS) persist in the environment and have long serum half-lives in humans (Wang 2017). PFAS contamination of drinking water is widespread in the U.S. For example, one report indicated that at least six million residents were served by 66 public water supplies that had at least one sample at or above the US EPA Lifetime Health Advisory for PFOA and PFOS (individually or combined) of 70 ng/L (Hu 2016). Industrial facilities that manufacture or use PFAS have contaminated drinking water in surrounding communities in West Virginia, Ohio, New York, Minnesota, Alabama, Vermont, New Hampshire, and New Jersey(Kray 2018). An alternative method of estimating PFAS drinking water contamination put the number of people potentially exposed to PFAS at concentration over 2.5 ng/L at about 110 million (Environmental Working Group 2018).PFOS, PFOA, PFHxS and other PFAS chemicals are constituents in aqueous film-forming foam (AFFF), used to extinguish flammable liquid fires. Since the 1970s, military bases in the U.S. have used AFFF with PFAS constituents for firefighting training as well as to extinguish fires. At some military bases, AFFF use has resulted in the migration of PFAS chemicals through soils to ground water and/or surface water sources of drinking water for the bases and/or surrounding communities (ATSDR 2017a). The Air Force and Navy have identified at least 24 bases with contaminated drinking water in Alaska, California, Colorado, Delaware, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Virginia, and Washington (Kray 2018).

A detailed review of epidemiological studies published up through 2016 was included in the ATSDR Feasibility Assessment for Epidemiological Studies at Pease International Tradeport, Portsmouth, New Hampshire (ATSDR 2017a; released Nov 2017). Health effects of PFAS exposure in children were also recently reviewed by Rapazzo (2017). The scientific evidence linking PFAS exposures with adverse health effects is rapidly growing. Epidemiological studies have found associations with changes in lipids (Steenland 2009; Zeng 2015, Mora 2018), levels of uric acid (Steenland 2010), thyroid and sex hormones (Wen 2013; Lopez-Espinosa 2016, Preston 2018), liver (Darrow 2016, Mora 2018), and immune function (Grandjean 2012, 2017), as well as reduced birth weight (Bach 2015, Verner 2015), reproductive effects (Lopez-Espinosa 2011, Bach 2016) and some cancers (; Barry 2013). However, findings across studies have been inconsistent for a variety of reasons, including differences in exposure levels, methods of

ascertaining diseases and the exposure and effect biomarkers measured. For some health endpoints, only one or a few studies currently exist.

Most studies of the human health effects from PFAS exposures have focused on PFOA and PFOS. These include studies that evaluated data from the National Health and Nutrition Examination Survey (NHANES), occupational studies, and national surveys conducted in other countries where exposures to PFAS were found mostly from consumption of food and beverages in PFAS-contaminated packaging. Studies of West Virginia and Ohio residents and workers exposed to PFOA from a chemical plant (the "C8" studies) have provided extensive and high quality information on PFOA (and to a lesser extent, PFOS), studying a large cohort of highly exposed residents (60,000+) and workers living in the vicinity of the production facility. However, other PFAS such as PFHxS and PFNA were not a primary focus of the C8 studies. Except for the C8 studies, there is scant information on the health effects of exposures to PFAS-contaminated drinking water.

1.1.2 Health Study Feasibility Assessment

In 2017, ATSDR published a feasibility assessment of possible future drinking water epidemiological studies at the Pease International Tradeport, Portsmouth, New Hampshire (ATSDR 2017a). Drinking water supply wells serving the Pease Tradeport were contaminated with PFAS from the use of AFFF at the former Pease Air Force Base. As part of this feasibility assessment, ATSDR reviewed the available information on the Pease Tradeport population and exposures (e.g., population size and demographics, PFAS biomonitoring results, and drinking water data) as well as conducted sample size calculations. The ATSDR feasibility assessment concluded that there was a need for additional epidemiological research on the health effects of PFAS exposures to address several research gaps and issues: (1) the small number of studies for some health endpoints, (2) the inconsistency of findings across studies for some health endpoints, (3) the lack of drinking water studies other than the C8 studies, and (4) the need to conduct studies that evaluate PFHxS and PFNA as well as other PFAS chemicals in addition to PFOA and PFOS (ATSDR 2017a).

In addition, ATSDR determined that cross-sectional epidemiological studies of children and adults at one site (e.g., at the Pease Tradeport) were feasible for some health endpoints (e.g., lipids, kidney function), but the size of the populations would be insufficient for other important health endpoints (e.g., thyroid, liver and immune function, autoimmune diseases). Therefore, the feasibility assessment concluded that: (1) a multi-site PFAS study of children and adults was necessary, (2) the study should be cross-sectional and involve separate evaluations of children (ages 4-17) and adults (ages ≥18), and (3) the study should

focus on communities impacted by PFAS-contaminated public drinking water supply wells and/or private wells. A cross-sectional study design was chosen because this design is especially suitable for assessing effect biomarkers and the prevalences of nonfatal diseases, in particular, diseases with no clear point of onset (Checkoway 2004). Additionally, the cross-sectional design can generate data for hypotheses that can be tested in subsequent longitudinal studies.

1.1.3 Summary of Study Goals

The main goal of the cross-sectional multi-site study is to evaluate associations between measured and historically reconstructed serum levels of PFAS including PFOA, PFOS, and PFHxS (see **Section 3.10**), and selected health outcomes as described below and detailed in study hypotheses (see **Section 2.5.2**). The study will attempt to recruit at least 2,000 children and 6,000 adults (equally of both sexes for both children and adults) from communities exposed to PFAS-contaminated drinking water. The criteria for selecting study sites are detailed in **Section 2.3** and would include:

1. Documented past or present PFAS drinking water concentrations at the tap,
2. The magnitude of past or present PFAS concentrations at the tap,
3. Size of the population exposed,
4. Amount of information available on the contaminated drinking water system or private wells, and
5. If biomonitoring for PFAS has previously occurred at the site.

Possible candidate sites include communities whose drinking water was impacted by AFFF use at military bases or by industrial PFAS emissions. Site selection process will consider the levels of PFAS drinking water concentrations at a site. The aim will be to select sites so that a wide range in PFAS exposures levels are included in the study in order to enable the evaluation of exposure-response trends including effects at the lower range of exposures.

For those sites with complex drinking water systems (e.g., where individual supply wells serve particular areas of the distribution system, or when there is uncertainty concerning which areas in the distribution system received contaminated water) or sites with groundwater contamination affecting private wells where there is uncertainty concerning which wells are contaminated, it may be necessary to use modeling

methods (e.g., ground water contaminant fate and transport models, water system distribution system models) to identify the areas with contaminated drinking water. A targeted PFAS biomonitoring approach is essential to confirm results from groundwater and/or distribution system modeling approaches. Modeling may also be necessary to determine the period when the drinking water was contaminated and to historically reconstruct PFAS contaminant concentrations during this period (Shin 2011).

The study will obtain blood samples from participants to measure PFAS serum levels and several effect biomarkers such as lipids, and thyroid, kidney, immune and liver function. The study will also obtain urine samples from participants to measure PFAS levels and kidney function biomarkers. The study will archive serum and urine samples in order to conduct analyses of additional PFAS chemicals and specific effect biomarkers. Adult participants and a parent of the child participant will complete a questionnaire that includes a residential history, medical history, occupational history and water consumption habits. The study will access medical and school records to confirm adverse health outcomes reported in the questionnaire. To facilitate access to these records, the recipient will reach out to local medical societies, the public school system and private schools to enlist their cooperation with the study.

Participants will be categorized based on the measured serum concentration of PFAS compounds or on modeled estimated historical serum levels (e.g., referent or low, medium, high). Estimated and measured PFAS serum levels will also be evaluated as continuous variables. At sites with preceding PFAS biomonitoring, the study will evaluate changes in PFAS concentration over time. The study will reconstruct historic serum PFAS concentrations by estimating half-lives and elimination rates as well as water contamination modeling to inform the pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) modeling. Historical serum PFAS reconstruction will enable the evaluation of exposure lags and vulnerable periods as well as statistical analyses that can control for confounding and reverse causation due to physiological factors (Dhingra 2017, Weisskopf 2017).

In order to restrict this study to drinking water exposures, adults occupationally exposed to PFAS will not be eligible for the study (e.g., ever firefighters or worked in an industry using PFAS chemicals in its manufacturing process). Likewise, children whose birth mothers were occupationally exposed will not be eligible.

Based on ATSDR's literature review of epidemiological studies of PFAS, the study will examine associations between PFAS compounds and lipids, renal function and kidney disease, thyroid hormones and disease, liver function and disease, glycemic parameters and diabetes, as well as immune response and function in both children and adults. In addition, the study will investigate PFAS differences in sex hormones and

sexual maturation, vaccine response, and neurobehavioral outcomes in children. In adults, additional outcomes of interest include cardiovascular disease, osteoarthritis and osteoporosis, endometriosis, and autoimmune disease.

These health endpoints were not selected based on power calculations, but rather on epidemiological and scientific bases: (1) endpoints that have been evaluated in previous PFAS research and need follow-up; (2) endpoints observed to be elevated in studies of other chemicals with similar *in vitro/in vivo* activity; and (3) results from toxicological and epidemiological studies of PFAS. With the proposed sample sizes for the multi-site study there should be sufficient power to detect mean differences and odds ratios in the ranges of those observed in other well designed epidemiologic studies.

1.2 Study Investigators and Roles

This cooperative research is being conducted under the ATSDR Notice of Funding Opportunity (NOFO) No. CDC-RFA-TS-19-002, titled "Multi-Site Study of the Health Implications of Exposure to PFAS-Contaminated Drinking Water." The expected number of research recipients[1] is six. The program will be administered by the CDC Extramural Research Program Office (ERPO).

Given that the single IRB mandate under the revised 2018 Common Rule will take effect on January 19, 2020, this research program shall be managed under the review of a single IRB for cooperative research. See §46.114 (Cooperative Research).

Projects that involve the collection or generation of data with federal funds must develop, submit, and comply with a Data Management Plan (DMP) prior to the collection or generation of public health data, and, to the extent appropriate, provide public access to and archiving/long-term preservation of collected or generated data.[2]

This protocol also represents CDC-supported research in which identifiable, sensitive information is collected and is issued a Certificate of Confidentiality (CoC). Thus, ATSDR and recipients are required to protect the privacy of individuals who are subjects of such research in accordance with Section 301(d) of the Public Health Service (PHS) Act.[3]

[1] A "recipient" is defined as a "non-Federal entity that receives a Federal award directly from a Federal awarding agency to carry out an activity under a Federal program." (see Grants.gov at https://www.grants.gov/learn-grants/grant-terminology.html#R; accessed 02/04/2019).
[2] https://www.cdc.gov/grants/additional-requirements/ar-25.html
[3] https://www.cdc.gov/grants/additional-requirements/ar-36.html

This protocol represents the core research that all recipients must conduct at their sites. Recipients will tailor their site-specific informed consent forms based on the ATSDR template (**Attachment 7b**).

ATSDR and NCEH Roles: The health study team at ATSDR is responsible for the development of and for external peer review requirements for the core protocol for the PFAS multi-site study. The study protocol will be submitted by ATSDR for review and approval by the CDC Institutional Review Board (IRB) under CDC's Federal wide Assurance (FWA) No. 00001413) and by the Office of Management and Budget (OMB). ATSDR will also seek comments from community organizations involved with PFAS (e.g., "Testing for Pease" - a community group in Portsmouth, NH active on the Pease International Tradeport site).

Serum specimens for PFAS analyses will be submitted to the CDC NCEH DLS, Atlanta, GA. Core clinical and research effect biomarkers will be analyzed by commercial laboratories as specified in the protocol. Urine specimens will be collected and stored for future analysis and study. ATSDR will conduct data analyses of the combined core data from all the study sites with the recipient participation.

Recipient Role: Data collection at each study site will be conducted by the recipient via cooperative agreement with the ATSDR. The recipient will conduct historical reconstruction of PFAS concentrations in the drinking water at Pease and will estimate historical PFAS serum levels. The recipient will conduct participant sampling, obtain informed consent, and administer a questionnaire. The recipient will verify reported health conditions with participant's health care providers and approach appropriate school district to abstract special education records. The recipient will obtain a blood and urine sample from each participant and will be responsible for specimen shipment to the CDC NCEH DLS and commercial laboratories. The recipient will deliver the core data and personal identifier information ("PII") such as social security number, full name and date of birth, to ATSDR. Each recipient may conduct analyses of the data from the recipient's site. Each recipient shall maintain PII data in a secure manner, and delete PII data after the study is completed.

2. INTRODUCTION

2.1 Authority

ATSDR is authorized to conduct the PFAS multi-site study under Section 316(a) of the National Defense Authorization Act for Fiscal Year 2018 (Public Law 115-91), and research in general, under the 1980

Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the 1986 Superfund Amendments and Reauthorization Act (SARA) (42 U.S.C. 9601, 9604).

2.2 Background

Starting in the 1950s, PFAS have been used in a wide variety of products and applications including fluoropolymer manufacturing, stain and water repellant coatings, cleaners, and paints. PFAS are also components of aqueous film-forming foam (AFFF) used to extinguishing flammable liquid fires. From approximately the early 1970s, AFFF was used for firefighting training and to extinguish fuel-based fires at a number of military and non-military sites (e.g., airports) around the country. PFAS components of AFFF include perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonate (PFHxS).

PFAS contamination of drinking water is widespread with at least six million U.S. residents receiving water having concentrations of PFOA and PFOS (individually or combined) exceeding the EPA's Lifetime Health Advisory of 70 parts per trillion (Kray 2018). Sources of the drinking water contamination include emissions from manufacturing facilities and the use of AFFF at military bases and airports. For example, the Air Force and Navy have identified at least 24 bases with contaminated drinking water in several states including Alaska, California, Colorado, Delaware, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Virginia and Washington (Kray 2018). At these bases, PFAS chemicals in the AFFF likely leached into the soil and ground water and migrated to drinking water supply wells.

An example of a community drinking water supply contaminated via the use of AFFF at a military base is the Pease International Tradeport, Portsmouth, New Hampshire. In 2014, a drinking water supply well had measured PFOS, PFOA and PFHxS concentrations of 2.5 µg/L, 0.35 µg/L, and 0.96 µg/L, respectively. The source of the contamination was use of AFFF at the former Pease Air Force Base. In 2015, NH DHHS established a Pease biomonitoring program for PFAS. The program obtained blood specimens for PFAS analyses from 1,578 persons (NH DHHS 2016, Daly 2018). The results from the blood-testing program indicated that the exposed population had serum levels of PFOS and PFHxS that were about two to three times higher than the U.S. population based on data from NHANES 2013-4 and from other epidemiological studies in the U.S. In analyses conducted by NH DHHS (Daly 2018), geometric mean PFHxS serum levels were higher for persons who drank ≥4 cups of water per day compared to those who drank <4 cups per day (4.76 µg/L versus 3.77 µg/L). NH DHHS measured 8 to 14 PFAS congeners at 3 analytical laboratories.

Among PFOA, PFOS, PFHxS and PFNA concentrations, water consumption had the strongest effect on PFHxS serum levels. In particular, water consumption had the highest effect on PFHxS serum levels among persons aged ≤19 years (β = 0.31, SE = 0.15, marginal effect = 36.4%). Geometric mean PFOS and PFOA serum levels were also higher among persons who drank ≥4 cups of water per day compared with those who drank <4 cups per day (NH DHHS 2016, Daly 2018). Linear trends were observed for geometric mean serum levels of PFOS, PFOA, and PFHxS and increasing time spent at the Pease Tradeport. The trend was strongest for PFOS and PFHxS (NH DHHS 2016, Daly 2018).

2.3 Selection of Sites

Possible candidate sites include communities whose drinking water was impacted by AFFF use at military bases or by industrial PFAS emissions. The criteria for selecting study sites would include:

1. Documented past or present PFAS drinking water concentrations at the tap,
2. The magnitude of past or present PFAS concentrations at the tap,
3. Size of the population exposed,
4. Amount of information available on the contaminated drinking water system or private wells, and
5. If biomonitoring for PFAS has previously occurred at the site.

In order to determine the feasibility of a site for inclusion in the multi-site study, information on the following parameters should be included in the application

1. For public water systems using ground water sources, enumeration of supply wells that provided drinking water to the site. Information on each supply well should include years of operation, well capacity, and daily or monthly pumping rates. This information can be used to determine the monthly proportion of the total water supply provided by each well during the period when PFAS contamination occurred. Information is also necessary about changes to the water system (e.g., closure of contaminated supply wells) after the contamination was detected.
2. For a water system supplied by surface water, characteristics of this source.

3. For a water system purchasing water from another system, characteristics of this source, the period of time purchased, and daily or monthly amount purchased in order to determine the proportion of the total water supply provided by the purchased water.
4. Characteristics of the drinking water distribution system. For example, for systems using supply wells, it is important to obtain information on whether mixing from the supply wells occurred at the treatment plant before entering the distribution system or if each supply well served a specific area in the system. If water was purchased from another system, then information on the area of the distribution system served by purchased water is necessary. For systems in which PFAS concentrations throughout the distribution system cannot be assumed to be similar (e.g., if all water is not mixed at the treatment plant before distribution), then It may be necessary to obtain sufficient information on the distribution system (e.g., pipe network, elevation and water demand at each node, pipe length and diameter, etc.) so that preliminary modeling using software such as EPANET can be used to estimate PFAS concentrations at various areas in the distribution system.
5. Description of when and how PFAS samples from monitoring or supply wells (or surface water) were obtained, the location of the wells, and the measured concentrations of PFAS including description of analytical methods used by the laboratory.
6. If the distribution system was sampled, which PFAS were detected, when, and the measured levels of concentration.
7. For sites involving private well contamination, the number and locations of the wells, periods of operation, any information on the source of contamination and the PFAS groundwater plume, and the dates of PFAS sampling and the measured concentrations.
8. Any information on the historical use of AFFF (e.g., amount purchased/used, location and frequency of training exercises, fire incidents, spills, etc.) at the site or in the vicinity of the site (e.g., military base airstrip) which was the source of the drinking water contamination. Any information on the soil and ground water characteristics in the vicinity of AFFF use. Any information on the groundwater PFAS plume.
9. If previous human PFAS biomonitoring program was conducted, the PFAS serum results, dates of blood or urine collection, and possible descriptive/predictive factors of the serum concentrations (e.g. volume of water consumed, length of residence at site, differences in age, race, or other population characteristics).

For those sites with complex drinking water systems (e.g., where individual supply wells serve particular areas of the distribution system, or when there is uncertainty concerning which areas in the distribution

system received contaminated water) or sites with groundwater contamination affecting private wells where there is uncertainty concerning which wells are contaminated, a targeted PFAS biomonitoring approach may be useful to confirm results from groundwater and/or distribution system modeling approaches. Possible candidate sites include communities whose drinking water was impacted by AFFF use at military bases or by industrial PFAS emissions.

2.4 General Approach for Study Recruitment

In considering possible study designs, ATSDR focused on the methods used in previous epidemiological research of PFAS exposures (ATSDR 2017a). Adopting study design methods consistent with previous research facilitates the interpretation and synthesis of findings across studies. Most of the epidemiological studies of PFAS exposures were cross-sectional and evaluated serum PFAS measurements. Some studies also evaluated cumulative PFAS serum levels estimated from historical reconstruction models. ATSDR concluded that the multi-site study should be cross-sectional and evaluate measured serum PFAS measurements as well as historically reconstructed estimates of cumulative PFAS serum levels. ATSDR also concluded that methods used to evaluate health-related endpoints in the study should be consistent with methods used in previous epidemiological research of PFAS exposures, given adequate sample size and power. In the future, the follow up to the cross-sectional studies of health-related outcomes proposed to be studied in the longitudinal studies.

The recipient should work closely with local and state agencies (e.g., public school systems, local and state health departments), local community organizations, and local media to conduct outreach about the study to encourage participation and community engagement with all local stakeholders. For those sites involving a contaminated public water system, the recipient should request that the water purveyor include a flyer about the study in its billing mailings and email notices.

The recipient should identify and enumerate all households served by the contaminated drinking water supply in the selected community in order to recruit potential participants to meet the sample size requirements for children and adults. If the selected community is served by a PFAS-contaminated public water system, then the recipient should obtain a list of households served by the water purveyor from its billing records. If the community is served by contaminated private wells, then the recipient should obtain a list of households with contaminated wells from the local and/or state health and environmental agencies.

Statistical sampling methods (e.g., a two stage cluster sample) may be used for recruitment of study participants if all the affected households can be enumerated. However, a simple random sample may not be appropriate if the PFAS drinking water concentrations vary widely across the community. In these situations, a random sample of households stratified by PFAS concentration levels would be more appropriate. To ensure a wide distribution of exposure levels among study participants, the recipient should consider oversampling areas with higher PFAS concentrations.

Although a recruitment process based on a statistically-based sampling approach may be theoretically ideal, in practice it may not be feasible. For example, enumeration of all households may not be possible. Moreover, if participation rates are not high, then in order to achieve the sample size objective, it will be necessary to recruit volunteers (i.e., include a "convenience sample"). Therefore the recipient should consider non-probabilistic sampling approaches such as "judgement" and "snowballing" sampling approaches (Tyrer 2016).

If the PFAS concentrations in drinking water are generally uniform throughout the community (e.g., if drinking water from all sources is mixed at the treatment plant prior to distribution), then a targeted sampling approach may not be necessary. On the other hand, if PFAS concentrations are not likely to be uniform throughout the distribution system or among private wells in the affected area, then a targeted sampling approach will probably be necessary with oversampling in areas with higher PFAS drinking water concentrations. To enable a targeted sampling approach, the recipient should use available information and, if necessary, preliminary modeling methods, to classify households in the community by past or present PFAS concentration levels in the drinking water. For contaminated public water systems, the recipient should request distribution system information from the water purveyor in order to identify areas with higher and lower PFAS concentrations in the drinking water. For contaminated private wells, the recipient should request information on the ground water PFAS contamination plume affecting the wells from the local or state environmental agency.

The recipient should request assistance from local and state health departments in its recruitment efforts. In addition, the recipient should engage community organizations to assist in conducting outreach about the study and recruitment of participants. In addition, the recipient may establish a community assistance panel ("CAP") to review and provide comments on the study protocol and to facilitate the involvement of the affected community in decisions related to outreach about the study, participant recruitment strategies, and study logistics. The CAP would also assist the recipient in the dissemination of study findings to the community.

2.5 Study Objectives and Study Questions

The main goal of the multi-site study of children and adults is to evaluate the associations between specific health effects and serum PFAS concentrations among those exposed to PFAS-contaminated drinking water.

2.5.1 Literature Review

A literature review was conducted for the Pease feasibility assessment and can be accessed in the final feasibility report (ATSDR 2017a). The literature review from the Pease feasibility assessment concluded that most information on potential health effects concerned exposures to PFOA. In particular, numerous studies have been conducted of West Virginia and Ohio residents and workers exposed to PFOA from a chemical plant via contaminated drinking water and occupationally, respectively (the "C8" studies) (Frisbee 2009). Studies of other workforces also focused primarily on PFOA exposures. The literature review found that less information was available about the potential health effects of PFOS exposures, and little information was available on the potential health effects of exposures to PFHxS. PFHxS and PFOS are often major contaminants in drinking water impacted by AFFF. Except for the C8 studies, there is scant information on the health effects of exposures to PFAS-contaminated drinking water.

The literature review identified many health-related endpoints evaluated in previous epidemiological studies of PFAS exposures. These included cancers, changes in lipids, effects on thyroid and immune function, and developmental delays. They also included effects on kidney and liver function and sex hormones, and diseases such as endometriosis, ulcerative colitis and osteoporosis (ATSDR 2017a).

The literature review found that most of the epidemiological studies of PFAS exposures were cross-sectional and evaluated serum PFAS measurements. Some studies also evaluated cumulative PFAS serum levels estimated from modeling methods. ATSDR concluded that studies of populations exposed to the PFAS-contaminated drinking water should be initially be cross-sectional to be comparable with other studies and to establish a baseline for potential follow-up longitudinal studies. Studies should also evaluate measured serum PFAS measurements as well as estimated cumulative PFAS serum levels, and use methods for the evaluation of health-related endpoints that are consistent with methods used in previous epidemiological research of PFAS exposures.

2.5.1.1 Health Effects in Children

There is some evidence that PFAS exposures are associated with decreased birth weight, small birth size for gestational age, measures of intrauterine growth retardation, and preterm birth. In particular, several meta-analyses have found an overall decrease in birthweight associated with PFOA and PFOS (Johnson 2014, Negri 2017, Verner 2015; Bach 2015). However, the findings across studies are inconsistent for adverse birth outcomes, and few studies have evaluated PFHxS. Several studies of infants have found that prenatal PFAS exposures affect thyroid function, but only two studies have evaluated thyroid function in older children (Lopez-Espinosa 2012; Lin 2013, Preston 2018).

A few studies of children have found elevated uric acid with PFAS exposures, but the possibility of reverse causation exists (Geigere 2013; Kataria 2015; Qin 2016). Positive findings occurred in some of the four studies of PFAS exposures and testosterone and other sex hormones, but the findings were not consistent across studies and further research is necessary (Maisonet 2015; Lopez Espinosa 2016, Zhou 2016). Growing evidence suggests that exposure to per- and polyfluoroalkyl substances (PFASs) may disrupt lipid homeostasis and liver function, but data in children are limited. Indicators of adiposity and glucose metabolism were also linked with PFAS in a large follow up study of children and adolescents (Domazet 2016). Recent study (Mora, 2018) suggests that prenatal and mid-childhood PFAS exposure may be associated with modest, but somewhat conflicting changes in the lipid profile and ALT levels in children.

There is some evidence from four studies that PFAS exposures might be associated with attention deficit hyperactivity disorder (ADHD), but findings have not been consistent across studies (Stein 2011; Liew 2015; Ode 2014; Hoffman 2010). In the Stein (2011) study, the ORs for ADHD and PFOS and PFHxS were 1.3 and 1.6, so there was some evidence of an increased risk, although not strong. A study using NHANES data obtained an OR of 1.6 for PFOS and ADHD (Hoffman 2010). Other studies have found conduct and coordination problems associated with PFOS (Fei 2011) and executive function deficits with PFOS and

PFHxS (Vuong 2016). Evaluating the evidence for PFAS exposures and neurobehavioral outcomes is difficult for several reasons: 1) the studies used different methods to measure the outcomes, 2) studies are inconsistent in the outcomes evaluated, and 3) too few studies exist. For example, there is little evidence that PFAS affects IQ, primarily because only two studies evaluated it; one in Taiwan, which observed deficits (Lien 2016), and one at C8 which did not (Stein 2011). We believe it is worth evaluating whether the PFAS mixture at Pease (and other sites with contamination due to AFFF use) is associated with IQ deficits or other neurobehavioral outcomes.

A few studies have found associations between PFAS exposures and a decline in antibody response to specific vaccines (Grandjean 2012, 2016), but only two studies evaluated the same vaccine (i.e., rubella; Granum 2013, Stein 2016).

In summary, there are considerable data gaps concerning the health effects in children of PFAS exposures. This is because of the small number of studies conducted, inconsistencies in methods and findings across studies, and limited sample sizes in some studies. As for other adverse outcomes, few studies have evaluated the effects on children of PFHxS exposures.

A recent systematic review of PFAS studies of children concluded that there was "…generally consistent evidence for PFAS' association with dyslipidemia, immunity including vaccine response and asthma, renal function, and age at menarche" (Rappazzo 2017). The review noted the limited number of studies for any one particular health outcome, the variability in outcome measurement, and the need for longitudinal studies.

2.5.1.2 Health Effects in Adults

Based on its detailed assessment of the epidemiological literature, ATSDR concluded that there was limited information concerning associations with PFAS exposures and most cancers and other adult diseases (ATSDR 2017a).

Epidemiologic studies of subjects exposed to PFOA and PFOS at background levels and at occupational settings have reported positive associations with number of health outcomes and conditions. Lipid and cholesterol concentrations were associated with increased PFOA or PFOS (Frisbee 2010; Nelson 2010; Fletcher 2011; Steenland 2015), as were increased uric acid levels (Costa et al., 2009; Steenland 2010; Shankar 2011; Geiger 2013; Gleason 2015), concentrations of thyroid and sex hormones (Olsen and Zobel

2007; Knox 2011; Jain 2013; Wen 2013; Winquist and Steenland 2014), immune parameters (Dalsager2016), and reproductive effects (Joensen 2013; Kristensen 2013; Crawford 2017).

Associations with liver enzymes were found with PFAS in most cross-sectional studies (Olsen 2000; Sakr2007; Lin 2010; Gallo 2012; Gleason 2015) but were weaker or found no association in the cohort studies of liver enzymes (Sakr 2007b, Darrow 2016). Structural protein cytokeratin 18 (CK-18) and its components have been used as a new non-invasive serum biomarker for non-alcoholic fatty liver disease and suspected steatohepatitis for adults and children (Fieldstein 2013, Shen 2012, Vos 2008). Prevalent coronary heart disease was positively associated in a cross sectional examination of NHANES (Shankar 2012) but not in cohort designs (Winquist 2014b; Mattsson 2015).

Two studies of osteoarthritis show association with PFOA in cross sectional analyses (Innes 2011, Uhl 2013) but no association in longitudinal analyses (C8 Science Panel 2012a). Another cross-sectional NHANES study (Khalil 2016) found an association with osteoporosis among women for PFHxS. Two NHANES studies (Lin 2014, Khalil 2016) also found associations with bone mineral density. Although, these studies are cross-sectional, they provide important evidence for a link between PFAS exposures and osteoarthritis and osteoporosis unless there is evidence that confounding or reverse causation can explain these results.

In evaluation of kidney function, data from Watkins (2013) and Dhingra (2017) showed that while measured PFOA showed positive association, modeled PFOA concentrations had no relation to eGFR illustrating example of potential reverse causality. C8 Science panel found no association with the nonmalignant renal disease in their cohort study (2021b)

There is increasing evidence showing associations between PFAS and markers of glucose homeostasis and insulin resistance, and associations with adult type 2 diabetes risk in men and women (Cardenas 2017; He 2018; Sun 2018); strengthening the case for adverse metabolic activity of these compounds.

Roles of inflammatory cytokines and adipokines have been explored several studies of liver disease such as non-alcoholic fatty liver disease/steatohepatitis and in atherosclerosis (Hennig 2007, Wahlang 2016, Clair 2018). Proinflammatory responses, alteration in leptin signaling, and increases in TNF-alpha and IL-2 were reported in mechanistic studies with various persistent organohalogen pollutants in relation to diabetes and metabolic syndrome (Ferrante 2014; Wieser 2013). These associations have not yet been explored specifically with PFAS compounds.

Some positive associations have also been found for cancer outcomes; with C8 studies finding strong associations for liver, kidney, and testicular cancer (Alexander and Olsen 2007; Barry2013; Bonefeld-Jorgensen2014; Hardell2014; Steenland2015).

Some studies have found no association between PFAS exposure and health effects such as specific cancers (Alexander and Olsen 2007; Lundin 2009), lipids or metabolic function (Fisher, 2013). Effects of counfounding, bias, and chance on observed associations with PFAS compounds were explored in reviews of immune and cancer outcomes (Chang 2014, Chang 2015) and in studies of PFAS and menopause and endometriosis (Dhingra 2017, Ruark 2017, Ngueta 2017).

Few studies have evaluated PFHxS exposures and the risk of cancers and other adult diseases. Although epidemiological studies have primarily evaluated PFOA and PFOS, there remain considerable data gaps concerning the health effects of exposures to these chemicals in adults. There have been inconsistencies in findings across studies and limited sample sizes in some studies. For some adverse outcomes, only one or a few studies have been conducted. Finally, except for the C8 studies, there are no published individual-level epidemiological studies in adults that have evaluated the health effects from exposures to PFAS-contaminated drinking water. Therefore, additional research is necessary to determine whether drinking water exposures to PFHxS, PFOS, and PFOA increase the risk of non-cancer diseases. The proposed scope of the funding and sample size estimated for this health study would be too small and insufficient to evaluate cancer health outcomes.

2.5.2 Hypotheses

For children (aged 4-17 years), the Multi-site Study will evaluate the following main hypotheses, following the outline of the biochemical analytical plan (**Attachment 2**):

Higher serum levels of PFOA, PFOS, PFHxS, or other PFAS are associated with:

1. Lipids (higher total cholesterol, low-density lipoprotein, and triglycerides, and higher prevalence of hypercholesterolemia; higher prevalence of obesity).
2. Impaired renal function (a higher level of uric acid, a higher prevalence of hyperuricemia, and a lower estimated glomerular filtration rate (eGFR).

3. Liver function/damage biomarkers (alanine transaminase (ALT), γ-glutamyltransferase (GGT), direct bilirubin, cytokeratin-18 (CK-18)), and non-alcoholic fatty liver disease/steatohepatitis.
4. Glycemic parameters (glucose, insulin, glycosylated hemoglobin (HbA1c), auto-antibodies [glutamic acid decarboxylase (GAD-65) and islet antigen 2 (IA-2)], C-peptide, pro-insulin) and diabetes (type 1 and 2).
5. Measures of thyroid function (differences in thyroid stimulating hormone - TSH, total thyroxin - TT4, free thyroxin - FT4, and TT3; higher prevalence of hypothyroidism/hyperthyroidism).
6. Differences in sex hormones, growth and sexual maturation (testosterone, estradiol, and sex hormone-binding globulin (SHBG); insulin-like growth factor - 1 (IGF-1), age at menarche, delayed puberty).
7. Immune response including prevalence of hypersensitivity-related outcomes (e.g., asthma, atopic dermatitis; higher levels of immunoglobulins (IgG, IgA and IgM) and lower antibody responses to rubella, mumps, and diphtheria vaccines).

Neurodevelopmental outcomes (lower intelligence quotient (full scale IQ), attention-deficit and hyperactivity disorder (ADHD).

For adults (aged ≥18 years), the Multi-site Study will evaluate the following main hypotheses.

Higher serum levels of PFOA, PFOS, PFHxS, or other PFAS are associated with:

1. Lipids (higher total cholesterol, low-density lipoprotein and triglycerides) and a higher prevalence of hypercholesterolemia).
2. Higher prevalence of coronary artery disease and hypertension (including hypertensive disorders of pregnancy).
3. Renal function (higher level of uric acid and a higher prevalence of hyperuricemia, lower estimated glomerular filtration rate (eGFR)) and higher prevalence of kidney disease.
4. Glycemic parameters (glucose, insulin, glycosylated hemoglobin (HbA1c), auto-antibodies (GAD-65 and IA-2), C-peptide, pro-insulin) and diabetes (type 1 and 2).
5. Differences in thyroid hormones (thyroid stimulating hormone (TSH), TT4, FT4, and TT3), and higher prevalence of hypothyroidism/ hyperthyroidism.

6. Liver function/damage biomarkers (alanine transaminase (ALT), γ-glutamyltransferase (GGT), direct bilirubin, cytokeratin-18 (CK-18)) and liver disease.
7. Higher prevalence of osteoarthritis and osteoporosis.
8. Higher prevalence of endometriosis.
9. Measures of immune response and inflammation (serum levels of IgA, IgE, IgG, IgM, C - reactive protein (CRP), antinuclear antibodies (ANA), inflammatory cytokines and adipokines (interleukin 1-β (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor α (TNFα), leptin, adiponectin, resistin, plasminogen activator inhibitor-1 (PAI-1).
10. Higher prevalence of autoimmune diseases such as ulcerative colitis, rheumatoid arthritis, lupus, and multiple sclerosis.

2.6 Intended Use of Study Findings

Given that epidemiological research on the health effects of drinking water exposures to PFAS other than PFOA is at an early stage, the Multi-site Study should make an important contribution to the scientific literature, expand knowledge in this field, and help addressing concerns about past exposure.

Additionally, the Multi-site Study will provide the PFAS serum level and the results of the clinical tests and effect biomarker tests to each study participant. The participant can use this information for medical decision-making. Advice and assistance (e.g. workshops and or training programs) to clinicians in each community be provided by recipients and ATSDR as a part of the community engagement efforts to be able to answer questions about the potential effects of elevated PFAS levels on health, interpreting results, additional test or treatments. ATSDR will provide summaries of the study findings to the participating affected communities and will also provide assistance in interpreting each of these results.

3. METHODS

3.1 Study Design

The Multi-site study will be cross-sectional with separate evaluation of children (ages 4 – 17 years) and adults (aged ≥18 years). The participants will be recruited from lists of residences served by PFAS-contaminated drinking water.

- The recipient will obtain adult consent and parental permission (ages 4-17) and child assent (ages 7 -17), to participate in this research study (including consent to be contacted for any future studies).
- The recipient will administer adult and child questionnaires, and seek medical records verification of self-reported diseases and medical histories (including neurobehavioral diseases).
- The recipient will administer neurobehavioral test batteries to the children and their parents and seek to abstract children's school records, in particular, special education records.
- The recipient will obtain blood samples from each participant for analyses of PFAS and a number of effect biomarkers.
- As part of the current protocol, both children and adults will be asked to provide a urine sample for future analyses of PFAS and relevant effect biomarkers. The recipient will ship the urine samples to CDC biorepository for analysis at a later time when more knowledge is gained about urinary PFAS and effect biomarkers and until the laboratory methods are developed.
- The recipient will seek consent to store residual blood and urine samples for future analyses of other PFAS and/or relevant effect biomarkers yet to be identified.

3.2 Study Populations and Eligibility

The target areas for the Multi-site Study are those served in the present or past by public water systems and/or private wells with documented past or present PFAS concentrations at the tap. The target populations consist of those residing in households in the target areas. Those eligible for the study include individuals aged ≥4 years at the start of the study who reside in a household in the target area and whose last exposure to PFAS-contaminated drinking water was no more than 15 years prior to the start of the study. In addition to those who resided in households served by contaminated drinking water, individuals exposed in utero and during breastfeeding when the mother resided in the household would also be eligible if the exposure occurred within 15 years of the start of the study. The limit of 15 years since last exposure was chosen to take into account the estimated half-lives in the body of PFOA, PFOS and PFHxS and to ensure that exposures to the contaminated drinking water are relatively recent.

Firefighters and others with occupational PFAS exposure from sources other than the drinking water will not be included in the study. In addition, children whose birth mothers had occupational exposures to PFAS from sources other than drinking water will be excluded. The goal is to enroll at least 2,000 children (ages 4-17) and 6,000 adults aged ≥18 years with drinking water exposure to PFAS.

3.2.1 Children

The eligibility criteria for children is as follows:

1. Aged 4 – 17 years at the start of the study,
2. Resided in areas with documented past or present PFAS drinking water concentrations at the tap, or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water,
3. Drinking water exposure occurred within 15 years of the start of the study.
4. Children will be excluded if their birth mothers were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process.

The requirement that the child's last exposure be within 15 years of the start of the study takes into account the half-lives of about 3 years for PFOA and PFOS, and about 5 years for PFHxS, observed in a recent study of drinking water exposures caused by AFFF use at a military facility in Sweden (Li 2017). Slightly longer half-lives for individual PFAS (5 to 8 years) were derived in the draft ATSDR toxicological profile (ATSDR 2018). Based on these half-lives, those last exposed more than 15 years ago will have greatly diminished current serum levels of these PFAS chemicals, making the use of these serum measurements to predict past exposures more problematic.

The age range for the child study (4-17 years) was determined by taking into account the age ranges in previous PFAS studies and the age range appropriate for the candidate endpoints. The study will limit inclusion to those ≥4 years of age because most of the neurobehavioral tests that will be used in the study are appropriate for children aged ≥4 years of age.

3.2.2 Adults

The eligibility criteria for adults is as follows:

1. Aged ≥18 years at the start of the study.
2. Resided in areas with documented past or present PFAS drinking water concentrations at the tap,
3. Drinking water exposure occurred within 15 years of the start of the study.
4. Persons ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

3.3 Sample Size Considerations

The Pease feasibility assessment included sample size calculations for a wide range of health related outcomes (ATSDR 2017a). Sample size calculations selected a type 1 ("α error") of .05 and type 2 error ("β error") of .20. The tables present sample sizes per stratum for specific outcomes for children (Table 1) and for adults (Table 2). To determine effect sizes that are reasonable to detect, we selected epidemiological studies using NHANES data. For those outcomes not included in NHANES studies, the C8 studies were used. The C8 results were considered more representative of U.S. populations (e.g., in background disease rates and prevalence of non-PFAS risk factors) than studies conducted in other countries, although the PFOS, and especially the PFOA, serum levels in the C8 studies were higher than might occur at other sites. For outcomes not evaluated by NHANES or C8 studies, it was necessary to use studies conducted in other countries. The total sample sizes for children and adults should allow for the categorization of PFAS serum levels (or cumulative PFAS serum levels) into e.g. quartiles of exposure: reference level, low, medium and high.

Attachment 3 includes additional information and assumptions pertinent to selected health outcomes to be studied.

3.3.1 Children

For children, **Table 1** (and **Attachment 3a**) provide the sample size calculations for several health outcomes of interest assuming a type 1 ("α error") of .05 and type 2 error ("β error) of .20. It was considered important that a study have a total sample size so that exposures could be categorized into

tertiles (i.e., reference, medium, and high) or preferably into quartiles (i.e., reference, low, medium and high). Per stratum estimates of needed sample size have been calculated based on different prevalence of outcomes and detected odds ratios or mean difference.

The proposed sample size of 2,000 children (equally of both sexes) is large enough to effectively evaluate many of the health outcomes identified in the Pease Feasibility Assessment literature review and the recent systematic review (Rapazzo 2017) as potentially associated with PFAS in children. The health outcomes and biomarkers studied would include mean difference in total cholesterol (ranging from 156 to 637 per stratum), uric acid levels (556 per stratum), estimated glomerular filtration rate (eGFR; 275 per stratum), testosterone (about 400 per stratum) and insulin growth factor-1 (IGF-1; 146 per stratum). Based on our estimations, we would also be able to detect differences in risk for obesity and atopic dermatitis. A sample size of 2,000 children would be larger than many of the PFAS studies that evaluated neurobehavioral outcomes such as IQ and ADHD (Wang 2015, Stein 2013, 2014, Fei 2011, Hoffman 2010, Strom 2014).

An NHANES study of estimated glomerular filtration rate observed statistically significant findings with a total sample size of just under 2,000 children (Kataria 2015). For thyroid function, estradiol, delayed puberty, and asthma, a total sample sizes of 2,000 children may be sufficient, although larger sample sizes would be optimal (Lopez-Espinosa 2011, 2012; Stein 2016).

In summary, a total sample size of ≥2,000 would be sufficient to evaluate a wide range of biomarkers and outcomes including lipids (and hypercholesterolemia), uric acid (and hyperuricemia), estimated glomerular filtration rate, testosterone, IGF-1, neurobehavioral measures (executive function, attention, IQ) and ADHD, rhinitis, and obesity.

Table 1. Sample size estimations for selected health-related endpoints in Child Study (ages 4-17 years)

Health-related Endpoint	Relevant Study	Observed Effect Size	Assumptions	Sample Size/Stratum α error = .05 β error = .20
Total Cholesterol (mg/dL)	Frisbee 2010, C8 Study 1,971 boys <12 yrs 2,773 boys 12-18 yrs 1,886 girls <12 yrs 2,520 girls 12-18 yrs	PFOS: 5th vs 1st quintile Age: <12 yrs 12-18 Boys: +6.2 +9.3 Girls: +4.6 +9.4	Mean PFOS serum levels were about 20 µg/L. SD for total cholesterol=29.3 mg/dL	+4.6: 637/stratum +9.3: 156/stratum
High cholesterol		OR = 1.6	Prevalence=34.2%	300/stratum

Thyroid function TT_4 Thyroid disease	Lopez-Espinosa 2012, C8 1,078 1-5 yrs 3,132 6-10 yrs 6,447 >10 – 17 yrs	PFOS, 4th vs 1 quartile: 2.3% change (mean difference = 0.17 µg/dL) PFOA: OR=1.44 (PFOS: OR < 1.0)	Mean PFOS serum levels were about 20 µg/L. SD for TT_4 as estimated at 1.4. Percent change in TT_4 was converted to mean difference assuming the median TT_4 was ref. level. Prevalence=0.6% (used PFOA results)	1,080/stratum >16,000/stratum
Uric Acid	Kataria 2015, NHANES 1,960; 12-18 yrs	PFOS: 4th vs 1st quartile = +0.19 mg/dL	Mean PFOS serum level = 12.8 µg/L. SD = 1.19.	556/stratum
Hyperuricemia	Geiger 2013, NHANES 1,772; 12-18 years	PFOS: 4th vs 1st quartile, OR=1.65	Mean PFOS serum level =16.6. Prevalence=16%	400/stratum
eGFR	Kataria 2015 1,960; 12-18 yrs	PFOA mean serum level =3.5 µg/L. mean difference= -6.6	Standard deviation=27.6	275/stratum
Testosterone	Lopez-Espinosa 2016, C8 1,169 boys; 6-9 yrs 1,123 girl; 6-9 yrs	PFOS (IQR): -5.8% boys (diff=1.9) -6.6% girls (diff=2.45)	Percent change was converted to mean difference assuming median testosterone level was ref. level. SD estimated at 11.85 for girls and 9.63 for boys.	Boys: 404/stratum Girls: 368/stratum
IGF-1 (Insulin-like growth factor – 1)	Lopez-Espinosa 2016, C8	PFHxS (IQR): Boys: -2.5% (diff=17.3) Girls: -2.1%	Percent change was converted to mean difference assuming median IGF-1 in boys as ref. level. SD estimated as 52.6	146/stratum
Delayed Puberty	Lopez-Espinosa 2011. C8 3,072 boys, 8-18 yrs 2,903 girls, 8-18 yrs	PFOS: mean serum level was about 19 µg/L.	OR for delayed puberty and the number of days delayed puberty had narrow CIs	Insufficient information to calculate sample size, but sample sizes in this study were enough for sufficient precision.
ADHD	Stein 2011, C8 10,546; aged 5-18 yrs.	PFHxS mean serum level was 5.2 µg/L. 4th vs 1st quartile, OR=1.5	Prevalence: ADHD Dx: 12.4%	764/stratum
Asthma	Stein 2016, NHANES 640; 12-19 yrs	PFOA mean serum level = 3.6 µg/L. OR=1.2	Prevalence = 11%	2,400/stratum
Atopic dermatitis	Wang 2011 (Taiwan) 244; infants, 2 yrs	PFOS mean serum level=5.5 µg/L., 4th quartile OR=2.19	Prevalence=10.7%	220/stratum
Obesity	Karlsen 2017 (Faroes)	PFOA mean serum level=2.22 µg/L. OR=1.88	Prevalence=17%	250/stratum

Note: Observed effect sizes focused on the results for serum levels of PFOS and/or PFHxS.

¶ eGFR –estimated glomerular filtration rate, TT4 – total thyroxine; IGF-1 – insulin-like growth factor 1; ADHD – attention-deficit and hyperactivity disorder.

3.3.2 Adults

For adults, **Table 2** (and **Attachment 3b**) provide the sample size calculations for several health outcomes of interest assuming a type 1 ("α error") of .05 and type 2 error ("β error) of .20. In this exposure based study we assume an appropriate coverage of range of exposures that will enable stratification/categorization to tertiles or quartiles of exposure. Per stratum estimates of needed sample size (e.g. first vs. fourth quartile) have been calculated based on different measures of association such as odds ratios or detected mean difference.

The proposed sample size of 6,000 adults (equally of both sexes) is large enough to effectively evaluate many of the health outcomes identified in the Pease Feasibility Assessment literature review. For example, for outcomes like elevated lipids levels (cholesterol) or uric acid, the range of 229 to 660 participants per stratum (i.e. quartile) or 200 to 550 per stratum, respectively, given observed differences would be needed. That would translate to overall sample size of about 800 to 2,600 participants being sufficient to detect differences at the specified level of precision and power (Steenland, 2009, 2010; Fisher 2013; Shankar 2011). Similar sample sizes would also be required to compare other common health outcomes such as cardiovascular disease (Shankar 2012). Larger samples sizes would be needed for liver function or osteoarthritis, with a total sample in the range of 3,000 to 4,000 subjects (Uhl 2013; Gallo 2012; Steenland 2010).

For thyroid disease and thyroid function, a total sample size of 6,000 may be sufficient although probably not optimal. However, NHANES studies of thyroid function and thyroid disease obtained statistically significant findings with total sample sizes considerably less than 6,000 (Melzer 2010; Wen 2013). NHANES studies of liver function also obtained statistically significant findings with total sample sizes considerably less than 6,000 (Gleason 2015; n=4333). For biomarkers of immune function (e.g., immunoglobulins, C-reactive protein and cytokines) and fatty liver disease, there was insufficient information to calculate sample sizes. However, a total sample size of 6,000 should be sufficient to evaluate these biomarkers as we assumed similar endpoint differences of those outcomes.

For ulcerative colitis, a sample size of 6,000 might be sufficient if the effect size in the C8 study (i.e., OR=3.05) was consistent for PFOA serum levels considerably lower than those in the C8 study. For more

modest effect sizes (e.g., ORs < 2.75), a total sample size of 6,000 would not be adequate to evaluate associations with ulcerative colitis.

In addition, several epidemiological studies of adults exposed to PFAS that reported robust statistical associations with these health outcomes had smaller sample sizes than the one proposed for the Multi-site Study, e.g., NHANES studies (Nelson 2010, Wen 2013), a C8 longitudinal study (Fitz-Simon 2013), a C8 immune study (Looker 2014), and studies in China (Fu 2014) and Korea (Ji 2012).

In summary, a total sample size of ≥6,000 in multi-site study should be sufficient to evaluate a broad range of biomarkers and outcomes such as lipids (and hypercholesterolemia), uric acid (and hyperuricemia), cardiovascular disease, osteoarthritis, immune biomarkers and biomarkers for fatty liver disease. It also may be sufficient to evaluate thyroid disease, thyroid function and liver function.

Table 2. Sample size estimations for selected health-related endpoints in Adult Study.

Health-related Endpoint	Relevant Study	Observed Effect Size	Assumptions	Sample Size/Stratum α error = .05 β error = .20
Total Cholesterol (mg/dL) High cholesterol	Steenland 2009, C8 46,294 aged ≥18 yrs	PFOS, mean serum level = 19.6 µg/L, 10th vs 1st decile:+11 mg/dL 4th vs 1st quartile, OR=1.51	SD=41.9 Prevalence=15%	228/stratum 660/stratum
High Cholesterol	Fisher 2013, Canada	PFHxS, mean serum level = 2.2 µg/L, 4th vs 1st quartile, OR=1.57	Prevalence=44%	290/stratum
Cardiovascular disease	Shankar 2012, NHANES 1,216 aged ≥40 years	PFOA mean serum level = 4.2 µg/L, 4th vs 1st quartile: OR=2.01	Prevalence = 13%	250/stratum
Uric Acid	Steenland 2010, C8 53,458 aged ≥20 yrs	PFOS mean serum level = 20.2 µg/L, 10th vs 1st decile: +0.22 mg/dL Hyperuricemia, 5th vs 1st quintile: OR=1.26	SD=1.55 Prevalence:24%	780/stratum 1,525/stratum
Uric Acid	Shankar 2011, NHANES 3,883 aged ≥20 yrs	PFOA mean serum level = 3.5 µg/L, 4th vs 1st quartile: +0.44 mg/dL Hyperuricemia, 4th vs 1st quartile: OR=1.97 PFOS mean serum level = 17.9 µg/L	SD = 2.5 Prevalence: 19.2%	507/stratum 200/stratum 550/stratum

		Hyperuricemia, 4th vs 1st quartile: OR=1.5		
Liver function Elevated ALT	Gallo 2012, C8 46,452 aged ≥18 yrs	PFOA and PFOS mean serum levels were 28 µg/L and 20.3 µg/L, respectively. PFOA: OR=1.54 PFOS: OR=1.25	Prevalence = 11.2%	 725/stratum 2,917/stratum
Liver function ALT (µIU/mL)	Gallo 2012, C8 46,452 aged ≥18 yrs	The top quintile of serum PFOS in the Pease population was 15 µg/L. This would approximately correspond to a mean difference in ALT of +1.8 µIU/mL	SD=1.47	1,958/stratum
Liver function Elevated ALT	Gleason 2015, NHANES 4,333 aged ≥12 yrs	PFHxS mean serum level = 1.8 µg/L. 4th vs 1st quartile: OR=1.37	Assumed similar prevalence as in the C8 study	1,570/stratum
Thyroid disease	Melzer 2010, NHANES 1,900 men, aged ≥20 yrs 2,066 women, aged ≥20 yrs	PFOA, mean serum level=3.5 µg/L, 4th vs 1st quartile: Thyroid disease ever: Women, OR=1.64 Men, OR=1.58 Thyroid disease with current meds Women, OR=1.86 Men, OR=1.89	Prevalences: 16.18% 3.06% 9.89% 1.88%	 410/stratum 2,035/stratum 365/stratum 1,575/stratum
Subclinical hypothyroidism	Wen 2013, NHANES 672 males aged ≥20 yrs 509 females aged ≥20 yrs	PFHxS mean serum level averaged about 2 µg/L. Unit increase in Ln(PFHxS): Women, OR=3.10 Men, OR=1.57	Prevalences: 1.6% 2.2%	 475/stratum 2,918/stratum
Osteoarthritis	Innes 2011, C8 49,432 aged >20 yrs	OR=1.42	Prevalence=7.6%	1,580/stratum
Osteoarthritis	Uhl 2013, NHANES 4,102 aged 20-84	PFOA mean serum level = 5.4 µg/L , 4th vs 1st quartile: OR=1.55 PFOS mean serum level = 24.6 µg/L, 4th vs 1st quartile: OR=1.77	Assumed similar prevalence as in the C8 study	978/stratum 550/stratum
Ulcerative colitis	Steenland 2013, C8 28,541 community and 3,713 worker cohorts	OR=3.05	Prevalence=0.5%	1,480/stratum

For rare health outcomes such ulcerative colitis, other autoimmune diseases, or cancer the sample size of 6,000 adults is too small to detect reasonably expected increases in the ORs.

It should be noted that the number of PFAS epidemiological studies available for each of the outcomes is limited, and the actual differences in clinical and research parameters may be quite different in the Multi-

site study than have been observed in the PFAS literature. Sample size estimates provide guidance and may be useful for planning purposes but should be interpreted with caution, especially given the limited nature of the PFAS literature.

Attachment 3 provides further information and details on the derivation of the sample size calculations for Table 2 and also estimates of detectable mean difference and odds ratios for selected clinical tests and health outcomes.

3.4 Study Roll Out and Communication Plan

The recipient will work with local and state health and environmental agencies as well as local and state-wide community groups in conducting outreach to encourage participation in the study. The recipient may establish a community assistance panel (CAP) at each site, (or covering several nearby sites), to assist in outreach efforts. The recipient may also establish a multi-site "umbrella" CAP, with community representatives from each of the sites included in the study, to develop a coordinated, across-site, approach to conducting outreach about the study.

Community involvement via a CAP or an alternative participatory mechanism will be crucial in achieving a high participation rate at each site and the sample size requirements of the study. In advance of the start of the study, outreach and engagement will involve announcements to local elected officials, medical societies/community health clinics, local media, community organizations, local unions, the public school system, and local private schools (**Attachment 5**). Outreach may also involve meetings with community representatives, medical societies, school officials, and/or public meetings. Although active in outreach, state and local agencies, CAPs, unions and community organizations will not directly obtain consent, intervene, or interact with research participants. As part of the outreach, the recipient will prepare a factsheet for distribution to state and local agencies, unions, and community groups (**Attachment 5, Attachment 7c**).

3.5 Recruitment

For sites with a contaminated public water supply, the recipient will request a list of residences served by the water purveyor. The information requested will include the name of the person on the residential account and the street address of the residence. The recipient will also request information from the

water purveyor on the distribution system characteristics, in particular, whether the PFAS concentrations can be assumed to be relatively uniform throughout the system or whether the system had specific areas with substantially higher or lower PFAS concentrations. If uniform PFAS concentrations can be assumed, then a random sample of households may be conducted and recruitment letters mailed to these households. If the system has specific areas with substantially higher PFAS concentrations, then households in these areas will be targeted (oversampled) for recruitment letters.

For sites with contaminated private wells, the recipient will request information on the impacted residences and the results of PFAS sampling of their private wells from the state and/or local health and environmental agencies. Sampling will target households based on the magnitude of the PFAS concentrations in their private wells – i.e., wells with higher concentrations will be oversampled.

Recruitment letters will provide a phone number to call for information about the study and to accept the invitation to participate in the study. The recipient will screen each interested caller using an eligibility screening script (**Attachment 4**). If necessary to achieve a high participation rate and the sampling size goal for the site, study staff may visit the sampled households to recruit participants.

Sampled households may have more than one eligible adult and/or child, and some parents may want to enroll in both of the adult and child studies. Trained study staff will use the recruitment tracking form (**Attachment 6**) to track recruitment success and to calculate non-response bias.

3.5.3 Enrollment Procedures

Once potential recruits express interest and are screened for eligibility, study staff will schedule appointments for them at the central study office, or alternatively for a home visit for some who are unable or unwilling to attend an office visit and who live a reasonable distance to the office. The study staff will establish a toll-free telephone line for interested recruits to schedule appointments at their convenience. Once the appointment is scheduled, study staff will mail an Appointment Packet (containing an Appointment Reminder Card (**Attachment 7a**), the Informed Consent materials (**Attachment 7b**), a Study Fact Sheet (**Attachment 7c**) with a description to arrive fasting, and to bring medications and a urine sample to the appointment**.** Interested recruits will be mailed urine collection supplies. They will be instructed to collect a first-morning voided urine sample on the day of their appointment. An advance copy of the Informed Consent Form will provide an extra opportunity for the interested recruit to read

and more fully understand his or her rights in the study and to ask any questions before the scheduled appointment.

Study staff will give the interested recruit a reminder telephone call one to two days before the scheduled appointment (**Attachment 8**). The study protocol will provide the flexibility to schedule or re-schedule office or home visits within the study period. Interested recruits who are unable or unwilling to come to the study office, and live within a one-hour drive of the study office, will be offered an in-home appointment by trained study staff to complete the study. Interested recruits who request or require a home interview, blood draw, and urine collection, should reside within a one-hour drive from the study office. The study staff will make up to five contact attempts to an interested recruit who misses an appointment in order to reschedule the appointment and maximize the number of completed appointments (**Attachment 9**).

3.6 Data Collection Procedures

The study will establish a central office in each study site to obtain informed consent, blood and urine specimens, administering the neurobehavioral batteries to parents and children, and providing a space for completion of the questionnaire. Study staff will be available to answer any questions concerning the study. All study staff will receive training on the goals and purposes of informed consent, administration of the questionnaire, administration of the neurobehavioral test batteries, collection methods for the blood specimens, and on proper documentation of data collection procedures. Study staff will receive certified training on Human Subjects Protection (e.g., Collaborative Institutional Training Initiative [CITI] Program) and sign a confidentiality agreement prior to contact with potential recruits and enrolled participants.

Trained study staff will attend dedicated telephone lines to respond to questions and to address concerns from potential recruits, enrolled participants, and the public. Study staff will ask participants to attend their appointment in at least an eight-hour fasting state; therefore, most recruits will likely schedule appointments in the early morning. The steps of the data collection will include:

1. Check-in procedures;
2. Informed consent;
3. Data collection procedures;
4. Exit procedures; including provision of a gift card as a token of appreciation for participation.

3.6.1 Check-in Procedures

Trained study staff will document the completion of each step from check-in to the provision of gift cards on a hard copy form (**Attachment 9**). This hardcopy form will be stored with the participant's signed Informed Consent Form (**Attachment 7b**) in locked files and in secure rooms. Staff will securely ship all files to ATSDR at the end of data collection. All files and biological samples will be securely stored at the study office prior to shipment.

3.6.2 Informed Consent Process

The informed consent includes a description of study procedures and risks and benefits of participation (**Attachment 7b**), including a Privacy Act Statement (**Attachment 7b1**). A study factsheet will inform the adult participant and the child participant and parent of the chemical tests and clinical outcomes to be measured (**Attachment 7c**). Study staff will emphasize the voluntary nature of participation and will answer any questions the participant, or parent of the child participant, has prior to obtaining signatures.

3.6.2.1 Consent for Specimens and Data

The recipient will obtain fasting blood specimens from each participant for analyses of PFAS and several effect biomarkers. In addition, all participants will be asked to provide a morning void urine sample on the same day as their blood draw. After all the current laboratory analyses on blood are completed, the recipient will ask for permission to archive any residual blood specimens and the urines for future analyses of PFAS and/or effect biomarkers.

If a study participant previously had a PFAS serum measurement, the recipient will ask the participant for the results.

3.6.2.2 Child Consent

Before any data collection can begin in the child study, trained study staff will review the hardcopy Parental Permission and Assent Form (**Attachment 7b2**) with the parent who is interested in having the child participate. The study staff will explain to the parent and child the purpose of the study and request that the parent sign the permission forms. If the child is seven years of age or older, the study staff will request that the child give an assent to participate in the study.

The recipient will request that the parent complete a questionnaire about the child and complete a parental neurobehavioral test battery on behalf of the child. The permission form will request that the

parent allow the child to donate a fasting blood specimen and store any residual specimens for future analyses. The parental permission form will allow the investigators to administer a neurobehavioral test battery to the child, access the child's medical and school records (including special education records) (**Attachments 7b2, 7b3 & 7b5**), and to contact the child and parent for possible future studies. Once the parent signs the consent and permission forms (and the child aged ≥7 years gives assent to participate), the parent and/or the child become study participants in the future.

3.6.2.3 Adult Consent

Before any data collection can begin in the adult study, trained study staff will review the hardcopy Adult Consent Form with the interested recruit (**Attachment 7b4**). The study staff will explain the purpose of the study and obtain written informed consent for the completion of a questionnaire, the collection of a new fasting blood specimen, the storage of this blood specimen for future analyses, access to medical records (**Attachment 7b5**), and permission to contact the participant in the future for a possible study . After signing the consent form, the adult will become a study participant.

3.6.2.4 Risks and Benefits

As further described in **Section 3.8.1**, the recipient will inform the participant that his or her participation is protected by a Certificate of Confidentiality under Section 301(d) of the Public Health Service Act as amended by Section 2012 of the 21st Century Cures Act. The recipient will further inform the participant that access to identifiable occupational history, private medical records, and to school records are protected from certain disclosures under Section 301(d) of the PHSA.

The risks of participation in this study are minimal (defined in 45 CFR 46.110). In-home urine collections are minimal risk. This study plans for a one-time 23-ml (5 teaspoons) volume of fasting blood collected from the child and a one-time 33-ml volume of fasting blood collected from the adult. These amounts of blood are the minimum necessary to conduct analyses for PFAS and the effect biomarkers (**Attachment 2**). After the blood draw, the participant will be offered a small snack, thereby allowing monitoring of adverse events due to phlebotomy.

Participants in this study will not receive any direct benefit from taking part in this research. Their taking part in this research will provide the scientific community and the public a better understanding of how exposures to PFAS-contaminated drinking water may affect human health. Each adult participant and the parent of the child participant will receive the results of the analyses of serum PFAS levels and effect

biomarkers. They will receive the results of their urine PFAS and effect biomarker levels, if ATSDR identifies meaningful urinary analyses to perform.

3.6.3 Update Contact Information and Medication List

The adult participant and the parent of the child participant will be asked to verify and update his or her current contact information for results reporting and potential future contact (**Attachment 10**).

The study staff will request that the adult participant and the parent of the child participant bring all current prescription and over the counter medications prior to the study office. This will help the study staff to complete the medications list (**Attachment 11**).

3.6.4 Body and Clinical Measurements

Trained study staff will perform the body and clinical measurements and specimen collections as described in the Manual of Procedures (**Attachment 12**).

Body Measurements: Trained study staff will perform body measurements, blood pressure measurements, and blood draws. Three blood pressure (BP) measurements will be taken and averaged. The measured BP level is subject to biological and observer variability; therefore, the study will use three different sizes of the manual cuffs in the measurements; the appropriate cuff size will be selected for each participant and administered 3 times. The purpose of a specific measurement protocol, or training and certifications of technicians and of ongoing quality control is to minimize variability due to known exogenous factors and to reduce imprecision and biases in measurement. Measurement of resting blood pressure, height, weight, and waist and hip circumference can occur in any order, but the BP measurement should occur after the subject has been in the seated position for at least five minutes. BP measurement will occur before venipuncture if the activities are scheduled consecutively. Trained study staff will record the measurements in the Body and Blood Pressure Measures Form (**Attachment 13**).

Fasting Blood Specimen and First Morning Urine Void Collection: Participants will transport their urine sample to study office for collection. Trained staff will collect and record the urine specimen intake (**Attachment 14)**. The blood collection procedure consists of administering and recording responses to a blood draw screening questionnaire for conditions that exclude the participant from the blood draw (hemophilia, skin condition, or chemotherapy in the past four weeks, and pregnancy), ask about having diabetes, taking blood thinning medications, participant's weight, and fasting status (**Attachment 14**).

Next, phlebotomists will draw 23-ml (0.8 ounces or about 5 teaspoons) of blood from the child participant and 33-ml (1.1 ounces or about 7 teaspoons) of blood from the adult participant using standard venipuncture techniques (**Attachment 12**) and record the outcome (**Attachment 14**). If a person is unable to provide the desired volume of blood, a smaller amount can be drawn and documented. Trained study staff will record the phlebotomy and urine collection result on the Blood Draw and Urine Collection Form (**Attachment 14**).

Common adverse events from blood draws include bruising, bleeding, and fainting. No serious adverse events are anticipated in drawing these volumes of blood. Fasting diabetic participants who use insulin will receive priority appointments for their blood draw. Light snacks will be provided following blood collection. While each participant will be asked to provide a fasting sample, it is recognized that some may not be able to fast. Variations in lipids levels due to fasting will affect PFAS compounds measurements to a lesser extent as PFAS in serum are bound to proteins not the lipid fraction. . In the C8 Science Panel studies, about 25% of participants fasted – but they were not asked to do so (Frisbee 2009).

Phlebotomists will extract serum, and label and prepare the serum and urine specimens for secure storage and transport from the study office to the CDC NCEH laboratory in Atlanta, GA (**Attachment 12**).

The NCEH laboratory will perform the analyses of serum PFAS according to the biochemical analytical plan (**Attachment 2**) and approved laboratory methods (Kuklenyik 2015). The NCEH laboratory staff will also aliquot and ship blood and serum specimens to participating laboratories for the analyses of the effect biomarkers according to the plan. The recipient will store the urine samples and conduct analyses at a later date when more knowledge is gained about urinary PFAS and effect biomarkers and until the laboratory methods are developed. Residual blood and urines will be archived at NCEH so that additional PFAS or effect biomarkers can be analyzed as new knowledge and analytical methods become available.

3.6.5 Questionnaire

Each adult participant, and a parent of the child participant, will complete a questionnaire during the appointment for the blood draw.

3.6.5.1 Children and Parents

Study staff will request that the parents of the child participant complete the questionnaire. The questionnaire will obtain demographic information (e.g., education, primary occupation), residential

history, water consumption habits, medical history of the mother and child, the child's medications, the mother's reproductive history (including maternal age at birth of the participating child) and any occupational exposures the mother may have had to PFAS. The questionnaire will be administered in two formats: a form for the child whose parent is not also a participant (**Attachment 15**), and an abbreviated form for the child whose parent is also an adult participant (**Attachment 15a**).

The questionnaire will obtain the mother's and child's residential history in the study area, and the dates and length of time of the pregnancy and breastfeeding of the child. The questionnaire will also obtain information on the water consumption habits (including use of water for formula, juices, etc., bottled water use) of the mother and child when they resided in the study area. Information on the mother's workplaces in the study area (location and dates) and the child's daycare and schools in the study area (location and dates) will be obtained.

The questionnaire will request information on the child's height and weight, vaccination history, and whether the child regularly exercises, currently smokes (and the number of cigarettes/day), or consumes alcohol (and the number of drinks/week). The questionnaire will ask when the female child first began to menstruate. The questionnaire will include specific questions addressing health outcomes of interest. For example, for ADHD, the questionnaire will ask, "Has a doctor or health professional ever told your child that your child has/had ADD or ADHD?" If the answer is "yes," a second question will ask for a list of medications the child took for the condition. The questionnaire will ask if the child had learning or behavioral problems, and if so, the type of problem and the treatment used. Questions would be included for the hypersensitivity-related outcomes, asthma, atopic dermatitis (or atopic eczema), and allergies. The study will attempt to confirm diseases and conditions reported in the questionnaire by accessing medical records sending abstraction forms (**Attachments 17&17a**) to the medical care provider identified by the participants on their consent forms (**Attachment 7b5**).

3.6.5.1.1 Child/Parent Neurobehavioral Assessments

Table 3 provides the neurobehavioral test battery for children enrolled in the Multi-site Study.

Trained professionals will administer the following tests to children:

- The Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI – II) test will be administered to measure Full Scale IQ (FSIQ) among children 6-17 years (15 minutes). Intelligence testing of children aged 4 – 5 years will not be conducted.

- Each child 4-16 years will complete the NEPSY-II selected tests. Except for Theory of Mind, these additional tests are short and useful to assess memory and inhibition. For all the NEPSY – II tests, children 4 years would take about 52 minutes, and children ≥5 years, about 70 minutes.
- Children aged 4 – 7 years will complete the Connors Kiddie Continuous Performance Test (K-CPT – 2) (8 minutes), and children aged >7 years will complete the Connors CPT – 3 (14 minutes).

Trained professionals will administer the following tests to parents about their children:

- Strengths and Difficulties Questionnaire (SDQ) (5 minutes).
- Behavior Rating Inventory of Executive Function® (BRIEF®) to assess the child's emotional, conduct, and peer relationship problems as well as problems with hyperactivity, inattention and executive function.
    - Parents of children aged 4 – 5 years will complete the preschool version (BRIEF®-P) (10 minutes).
    - Parents of children aged >5 years will complete the BRIEF® (10 minutes).

A summary of the neurobehavioral test battery is found in **Attachment 18**. Each child will spend an average of 90 minutes to complete the child battery of tests. Each parent will spend an average of 15 minutes to complete the parent battery of tests. Overall, each parent/child pair will take 105 minutes to complete the neurobehavioral test battery (**Attachment 18a**).

Table 3. Neurobehavioral Test Battery for Children

Neurobehavioral Test	Domain	Age	Administration	Time to Administer
Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI - II)	Two Subtest Form (FSIQ)	6 – 17*	Child	15 minutes
A Developmental Neuropsychological Assessment – 2nd edition (NEPSY – II) subtests * from Core Assessment	Auditory Attention and Response* (reduced attention)	5 – 16	Child	7 – 11 minutes
	Inhibition*	5 – 16	Child	8 – 11 minutes
	Comprehension of Instructions* (receptive language, trouble following multi-step commands)	4 – 16	Child	6 – 8 minutes
	Speeded Naming* (expressive language, processing speed)	4 – 16	Child	2 – 7 minutes
	Word List Interference* (verbal memory)	7 – 16	Child	6 – 8 minutes
	Narrative Memory* (comprehension, verbal memory)	4 – 16	Child	6 – 11 minutes
	Design Copying* (visuospatial processing)	4 – 16	Child	7 – 10 minutes
	Theory of Mind (social perception)	4 – 16	Child	10 – 13 minutes

	Sentence Repetition (verbal memory)	4 – 6	Child	4 minutes
	Statue (inhibitory control)	4 – 6	Child	3 minutes
	Word Generation (expressive language, executive control)	4 - 16	Child	4 – 6 minutes
Conners Kiddie Continuous Performance Test, 2nd Edition (Conners K-CPT 2)	Inattentiveness, Impulsivity, Sustained Attention, Vigilance	4-7	Child	8 minutes
Conners Continuous Performance Test 3rd edition (CPT 3)	Inattentiveness, Impulsivity, Sustained Attention, Vigilance	8-17	Child	14 minutes
Strengths and Difficulties Questionnaire© (SDQ©)	Double-sided form with impact supplement (behavioral problems)	4 – 17	Parent about Child	5 minutes
Behavior Rating Inventory of Executive Function® (BRIEF®)	Executive Function	6-17	Parent about Child	10 minutes
Behavior Rating Inventory of Executive Function® – Preschool Version (BRIEF®-P)	Executive Function - Preschool	4-5	Parent about Child	10 minutes

For each child, the recipient will also review and abstract school records, including special education records, to identify learning problems and behavioral problems (**Attachment 18b**). If the parent reports that the child has a developmental disability (e.g., ADHD, autism, or a learning disability), then the recipient shall obtain and abstract the special education records for the child including the individualized education program (IEP), the IEP evaluation report ("Full Individual Evaluation" or "FIE"), and if available, the Independent Educational Evaluation.

3.6.5.2 Adults

Each adult participant will complete a questionnaire requesting demographic information, residential history, water consumption habits, occupational history, medical history and reproductive history (**Attachment 16**). In particular, the questionnaire will ask if the participant ever had kidney disease, liver disease, cardiovascular disease, hypertension, high cholesterol, thyroid disease, diabetes, autoimmune diseases, osteoporosis, osteoarthritis, pregnancy-induced hypertension, infertility, and endometriosis. For each reported disease or condition, the questionnaire will ask about the date of diagnosis, the medical provider who made the diagnosis, and the medications used for treatment the questionnaire will ask the participant about conditions that might affect PFAS serum levels such as date of menopause, menstrual

cycle information, blood transfusions, and blood donations. The study will attempt to confirm diseases and conditions reported in the questionnaire by medical records review (**Attachments 17&17a**).

3.6.6 Exit Procedures

At the end of the data collection, study coordinators or staff will review recorded items in the participant's Appointment Tracking Form for completeness (**Attachment 9**).

The adult participant or the parent of the child participant will receive a copy of the participant's Body and Blood Pressure Measures Report (**Attachment 19**). These results will be immediately available and will require no further evaluation or interpretation with two exceptions. The adult participant or the parent of the child participant will receive a supplemental notice if the participant has a critical blood pressure measure (diastolic blood pressure > 120 mm Hg, or systolic blood pressure >180 mm Hg). In this case, a Critical Hypertension Notice will be appended to the Body and Blood Pressure Measurements Report along with written and verbal recommendations to obtain immediate medical attention. If the participant does not have a personal physician, the study coordinator will provide a referral. If the participant has an elevated but non-critical blood pressure measure (resting blood pressure > 140/90), an Elevated Hypertension Notice will be appended to the Body and Blood Pressure Measures Report with written and verbal recommendations to obtain clinical follow-up.

3.6.6.1 Gift Cards as a Token of Appreciation for Participation

As a token of thanks for participation, the recipient will offer gift cards according to the following schedule:

- $25 for body and blood pressure measures, and for blood and urine collection;
- $25 for completed questionnaire; and
- $25 for child/parent completion of the neurobehavioral test battery

Trained study staff will document provision of gift cards on the hard copy form (**Attachment 9**). As part of the exit procedures, the participant will sign this form to document receiving the gift card.

3.6.7 Adverse Events

The risks associated with this study are minimal. There is a small chance of unexpected or adverse events occurring during the course of this project. Unanticipated problems involving risk to the subjects or others

will be reported to the CDC Human Institutional Review Board (IRB) in accordance with institutional policies and procedures.

The most likely adverse event is a participant feeling lightheaded or fainting during blood collection. The phlebotomist will receive training to respond to such situations. The tests and procedures conducted by trained study staff are for research purposes only and are not diagnostic exams. They are not a substitute for an evaluation by a medical professional. The study will not perform any clinical treatments or health interventions as part of the study.

If a participant loses consciousness, falls, is unable to stand, or experiences chest pain the study staff will decide whether to advise the adult participant or the parent of the child participant to seek immediate medical treatment or to contact emergency medical services. Study staff have identified appropriate local medical care providers that participants may be referred to if clinical results suggest medical attention is needed (**Attachment 12**).

3.7 Biochemical Analyses

Serum PFAS: The study's biochemical analytical plan is found in **Attachment 2**. The study will analyze 12 PFAS in fasting serum including PFOA (linear and the sum of branched isomers of PFOA), PFOS (linear and the sum of perfluoromethylheptane sulfonate isomers, and PFHxS (Kuklenyik 2015). Other PFAS analyzed will include: perfluorooctane sulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH), 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH), perfluorobutane sulfonic acid (PFBuS), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic acid (PFDoA).

{Note: the study may include measurement of additional PFAS if methods become available by the start of the study. Addition of new analytes will be submitted to the CDC IRB for approval of amendments}

Urinary PFAS: The study will also analyze PFAS compounds in first morning void urines at later time on stored urine samples. Urine is an important excretion pathway for human metabolism and PFAS urine elimination may be important influencing serum concentrations (Harada 2005, Zhang 2015). The PFAS compounds to be measured in the future are listed in **Attachment 3**.

3.7.1 Children

The study will analyze fasting serum for the following biomarkers of lipids, thyroid, glycemic, liver, and kidney function, sex hormones, and immune function **(Attachment 2**)**:**

- Total cholesterol, low density lipoprotein, high density lipoprotein, total triglycerides,
- Uric acid, creatinine,
- Thyroxine (TT4, FT4), T3, thyroid stimulating hormone (TSH),
- Glucose, insulin, glycosylated hemoglobin (HbA1c), auto-antibodies (GAD-65 and IA-2), C-peptide, pro-insulin,
- Alanine transaminase (ALT), γ-glutamyltransferase (GGT), direct bilirubin, and cytokeratin-18 (CK-18),
- Testosterone, estradiol, sex hormone-binding globulin (SHBG), follicle stimulating hormone, insulin-like growth factor,
- Immunoglobulin G (IgG), IgA, and IgM; antibodies to measles, mumps, rubella, tetanus, and diphtheria.

The child study will use the cut points of 50 ng/dL of total testosterone and 20 pg/mL of estradiol to identify sexual maturation in boys and girls, respectively (Lopez-Espinosa 2011). The child study will measure IgG antibodies for measles, rubella, and diphtheria to determine vaccine responses. It will analyze allergen-specific IgE (mold, dust mites, dog, cat, cow's milk, peanut, hen's egg, and birch). The study will analyze serum levels of thyroid stimulating hormone (TSH) and total/free T4 separately and use these measurements to determine clinical and subclinical hypothyroidism and hyperthyroidism. The study will measure uric acid, total cholesterol, low-density and high-density lipoprotein, and triglycerides. We also propose to measure liver enzymes and CK-18 (Feldstein 2013, Mora 2018, and Santoro 2013).

3.7.2 Adults

The study will analyze the following biomarkers in the adult fasting serum (**Attachment 2**)**:**

- Total cholesterol, low density lipoprotein, high density lipoprotein, total triglycerides,
- Uric acid, creatinine,
- Thyroxine (TT4, FT4), T3, thyroid stimulating hormone (TSH),
- Glucose, insulin, glycosylated hemoglobin (HbA1c), auto-antibodies (GAD-65 and IA-2), C-peptide, pro-insulin,

- Alanine transaminase (ALT), γ-glutamyltransferase (GGT), direct bilirubin, and cytokeratin-18 (CK-18),
- Immunoglobulin G (IgG), IgA, IgE and IgM; C reactive protein, and antinuclear antibodies (ANA),
- Cytokines and adipokines (e.g. IL-1β, IL-6, IL-8, MCP-1, TNFα, leptin, adiponectin, resistin, PAI-1).

3.7.3 Quality Control/Quality Assurance

To maintain the integrity of the lab results, a backup generator will be available for the refrigerator and freezer at the study office. All serum, blood, and urine specimens will be securely stored at the study office until shipped to the NCEH laboratory.

The NCEH and other participating laboratories will fulfill quality assurance/quality control criteria (QA/QC) including a documented quality assurance plan and adherence to required quality control procedures specified in an approved method. The laboratories will ensure that the analytical data are scientifically valid, defensible, and of known and acceptable precision and accuracy. QA/QC procedures, including appropriate calibration of instruments, running standards and blanks, reporting limits of detection, and other parameters will be in place before specimens are tested. Specimen collection, storage, and transportation techniques are specified in the Manual of Procedures to ensure the integrity of the specimens (**Attachment 12**). Specimens will be stored at the proper temperature and isolated from potential sources of contamination.

The Standard Operating Procedure (SOP) for each analytical method is kept on file by the PI, and is available for review upon request.

3.7.4 Reference Values

The participating laboratories will provide reference values and action levels for the effect biomarkers which will be reported in **Attachments 20&21**. The recipient will report the participant's PFAS results using reference values from the most recent NHANES report (**Attachment 22**). Currently, the 2013-14 report is available and provides reference values for children. **Section 4** provides additional descriptions of the procedures for advance and final results reporting.

3.8 Data Handling

3.8.1 Certificate of Confidentiality

ATSDR requests to issue a Certificate of Confidentiality (CoC) under Section 301(d) of the Public Health Service (PHS) Act, as amended by Section 2012 of the 21st Century Cures Act, P.L. 114-255 (42 U.S.C. 241(d)), states that the Secretary shall issue CoCs to persons engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. In furtherance of this provision, CDC research commenced or ongoing after December 13, 2016 and in which identifiable, sensitive information is collected, as defined by Section 301(d), is deemed issued a CoC and therefore researchers are required to protect the privacy of individuals who are subjects of such research in accordance with Section 301(d) of the PHSA.

Consistent with Section 301(d), ATSDR determined that a CoC applies to this research by answering the following questions:

1. Is the activity biomedical, behavioral, clinical, or other research? YES
2. Does the research involve Human Subjects as defined by 45 CFR Part 46? YES
3. Is ATSDR collecting or using biospecimens that are identifiable to an individual as part of the research? YES
4. If collecting or using biospecimens as part of the research, is there a small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual? YES
5. Does the research involve the generation of individual level, human genomic data? NO

Since the answer to any one of Questions 2-5 is YES, ATSDR determined that a CoC will apply to the research; therefore, in accordance with subsection 301(d) of the Public Health Service Act, ATSDR and any of its cooperative agreement recipients shall not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive

information about such an individual and that was created or compiled for purposes of the research.

Disclosure is permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

ATSDR and its cooperative agreement recipients conducting this research are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the research contract is managed in compliance with Federal statutes, regulations, and the terms and conditions of the award (**Attachment 12**). Recipients are also required to ensure: 1) that any investigator or institution not funded by CDC/ATSDR who receives a copy of identifiable, sensitive information protected by this CoC, understands that it is also subject to the requirements of subsection 301(d) of the PHS Act; and 2) that any subrecipient that receives funds to carry out part of this CDC award involving a copy of identifiable, sensitive information protected by a Certificate understands that it is subject to subsection 301(d) of the PHS Act.

For studies in which informed consent is sought, ATSDR and its cooperative agreement recipients shall inform research participants of the protections and the limits to protections provided by this CoC (**Attachment 7b**). Therefore, all study staff will receive training on the importance of protecting the confidentiality of human research subjects and of personal information acquired, including the collection of biological specimens. The study will minimize the risk of loss of confidentiality and privacy through careful attention to procedures for such protections in the collection, handling, and reporting of individually identifiable and sensitive data (**Attachment 12**).

3.8.2 Data Management and Security

Data management for this study described below includes guidance on:

1. Use and protection of information in identifiable form (IIF);
2. Security access (physical, technical, and administrative) controls for ATSDR and its contractor;
3. Appropriate data delivery; and
4. Data ownership and data sharing.

Collection of IIF. The study staff will collect, manage and store IIF in an already established record system (System of Records Notice [SORN] No. 09-19-0001 titled "Records of Persons Exposed to Toxic or Hazardous Substances"). ATSDR will use IIF to report results to each parent of a child participant or adult participant. ATSDR will be the final recipient of the IIF (to keep for potential re-contacting of participants).

The study staff will deliver all field-collected records to ATSDR headquarters at the end of the study. ATSDR will retain IIF such as name, Social Security Number (SSN), current address, phone number, email address, date of birth, and the date of the participant's blood draw and questionnaire completion. ATSDR will store the IIF in a separate master key dataset along with a study-generated ID. This dataset will be separate from the dataset containing the questionnaire data and other data used in the statistical analyses. The study-generated ID will be the variable that can link the two datasets if necessary. IIF will not be linked with files used for statistical analysis and will not appear in any reports generated from this data set.

3.8.3 Impact on Privacy

Because the study staff will collect, store, manage, and maintain IIF on an already established record system, there would be a likely effect on the participant's privacy if a breach of data security occurred. Therefore, its established record system has stringent safeguards in place as described in the following section. Research datasets will include only coded information that might be sensitive, such as questions on reproductive outcomes, fertility, or fecundability. These files will not have associated information that might directly identify these participants. IIF will be stored in a separate master key dataset, which will enable ATSDR investigators to link the participant's research data with his or her IIF via a study-generated ID. Maintaining this contact information is necessary to provide results of the tests or re-contact them in the future for a longitudinal study. Therefore, stringent data security measures will be in place, including administrative, physical, and technical controls as described below.

All laboratories involved in biochemical analyses will receive biological specimens with participants' study-generated ID only. Nondisclosure agreements will be executed between the recipient and laboratories that will not be engaged in research.

3.8.3.1 Access Controls and Security

The recipient PI and Project Manager will be responsible for all required staff training and certification, periodic checks of procedures and data collection methods, privacy, and security of data, as well as access of assigned personnel to different types of data. For this information collection, all study staff will be under the direct supervision of the ATSDR on-site supervisor. The study staff will obtain appropriate office space for the blood draws, clinical assessments, questionnaire, neurobehavioral batteries administration, secure storage of questionnaires, medical and school records, and storage of blood specimens (including refrigeration) prior to shipment to the NCEH laboratory. All data and biological specimens collected in the study are the property of ATSDR. Methods to ensure least privilege access to the study information will be in place; therefore, access to identifiable information will be role-based on a need-to-know basis for the recipient investigators.

The study staff will provide details on its data security technology and methods including password protection, desktop firewalls, daily backups and server based storage, intrusion detection, vulnerability scans of personal computers and server, laptop security, and computer encryption procedures to the CDC security office.

Once collected from the participant, all hardcopy informed consents and data collection forms will be stored in locked files in locked rooms in the study office and at ATSDR. Informed consent will also be scanned into electronic form and transferred to ATSDR to provide backup in the case of incidental damage to the paper forms.

Upon completion of the project and once the ATSDR has received all approved study related paper documents, the recipient will destroy those hardcopy documents not necessary to complete the study analyses or to contact study participants.

Data security measures at ATSDR will comply with the *CDC/ATSDR Protection of Information Resources Policy* and the *CDC/ATSDR IT Security Program Implementation Standards.* These policies apply to all authorized ATSDR employees. All incidents involving a suspected or confirmed breach of IIF must be

reported to OCISO according to the policy titled *OCISO/CDC Standard for Responding to Breaches of Personally Identifiable Information (PII).*

Physical controls – The CDC/ATSDR issues identity credentials based on the Federal Information Processing Standards (FIPS) Publication 201 for Personal Identity Verification (PIV) authentication of government employees' identities. Security measures for physical access to secured facilities include the use of PIV Cards, security guards, and closed circuit TV monitoring.

Technical Controls – CDC/ATSDR policy requires employees to gain authorized logical access to its information systems through a unique electronic identity (User ID). The computer-controlled limits on what can be done by the user are assigned based on program roles and privilege requirements.

Administrative Controls –Authorized recipient researchers and CDC/ATSDR employees are required to:

- Complete required privacy and information security refresher training.
- Read, acknowledge, sign (if online completion is not available), and comply with the HHS Rules of Behavior, as well as other applicable CDC/ATSDR- and system-specific rules of behavior before gaining access to the CDC/ATSDR's systems and networks.
- Adhere to the requirements set forth in the *CDC/ATSDR IT Security Program Implementation Standards*, and other security policies and procedures that minimize the risk to CDC systems, networks, and data from malicious software and intrusions.
- Abide by all applicable acceptable use policies and procedures regarding use or abuse of CDC/ATSDR IT resources.

All study records are subject to the ATSDR Comprehensive Record Control Schedule (CRCS), B-371, which contains authorized disposition instructions for ATSDR's administrative and program records. ATSDR is legally required to maintain its program-related records in accordance with disposition instructions contained in this comprehensive records control schedule. These retention periods have a direct impact on completing Freedom of Information Act (FOIA) requests and in applying the requirements of the Privacy Act. The current schedule requires ATSDR to retain and archive program records for a period of 75 years after the end of the study activities.

3.8.4 Data Delivery

Study staff will follow checks and quality control procedures for data entry. Only authorized study staff will receive permission to enter or manipulate the study data. Data entry from hardcopy documents will involve double entry with discrepancies compared and corrected.

Study staff will prepare draft datasets to record questionnaire responses and medical record/school record data to send to ATSDR for review and approval. ATSDR will work with the study staff to resolve missing values and other data issues. The study staff will also keep and deliver a shipping log of blood specimens sent to the NCEH laboratory in Microsoft Excel format (**Attachment 12**). The log will include the include vial type, volume, ID code, date, and carrier details. ATSDR will receive lab results from the participating laboratories. The lab dataset will be merged by study ID with the questionnaire data to create a combined questionnaire and lab dataset.

All dataset formats will be transformed to SAS datasets (SAS 9.3, Cary NC). All final data management will be performed on this platform. Site investigators may also use other CDC approved statistical software before converting to SAS. Final datasets will be sent to ATSDR using encrypted, password coded spreadsheets through a password protected data sharing facility. The contractor will deliver to ATSDR the code and the master key dataset by which the response data are potentially relinkable to PII.

Consent forms that collect the signatures of participants will be paper instruments and the adult participant or parent of the child participant will receive a copy of the consent form; scanned electronic copy will be sent to CDC. Height, weight, and other applicable body measures and blood pressure will be recorded on a paper form and transferred to an electronic form.

3.8.5 Data Ownership and Data Sharing

Coded research datasets will be available to all ATSDR study investigators listed in **Attachment 1**. We will produce coded datasets by removing the following: name, SSN, date of birth, address, former address (es), phone number, and date of completion of the blood draw and questionnaire. SSN will be collected at enrollment for linkage to medical records and school records. Once the linkage has occurred, the SSN will be kept with other PII in a separate access restricted secure database. Age will replace date of birth in the data analysis file because it is the necessary variable in exposure and health outcome analyses.

Release of de-identified multi-site combined data to outside investigators including recipients must be approved by ATSDR. A data use agreement (DUA) will be prepared, detailing the condition of use of the data and proposed analyses for each outside project. The DUA condition of use will specify that ATSDR will not release the link between the study IDs and the participants' PII to the outside researchers. The DUA will also specify that:

1. Our data cannot be merged with public data in such a way that individuals may be identified;
2. Our data cannot be enhanced with public data sets with identifiable, or potentially identifiable, data;
3. One of the study investigators listed **in Attachment 1** must be a co-investigator on any outside research project to guarantee adherence to the agreed conditions of use; and
4. Each data release will be cleared by a specific IRB request to the investigator's home institution prior to data release.

After the approved project with the outside researchers is completed, further or secondary analyses of electronic datasets can only be undertaken with additional approval(s) from ATSDR. Written confirmation of understanding the conditions of use will be required from the lead scientist and institution. Copies of statistical code and datasets used in statistical analyses by the outside investigators will be kept by ATSDR.

3.8.6 Storing Residual Blood for Future Use

After performing the chemical and clinical tests, there may be some residual blood. In the consent form, we will ask participant's permission to save this residual blood for additional future analyses of PFAS and possibly additional effect biomarkers. We will only store blood of those participants who will consent to have their blood archived for additional PFAS and effect biomarker analyses.

The residual blood specimens will be stored with the study-generated ID only. ATSDR will keep a separate dataset that can link the study ID with the participant's name. If participants change their minds later about letting their blood used for additional analyses, they can contact ATSDR and we will remove their specimens. We do not plan to provide participants the results of these future tests, but we may contact them if we learn something that is important.

3.8.7 Future Exploratory Analyses

CDC IRB approval will be sought for this additional research either as a protocol amendment or under a new research protocol prior to undertaking this plan.

3.9 Exposure Estimation

The study will use the fasting serum PFAS measurements obtained from study participants to estimate exposures. In addition, the study will estimate each participant's cumulative PFAS serum level, using:

- PFAS serum measurements obtained in the study,
- Historical reconstruction of PFAS concentrations in the drinking water consumed by the participant,
- Questionnaire data on the participant's consumption of PFAS-contaminated drinking water and factors that might affect PFAS serum levels,
- Age-, sex-, and calendar year-specific "background" PFAS serum levels from NHANES, and
- Physiologically based pharmacokinetic (PBPK) models.

If previous PFAS serum measurements are available for some of the participants (e.g., from a biomonitoring program), then these results will be used to validate the modeled historical PFAS serum estimates.

The C8 studies used PBPK modeling to estimate cumulative serum levels of PFOA and PFOS (Shin 2011). The model incorporated information from the historical reconstruction of PFAS concentrations in the drinking water serving the C8 areas, questionnaire data on each participant's water consumption, and the serum levels of PFOA and PFOS obtained from study participants. A recent effort to reconstruct historical exposures worked well for PFOA and PFOS; the model for PFHxS serum levels using biomonitoring data in the US and Australia did not work as expected (Gomis 2017). Low environmental concentrations, lack of decline in older population, possible ongoing exposure in children/younger adults, and scarcity of time-trend data in consumer products were cited as reason for poor prediction characteristics of PFHxS models (Gomis 2017). However, if there are high correlations in serum levels between PFHxS and PFOS and/or PFOA, then it may be possible to estimate cumulative PFHxS serum levels based on the historical estimates for serum PFOS and/or PFOA.

Recently, an online serum PFOA calculator for adults became available using a modified one-compartment exponential decay model to estimate PFOA serum levels from PFOA concentrations in drinking water (Bartell 2017). Developing a similar calculation for serum PFOS is possible. The studies of children and

adults by ATSDR and recipients will explore this approach to estimate serum PFOA, PFOS, PFHxS and PFNA levels and make comparisons with serum levels from the blood specimens obtained in this study (and if available, previous PFAS serum measurements). The recipient may consider the use of a one-compartment PBPK model similar to one used by Shin (2011) and Avanasi (2016), and also used as the basis for a recent PFOA serum calculator (Bartell SM 2017).

A number of improvements in PBPK modeling approaches, especially as related to multi-compartment models, have been developed recently and the recipient should take those into consideration (Loccisano 2013, Fabrega 2014, 2016; Verner 2015, 2016).

The recipient should attempt to integrate a broad range of information on individuals' sociodemographics (birth year, age, sex, ethnicity), PFAS pharmacokinetics (e.g. tissue partitioning and distribution volumes, elimination rates), as well as exposure sources as pertain for the general population (e.g. breastfeeding, water consumption, blood transfusion) and secretion routes (e.g. parity, breastfeeding history, and menstruation in women; donating blood) which will be collecting in the adult and child questionnaire. Questionnaires also includes detailed information on menstruation cycles for women (regular/irregular, length, heavy/light flow, last menstruation before blood draw; Wong 2015, Verner and Longnecker 2015). The recipient can assume the contributions from dietary intake, cookware, cleaning supplies, etc. to be similar to the background US population (Domingo 2012, Christensen 2017). The recipient can also assume that NHANES calendar year-, age- and sex-specific PFAS serum concentrations reflect these background exposures (Calafat 2007, Ye 2017).

In order to estimate historical concentrations of PFAS in the drinking water and historical PFAS serum levels, it is necessary to obtain as much information as possible on the source of the PFAS contamination. If the source is environmental emissions from an industrial facility, then the recipient should request information from the facility about these emissions (e.g., periods, locations, frequencies and amounts of emissions, and whether the emissions are to surface water, ground water and/or air). If the source is AFFF use at a military base, airport or fire training area, then the recipient should seek information on the period and location of use, the annual amount of AFFF used, and any accidental or non-routine use (e.g., to extinguish a major fire, or a major spill) and the date, location and amount used.

Once information on the source is obtained, the recipient should seek information on how the PFAS contamination migrated from the source to the drinking water supply. For example, the recipient should request information on the soil, ground water and/or surface water characteristics in the vicinity of the

industrial emissions or AFFF use, as well as the location of drinking water intakes, supply wells (and nearby monitoring wells), and/or private wells serving the study area. If the PFAS contamination migrated from the source via ground water, then the recipient should seek information on the extent of the contamination plume from the state environmental agency, EPA, and/or the industrial facility.

If the contaminated drinking water is from a municipal system, then the characteristics of the distribution system will be obtained from the water purveyor. If supply wells are used, then the recipient will request historical and current information on these wells including monthly or daily production logs and dates of operation. If a surface water source is used or if water is purchased from another purveyor, then the recipient will request information about this source.

The recipient will also request the results of all relevant PFAS sampling: in the surface water near the drinking water intakes, in the distribution system, in the supply wells and nearby monitoring wells, in purchased water from other water purveyors, and in the private wells in the study area.

3.10 Statistical Analyses

ATSDR staff will perform statistical analyses with the participation of the recipients using SAS, R and STATA on the combined multi-site study dataset. ATSDR staff may also use SPSS for data management. ATSDR staff will calculate descriptive statistics (including means, geometric means, medians, standard deviations, and percentiles) to identify the presence and distribution of PFAS and effect biomarker analytes. Statistical methods will include multiple linear regression of continuous (untransformed and natural log transformed) effect biomarkers on continuous (untransformed and natural log transformed) PFAS serum levels and categorized PFAS serum levels, and logistic regression of categorized effect biomarkers (e.g., hypercholesterolemia) or disease prevalence on continuous (untransformed and natural log transformed) and categorical PFAS serum levels. ATSDR staff will use restricted cubic spline methods (or generalized additive models using cubic regression splines) for linear and logistic regression to obtain flexible, smoothed exposure-response curves. To identify risk factors that may act as confounders for a particular health outcome, the analysis will implement a “10% change in the estimate” rule (Maldonado 1993).

Primary analyses will focus on estimated cumulative PFAS serum levels. Supplemental analyses will evaluate PFAS serum levels in the blood specimens obtained in the study as well as estimated maximum and average PFAS serum levels. The primary analyses will evaluate each PFAS chemical separately; sum

of PFAS measures may also be considered. Statistical analyses using prevalent cases in a cohort design which takes into consideration the times of diagnosis will also be conducted. ATSDR will explore the use of methods for evaluating multi-pollutant mixtures, such as the hierarchical Bayesian model, to analyze the effects of exposures to the PFAS mixtures. ATSDR will use quantitative methods to assess the impact of possible selection bias and possible confounding due to unmeasured risk factors (Lash 2009). There are several caveats and recommendations in conducting analyses of mixtures to determine the optimal method that avoids amplifying bias due to confounding (Weisskopf et al 2018). For the bias analyses, ATSDR will identify "negative control" diseases with no known association with PFAS exposures (Lipsitch 2010). ATSDR conducted a literature search to identify these negative control diseases and included them in the questionnaire.

ATSDR will interpret the findings from this study based on the magnitude of the effect estimates (e.g., the linear regression coefficient for continuous outcomes or the odds ratio for categorical outcomes) of the exposure-response relationship, consistency with findings from other studies, and the possible sources of bias (Rothman 2014). The analyses will construct confidence intervals to indicate the level of precision (or uncertainty) in the effect estimates.

The studies will use statistical significance testing to interpret findings but will not use it as a sole factor in determining scientific and public health significance (Rothman et al. 2008, 2010; Stang et al. 2010). A finding that fails to achieve statistical significance can still provide evidence for a causal association, and a finding that achieves statistical significance can lack any such significance (Porta 2014).

4. RESULTS REPORTING

4.1 Notification of Individual Results

Some of the clinical tests may include results that indicate disease or serious medical condition. Due to the scheduled timespan between blood specimen collection and the actual laboratory analyses, we are unable to report study results in a short period. Study staff will report to the participant the result of a clinical test that clearly indicates the potential for a serious health consequence immediately after receiving the result from the laboratory. An advance notification phone call from the study investigators (**Attachment 22**) with a subsequent letter of clinical tests results will be sent to the participant when the abnormal result are identified, processed, and checked for accuracy (**Attachment 22a**). Study staff will advise the participants to consult his/her physician, or to contact the physician associated with the study for explanation of clinical findings.

Participants will also receive results of their effect biomarker tests after the study is completed. Contract labs will provide their clinical reference abnormal or 'high' levels, if available, for interpretation of clinical test results (**Attachment 23**). Participants will receive their PFAS test results. The recipient will provide to the 50th and 95th percentiles from NHANES for comparison to the U.S. population (CDC, 2018). Study staff will advise participants to consult ATSDR with questions about their results if they wish to do so.

4.2 Disseminating Results to the Public

The recipient will consult with the local and/or state health agency, local community groups, and the National PFAS Contamination Coalition to determine the most effective method of disseminating the results to the participants and the public. If the recipient establishes a community assistance panel (CAP) in the study area, then the CAP will participate in study community outreach and recruitment activities as well as provide advice on effective methods of results dissemination.

The recipient may consider using a user-centered digital interface developed by the Silent Spring Institute for reporting results to each participant. The recipient will present study results to the community in public meetings, printed community handout materials, participating in local radio programs and in informal activities. The recipient also will provide a study website with information about the study findings and general information about any future follow up studies.

Generally, ATSDR will publish study results only as group data analyses in peer-reviewed scientific journals or government reports. If individual data are presented, those will not be linked to participants' identities. In the event that some other exceptional characteristics would enable personal identification, those would be masked or modified as needed to protect individual privacy. ATSDR will use manuscripts published in peer-reviewed scientific journals and presentations at major scientific meetings to inform the scientific community about the results of the Multi-site studies.

5. STRENGTHS AND LIMITATIONS

Cross-sectional studies are especially suitable for assessing effect biomarkers and the prevalences of nonfatal diseases, in particular, diseases with no clear point of onset (Checkoway 2004). However, if the cross-sectional study concurrently measures the exposure and the outcome (i.e., the disease or effect biomarker), it might be difficult to determine whether the exposure caused the outcome or whether the

outcome influenced the measured exposure level (Flanders 1992, 2016). For example, as discussed above, the concurrent measurement of serum PFAS levels and kidney function biomarkers might raise the question of "reverse causation" because kidney function can affect the levels of PFAS in serum. One approach to minimize the problem of reverse causation or possible confounding due to health outcomes that affect PFAS serum levels is by estimating exposures based on the historical reconstruction modeling of serum PFAS levels. In addition, it might be possible to estimate exposures during critical vulnerable periods (e.g., in utero exposure) through the modeling of historical serum PFAS levels. However, the modeling of historical PFAS serum levels is subject to uncertainties and data limitations, and published methods currently are available only to model serum levels of PFOA and PFOS.

Other issues concerning cross-sectional study designs are similar to those that confront other observational study designs, such as cohort studies. These issues include: 1) the ability to clearly define, enumerate and recruit (without introducing selection bias) the exposed and comparison populations, 2) the comparability of the exposed and comparison populations on risk factors other than the PFAS exposures, 3) accurate exposure assessment, and 4) accurate measurement of effect biomarkers and ascertainment of diseases. In addition, a bias similar to the "healthy worker survival effect" bias could occur in a cross-sectional study because the study population consists of those who remained in the study area (and, for example, did not leave the study area due to health problems caused by exposure to the PFAS contaminated drinking water). While the resulting cohort is a 'survivor cohort', the studies have shown that the only if survival after incidence differs by exposure level can results be biased (Barr 2015) for the non-fatal and even in the case of fatal disease...

All epidemiological studies of environmental exposures and health outcomes have limitations and uncertainties. Whether a study will find an association between an environmental exposure and health effects is unknown prior to conducting the study. No single study will provide definitive answers to the community about whether their exposures to the PFAS-contaminated drinking water caused their health problems. The ability of the multi-site study to provide useful information will depend largely on the success of recruiting a sufficient number of study participants and obtaining sufficient information on the PFAS contamination to estimate historical PFAS serum levels with reasonable accuracy.

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Attachment 1. Investigators and Key Study Personnel

Protocol Title: *Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances: A multi-site cross-sectional study (Multi-site Study).* ***CDC Protocol No. xxxx*** ***CDC FWA No. 00001413***	
Name	Affiliation
PRINCIPAL INVESTIGATORS	
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Kyle Steenland, PhD • April 12, 2018	Emory University Rollins School of Public Health Department of Environmental Health and Department of Epidemiology
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Mark Strynar, PhD • September 6, 2018	US EPA National Research Exposure Laboratory (NERL), Office of Research and Development (ORD)
Philippe Grandjean, MD, DMSc • October 11, 2018	University of Southern Denmark, Environmental Medicine; University of Rhode Island Superfund Research Center; Harvard TH Chan School of Public Health

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Biochemical analytical plan in children and adults: performing laboratories, reference levels, reporting ranges, clinical guidelines, and critical values.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	NHANES [1] (µg/L) 2013 - 2014	
Children and Adults						
NCEH/Division of Laboratory Sciences* *Contact: Dr. Antonia Calafat*	*Per- and Poly-fluoroalkyl Substances (PFAS)*	Yes	Serum	1 ml (for all PFAS); 1 ml reserve (for future PFAS analyses)	**Age Group (years):**	**50th to 95th %**
	perfluorooctanoic acid (PFOA)‡				3-5: 6-11: 12-19: 20+:	1.80 – 5.58 1.94 – 3.84 1.67 – 3.47 2.07 – 5.60
	n-PFOA - linear isomer				3-5: 6-11: 12-19: 20+:	1.72 – 5.32 1.84 – 3.77 1.60 – 3.40 2.00 – 5.40
	Sb-PFOA - serum branched isomer				3-5: 6-11: 12-19: 20+:	< LOD – 0.280 < LOD – 0.230 < LOD – 0.200 < LOD – 0.200
	perfluorooctane sulfonic acid, (PFOS)‡				3-5: 6-11: 12-19: 20+:	3.41 – 8.82 4.02 – 12.4 3.60 – 9.30 5.60 – 19.5
	n-PFOS – linear isomer				3-5: 6-11: 12-19: 20+:	2.11 – 6.19 2.65 – 8.41 2.70 – 7.10 3.70 – 15.1
	Sm-PFOS – serum branched				3-5: 6-11: 12-19: 20+:	1.00 – 3.60 1.41 – 4.25 1.00 – 2.30 1.60 – 5.30

Limit of detection (LOD, see Data Analysis section) for Survey year 13-14 is 0.1. < LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

[1] CDC. 2018. 2013-2014 NHANES 50th to 95th percentiles among children 12-19 years and adults 20+ years old from the Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018. Accessed April 13, 2018 at (https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf).

‡ See Calculation of PFOS and PFOA as the Sum of Isomers for additional information in March 2018 Updated Tables.

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	NHANES [1] (µg/L) 2013 - 2014	
Children and Adults						
NCEH/Division of Laboratory Sciences* *Contact: Dr. Antonia Calafat*	*Per- and Poly-fluoroalkyl Substances (PFAS) (continued)*	Yes	Serum	1 ml (for all PFAS); 1 ml reserve (for future PFAS analyses)	**Age Group (years):**	**50th to 95th %**
	perfluorohexane sulfonic acid (PFHxS)				3-5: 6-11: 12-19: 20+:	0.740 – 1.62 0.850 – 4.14 1.10 – 6.30 1.40 – 5.50
	perfluorooctane sulfonamide (PFOSA)				3-5: 6-11: 12-19: 20+:	< LOD – 0.110 < LOD - < LOD n/a ‡ n/a ‡
	2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSAA)				3-5: 6-11: 12-19: 20+:	0.110 – 1.02 0.110 – 0.940 0.100 – 0.600 < LOD – 0.600
	2-(N-ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSAA)				3-5: 6-11: 12-19: 20+:	< LOD - < LOD < LOD - < LOD n/a ‡ n/a ‡
	perfluorobutane sulfonic acid (PFBS)				3-5: 6-11: 12-19: 20+:	< LOD - < LOD < LOD – 0.130 < LOD - < LOD < LOD - < LOD
	perfluoroheptanoic acid (PFHpA)				3-5: 6-11: 12-19: 20+:	< LOD – 0.310 < LOD – 0.170 < LOD – 0.200 < LOD – 0.100

Limit of detection (LOD, see Data Analysis section) for Survey year 13-14 is 0.1. < LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample. ‡ Not measured after Survey Years 2011-2012.

[1] CDC. 2018. 2013-2014 NHANES 50th to 95th percentiles among children 12-19 years and adults 20+ years old from the Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018. Accessed April 13, 2018 at (https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf).

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	NHANES [1] (µg/L) 2013 - 2014
Children and Adults					
NCEH/Division of Laboratory Sciences* *Contact: Dr. Antonia Calafat*	*Per- and Poly-fluoroalkyl Substances (PFAS) (continued)*	Yes	Serum	1 ml (for all PFAS); 1 ml reserve (for future PFAS analyses)	**Age Group (years): 50th to 95th %**
	perfluorononanoic acid (PFNA)				3-5: 0.620 – 3.49 6-11: 0.750 – 3.19 12-19: 0.500 – 2.00 20+: 0.700 – 2.00
	perfluorodecanoic acid (PFDA)				3-5: 0.100 – 0.370 6-11: < LOD – 0.350 12-19: 0.100 – 0.400 20+: 0.193 – 0.800
	perfluoroundecanoic acid (PFUnDA)				3-5: < LOD – 0.370 6-11: < LOD – 0.250 12-19: < LOD – 0.200 20+: < LOD – 0.500
	perfluorododecanoic acid (PFDoA)				3-5: < LOD - < LOD 6-11: < LOD - < LOD 12-19: < LOD – 0.200 20+: < LOD – 0.200
Laboratory and Contact	**Proposed Biospecimen Bank for Future Analytes**	*** CLIA Cert.**	**Matrix**	**Volume**	**NHANES [TBD] (µg/L) 20xx – 20xx**
Children and Adults					
NCEH/Division of Laboratory Sciences* *Contact: Dr. Antonia Calafat*	*Per- and Poly-fluoroalkyl Substances (PFAS)*	Yes	Spot Urine (morning void)	1 ml (for PFAS); 15 ml for creatinine/or specific gravity)	**Age Group: 50th to 95th %**
	To be determined (TBD) when analytical methods are developed (Including but not limited to the following 18 analytes: PFOA [n-PFOA;, Sb-PFOA], PFOA [n-PFOS, Sm-PFOS], PFHxS, PFBS, PFHpA, PFNA, PFDA, PFUnDA, PFPrS, PFHpS, PFBA, PFPeA, PFHxA, HFPO-DA (GenX), DONA, 9Cl-PF3ONS)				3-5: TBD 6-11: TBD 12-19: TBD 20+: TBD
	Creatinine (for urinary creatinine correction; may be contracted)				TBD

Limit of detection (LOD, see Data Analysis section) for Survey year 13-14 is 0.1. < LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample. ‡ Not measured after Survey Years 2011-2012.

[1] CDC. 2018. 2013-2014 NHANES 50th to 95th percentiles among children 12-19 years and adults 20+ years old from the Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018. Accessed April 13, 2018 at (https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf).

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	Reportable Range, Guidelines, Critical Values *Reference ranges will be updated when commercial lab is selected.*
Children and Adults					
Commercial Laboratory (to be determined)* *Contact:*	*Lipids*	Yes	Serum	0.5 ml (for all)	
	Total cholesterol, fasting				Coronary Heart Disease Risk (CHD)[1] Adult, 18+ years: Desirable: <200 mg/dL Borderline High: 200-239 mg/dL High: ≥240 mg/dL Child, 2-17 years: Acceptable: <170 mg/dL Borderline high: 170-199 mg/dL High: ≥200 mg/dL
	Triglycerides, fasting				CHD Risk[1] Adult, 18+ years: Normal: <150 mg/dL Borderline High: 150-199 mg/dL High: 200-499 mg/dL Very High: ≥500 mg/dL **Critical Value: >1,000 mg/dL** Child, 2-9 years: Acceptable: <75 mg/dL Borderline high: 75-99 mg/dL High: ≥100 mg/dL Child, 10-17 years: Acceptable: <90 mg/dL Borderline high: 90-129 mg/dL High: > or =130 mg/dL
	Low Density Lipoprotein (LDL), fasting				CHD Risk[1]

[1] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8320

Attachment 2. Biochemical Analytical Plan in Children and Adults.

					Adult, 18+ years: Desirable: <100 mg/dL Above Desirable: 100-129 mg/dL Borderline high: 130-159 mg/dL High: 160-189 mg/dL Very high: ≥190 mg/dL Child, 2-17 years: Acceptable: <110 mg/dL Borderline high: 110-129 mg/dL High: ≥130 mg/dL
	High Density Lipoprotein (HDL), fasting				<u>CHD Risk</u>[1] Adult, 18+ years: Males: ≥40 mg/dL Females: ≥50 mg/dL Child, 2-17 years: Low: <40 mg/dL Borderline low: 40-45 mg/dL Acceptable: > 45 mg/dL

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	Reportable Range, Guidelines, Critical Values *Reference ranges will be updated when commercial lab is selected.*
Children and Adults					
Commercial Laboratory (to be determined)* *Contact:*	*Uric Acid*	Yes	Serum	1 ml	Males[2] ≤ 8.0 mg/dL Females ≤ 6.1 mg/dL
	Creatinine (to estimate glomerular filtration rate [eGFR])				Males[3] 1-2 years: 0.1-0.4 mg/dL 3-4 years: 0.1-0.5 mg/dL 5-9 years: 0.2-0.6 mg/dL 10-11 years: 0.3-0.7 mg/dL 12-13 years: 0.4-0.8 mg/dL 14-15 years: 0.5-0.9 mg/dL > or =16 years: 0.8-1.3 mg/dL Reference values have not been established for patients that are <12 months of age. Females 1-3 years: 0.1-0.4 mg/dL 4-5 years: 0.2-0.5 mg/dL 6-8 years: 0.3-0.6 mg/dL 9-15 years: 0.4-0.7 mg/dL > or =16 years: 0.6-1.1 mg/dL Reference values have not been established for patients that are <12 months of age. ESTIMATED GFR >60 mL/min/BSA **Note:** eGFR results will not be calculated for patients <18 or >70 years old.

[2] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8440
[3] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8472

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	Reportable Range, Guidelines, Critical Values *Reference ranges will be updated when commercial lab is selected.*
Children and Adults					
Commercial Laboratory (to be determined)* *Contact:*	*Thyroid Hormones*	Yes	Serum	0.5 ml	
	Thyroid Stimulating Hormone (TSH)				0.30-3.0 mIU/L [4]
	Free Total Thyroxine (Free T4)				0.8-2.0 ng/dL
	Total Thyroxine (TT4)				4.5-12.5 µg/dL
	Total Triiodothyronine (TT3)				80-180 ng/dL
Commercial Laboratory (to be determined)* *Contact:*	*Liver Tests*	Yes	Serum	0.5 ml standard tests; 1 ml CK18	
	Alanine transaminase (ALT)				15-65 U/L [5]
	Aspartate transaminase (AST)				5-40 U/L
	Alkaline phosphatase (ALP)				Female: 50-136 U/L; Male: 40-136 U/L
	Gamma-glutamyltransferase (GGT)				Female 5-55 U/L; Male 5-85 U/L
	Albumin (Alb)				3.4-5.0 g/dL **Critical Value: <1.5 g/dL** **Critical Value: >7.9 g/dL**
	Total bilirubin (TBIL)				0.0 – 1.0 mg/dL **Critical Value: >12.9 mg/dL**
	Direct bilirubin (Conjugated Bilirubin)				0.0-0.3 mg/dL
	Non-alcoholic fatty liver disease (NAFLD)/steatohepatitis				
	Cytokeratin 18 M30 (CK-18 M30) Cytokeratin 18 M65 (CK-18 M65)				No evident liver disease: M30 <200 U/L and M65 <300 U/L TASH: M30<200 U/L and M65 >300 U/L Other liver disease: M30: >200 U/L

[4] University of Southern California Clinical Laboratories Endocrine Services.

[5] University of Louisville Department of Medicine, Gastroenterology (updated 14 October 2015).

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	Reportable Range, Guidelines, Critical Values *Reference ranges will be updated when commercial lab is selected.*
Children and Adults					
Commercial Laboratory (to be determined)* *Contact:*	*Sex Hormones*	Yes	Serum	0.5 ml	
	Testosterone				Males[6] 4-9 years: <7-20 ng/dL 10-11 years: <7-130 ng/dL 12-13 years: <7-800 ng/dL 14 years: <7-1,200 ng/dL 15-16 years: 100-1,200 ng/dL 17-18 years: 300-1,200 ng/dL ≥19 years: 240-950 ng/dL Females 4-9 years: <7-20 ng/dL 10-11 years: <7-44 ng/dL 12-16 years: <7-75 ng/dL 17-18 years: 20-75 ng/dL ≥19 years: 8-60 ng/dL
	Estradiol				CHILDREN[7] Males **Tanner Stages** — **Reference Range** Stage I (>14 days and prepubertal) — <LOD-13 pg/mL Stage II — <LOD-16 pg/mL Stage III — <LOD-26 pg/mL Stage IV — <LOD-38 pg/mL Stage V — 10-40 pg/mL

[6] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83686
[7] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81816

Attachment 2. Biochemical Analytical Plan in Children and Adults.

					Females **Tanner Stages** — **Mean Age** Stage I (>14 days and prepubertal) — 7.1 years Stage II — 10.5 years Stage III — 11.6 years Stage IV — 12.3 years Stage V — 14.5 years ADULTS Males: 10-40 pg/mL Females Premenopausal: 15-350 pg/mL** Postmenopausal: <10 pg/mL **E2 levels vary widely through the menstrual cycle.
	Sex hormone-binding globulin (SHBG)				CHILDREN[8] Males Tanner Stages — Reference Range Stage I — 31-167 nmol/L Stage II — 49-179 nmol/L Stage III — 5.8-182 nmol/L Stage IV — 14-98 nmol/L Stage V — 10-57 nmol/L Females Tanner Stages — Reference Range Stage I — 43-197 nmol/L Stage II — 7.7-119 nmol/L Stage III — 31-191 nmol/L

[8] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9285

Attachment 2. Biochemical Analytical Plan in Children and Adults.

					Stage IV 31-166 nmol/L Stage V 18-144 nmol/L ADULTS Males: 10-57 nmol/L Females (non-pregnant): 18-144 nmol/L
	Follicle stimulating hormone (FSH)				Males[9] 4-6 years: < or =6.7 IU/L 7-8 years: < or =4.1 IU/L 9-10 years: < or =4.5 IU/L 11 years: 0.4-8.9 IU/L 12 years: 0.5-10.5 IU/L 13 years: 0.7-10.8 IU/L 14 years: 0.5-10.5 IU/L 15 years: 0.4-18.5 IU/L 16 years: < or =9.7 IU/L 17 years: 2.2-12.3 IU/L ≥18 years: 1.0-18.0 IU/L Females 15 days-6 years: < or =3.3 IU/L 7-8 years: < or =11.1 IU/L 9-10 years: 0.4-6.9 IU/L 11 years: 0.4-9.0 IU/L 12 years: 1.0-17.2 IU/L 13 years: 1.8-9.9 IU/L 14-16 years: 0.9-12.4 IU/L 17 years: 1.2-9.6 IU/L ≥18 years: Premenopausal Follicular: 3.9-8.8 IU/L Midcycle: 4.5-22.5 IU/L Luteal: 1.8-5.1 IU/L Postmenopausal: 16.7-113.6 IU/L
	Insulin-like growth factor (IGF-1)				

[9] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8670

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Laboratory and Contact	Analyte	* CLIA Cert.	Matrix	Volume	Reportable Range, Guidelines, Critical Values *Reference ranges will be updated when commercial lab is selected.*
Children and Adults					
Commercial Laboratory (to be determined)* *Contact:*	*Immune Function*	Yes	Serum	1 ml	
	Ig A, Ig G, Ig M, Ig E				
Commercial Laboratory (to be determined)* *Contact:*	*Glycemic Parameters*	Yes			
	Glycosylated hemoglobin (HbA1c)		Whole Blood EDTA	1 ml; plus 1 ml reserve	Diabetes Risk[10] Normal: <5.7% Increased Risk Diabetes: 5.7-6.4% Diabetes: ≥6.5% (confirmation required)
	Glucose, fasting, 8-hour		Serum	0.5 ml Glucose/ Insulin; 1 ml antibodies	
	Insulin				<17 µU/ml [8]
	Glutamate Decarboxylase -65 (Anti-GAD 65)				Negative Antibody: DK≤33 [8] Positive Antibody: DK>33
	Thyrosine Phosphatase-like Protein Autoantibodies (Anti-IA2)				Negative Antibody: DK<5 [8] Positive Antibody: DK≥5
Children Only					
Commercial Laboratory (to be determined)* *Contact:*	*Antibodies to measles, mumps, rubella, tetanus, and diphtheria*	Yes	Serum	1 ml	
			Child Total	**Serum - 9ml Whole Blood – 2 ml Urine – 16 ml Red Top 2 x10 ml EDTA Lavender Top 3 ml**	

Adults Only					
	Autoimmune Parameters	Yes	Serum		

[10] American Diabetes Association. Standards of Medical Care in Diabetes - 2011. Diabetes Care. January 2011;34(Supplement 1):S11-S61 (subject to periodic update).

Attachment 2. Biochemical Analytical Plan in Children and Adults.

Commercial Laboratory (to be determined)* *Contact:*	Rheumatoid Factor (RF)			2 ml (for all)	< 15 IU/mL[11]
	Antinuclear Antibody (ANA) screen				< or =1.0 U (negative)[12] 1.1-2.9 U (weakly positive) 3.0-5.9 U (positive) > or =6.0 U (strongly positive)
	Antinuclear Antibody (ANA) titer				
			Adult Total	**Serum – 11 ml Whole Blood – 2 ml Urine – 16 ml Red Top 3 x 10 ml EDTA Lavender Top 3 ml**	

[11] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9060
[12] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9026

Attachment 3 – Justification for Sample Size Calculations (Supporting information)

- **Attachment 3a – Child Sample Size Calculations**
- **Attachment 3b – Adult Sample Size Calculations**

Sample size calculations were conducted using OpenEpi Version 3.03 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com, updated 2014/09/22). For some health-related endpoints, calculations could not be conducted because of a lack of information in the studies on the parameters needed to make the calculations.

Sample size calculation for mean difference:

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2 / \kappa)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_2 = \frac{(\kappa * \sigma_1^2 + \sigma_2^2)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

The notation for the formulae are:

n_1 = sample size of Group 1

n_2 = sample size of Group 2

σ_1 = standard deviation of Group 1

σ_2 = standard deviation of Group 2

Δ = difference in group means

κ = ratio = n_2/n_1

$Z_{1-\alpha/2}$ = two-sided Z value (eg. Z=1.96 for 95% confidence interval).

$Z_{1-\beta}$ = power

Where N_2/N_1 is the ratio of the two sample sizes. Then N_2 is simply this ratio multiplied by N_1. For a type 1 error (or α error) of .05, the $Z_{1-\alpha/2}$ value is 1.96. This calculation is for a two-tailed hypothesis test and equivalent to using a 95% confidence interval to determine statistical significance. For a one-tail test with α =.05, the $Z_{1-\alpha/2}$ in the above equation is replaced by $Z_{1-\alpha}$ and its value is 1.65, equivalent to using a 90% confidence interval to determine statistical significance. The $Z_{1-\beta}$ in the above equation is the Z value for the selected power. For 80% power, $Z_{1-\beta}$ = 0.84, for 90% power, $Z_{1-\beta}$ = 1.28, and for 95% power, $Z_{1-\beta}$ = 1.65. (See Rosner B. Fundamentals of Biostatistics, 7th Edition, equation 8.27, p. 302).

Fleiss JL. Statistical Methods for Rates and Proportions. John Wiley & Sons, 1981.

Note: In some studies, the standard deviation is not presented but instead, the interquartile range (IQR) is given. Assuming a normal distribution for the outcome under evaluation (e.g., thyroid function measures), the standard deviation can be calculated by dividing the IQR range by 1.35. However if the outcome is not normally distributed, this formula could underestimate the standard deviation. In particular, if the outcome under evaluation has been log-transformed presumably to achieve a normal distribution, the untransformed outcome is unlikely to have a normal distribution. Therefore, using this formula when the outcome does not have a normal distribution may underestimate the SD by as much as 20% according to simulations conducted in Wan X. 2014. A higher SD would increase the sample size requirement.

Attachment 3a. Sample Size for Child Study

The following notes provide comments and information on the parameters (e.g., standard deviation, disease prevalence) used in the sample size calculations provided in Table 1 for the children study.

Sample size calculations were conducted with type 1 ("α error") set at .05 and type 2 error ("β error) set at .20. Sample sizes per stratum group were calculated. It was considered important that a study have a total sample size so that exposures could be categorized into tertiles (i.e., reference level, medium level, and high level) or quartiles (i.e., reference level, low, medium and high).

Studies were selected that were considered the most representative of U.S. populations exposed via drinking water to PFOA, PFOS and/or PFHxS as a result of the migration of these PFAS chemicals into ground water or surface water sources from the use of aqueous film forming foam (AFFF). The PFOS, PFOA and PFHxS results in the NHANES studies were used in many of the sample size calculations. For those outcomes not included in NHANES studies, the C8 studies were used. Where applicable studies from Taiwan or other major industrialized countries were also used.

Examples:

Lipids

In the C8 study (Frisbee 2010), the mean total cholesterol level in the study population was 160.7 mg/dL and the standard deviation (SD) was 29.3. The sample size calculations assumed the same SD in children exposed and the unexposed group. For hypercholesterolemia (total cholesterol ≥ 170 mg/dL), the prevalence in the C8 study was 34.2%.

Uric Acid

In the NHANES study (Geiger 2013), the mean uric acid level in the study population was 5.07 mg/dL with a SD of 1.19. The sample size calculations assumed the same SD in the exposed children and the unexposed group. The prevalence of hyperuricemia (uric acid ≥ 6 mg/dL) in the NHANES study was 16%.

Kidney Function

The mean estimated glomerular filtration rate (eGFR) in the C8 study of children and adolescents (Watkins 2013) was 133 mL/min/1.73 m^2 with a SD of 23.9. The sample size calculations assumed the same SD in the exposes children and the unexposed group.

Attention Deficit/Hyperactivity Disorder (ADHD)

In the C8 study (Stein 2011), the prevalence of participant-reported ADHD was 12.4% and the prevalence for participant-reported + used medications for ADHD was 5.1%. Sample size calculations used the 12.4% prevalence.

Hypersensitivity-related Outcomes

From an NHANES study (Stein 2016), the prevalence of current asthma and rhinitis among those aged 12-19 were 10.9% and 25.6%, respectively. For atopic dermatitis, the prevalence for children and adolescents (ages 5-17) is about 12% based on data from the National Health Interview Survey.

Sex hormones and Insulin-like growth factor – 1 (IGF-1)

C8 study of children (Lopez-Espinosa 2016)

a. Testosterone

For PFOS, there was a -6.6% difference in the natural log testosterone among girls (per interquartile range of the natural log of PFOS). Among girls, the median testosterone level was 15 ng/dL with an IQR of <LOD, 21 and the LOD of 10 ng/dL. For the sample size calculation of mean difference, the standard deviation was assumed to be equal for the exposed and unexposed groups and equal to 11.85. (Assuming LOD/2 was the lower limit of the IQR, the range = 21 - 5 = 16. Assuming a normal distribution, dividing 16 by 1.35 converts the IQR to a standard deviation, which equaled 11.85)[1]. To obtain the mean difference, the median testosterone level (15 ng/dL) was assumed to be the reference level (i.e., the level among the unexposed). The natural log of the median equals 2.71. A 6.6% decrease equals 2.53. Exponentiating 2.53 equals 12.55. The mean difference is then 15 – 12.55 = 2.45.

Assuming a 95% CI and 80% power, the sample size = 368/group; for a ratio of 2, the sample sizes = 552 and 276.

b. IGF-1

For PFHxS, there was a -2.5% difference in the natural log IGF-1 among boys (per interquartile range of the natural log of PFHxS). Among boys, the median IGF-1 level was 147 ng/mL with an IQR of 116, 187. For the sample size calculation of mean difference, the standard deviation was assumed to be equal for the exposed and unexposed groups and equal to 52.6. (The IQR range was 187 – 116 = 71. Assuming a normal distribution, dividing 71 by 1.35 converts the IQR to a standard deviation, which equaled 52.6)[1]. To obtain the mean difference, the median IGF-1 level (147 ng/mL) was assumed to be the reference level (i.e., the level among the unexposed). The natural log of the median equals 4.99. A 2.5% decrease equals 4.865. Exponentiating 4.865 equals 129.7. The mean difference is then 147 – 129.7 = 17.3.

Assuming a 95% CI and 80% power, the sample size = 146/group; for a ratio of 2, the sample sizes = 218 and 109.

For PFOS, there was a -5.9% difference in the natural log IGF-1 among boys (per interquartile range of the natural log of PFOS). This would require considerably smaller sample sizes for IGF-1 than those for PFHxS.

Thyroid function – Children/Adolescents

Taiwan study of children. (Lin 2013)

a. For males aged 12-19, there was a mean difference in the log TSH of -.50 mIU/L for PFOA levels in the 90th percentile (>9.71 ng/ml) compared to the reference level of PFOA exposure. The standard error for the reference group was 0.26 with N=32 in this group; and the standard error for the 90th percentile group was 0.33

with N=6. The standard deviations for the reference and 90th percentile groups were therefore 1.47 and 0.81, respectively.

Assuming a 95% CI and 80% power, the sample size = 89/group; for a ratio of 2, the sample sizes = 158 and 79.

b. For females aged 12-19, there was a mean difference in the log TSH of -.35 mIU/L for PFOA levels in the 90th percentile (>9.71 ng/ml) compared to the reference level of PFOA exposure. The standard error for the reference group was 0.18 with N=71 and the standard error for the 90th percentile group was 0.24 with N=14. The standard deviations for the reference and 90th percentile groups were therefore 1.52 and 0.90, respectively.

Assuming a 95% CI and 80% power, the sample size = 200/group; for a ratio of 2, the sample sizes = 348 and 174.

Additional notes:

Sample sizes for the categorical outcomes in Table 1 were based on the following prevalence in children (also listed in Appendix C Table 1):

Hypercholesterolemia: 34.2%
Hyperuricemia: 16%
Thyroid disease: 0.6%
ADHD 12.4% reported only; 5.1% reported with additional reporting on medications used for ADHD
Asthma: 11%
Rhinitis: 25.6%
Atopic dermatitis: 10.7%
Hypertension: 23.4%
Obesity: 17%

Attachment 3b. Adult Study

The following provides information on the parameters and sample size calculation used in Table 2 for the adult study.

Sample size calculations were conducted with type 1 ("α error") set at .05 and type 2 error ("β error) set at .20. It was considered important that a study have a total sample size so that exposures could be categorized into tertiles (i.e., reference level, medium level, and high level) or preferably into quartiles (i.e., reference level, low, medium and high).

Studies were selected that were considered the most representative of U.S. populations exposed via drinking water to PFOA, PFOS and/or PFHxS as a result of the migration of these PFAS chemicals into ground water or surface water sources from the use of aqueous film forming foam (AFFF). The PFOS, PFOA and PFHxS results in the NHANES studies were used in many of the sample size calculations. For those outcomes not included in NHANES studies, the C8 studies were used. Where applicable studies from Taiwan or other major industrialized countries were also used.

Example:

Liver Function – Adults

In the C8 study (Darrow 2016), the mean alanine aminotransferase (ALT) level was 26 IU/L and the standard deviation was 19. The linear regression coefficient for the natural log ALT in the fifth quintile level of cumulative natural log PFOA was 0.058. Assuming that the reference group had an ALT level equal to the mean, the natural log of the mean ALT would be 3.26. Therefore the natural log of ALT for the fifth quintile cumulative log PFOA would be 3.32. Exponentiating 3.32 equals 27.6. The mean difference in the untransformed ALT is then 1.6.

Assuming a 95% CI and 80% power, the sample size = 2,214/group.

Thyroid Function – Adults (not included in Table 2)

In a study done by Shrestha 2015, the sample size was 87 adults aged 55-74. Mean and SD for TSH was 2.58 µIU/mL and 1.47, respectively. The linear regression of the natural log TSH resulted in a coefficient for the natural log PFOS of 0.129. Using a PFOS level of 15 ng/mL, the natural log of 15 is 2.71; multiplied by 0.129 equals 0.35. The reference level TSH was assumed to be the median TSH of 2.15 µIU/mL. The natural log of 2.15 is 0.77; adding 0.35 equals 1.12. Exponentiating 1.12 equals 3.06. The mean difference is then 3.06 – 2.15 = 0.91. The standard deviation of 1.47 was used for each group.

Assuming a 95% CI and 80% power, the sample size = 41/group.

Assuming a 95% CI and 95% power, the sample size = 68/group.

a. TSH

In Ji 2012, the sample size was 633, ≥12 years of age and the median TSH level was 1.37 µIU/mL with an IQR of 0.90, 2.01. The standard deviation was estimated as the IQR range divided by 1.35: (2.01 - .90)/1.35 = 0.82. This standard deviation was assumed for each group. For TSH, the linear regression coefficients for PFOS and PFHxS were 0.062 and 0.013, respectively. Using a PFOS level of 15 ng/mL and a PFHxS level of 9 ng/mL, the mean difference for PFOS and PFHxS are 0.93 and 0.12, respectively.

Assuming a 95% CI and 80% power, the sample size = 13/group for PFOS

Assuming a 95% CI and 80% power, the sample size = 733/group for PFHxS

b. TT_4 (total thyroxine)

In Ji 2012, the sample size was 633, ≥12 years of age and the median TT_4 level was 7.4 µg/dL and the IQR was 6.7, 8.1. The standard deviation was estimated: (8.1 – 6.7)/1.35 = 1.04. This standard deviation was assumed for each group. For TT_4, the linear regression coefficients for PFOS and PFHxS were -0.021 and -0.007, respectively. Using a PFOS level of 15 ng/mL and a PFHxS level of 9 ng/mL, the mean difference for PFOS and PFHxS are -0.32 and -0.06, respectively.

Assuming a 95% CI and 80% power, the sample size = 166/group for PFOS

Assuming a 95% CI and 80% power, the sample size = 4,716/group for PFHxS

Sample sizes for the categorical outcomes in Table 2 were based on the following prevalences in adults:

Hypercholesterolemia: 15%
Hyperuricemia: 24%
Thyroid disease: 6.5% (reported and confirmed by medical records); 11.5% (reported only)
Elevated ALT: 11.2%
Elevated GGT: 14%
Elevated bilirubin: 1.1%
Osteoporosis: 5%
Osteoarthritis: 7.6%
Cardiovascular disease: 13%
Ulcerative colitis: 0.5%
Rheumatoid arthritis: 1.2%

Health related Endpoints Not shown in Table 2:

Chronic kidney disease: 1.4%
Liver disease: 2%
Hypertension: 37%

Pregnancy-induced hypertension: 8.5%
Endometriosis: 7%
Lupus: 0.2%
Multiple sclerosis: 0.32%
Kidney cancer: 0.3%

Multi-site Study
Eligibility Screening Script
Flesch-Kincaid Readability Score – 5.8

Attachment 4.

Multi-site Study –Eligibility Screening Script

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

(This script will be used to screen adult and parent/child volunteers who respond to the NH DHHS Invitation Letter to former Biomonitoring Program participants. They will be instructed to call ATSDR on the toll-free number.) [**SHADED TEXT DENOTES INFORMATION COLLECTION**]

Hello. My name is _____. I'd like to thank you for calling about the **Multi-site PFAS Health Study**.

I understand that you received a letter from the [insert institution name] about volunteering for the Multi-site Study. As you know, the Agency for Toxic Substances and Disease Registry, or ATSDR for short, is funding the study and [insert study investigators institution name] would like to recruit people for the Multi-site Study who reside at [insert site]. If there are more people in your house who took part and are interested, I'd like to start with you first.

[Screening Questions for ADULT – If a PARENT calls who is not going to enroll as an ADULT > go directly to Screening Questions for PARENT/CHILD]

A1. I'm happy to hear that you received the invitation letter as a resident of [insert site]. Are you 18 years or older?

- **YES** > *go to A2.*
- **NO (under 18)** > OK, can I speak to your parent or guardian? [becomes PARENT ONE] > *go to Screening Questions for PARENT/CHILD.*

A2. Have you ever worked as a firefighter or ever participated in training exercises using firefighting, or AFFF, foam?

- **YES** > I'm sorry. People who ever worked as a firefighter or used firefighting foam are not eligible for this study. > *go to Screening Questions for PARENT/CHILD.*
- **NO** > *go to A3.*

A3. Have you ever worked at industrial facilities that used PFAS chemicals in the manufacturing process?

- **YES** > I'm sorry. People who ever worked at facilities using PFAS chemicals are not eligible for this study. > *go to Screening Questions for PARENT/CHILD.*
- **NO** > Thank you very much. You are eligible to take part in the Multi-site Study as an adult participant. > *go to A4.*

A4. Are you in prison or under house arrest?

- **YES** > I'm sorry. The federal regulations say that people who are in prison or under house arrest cannot be in this study. > *go to Screening Questions for PARENT/CHILD.*
- **NO** > Thank you very much. You are eligible to take part in the Multi-site as an adult participant. > *go to A4.*

A5. If you want to enroll in the Multi-site Study as an adult participant, I will need your contact information to send you some recruitment materials and to set up an appointment.

Record ADULT Contact Information

Attachment 4.

- **FIRST NAME** |_____|
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____|
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **DATE OF BIRTH** |__|__|/|__|__|/|__|__| > *verify age eligibility*
- **WORK PHONE NUMBER** |_____|
- **HOME PHONE NUMBER** |_____|
- **CELL PHONE NUMBER** |_____|
- **EMAIL** |_____|

After the call is over, enter the assigned ADULT STUDY ID number to begin tracking enrollment and biospecimen sample logistics. Be sure to link the ID numbers for an individual who has both an ADULT STUDY ID and one or more PARENT STUDY IDs.

- ***ADULT STUDY ID*** |_____|

A6. The study interview will take place at our central study office at (address). We would like to conduct the study there, but we know some people may find it difficult to travel. For some cases, we are willing to send an interview team to their homes as long as it is within a one-hour drive from the central office. Which location works best for you?

Record Appointment Location

- **CLINIC OFFICE**
- **ADULT HOME**

A7. Let's pick a good day and time for you. > *Record Appointment Information*

- **DAY** |_____|
- **DATE** |__|__|/|__|__|/|__|__|
- **TIME** |__|__|:|__|__| **AM PM**

A8. Thank you for your interest. We will mail you a packet of information including consent forms that shows what to expect at your appointment. We will also mail instructions. They will tell you how to prepare and what to bring.

A8. Adult participants may also enroll as parents of children in this research. Are there any children in your household who received an invitation letter?

- **YES** > *go to Screening Questions for PARENT/CHILD.*
- **NO** > OK. Thank you very much for your interest. We will mail your Appointment Packet shortly. If there are any other adults in your household who received an invitation letter, I will be happy to speak to them now, or at another more convenient time. Thanks again. > *When additional adults are available, begin at A1.*

[Screening Questions for PARENT/CHILD]

For this research study, ATSD and [insert study investigators institution name] are recruiting children who reside at [insert site] and received an invitation letter from the [insert state; whom?] Health Department. We are looking for about [insert as applicable] interested parent/child pairs to enroll. A parent may also enroll with more than one child.

Attachment 4.

P1. For each child, 4-17 years old, who received a letter and is interested in taking part in the Multi-site Study, I need to speak to the parent or guardian who wants to enroll with his or her child. We think it is best if the child's birth mother enrolls. That is because we will ask a lot of questions about when your child was a baby. Am I speaking to the right person?

- **YES** > Thank you. I need to find out a bit more about each child who wants to be in the Multi-site Study. If you have more than one, let's start with the youngest.
- **NO** > OK, I'd like to speak to that parent or guardian. If this isn't a good time, he or she can call our office later. If now is a good time, let's start with the youngest.
    - *If correct parent not available, stop* > OK, we will be waiting for that parent to call our office. Thanks very much for your interest.
    - *If correct parent available, go to P2.*

P2. How old is [CHILD 1; CHILD 2; CHILD 3; etc.]?

- **AGE** |__|__| **years** > *eligible age is 4-17 years* >
    - *If not age eligible,* go to P2a.
    - *If age eligible, go to P3.*

    P2a. I'm sorry. We are looking for children 4-17 years. Do you have other children who are 4-17 years?

    - **YES** > OK, let me find out more about them. > *go back to P2.*
    - **NO** > Thank you very much for calling us today. It appears that your children are not eligible to take part in the Multi-site Study. We appreciate your interest in this research.

    [ADD IF EXPOSURE OCCURRED WITHIN 15 YEARS OF START OF THE STUDY]

P3. Has [CHILD 1; CHILD 2; CHILD 3; etc.]'s birth mother ever worked as a firefighter or ever participated in training exercises using firefighting, or AFFF, foam?

- **YES** > I'm sorry. Children whose birth mother ever worked as a firefighter or used firefighting foam are not eligible for this study. If you have other children who are 4-17 years, let me ask these same questions about him or her. > *go back to P2. If no more children, go to P3a.*

    P3a. Thank you very much for calling us today. It appears that your children are not eligible to take part in the Multi-site Study. We appreciate your interest in this research.

- **NO** > *go to P4.*

P4. Has [CHILD 1; CHILD 2; CHILD 3; etc.]'s birth mother ever worked at industrial facilities that used PFAS chemicals in the manufacturing process?

- **YES** > I'm sorry. Children whose birth mother ever worked at facilities using PFAS chemicals are not eligible for this study. If you have other children who are 4-17 years, let me ask these same questions about him or her. > *go back to P2. If no more children, go to P4a.*

    P4a. Thank you very much for calling us today. It appears that your children are not eligible to take part in the Multi-site Study. We appreciate your interest in this research.

- **NO** > OK. You and your child are eligible to enroll in the Multi-site Study as a child/parent pair. > *go to P5.*

P5. Is your child in prison or under house arrest?

Attachment 4.

- **YES** > I'm sorry. The federal regulations say that people who are in prison or under house arrest cannot be in this study. *> go to Screening Questions for PARENT/CHILD.*
- **NO** > Thank you very much. Your child is eligible to take part in the Multi-site Study as a participant. *> go to P6.*

P6. I will need your contact information to send you some recruitment materials and to set up an appointment.

P5a. *Record PARENT 1 Contact Information*

- **FIRST NAME** |_____|
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____|
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **WORK PHONE NUMBER** |_____|
- **HOME PHONE NUMBER** |_____|
- **CELL PHONE NUMBER** |_____|
- **EMAIL** |_____|

P6b. *Record CHILD 1 Contact Information*

- **FIRST NAME** |_____|
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____|
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **DATE OF BIRTH** |__|__|/|__|__|/|__|__| > *verify age eligibility*

- ***PARENT 1 STUDY ID*** |_____|
- ***CHILD 1 STUDY ID*** |_____|

P6c. The study interview will take place at our central study office at (address). We would like to conduct the study there, but we know some people may find it difficult to travel. For some cases, we are willing to send an interview team to their homes as long as it is within a one-hour drive from the central office. Which location works best for you?

Record Appointment Location

- **CLINIC OFFICE**
- **ADULT HOME**

P6d. Let's pick a good day and time for you. > *Record Appointment Information*

- **DAY** |_____|
- **DATE** |__|__|/|__|__|/|__|__|
- **TIME** |__|__|:|__|__| **AM PM**

Attachment 4.

P7. If you have another eligible child who would like to enroll, I will fill in his or her contact information, too. Let me go back through the screening questions. > *go back to P2. If no more children, go to P6a.*

P7a. Thank you very much for your interest. We will mail your child's Appointment Packet shortly. Thanks again.

P7b. *Record PARENT 2 Contact Information*

- **FIRST NAME** |_____| (enter "SAME AS PARENT 1" if applicable > go to P6c)
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____|
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **WORK PHONE NUMBER** |_____|
- **HOME PHONE NUMBER** |_____|
- **CELL PHONE NUMBER** |_____|
- **EMAIL** |_____|

P7c. *Record CHILD 2 Contact Information*

- **FIRST NAME** |_____|
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____| (enter "SAME AS PARENT 1" if applicable > go to P6d)
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **DATE OF BIRTH** |__|__|/|__|__|/|__|__| > *verify age eligibility*

- ***PARENT 2 STUDY ID*** |_____|
- ***CHILD 2 STUDY ID*** |_____|

P7d. Which location for your interview works best for you?

Record Appointment Location

- **CLINIC OFFICE**
- **ADULT HOME**

P7e. Let's pick a good day and time for you. > *Record Appointment Information*

- **DAY** |_____|
- **DATE** |__|__|/|__|__|/|__|__|
- **TIME** |__|__|:|__|__| **AM PM**

P8. If you have another eligible child who would like to enroll, I will fill in his or her contact information, too. Let me go back through the screening questions. > *go back to P2. If no more children, go to P7a.*

P8a. Thank you very much for your interest. We will mail your children's Appointment Packets shortly. Thanks again.

Attachment 4.

P8b. *Record PARENT 3 Contact Information*

- **FIRST NAME** |_____| (enter "SAME AS PARENT 1" if applicable > go to P7c)
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____|
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **WORK PHONE NUMBER** |_____|
- **HOME PHONE NUMBER** |_____|
- **CELL PHONE NUMBER** |_____|
- **EMAIL** |_____|

P8c. *Record CHILD 3 Contact Information*

- **FIRST NAME** |_____|
- **LAST NAME** |_____|
- **STREET ADDRESS** |_____| (enter "SAME AS PARENT 1" if applicable > go to P7d)
- **CITY** |_____|
- **STATE** |_____|
- **ZIP CODE** |_____|
- **DATE OF BIRTH** |__|__|/|__|__|/|__|__| > *verify age eligibility*

- ***PARENT 3 STUDY ID*** |_____|
- ***CHILD 3 STUDY ID*** |_____|

P8d. Which location for your interview works best for you?

Record Appointment Location

- **CLINIC OFFICE**
- **ADULT HOME**

P8e. Let's pick a good day and time for you. > *Record Appointment Information*

- **DAY** |_____|
- **DATE** |__|__|/|__|__|/|__|__|
- **TIME** |__|__|:|__|__| **AM PM**

P9. *(CLOSING REMARKS)* Thank you very much for your interest. We will mail your [child's/children's] Appointment Packet(s) shortly. Thanks again.

P10. Data Linkages

After the call is over, enter the assigned PARENT (1,2,3, etc.) STUDY ID number(s) to begin tracking enrollment and biospecimen sample logistics for each child. Be sure to link the ID numbers for an individual who has both an ADULT STUDY ID and one or more PARENT STUDY ID aliases.

- ***ADULT STUDY ID*** |_____| *(IF APPLICABLE ALIAS)*

Attachment 4.

- ***PARENT 1 STUDY ID*** _____
- ***PARENT 2 STUDY ID*** _____ *(IF APPLICABLE ALIAS)*
- ***PARENT 3 STUDY ID*** _____ *(IF APPLICABLE ALIAS)*

Attachment 5. Multi-site Study Recruitment Materials

- **Attachment 5a. Child invitation letter**
- **Attachment 5b. Adult invitations letter**
- **Attachment 5c. Multi-site Study Communication Plan Objectives**
- **Attachment 5d. Multi-site Study Overarching Communication Messages**
- **Attachment 5e. Multi-site Study Press Release – Launch**
- **Attachment 5f. Multi-site Study Website Flyer**
- **Attachment 5g. Multi-site Study Public Service Announcement**

Multi-site Study

Child Invitation Letter

Flesch-Kincaid Readability Score – 8.2
(delete authority; ATSDR spelled out)

Attachment 5a – Example - Child Invitation Letter

[ON LETTERHEAD]

[DATE]

[NAME OF ADULT]

[ADDRESS]

[CITY, STATE ZIP CODE]

Subject: Multi-site PFAS Health Study – Child Recruitment

Dear [NAME OF PARENT/GUARDIAN]:

Under the Under Section 8006 of the 2018 Consolidated Appropriations Act, Congress authorized the Agency for Toxic Substances and Disease Registry (ATSDR) to study if exposure to per- and polyfluoroalkyl substances (PFAS) in drinking water might affect human health. Thus, ATSDR is funding the Multi-site PFAS Health Study (CDC Protocol No. xxxx) conducted by [insert study investigators institution name].

ATSDR and [Insert study investigators institution name] will recruit 6,000 adults and 2,000 children who resided in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. Adults must be 18 years or older. Children must be 4 to 17 years old. Children whose birth mothers were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

[Insert site] was selected to be one of the study sites. Our records show that your child may be eligible take part in the Multi-site Study. If you and your child are interested, please call [insert study investigators institution name] directly at [study telephone number].

For questions about this research study, please call the study lead [insert name], at [study telephone number]. Please leave a message with your name, a telephone number, or an address.

Thank you for your interest.

[Insert Name?]

State Epidemiologist

[Insert State?] Department of Health and Human Services

Multi-site Study

Adult Invitation Le

Flesch-Kincaid R
(delete authority;

Attachment 5b –Adult Invitation Letter

[ON LETTERHEAD]

[DATE]

[NAME OF ADULT]

[ADDRESS]

[CITY, STATE ZIP CODE]

Subject: Multi-site PFAS Health Study – Adult Recruitment

Dear [NAME OF ADULT]:

Under the Under Section 8006 of the 2018 Consolidated Appropriations Act, Congress authorized the Agency for Toxic Substances and Disease Registry (ATSDR) to study if exposure to per- and polyfluoroalkyl substances (PFAS) in drinking water might affect human health. Thus, ATSDR is funding the Multi-site PFAS Health Study (CDC Protocol No. xxxx) conducted by [insert study investigators].

[Insert study investigators] will recruit 6,000 adults and 2,000 children who resided in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. Adults must be 18 years or older. Children must be 4 to 17 years old. Persons who were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

[Insert site] was selected to be one of the study site. Our records show that you may be eligible take part in the Multi-site Study. If you are interested, please call [insert study investigators] directly at [study telephone number].

For questions about this research study, please call the study lead [insert name], at [study telephone number]. Please leave a message with your name, a telephone number, or an address.

Thank you for your interest.

[Insert Name?]

State Epidemiologist

[Insert State?] Department of Health and Human Services

Attachment 5c.

Agency for Toxic Substances and Disease Registry (ATSDR)

Multi-site Study Communication Plan Objectives

Objectives	Activities/Methods	Responsible participant	Timetable	Objectives achieved
Objective 1:				
Identify and establish relationship with project stakeholders	• Establish and maintain collaborative partnership and alliances with local community groups and civic organizations • Develop plan to provide project updates • Establish and maintain links with community leaders and elected officials	Recipient, he Agency for Toxic Substances and Disease Registry (ATSDR)	Ongoing	Met with community groups, set up Community Assistance Panel (Multi-site CAP)
			Ongoing	Provided detailed information on planned study (developed research protocol, externally peer reviewed, revised – discussed content and changes).
			After Institutional Review Board (IRB) approval	Received extensive input from the community …. etc. Monthly calls with Multi-site CAP; meetings 2-3 times a year.

Objective 2:				
Develop and present project-related information	• Develop study-related information materials, forms, and reports for participants; submit materials, etc., for IRB and Office of Management and Budget (OMB) review • Describe planned activities for the study at informal meetings in Multi-site at civic or community clubs or other functions • Obtain comments on presenting study information from Multi-site CAP, community groups, and others • Describe project activities at professional scientific meetings	ATSDR, Study investigators	Ongoing	IRB and OMB approvals pending.
			After the IRB approval	Set up additional meetings with Multi-site CAP including representatives from local medical societies, school officials, and elected officials.
Objective 3:				
Develop and establish media relations	• Study PIs and staff should participate in local radio programs describing planned Multi-site Study • Use contacts from the Multi-site CAP to contact local press • Publish information about upcoming health study • Record short video message from the ATSDR director and Multi-site CAP to introduce the study and encourage participation	Study PIs and co-PIs	Ongoing Ongoing After the OMB approval	Call or meet the press and local radio and television representatives at the site.

Objective 4:				
Organize community meeting for former NH DHHS participants and other community members to announce the study	• Mail invitation letters and study fact sheet to recruits • Organize a public meeting at the appropriate/suitable venue • Use Multi-site CAP and local contacts to distribute material about upcoming meeting to schools, employers, and other stakeholders.	Study PIs, study staff	After OMB approval 2 months after OMB approval	Provide a forum for potential participants to find out more about the study and have study investigators answer questions.

Attachment 5d

Agency for Toxic Substances and Disease Registry (ATSDR)

Multi-site Study

Overarching Communications Messages

- ATSDR is conducting the Multi-site PFAS Study:
  - to learn more about the human health effects of exposures to drinking water contaminated with perfluoroalkyl substances (PFAS), and
  - to identify issues that must be addressed prior to starting a future multi-site health study of PFAS-contaminated drinking water.

- The Multi-site Study will include children aged 4-17 years and adults aged ≥18 years who were exposed to the contaminated drinking water at the [insert site]. Persons will be eligible for the study if they lived in a home, worked or attended childcare at the site, were exposed in utero or during breastfeeding, that was served by a PFAS-contaminated public water system or private well.

- The Multi-site Study will recruit 6,000 adults and 2,000 children combined from the sites exposed to the PFAS-contaminated drinking water.

- The Multi-site Study will determine the participant's blood levels of PFAS as well as health indicators such as cholesterol levels, liver function, thyroid function and immune function. The participant's test results will be provided to the participant along with information on how to interpret the results.

Attachment 5e.

Agency for Toxic Substances and Disease Registry (ATSDR)

Multi-site Study

Press Release - Launch

For Immediate Release:

Contact: ATSDR Media Office

770-488-0700

ATSDR launches a health study of adults and children exposed to drinking water contaminated with perfluoroalkyl substances ("PFAS") ….

The Agency for Toxic Substances & Disease Registry (ATSDR) is starting a study to determine the health effects of exposures to contaminated drinking water serving [insert site]. The public drinking water system at [insert site] was contaminated with perfluoroalkyl substances ("PFAS") from [insert as applicable].

The Multi-site Study will recruit at least 2,000 children aged 4-17 years and 6,000 adults aged ≥18 years who were exposed to PFAS contaminated drinking water. Birth mothers of eligible children cannot have a history of work exposure to PFAS.

"There is much that is unknown about the health effects of exposures to these chemicals," said Patrick Breysse, PHD, CIH, Director of ATSDR and the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC). "The Multi-site Study will advance the scientific evidence on the toxicity of PFAS and provide some answers to communities exposed to the contaminated drinking water."

Each participant will be asked to provide a blood and a urine sample for analysis of PFAS levels and health indicators such as cholesterol levels, liver function, thyroid function and immune function. The participant's test results will be provided to the participant along with information on how to interpret the results.

Attachment 5f.

Agency for Toxic Substances and Disease Registry (ATSDR)

Multi-site Study

Website Flyer** TO BE COMPLETED**

Multi-site Study

ATSDR is funding a health study of children and adults exposed to drinking water contaminated with perfluoroalkyl substances ("PFAS"): Multi-site PFAS Health study ("Multi-site Study").

The purposes of the study are to:

- *Learn more about the human health effects of exposures to drinking water contaminated with PFAS,*
- *Address some of the health concerns of the affected communities, and*
- *Identify issues that must be addressed prior to starting future health studies at sites where exposures to PFAS-contaminated drinking water have occurred.*

The Multi-site Study will recruit as many as 350 exposed children aged 4-17 years and 1,000 exposed adults aged ≥18 years. Persons will be eligible for the study if they worked or attended childcare at the Multi-site Tradeport prior to the closing of the Haven supply well in May 2014, were exposed in utero or during breastfeeding, or lived in a home near Multi-site that was served by a PFAS-contaminated private well. The study will also recruit a comparison group of 175 children and 100 adults from the Portsmouth area who were <u>not</u> exposed to PFAS-contaminated drinking water. Birth mothers of eligible Portsmouth children cannot have exposure to drinking water from Multi-site, and no adults in the study can have a history of work exposure to PFAS.

Frequently Asked Questions (FAQs)

1. Why is ATSDR doing the health study at Multi-site?

ATSDR is conducting a health study to evaluate the health effects from exposures to PFAS-contaminated drinking water at the Multi-site International Tradeport in Portsmouth, NH ("Multi-site"). The drinking water serving Multi-site was contaminated by the Haven supply well until the well was closed in May 2014. Based on the PFAS levels measured in the Haven well in April and May 2014, the estimated combined levels of two PFAS chemicals in the drinking water, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), exceeded the US EPA Lifetime Health Advisory Level of 70 parts per trillion.

The purposes of the study are to:

- *Learn more about the human health effects of exposures to drinking water contaminated with PFAS,*
- *Address some of the health concerns of the Multi-site community, and*
- *Identify issues that must be addressed prior to starting future health studies at sites where exposures to PFAS-contaminated drinking water have occurred.*

2. How was the drinking water at this site contaminated with PFAS?

The source of the PFAS contamination was the use of aqueous film-forming foam (AFFF), a fire suppressant agent, at the [insert site]. AFFF ingredients include PFAS. PFAS migrated from the soil into the ground water at the base and then to the [insert name(s)] supply well and the two other supply wells serving [insert site].

3. Who is eligible for the study?

Children aged 4-17 years and adults aged ≥18 years are eligible for the study if they worked or attended childcare at the site, were exposed in utero or during breastfeeding, or lived in a home near the site that was served by a PFAS-contaminated private well.

Persons with occupational exposures to PFAS (e.g., firefighters who used or trained with AFFF) and children whose mothers were occupationally exposed to PFAS are not eligible for the study.

Eligible females who are pregnant may enroll; however, the federal regulations say that people in prison, including those under house arrest, cannot take part in this type of study.

4. What is required in order to participate in the study?

Each participant (or the parent of a child participant) must sign a consent form. The consent form describes the study procedures and risks and benefits of participation. The consent form will request permission to obtain a blood and urine sample. These samples will be analyzed for PFAS and for health indicators such as cholesterol levels, liver function, thyroid function and immune function. The participant's test results will be provided to the participant along with information on how to interpret the results. The consent form will also request that the participant (or parent of the child participant) complete a health and exposure questionnaire. The consent form will ask permission to obtain body measurements (blood pressure, weight, height, waist and hip circumference). The consent form will request permission to obtain the participant's medical records and the child participant's special education records (e.g., IEP evaluation report or 504 Plan). Finally, the consent form for children participants will request permission to administer behavioral tests to the child and obtain information from the parent concerning the child's behaviors.

Attachment 5g.

Agency for Toxic Substances and Disease Registry (ATSDR)

Study

Public Service Announcement****

Did you live, work, or did your child attend day care at the Multi-site International Tradeport ("Multi-site") on or before May 2014? If so, you or your child could be eligible to participate in a study assessing the health effects of exposures to drinking water contaminated with perfluoroalkyl substances ("PFAS") at Multi-site. The Agency for Toxic Substances & Disease Registry (ATSDR) is funding the Multi-site PFAS Health Study.

The study includes children aged 4-17 years and adults aged ≥18 years who were exposed to the contaminated drinking water at [insert site].

Each participant will be asked to complete a questionnaire and provide a blood sample to test for PFAS levels as well as health indicators such as cholesterol levels, liver function, thyroid function and immune function. Test results will be provided to the participant.

Additional information on the study is available at http://www.atsdr.cdc.gov/.....

Attachment 6.

Multi-site Study
Recruitment Tracking Form

Adult Study ID No.	|_____| (record any alias study IDs to ensure linkages)
Parent Study ID No.	|_____|
Child Study ID No.	|_____|
	Contact Information Label

NW = Non-working Number	AN = Appointment Not Scheduled	CC = Consent Complete
NH = No One Home	AS = Appointment Scheduled (note date/time)	IP = Partial Interview
EN = Not Eligible	AR = Appointment Rescheduled (note date/time)	IC = Completed Interview
EY = Yes Eligible	AX = Appointment No-Show	O = Other (explain)

No.	DATE mm/dd/yy	TIME hh:mm	OUTCOME CODE(S)	COMMENTS	INTERVIEWER
1	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
2	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
3	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
4	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
5	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
6	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
7	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
8	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
9	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
10	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
11	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
12	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			

Multi-site Study
Appointment Reminder Card
Flesch-Kincaid Readability Score – 5.9

Attachment 7a. Appointment Reminder Card and Instructions

Multi-site PFAS Health Study
Appointment Reminder Card

Clinic Visit

Appointment Information for Your Multi-site Study Interview

[NAME OF LOCATION]

[Street Address]

[Local or Toll Free Telephone Number]

Day: |_____|

Date: |__|__|/|__|__|/|__|__|

Time: |__|__|:|__|__| ☐ **AM** ☐ **PM**

Study ID No.: |_____|

Please bring this paper with you.

We will draw a blood sample so please do not eat for at least 8 hours before your appointment. You may drink water during this time.

Don't forget to collect your urine sample in the morning. Bring your urine sample with you.

If you take diabetic medication, see special instructions.
Don't forget to bring all your medication for us to see.

[If you are a past participant in the [insert site] PFAS Blood Testing Program, please bring a copy of your results report.]

If you are unable to keep this appointment, please call to set up another time.

Toll-free (xxx)xxx-xxxx

Multi-site PFAS Study
Appointment Reminder Card

Home Visit

Appointment Information for Your Multi-site PFAS Study Interview

We will arrive at your home on the date and time below:

Day: |_____|

Date: |__|__|/|__|__|/|__|__|

Time: |__|__|:|__|__| ☐ **AM** ☐ **PM**

Study ID No.: |_____|

We will draw a blood sample so please do not eat for at least 8 hours before your appointment. You may drink water during this time.

Don't forget to collect your urine sample in the morning.

If you take diabetic medication, see special instructions.
Don't forget to gather all your medication for us to see.

[If you are a past participant in the [insert site] PFAS Blood Testing Program, please provide a copy of your results report.]

If you are unable to keep this appointment, please call to set up another time.

Toll-free (xxx)xxx-xxxx

Multi-site Study
Appointment Reminder Card – Instructions

Instructions for Study Participants

On the day of your appointment

Fasting: Do not eat or drink for at least 8 hours before your appointment. Do not have candy, gum, or soda. Drinking water is fine. Take all your medications with water only.

If you have diabetes and take insulin or other medications, we will schedule your appointment as early in the morning as possible. Please fast for at least 8 hours if your meal and medication plan allows. If you must eat before your appointment, please eat fat-free or low-fat items and take your medications as usual. Write down what you ate and when you ate it.

First Morning Voided Urine Collection: Using the supplies we sent in your Appointment Packet, collect a first morning voided specimen. Note the time of collection of the specimen on the label of the container. To reduce contamination, the specimen should be a clean catch "mid-stream" sample.

Medications: Please have all of your regular medications that you have taken for the past two weeks with you. Putting them in a plastic bag will make it easy. We want to know about:

- Prescriptions
- Over-the-counter medicines
- Supplements and vitamins
- Fish oil
- Herbal remedies
- If any of your medications need to be kept chilled, please leave them in your refrigerator. Make a note to tell us about them.

[Insert site] PFC Blood Testing Program Results: *We would like to record your prior results to compare with your current ones. Please provide a copy of the results report for us to see.[if applicable]*

Questions: If you have any questions, please contact us at our study phone number [INSERT TOLL FREE TELEPHONE NUMBER]. Thank you for taking part in this study.

Attachment 7b – Informed Consent Packet

- **Attachment 7b1 – Privacy Act Statement**
- **Attachment 7b2 – Parental Permission and Child Assent Forms**
- **Attachment 7b3 – Parental Consent to Release Student Information**
- **Attachment 7b4 – Adult Consent Form**
- **Attachment 7b5 – Parent/Child/Adult Permission for Medical Record Abstraction**

Multi-site Study
Privacy Act Statement at Consent
Flesch-Kincaid Readability Score – 8.5
(deleting authority; NCEH spelled out; SORN)

Attachment 7b1 – Privacy Act Statement

PRIVACY ACT STATEMENT
FOR THE
HUMAN HEALTH EFFECTS OF DRINKING WATER EXPOSURES TO PER- AND POLY-FLUOROALKYL SUBSTANCES (PFAS): A MULTI-SITE CROSS-SECTIONAL STUDY

This statement provides the notice required by the Privacy Act of 1974 (5 USC § 552a(e)(3)).

- **Authority:** The Agency for Toxic Substances and Disease Registry (ATSDR) has the authority to collect this information under § 8006 of the Consolidated Appropriations Act of 2018 (Public Law 115-141). ATSDR also conducts research under the ''Comprehensive Environmental Response, Compensation, and Liability Act of 1980'' (CERCLA) as amended by ''Superfund Amendments and Reauthorization Act of 1986'' (SARA) (42 U.S.C. 9601, 9604).

- **Purpose:** ATSDR is funding this research to study whether exposure to per- and polyfluoroalkyl substances (PFAS) from drinking water might be a public health concern. [Insert study investigators institution name] is collecting this information on you or your child for:
  - Adult consent, parental permission, and child assent to participate in surveys, tests, and blood and urine collections.
  - Consent for ATSDR and [institution name] to look at your child's school records. This will help to compare study results to school records.
  - Consent for ATSDR and [institution name] to look at your or your child's medical records. We will compare doctors' notes to survey results. This will improve the quality of the study results.
  - Sending your or your child's results back to you.
  - Contacting you for future studies.

- **Routine Uses:**
  - ATSDR will share these records with National Center for Environmental Health. NCEH may provide research or support staff, laboratory and statistical analysis, etc.
  - ATSDR and [institution name] may disclose these records to its contractors to locate individuals exposed or potentially exposed to PFAS, and to conduct interviews and other research activities. The contractor must also comply with the requirements of the Privacy Act to protect your or your child's records.
  - Other routine uses as described in Statement of Records Notice (SORN) No. 09-19-0001 - ''Records of Persons Exposed or Potentially Exposed to Toxic or Hazardous Substances." See https://www.gpo.gov/fdsys/pkg/FR-2011-01-25/pdf/2010-33004.pdf.

- **Disclosure:** Providing this information is voluntary. ATSDR and [institution name] need this information for you or your child to take part in the study. Both institutions need up-to-date contact information to send your or your child's study results. If you permit, ATSDR would like to keep your contact information for future studies.

Participant Initials: _____

Multi-site Study – Parental Permission/Child Assent
Flesch-Kincaid Readability Score –
KEY THINGS – 8.4
Overall – 7.9

Attachment 7b2.

Parental Permission and Child Assent Form

TITLE OF RESEARCH: *"**The Multi-site PFAS Health Study**" formally titled:*

"Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances (PFAS): A multi-site cross-sectional study "

PRINCIPAL INVESTIGATORS: Dr. Marian Pavuk, Dr. Frank Bove

CO-INVESTIGATOR: xxxxxxxx

SPONSOR: Agency for Toxic Substances and Disease Registry (ATSDR)

CDC Protocol #XXXX

KEY THINGS TO KNOW ABOUT THIS RESEARCH

AUTHORITY: Public Law 115-141, the "Consolidated Appropriations Act of 2018."

PURPOSE: To see if PFAS exposure from drinking water is related to children's health outcomes.

WHO CAN TAKE PART: About 2,000 eligible children, 4-17 years of age, and their parents.

- ATSDR and [institution name] are enrolling [# as applicable] children, 4-17 years of age, who were exposed to PFAS-contaminated water from the [insert site].
- ATSDR and its research partners plan to recruit at least 2,000 children for the Multi-site PFAS Health Study. Those children have had to reside in areas served by PFAS contaminated drinking water or were exposed *in utero* or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. The birth mothers for children cannot have or had contact with PFAS chemicals at work.
- Eligible girls who are pregnant may enroll.
- The federal regulations do not allow people who are prisoners or under house arrest to take part in this type of study.

Ideally, the parent should be the mother, who can best answer some survey questions about the child's exposures and about the mother's pregnancy and breastfeeding history. A parent can enroll with more than one child. In this case, ATSDR and [institution name] will enroll each child separately along with his or her parent. Parents, if eligible, may also enroll in the adult study.

ATSDR and [institution name] ask children and parents to come to our central study office. We will offer to meet some families at home, if they find travel difficult. They must live within a one-hour drive from the office.

EXPECTED TIME IN THE STUDY: About 2 hours. To save time, your child can do some parts of the study while you do the parent's parts.

PROCEDURES: Trained study staff will take your child's body measures and list your child's medications. You, as the parent, will answer survey questions and behavioral assessments about your child. At the same time, the child will complete his or her own assessments.

ATSDR and [institution name] will collect your child's blood and urine biospecimens. ATSDR will try to analyze blood for PFAS and health tests right away. Urines will be stored until such time that lab methods are developed and scientific evidence shows which PFAS tests will yield useful results. After all tests are done, ATSDR would like to save your child's leftover blood and urine for future studies, and only if you permit.

If you permit, ATSDR and [institution name] will ask the doctor to verify some of your child's medical history. ATSDR will also look at your child's school records to compare to the assessment results. If your child took part in any PFAS Blood Testing Program, ATSDR would like to get those results.

RISKS: The risks of taking part in this research are minimal. The main risk from taking part in this research is for the inadvertent disclosure of your or your child's identity. Study staff will be trained in ways to prevent disclosures from occurring. The risk of giving blood would be the same as in a doctor's office. It may hurt a little when the blood is drawn. Your child may get a bruise where the blood is drawn. These risks are about the same as those your child would face in daily life. We will do our best to prevent these problems.

BENEFITS: There are no direct benefits for your child to be in the study. We will give you the results of his or her blood and urinary PFAS and health tests that you may find helpful to share with your child's doctor. We also think that the study will help the [insert site] community better understand the connection between PFAS and health.

CONFIDENTIALITY: ATSDR and [institution name] has taken steps to protect your child's privacy. A Certificate of Confidentiality covers this research. ATSDR, [institution name], and its contractors cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you consent to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.

IT IS YOUR DECISION: You and your child may freely choose to, or refuse to, take part in this research. During your appointment, you can stop at any time. You and your child can refuse to answer any questions or have your child's blood drawn or urine collected. There is no penalty for refusing to take part or for leaving the study at any time.

FOR QUESTIONS ABOUT THIS STUDY: If you have any questions about the study, or if you and your child decide later that you do not want to take part, please contact Dr. Marian Pavuk or Dr. Frank Bove at (xxx) xxx-xxxx. They can provide a phone number for a consultation with a health care provider at no cost to you if you would like to discuss your child's results.

Participant Initials: _____

FOR QUESTIONS ABOUT YOUR CHILD'S RIGHTS IN RESEARCH OR ABOUT A RESEARCH-RELATED INJURY: For questions about your rights in taking part in this study, call the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814. Be sure to say your call is about CDC Protocol No. xxxx. Leave your name, contact information, and a description of your concern.

DETAILS ABOUT THIS RESEARCH

STUDY OVERVIEW/PURPOSE: ATSDR and [institution name] are inviting your child to take part in a research study to find out about the health effects of PFAS in the drinking water in your area.

GETTING READY FOR YOUR APPOINTMENT: When study staff screened and told you that your child was eligible, we scheduled your appointment and mailed you a packet with instructions on how to prepare for the appointment.

- On the morning of the appointment, we request that you help your child collect a clean first morning voided urine sample. Bring it to the appointment.
- We also request that your child not eat for at least 8-hours before his or her appointment so that we can collect a fasting blood sample.
- If your child is taking any medications or dietary supplements, we request that you bring them to the appointment. We also as that you note the dates of your child's vaccinations for us to write down.
- If your child participated in a PFAS biomonitoring program in the past, we ask that you bring a copy of the results to the appointment.

WHAT TO EXPECT AT YOUR APPOINTMENT: The whole appointment will take about two hours.

- We will measure your child's height, weight, waist, hip, and blood pressure.
- We will take in your child's urine sample, which you will help your child collect that morning.
- We will collect a fasting blood sample from your child. A trained phlebotomist will draw a small amount of blood from a vein in your child's arm (about 5 teaspoons). We will label your child's samples with a study ID only.

  Certain medical conditions might interfere with our drawing blood or might affect the results of our lab tests. If your child has of one of these conditions, he or she may not be able to take part in all parts of the study. However, he or she can still do the interviews and have a weight, height, waist, hip, and blood pressure measured.
- The questionnaire about your child's exposure and medical history should take about 30 minutes to complete. Parents who also enroll as adults will take a shorter 15-minute questionnaire.
- We will also ask you to complete an assessment of your child's attention and behaviors. It should take about 15 minutes.

Participant Initials: _____

- Trained professionals will give your child the behavioral assessments. Although some age groups will only need 30 to 60 minutes, the testing will take about 90 minutes for most children. The tests will be given at a relaxed pace and should not be tiring for your child.

We very much appreciate you and your child taking part in this study. If you complete all parts of the study, we will give you $75 in gift cards as our way of saying thank you. If you and your child complete parts of the appointment, we will provide the following gift cards:

- $25 for body and blood pressure measures, and for blood and urine collection;
- $25 for completed questionnaire; and
- $25 for child/parent completion of the neurobehavioral test battery

QUESTIONS WE WILL ASK: We will ask you questions about your child's health, medications, vaccinations, drinking water habits, and daycare attendance. If you report that your child had certain health conditions, we would like to review your child's medical records to confirm his or her health conditions. We will also ask you about his or her mother's health, pregnancies, and work history. We would like to know more about her pregnancy and breastfeeding of your child.

We will ask you to complete a parent's assessment of your child's attention and behaviors. We will ask your child to take assessment tests about his or her attention, memory, and behaviors. We will assess IQ for children older than 5 years of age. Education professionals have used these types of assessment tests for many years with thousands of children who often find them fun and enjoyable. We would like to compare your child's school records to the assessment results.

PFAS MEASURED IN BLOOD: We will send your child's blood sample for lab analysis. The lab will measure the levels of specific PFAS in your child's blood.

OTHER BLOOD TESTS: We will send your child's blood to the lab for health tests such as cholesterol, other lipids, liver enzymes, and thyroid hormones. We will also look at allergy markers and vaccine response. Doctors often use these types of tests. They will help us learn more about how PFAS might affect health.

PFAS MEASURED IN URINE: Scientists are learning more about PFAS every day. Your child's urine specimen will be stored until lab methods are developed and the scientific evidence shows which PFAS tests will yield useful results. It might be a year or more before ATSDR decides if and which PFAS tests in urine should be done as part of this research study.

YOUR CHILD'S TEST RESULTS: We will send you a letter with your child's blood PFAS and health test results. We think we will finish all of the lab tests in less than six months after we draw your child's blood. If your child's test results suggest a health problem, we will let you know before we mail the blood test results. Despite the anticipated time delay, ATSDR and [institution name] plans to send a report of your child's urine PFAS.

COSTS: You do not have to pay to let your child be part of this study. The blood tests are free.

Participant Initials: _____

MORE ABOUT CONFIDENTIALITY: ATSDR and [institution name] has taken steps to protect your privacy. A Certificate of Confidentiality covers this research. ATSDR is required to protect the privacy of persons who are subjects of this research under subsection 301(d) of the Public Health Service Act (PHSA) [42 USC §241(d)]. ATSDR and its research partners cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you consent to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.

You should also know that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow ATSDR or [institution name] to release it.

ATSDR and its research partners are required to ensure that any investigator or institution not funded by ATSDR who receives a copy of identifiable, sensitive information protected by a Certificate, understand they are also subject to the requirements of subsection 301(d) of the PHSA.

We will store your answers and test results using a study number, not your child's name. We will keep his or her records in locked files at the study office in [insert site]. ATSDR and its research partners will protect any computer files with your child's information. Only study staff with a need-to-know will have access to his or her information and test results. All study staff will take training on how to protect the privacy of people who take part in this research.

USE OF COLLECTED INFORMATION: We will write reports or scientific articles about the study results. We will combine everyone's responses to get a picture of the health issues of people across the sites as they relate to PFAS. These reports or articles will be available to the public after the study is finished. The report results will not identify who took part in the study.

STORING RESIDUAL BIOSPECIMENS AND MULTI-SITE PFAS HEALTH STUDY DATA FOR FUTURE USE:

ATSDR will keep your and your child's contact information and study ID number(s) in a restricted-access secure master dataset. All biospecimens and study data will be coded and stored only with study IDs for data analysis. If you change your mind later and decide not to let us use your biospecimens or data for other projects, you can contact us and we will remove you from the list.

We are ***seeking consent now and will not recontact*** you for the following activities:

- **Additional analyses of stored biospecimens related to this PFAS research:** After we test your child's blood and urine, there may be some left over. Because new scientific knowledge, tests, or methods may arise, we would like to save this leftover blood and urine for additional analyses on exposures or health conditions related to PFAS. We do not expect the results of these additional or future research tests to be clinically important to your health and we are not planning to report the individual test results to you.

Participant Initials: _____

- **Future analyses by outside investigators:** In addition, ATSDR/[institution name] may release your child's **de-identified research datasets or de-identified blood and urine** samples for future studies related to PFAS to outside investigators under a data use agreement that will prohibit any attempt to identify you or your child as a research subject. In this case, your individual test results will not be reported to you.

We would like ***to keep your contact information for future studies*.** We would like to recontact you to get additional consent for the following types of activities:

Studies that require collection of additional data or biospecimens. After we complete this study we may conduct new research studies. At that time, we may ask your consent to include your child, and your child's data or leftover biospecimens from this current study. We'd like to contact you at that time.

Your stored biospecimens will not be used for any commercial activities for profit. In addition, we do not anticipate your biospecimens to be used for whole genome sequencing (you would need to be recontacted to consent for such tests). All future analyses and studies must adhere to IRB review requirements.

If you do not understand what we are asking you to do, feel free to ask questions now. If you have no further questions and agree to be in this study, please sign the permission and assent form below.

Child Assent Information about the Multi-site Study

THINGS TO KNOW ABOUT THIS STUDY

WHO IS DOING THIS STUDY: ATSDR is a public health agency that does research at places like [insert site]. [Insert site] has a chemical that got into some of the drinking water. In [insert site], the chemical is called "PFAS."

PURPOSE: In this study, ATSDR and [institution name] will ask you to tell us about your health, to take some assessment tests, and to get your blood tested for PFAS. This way, when ATSDR and [institution name] investigators look at all the results together, we can see if any answers about children's health match with their PFAS results.

WHO CAN TAKE PART: ATSDR and [institution name] wants to enroll about [# as applicable] eligible children, 4-17 years of age, and their parents. We think it is best if your mother comes with you. That is because we will ask a lot of questions about when you were a baby.

EXPECTED TIME IN THE STUDY: About 2 hours. To save time, you can do some parts of the study at the same time as your parent. Before you come to the study, we ask that you not eat for 8 hours. We also ask that you pee in a lab cup at home and bring the sample with you.

WHAT WILL YOU DO: It will be a lot like going to the doctor's. We will measure how tall you are and how much you weigh. We will take your blood pressure and write down your medicines, if you take any. We will take your pee and draw a small blood sample. The blood draw might hurt a little, but for most children, it is not too bad.

Your parent will answer questions about you. At the same time, you will do the assessment tests. They are a lot like puzzles and thinking games that you might find fun to do.

IT IS YOUR DECISION: You are free to decide if you want to do the study. If you start, you can stop at any time. You can refuse to answer any questions. You can decide not to give a blood or urine sample. Nothing bad will happen to you or your parent if you don't join the study.

FUTURE STUDIES: ATSDR and [institution name] may plan to do more studies in the future. Sometimes, ATSDR and [institution name] might want to let you know about a new study or to get your permission to include you, your study data, or your leftover blood and urine, for a new study. To do this, we'd like to contact you then.

PARENTAL PERMISSION AND CHILD ASSENT (SIGNATURE PAGE 1 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances (PFAS): A multi-site cross-sectional study "*

CDC Protocol #XXXX

FOR OFFICE USE ONLY
Adult Study ID No. |_____| (alias)
Parent Study ID No. |_____|
Child Study ID No. |_____|

I have read and/or have been told about the purpose of the study. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I choose to take part in the study.

By signing below, I agree to the parts of the Multi-site Study that I have checked below:

[__] Answer study questions about my child.

[__] Complete a parent assessment of my child's attention and behaviors.

[__] Have my child take a test for attention and behaviors.

[__] Have my child, who is > 5 years of age, take an IQ test; **or** [__] My child is ≤ 5 years of age.

[__] Allow ATSDR and [institution name] to review my child's school records.

[__] Allow ATSDR and [institution name] to review my child's medical records.

[__] Give ATSDR and [institution name] a copy of any PFAS Blood Testing Program results; if available; [__] My child has not participated in a PFAS Blood Testing Program.

[__] Have my child provide a blood sample and have it tested.

[__] Have my child provide a urine sample and have it stored.

_____ Parent or Guardian's Name (Print)	_____ Child's Name (Print) (≥ 7 years old)
_____ Parent or Guardian's Signature Date	_____ Child's Signature Date
	|__|__|__| - |__|__|__| - |__|__|__|__| Child's Social Security Number

Participant Initials: _____

PARENTAL PERMISSION AND CHILD ASSENT (SIGNATURE PAGE 2 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances (PFAS): A multi-site cross-sectional study "*

CDC Protocol #XXXX

FOR OFFICE USE ONLY
Adult Study ID No. |_____| (alias)
Parent Study ID No. |_____|
Child Study ID No. |_____|

I have read and/or have been told about ATSDR's plans for using my child's study data and leftover biospecimens in the future. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I understand that ATSDR will follow CDC IRB requirements for these additional analyses or new studies.

By signing below, I agree to the additional uses of my child's Multi-site Study data and leftover biospecimens that I have checked below:

[__] ATSDR and [institution name] can use my child's study data and his or her leftover blood and urine for additional analyses related PFAS.

[__] I understand that ATSDR and [institution name] can share my child's de-identified data and leftover biospecimens with outside investigators for future research related to PFAS.

[__] ATSDR and [institution name] can contact me about new studies.

_____ Parent or Guardian's Name (Print)	_____ Child's Name (Print) (≥ 7 years old)
_____ Parent or Guardian's Signature Date	_____ Child's Signature Date

Participant Initials: _____

Multi-site Study
Parental Consent Release Student Info
Flesch-Kincaid Readability Score – 8.1

Attachment 7b3.

Multi-site Study

PARENTAL CONSENT TO RELEASE STUDENT INFORMATION

Under the Family Educational Rights and Privacy Act (FERPA), the Agency for Toxic Substances and Disease Registry (ATSDR) and [institution name] are seeking parental consent for the release of your child's school records. ATSDR and [institution name] will compare your child's school records to some of his or her research test results from the Multi-site PFAS Health Study.

The only type of information that is to be released under this consent is:
_____ Individualized Education Program (IEP)
_____ IEP Evaluation Report ("Full Individual Evaluation" or "FIE")
_____ Independent Educational Evaluation (IEE)

ATSDR and [institution name] plan to send trained study staff to the school indicated on this form. The staff will perform school record abstractions limited to the above information. You have a right to inspect any written records released pursuant to this consent. You may revoke this consent upon providing written notice to the Education Official and School that you permitted to release you child's school records. Until it is revoked, this consent shall remain in effect. Until such time, your child's school records will be provided to ATSDR and [institution name] until the study is over.

By signing below, you permit:

Name of Official: _____School: _____
to release your child's school records to the ATSDR Principal Investigators, Marian Pavuk, MD, PhD and Frank Bove, PhD. You may contact them with any questions at [study telephone number].

Name of Student (print): _____ ***Student ID No.*** _____

Address of Student: _____

City: _____ ***State:*** _____ ***Zip Code:*** _____

Name of Parent or Guardian (print): _____

Signature of Parent or Guardian: _____

Date of Consent: |__|__|/|__|__|/|__|__|

Child's Study ID No. |_____|

Participant Initials: _____

Attachment 7b4.

Adult Consent Form

TITLE OF RESEARCH: *""**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and poly-fluoroalkyl substances (PFAS): A multi-site cross-sectional study "*

PRINCIPAL INVESTIGATORS: Dr. Marian Pavuk, Dr. Frank Bove

CO-INVESTIGATOR: xxxxxxxx

SPONSOR: Agency for Toxic Substances and Disease Registry (ATSDR)

CDC Protocol #XXXX

KEY THINGS TO KNOW ABOUT THIS RESEARCH

AUTHORITY: Public Law 115-141, the "Consolidated Appropriations Act of 2018."

PURPOSE: To see if PFAS exposure from drinking water is related to adult health outcomes. Study methods will inform the design of future studies.

WHO CAN TAKE PART: Eligible adults, ≥ 18 years of age. ATSDR and [institution name] ask you to come to our central study office. We will offer to meet some adults at home, if they find travel difficult. They must live within a one-hour drive from the office.

- ATSDR and its research partners plan to recruit a total of 6,000 adults for the Multi-site Study. Those person had to reside in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water.

- Drinking water exposure must have occurred within 15 years of the start of the study. Persons who were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

- Eligible females who are pregnant may enroll.

- The federal regulations do not allow people who are prisoners or under house arrest to take part in this type of study.

- An eligible adult can also enroll as a parent of one or more eligible children.

We will ask you to come to our central study office. We will offer to meet some adults at home, if they find travel difficult. They must live within a one-hour drive from the office.

EXPECTED TIME IN THE STUDY: About 45 minutes.

PROCEDURES: Trained study staff will take your body measures and list your medications. You will answer survey questions.

ATSDR and [institution name] will collect your blood and urine biospecimens. ATSDR and [institution name] will try to analyze blood for PFAS and health tests right away. Urines will be stored until such time

that lab methods are developed and scientific evidence shows which PFAS tests will yield useful results. After all tests are done, ATSDR and [institution name] would like to save your leftover blood and urine for future studies, and only if you permit.

If you permit, study staff will ask the doctor to verify some of your medical history. If you took part in any PFAS Blood Testing Program, ATSDR would like to get those results.

RISKS: The risks of taking part in this research are minimal. The main risk from taking part in this research is for the inadvertent disclosure of your identity. Study staff will be trained in ways to prevent disclosures from occurring. The risk of giving blood would be the same as in a doctor's office. It may hurt a little when the blood is drawn. You may get a bruise where the blood is drawn. These risks are about the same as those you would face in daily life. We will do our best to prevent these problems.

BENEFITS: There are no direct benefits for you to be in the study. We will give you the results of your blood PFAS and health tests that you may find helpful to share with your doctor. We also think that the study will help the [insert site] community better understand the connection between PFAS and health.

CONFIDENTIALITY: ATSDR has taken steps to protect your privacy. A Certificate of Confidentiality covers this research. ATSDR and its research partners cannot be forced to release information that could identify you even under a court order or subpoena (unless you choose to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.

IT IS YOUR DECISION: You may freely choose to, or refuse to, take part in this research. During your appointment, you can stop at any time. You can refuse to answer any questions or have your blood drawn. There is no penalty for refusing to take part or for leaving the study at any time.

FUTURE STUDIES: ATSDR and [institution name] may plan to do more studies in the future. Sometimes, ATSDR and [institution name] might want to let you know about a new study or to get your permission to include you, your study data, or your leftover blood and urine, for a new study. To do this, we'd like to contact you then.

FOR QUESTIONS ABOUT THIS STUDY: If you have any questions about the study, or if you decide later that you do not want to take part, please contact Dr. Marian Pavuk or Dr. Frank Bove at (xxx) xxx-xxxx. They can provide a phone number for a consultation with a health care provider at no cost to you if you would like to discuss your results.

FOR QUESTIONS ABOUT YOUR RIGHTS IN RESEARCH OR ABOUT A RESEARCH-RELATED INJURY: For questions about your rights in taking part in this study, call the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814. Be sure to say your call is about CDC Protocol No. xxxx. Leave your name, contact information, and a description of your concern.

DETAILS ABOUT THIS RESEARCH

STUDY OVERVIEW/PURPOSE: ATSDR and [institution name] are inviting you to take part in a research study to find out about the health effects of PFAS in the drinking water in your area.

Participant Initials: _____

GETTING READY FOR YOUR APPOINTMENT: When study staff screened and told you that you were eligible, we scheduled your appointment and mailed you a packet with instructions on how to prepare for the appointment.

- On the morning of the appointment, we request that you collect a clean first morning voided urine sample. Bring it to the appointment.
- We also request that you not eat for at least 8-hours before your appointment so that we can collect a fasting blood sample.
- If you are taking any medications or dietary supplements, we request that you bring them to the appointment.

WHAT TO EXPECT AT YOUR APPOINTMENT: The whole appointment will take about 45 minutes.

- We will measure your height, weight, waist, hip, and blood pressure.
- We will take in your urine sample, which you will collect that morning.
- We will collect a fasting blood sample. A trained phlebotomist will draw a small amount of blood from a vein in your arm (about 7 teaspoons). We will label your samples with a study ID only.

  Certain medical conditions might interfere with our drawing blood or might affect the results of our lab tests. If you have of one of these conditions, you may not be able to take part in all parts of the study. However, you can still do the interviews and have a weight, height, waist, hip, and blood pressure measured.
- The questionnaire about your exposure and medical history should take about 30 minutes to complete.

We very much appreciate you taking part in this study. If you complete all parts of the study, we will give you $50 in gift cards as our way of saying thank you. If you complete parts of the appointment, we will provide the following gift cards:

- $25 for body and blood pressure measures, and for blood and urine collection; and
- $25 for completed questionnaire.

QUESTIONS WE WILL ASK: We will ask you questions about your health, medications, drinking water habits, and work history. If you report that you had certain health conditions, we would like to review your medical records to confirm these health conditions. For women, we will also ask your reproductive and breastfeeding history.

PFAS MEASURED IN BLOOD: We will send your blood sample for lab analysis. The lab will measure the levels of specific PFAS in your child's blood.

OTHER BLOOD TESTS: We will send your blood to the lab for health tests such as cholesterol, other lipids, liver enzymes, and thyroid hormones. We will also look at allergy markers. Doctors often use these types of tests. They will help us learn more about how PFAS might affect health.

PFAS MEASURED IN URINE: Scientists are learning more about PFAS every day. Your urine specimen will be stored until lab methods are developed and the scientific evidence shows which PFAS tests will yield useful results. It might be a year or more before ATSDR decides if and which PFAS tests in urine should be done as part of this research study.

YOUR TEST RESULTS: We will send you a letter with your blood PFAS and health test results. We think we will finish all of the lab tests in less than six months after we draw your blood. If your test results suggest a health problem, we will let you know before we mail the blood test results. Despite the anticipated time delay, ATSDR plans to send a report of your urine PFAS.

COSTS: You do not have to pay to be part of this study. The blood tests are free.

MORE ABOUT CONFIDENTIALITY: ATSDR and [institution name] have taken steps to protect your privacy. A Certificate of Confidentiality covers this research. ATSDR is required to protect the privacy of persons who are subjects of this research under subsection 301(d) of the Public Health Service Act (PHSA) [42 USC §241(d)]. ATSDR and its research partners cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you choose to such a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.

You should know that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow ATSDR to release it.

ATSDR, [institution name], and its contractors are required to ensure that any investigator or institution not funded by ATSDR who receives a copy of identifiable, sensitive information protected by a Certificate, understand they are also subject to the requirements of Subsection 301(d) of the PHSA.

We will store your answers and test results using a study number, not your name. We will keep your records in locked files at the study office in [insert site]. ATSDR and its research partners will protect any computer files with your information. Only study staff with a need-to-know will have access to your information and test results. All study staff will take training on how to protect the privacy of people who take part in this research.

USE OF COLLECTED INFORMATION: We will write reports or scientific articles about the study results. We will combine everyone's responses to get a picture of the health issues of people in [insert site] as they relate to PFAS. These reports or articles will be available to the public after the study is finished. The report results will not identify who took part in the study.

STORING RESIDUAL BIOSPECIMENS AND MULTI-SITE PFAS HEALTH STUDY DATA FOR FUTURE USE:

Participant Initials: _____

ATSDR will keep your contact information and study ID number(s) in a restricted-access secure master dataset. All biospecimens and study data will be coded and stored only with study IDs for data analysis. If you change your mind later and decide not to let us use your biospecimens or data for other projects, you can contact us and we will remove you from the list.

We are ***seeking consent now and will not recontact*** you for the following activities:

- **Additional analyses of stored biospecimens related to this PFAS research:** After we test your blood and urine, there may be some left over. Because new scientific knowledge, tests, or methods may arise, we would like to save this leftover blood and urine for additional analyses on exposures or health conditions related to PFAS. We do not expect the results of these additional or future research tests to be clinically important to your health and we are not planning to report the individual test results to you.

- **Future analyses by outside investigators:** In addition, ATSDR/[institution name] may release your **de-identified research datasets or de-identified blood and urine** samples for future studies related to PFAS to outside investigators under a data use agreement that will prohibit any attempt to identify you as a research subject. In this case, your individual test results will not be reported to you.

We would like ***to keep your contact information for future studies.*** We would like to recontact you to get additional consent for the following types of activities:

> **Studies that require collection of additional data or biospecimens.** After we complete this study we may conduct new research studies. At that time, we may ask your consent to include you, and your data or leftover biospecimens from this current study. We'd like to contact you at that time.

Your stored biospecimens will not be used for any commercial activities for profit. In addition, we do not anticipate your biospecimens to be used for whole genome sequencing (you would need to be recontacted to consent for such tests). All future analyses and studies must adhere to IRB review requirements.

If you do not understand what we are asking you to do, feel free to ask questions now. If you have no further questions and agree to be in this study, please sign the permission and assent form below.

ADULT INFORMED CONSENT (SIGNATURE PAGE 1 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled:*
"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): a multi-site cross-sectional study."

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____| (alias)
Child Study ID No. |_____|

I have read and/or have been told about the purpose of the study. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I choose to take part in the study.

By signing below, I agree to the parts of the Multi-site Study that I have checked below:

[__] Answer study questions.

[__] Allow ATSDR/[institution name] to review my medical records.

[__] Give ATSDR/ institution name a copy of my PFAS Blood Testing Program results if available; **or** give ATSDR/ institution name permission to get my child's results (if available); [__] I have not participated in a PFAS Blood Testing Program.

[__] Provide a blood sample and have it tested.

[__] Provide a urine sample and have it stored.

_____
Adult's Name (Print)

_____
Adult's Signature Date

|__|__|__| - |__|__|__| - |__|__|__|__|
Adult's Social Security Number

Participant Initials: _____

ADULT INFORMED CONSENT (SIGNATURE PAGE 2 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled:*
"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): a multi-site cross-sectional study."
CDC Protocol #XXXX

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____| (alias)
Child Study ID No. |_____|

I have read and/or have been told about ATSDR's plans for using my study data and leftover biospecimens in the future. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I understand that ATSDR and [institution name] will follow CDC IRB requirements for these additional analyses or new studies.

By signing below, I agree to the additional uses of my Multi-site Study data and leftover biospecimens that I have checked below:

- [__] ATSDR and [institution name] can use my child's study data and his or her leftover blood and urine for additional analyses related PFAS.
- [__] I understand that ATSDR and [institution name] can share my child's de-identified data and leftover biospecimens with outside investigators for future research related to PFAS.
- [__] ATSDR and [institution name] can contact me about new studies.

_____
Adult's Name (Print)

_____
Adult's Signature Date

Participant Initials: _____

Multi-site Study
Permission for Medical Record Abstraction
Flesch-Kincaid Readability Score – 11.7

Attachment 7b5.

Parent/Child/Adult Permission for Medical Record Abstraction
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR)
MULTI-SITE STUDY

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____|
Child Study ID No. |_____|

I authorize this health care provider or organization to release protected health information (PHI) for the uses listed below:

Information to be released by:	**Information to be released to:**
(Name of health care provider, health plan, or health care clearing house)	Marian Pavuk, MD, PhD, Principal Investigator (Name of person or organization)
(Address)	ATSDR Division of Toxicology and Human Health Sciences (DTHHS) 1600 Clifton Road, NE Mail Stop – F57 (Address) Atlanta, Georgia 30341
(Phone number)	770-488-3671 (Phone number)

The information is released for the following uses:

ATSDR is asking providers to verify diagnosis or treatment of certain health conditions and outcomes for the named individual. ATSDR lists the conditions on the back of this form.

ATSDR will not ask for the release of PHI about alcohol or drug abuse treatment, genetics, and about reportable diseases, including sexually transmitted diseases and HIV-AIDS.

By signing below, I understand that:

- I do not have to sign this authorization.
- My authorization will automatically end at the end of the study; or
- I have the right to end my authorization at any time by writing a letter to this office.
- Ending my authorization will not affect any earlier release of PHI.
- Ending my authorization will not bar me from taking part in the study.
- Under my authorization, I have a right to look at or copy any release of PHI.
- I have a right to a copy of this authorization.
- No study reports will reveal my identity.

_____ **(Signature of Individual or Authorized Representative)**	_____ **(Print Name of Individual)**
(Representative's Legal Authority to Individual)	**(Print Name of Authorized Representative)**
(Today's Date)	**(Address)**
(Phone Number)	
(Date of Birth of Individual)	|___|___|___| - |___|___|___| - |___|___|___|___| **(Social Security Number of Individual)**

The Privacy Rule issued under Health Insurance Portability and Accountability Act (HIPAA) is a regulation that provides protection for the privacy of certain individually identifiable health data ("protected health information"). HIPAA applies to covered entities, including health care providers who conduct electronic transactions, health plans (both public and private), and healthcare clearinghouses. CDC is generally not a covered entity; it is a public health authority. CDC/ATSDR may receive protected health information from covered entities, because CDC is a public health authority authorized by law to receive such information for public health purposes. Covered entities may, but are not required to, provide protected health information to CDC.

Participant Initials: _____

ATSDR or [institution name] may send a medical record abstraction form to be completed by the health care provider, health plan, or health care clearing house that you indicate on this form. Alternatively, ATSDR and NCEH staff or contractors may perform the medical record abstraction.

ATSDR and [institution name] are seeking information on the date of diagnosis or first treatment for the following health conditions (except as shown on Page 1). ATSDR and [institution name] are also seeking information if the individual is currently receiving treatment for these health conditions:

Diagnosis or Treatment of Health Conditions	***Adult***	***Child***
Osteoarthritis	√	--
Osteopenia and osteoporosis	√	--
Endometriosis	√	--
Heart Disease	√	--
Hypertension (including pregnancy-induced hypertension)	√	√
Autoimmune diseases (including ulcerative colitis, rheumatoid arthritis, lupus, and multiple sclerosis)	√	√
Diabetes (including gestational diabetes)	√	√
Kidney Function (including kidney disease)	√	√
Lipid Disorder (including high cholesterol)	√	√
Thyroid Hormones	√	√
Liver Function (including liver disease)	√	√
Immune Response and Inflammation	√	√
Hypersensitivity-related outcomes (including asthma, atopic dermatitis)	--	√
Antibody responses to rubella, mumps, and diphtheria vaccines	--	√
Sex hormones, growth, and maturation	--	√
Neurodevelopmental outcomes (lower intelligence quotient (full scale IQ), attention-deficit and hyperactivity disorder (ADHD).	--	√

Multi-site Study
Study Fact Sheet
Flesch-Kincaid Readability Score – 6.2

Attachment 7c.

Agency for Toxic Substances and Disease Registry
[Insert Investigators' Institution Name]

Multi-site Study Fact Sheet

What is this new study about? The Agency for Toxic Substances and Disease Registry (ATSDR) and [insert institution name] wants to learn how per- and polyfluoroalkyl substances (PFAS) in drinking water may have affected the health of [insert site] residents.

Who wants to know these things? Researchers from [insert study investigators institution name] are conducting this study. ATSDR is funding the study. The [insert state] Department of Health and Human Services (NH DHHS) is helping to recruit people for the Multi-site Study.

Why does ATSDR want me to join? [Insert study investigators institution name] is inviting adults, ≥ 18 years, and children, 4-17 years, with their parent, to take part in the Multi-site Study. ATSDR and [institution name] are inviting the following groups of people.

ATSDR and its research partners plan to recruit at least 6,000 adults and 2,000 children for the Multi-site Study. Those person had to reside in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. Persons who were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

It is best if the mother takes part with her child. That is because we will ask lots of questions about her child's exposures, especially about her pregnancy and breastfeeding. If another parent enrolls with his or her child, that is OK. We might need to ask a few more questions about the mother's history.

You might be eligible to take part as both an adult and as a parent. As a parent, you also might be eligible to enroll with more than one child. Either is OK.

If I decide to take part in this study, how can I join? We invite you to call [institution name] at [xxx-xxx-xxxx] to let us know you want to take part. Trained staff will ask you a few questions to make sure you are eligible. Since this is a study only about PFAS in drinking water, people who ever worked with PFAS chemicals at their jobs cannot take part. Eligible females who are pregnant may enroll; however, the federal regulations do not allow people who are in prison or under house arrest to take part in this type of study. If we find you eligible, ATSDR will make an appointment for you. We will mail you an appointment packet to help you get ready.

Where will I go to take part? We are offering appointments at our central study office at [xxxxx address]. The appointment will take about 45 minutes for adults and about 2 hours for children.

It is hard for me to come to the office. Can I still take part? If your house is within a one-hour drive from the study office, we can set up home visit.

How do I get ready for my appointment? We will provide a packet with instructions on how to prepare for the appointment.

- On the morning of the appointment, we request that you collect a clean first morning voided urine sample. Bring it to the appointment.
- We also request that you not eat for at least 8-hours before your appointment so that we can collect a fasting blood sample.
- If you are taking any medications or dietary supplements, we request that you bring them to the appointment. For your child, we will ask the dates of his or her vaccinations.

Why do I have to sign the consent form? By signing the consent form, you agree to be part of this study. We are required to have your signed consent form before we start any part of the study.

In addition to doing the parts of the study, you may have a health condition that we would like to ask your doctor to verify. ATSDR and [institution name] would also like to check a child's school records to compare to the child's assessments. We'd like your consent for [institution name] to get this additional information. This will improve the quality of the study results.

What will happen at my appointment? After you consent to take part in the Multi-site Study:

- We will measure your height, weight, waist, hip, and blood pressure.
- We will take in your urine sample, which you collect that morning.
- We will collect a fasting blood sample. A trained phlebotomist will draw a small amount of blood from a vein in your arm (about 5 teaspoons for children and 7 teaspoons for adults). We will label your samples with a study ID only.

  If we find that you have of a medical condition that will interfere with a blood draw or blood test, you may not be able to take part in all parts of the study. However, you can still do the interviews and have a weight, height, waist, hip, and blood pressure measured.
- The questionnaire about your exposure and medical history should take about 30 minutes to complete. If you are a parent who also enrolled as an adult, [institution name] will give you a 15-minute questionnaire about your child.
- If you are a parent, we will also ask you to complete an assessment of your child's attention and behaviors. It should take about 15 minutes.
- Trained professionals will give your child the behavioral assessments. Although some age groups will only need 30 to 60 minutes, the testing will take about 90 minutes for most children. The tests will be paced and should not be tiring for your child.

Can I do the interview by telephone? No. All parts of the study must be done face-to-face. We need to interview everyone the same way.

Can someone else interview for me? No. It is important that we interview only people who are eligible. Of course, [institution name] will ask parents to answer questions about their children. If you are having trouble speaking, a household member may assist you.

What questions will I be asked? We will ask about your health in general, your family health history, your jobs, and about other ways that you might be exposed to PFAS. For adults, we will also ask about health behaviors such as use of alcohol and tobacco. Parents and children will complete their behavioral assessments as well.

This is personal. Why do you need this information? Your personal information will be kept private. The research staff will combine your answers with everyone else's. We want to know if the health status and blood PFAS are different between groups of people.

What if I don't know how to answer the questions? If you do not know or do not remember the answer, you simply say so.

Will you measure PFAS in my blood? Yes. We will test your blood for the PFAS. We will let you know what your PFAS levels are. If you were part of any previous PFAS Blood Testing Program, we would like to compare those results to the Multi-site Study results.

Will you do other blood tests? Yes. We will test your blood for health markers like cholesterol, liver enzymes, kidney function, sex and thyroid hormones. These markers will help us learn more about how PFAS affect health. Doctors use most of these markers to assess health.

Will you measure PFAS in my urine? Scientists are learning more about PFAS every day. Your urine specimen will be stored until lab methods are developed and the scientific evidence shows which PFAS tests will yield useful results. It might be a year or more before ATSDR and institution name] decide if and which PFAS tests in urine should be done as part of this research study.

How will I learn about my test results? We will send your test results to you in a letter. We think it will be up to two years from the time of your blood draw when we finish all of the tests and send the letters. If one of your test results means you might have a health problem, we will contact you when the laboratory sends us the result.

How are you going to use my information? We will write reports or scientific articles about the study results. We will combine everyone's results to get a picture of the health issues of people in [insert site] and how they relate to PFAS. These reports or articles will be made public after the study is finished. The results in these reports will be presented in a way that people who take part cannot be identified.

What are the risks of taking part in the study? Your only risk from taking part in the study are from having your blood drawn. It may hurt a little when the blood is drawn and you may have some bruising afterward where the blood is drawn. We will do our best to avoid these problems.

Are there any costs to my taking part? You do not have to pay to be part of this study. The blood tests are free.

What benefit do I get for taking part? While there are no direct benefits for taking part in the study, we will give you the results of your blood PFAS and health tests that you may find helpful to share with your child's doctor. We also think that the study will help the affected communities better understand the connection between PFAS and health.

Will I be paid to take part? The study has different parts. We will give you a $25 gift card if you complete the questionnaire. We will give you a $25 gift card if you complete your body and blood pressure measures and donate blood and urine. If you are a parent with a child who completes a battery of assessment tests, we will give you a $25 gift card. This is our way of thanking you for taking part in the study.

Can I change my mind about taking part after I start? You can always choose whether you want to be part of this study, or not. You can stop at any time by telling the study staff that you do not want to go on. You also can refuse to answer any question or to have your blood drawn or donate urine. There is no penalty for refusal or withdrawal from the study.

Are you trying to sell me something? This study does not have anything to sell or buy. This is a study paid by ATSDR at no cost to you.

How will you protect information I provided? This research is covered under a Certificate of Confidentiality. That means that courts cannot compel ATSDR and [institution name] to reveal your identity, unless you consent to it.

All of the information that you give us will be kept private to the extent allowable by law. We will use a code number instead of your name for your answers and test results. We will keep your records under lock and key at the study office in [insert site]. ATSDR and [insert institution name] will protect any computer files with your information and keep them secure. Only study staff with a need-to-know will have access to your information and test results. Other scientists may request information from this study. If we share the information with them, we will first make sure that you cannot be identified.

How can I get more information about the study? To ask questions about the study call study investigators at [xxx-xxx-xxxx]. For questions about your rights related to this study, contact the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814. Please leave a message about the CDC Protocol No. xxxx, and a brief message about your concern of question.

Attachment 8.

Multi-site Study
Reminder Telephone Script
Flesch-Kincaid Readability Score – 7.6

Multi-site Study
Appointment Reminder Telephone Script

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

[**SHADED TEXT DENOTES INFORMATION COLLECTION**]

HELLO, my name is _____. I am calling on behalf of the [insert study investigators] conducting the "Multi-site PHAS Health Study."

May I speak to *[SELECT NAME FROM CORRECT SCENARIO BELOW]*?

- *ADULT PARTICIPANT*
- *PARENT/GUARDIAN OF CHILD PARTICIPANT*
- *ADULT WHO IS BOTH PARTICIPANT AND PARENT/GUARDIAN OF CHILD PARTICIPANT*

[IF NOT CORRECT PERSON]

- Please let me know the best time we can reach *[NAME]*.
- ***RECORD*** |_____| ***(day)***
  |__|__|/|__|__|/|__|__| ***(date)***
  |__|__|:|__|__| AM PM ***(time)***
- Thank you so much. I will call back then to speak to *[NAME]*.

[IF CORRECT PERSON] Hello. I am calling to remind you that [YOU have/ YOUR CHILD has/YOU and YOUR CHILD have] an appointment scheduled on _____ (date) at ____ (time) to participate in the Multi-site Study.

- Our records show that [your appointment is/your child's appointment is/both your appointments are] scheduled to take place at [our clinic office/your home at (verbally repeat address on file)/your child's home at (verbally repeat address on file)]. Is that correct?
  - o **YES**
  - o **NO** > OK, let me record the correct information for your appointment(s).
    - ***CORRECTED APPOINTMENT LOCATION –***
      - ***OFFICE***
      - ***HOME > Verify address > If incorrect, go to Attachments 8 and 12 to update.***
    - ***CORRECTED DATE AND TIME***
      RECORD |_____| ***(day)***
      |__|__|/|__|__|/|__|__| ***(date)***
      |__|__|:|__|__| **AM PM** ***(time)***

Attachment 8.

Thank you so much. To get you prepared for the appointment, I have just one more question about some medicines [you/your child/both you and your child] might be taking now.

- Are [you/your child/either you or your child] taking any medication for diabetes?
  - **YES** > Because [you/your child/both you and your child] take diabetes medication, we want to give special instructions about your appointment(s). We will be mailing out a reminder card. If [you/your child/both you and your child] can fast and take your medication without eating, please do. If [you/your child/both you and your child] cannot fast, please eat, and take your medications as usual. Please eat only fat-free or low-fat food, if possible. Please write down the time and the foods you eat. You may drink water during this time. *[GO TO CLOSING REMARKS]*

  - **NO** > Please remember not to eat for at least 8 hours before your appointment. You may drink water during this time. We also want to remind you to collect your urine sample(s) that morning and bring it. We will be mailing out a reminder card. *[GO TO CLOSING REMARKS]*

[CLOSING REMARKS FOR OFFICE VISIT] Don't forget to bring all your medications with you to your appointment. *[For children* – Don't forget to note the dates of (his/her) vaccinations. We will be asking about that.] Please let us know as soon as possible if you have to cancel your appointment. You can call at [STUDY TELEPHONE NUMBER] if you have to cancel your appointment. Thank you for being part of our study.

[CLOSING REMARKS FOR HOME VISIT] Don't forget to gather all your medications for your appointment. *[For children* – Don't forget to note the dates of (his/her) vaccinations. We will be asking about that.] Please let us know as soon as possible if you have to cancel your appointment. You can call at [STUDY TELEPHONE NUMBER] if you have to cancel your appointment. Thank you for being part of our study.

Note: This script cannot be used as a voicemail message.

Attachment 9

Multi-site Study
Appointment tracking form

Adult Study ID No. |_____| **Parent Study ID No.** |_____| **Child Study ID No.** |_____|	**Order Assigned by Coordinator**	**Comments**	**Completed**		**Clinic or In-field**
			Date mm/dd/yy	*Time hh:mm*	*0 clinic 1 home*
Informed Consent	1.		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Update Contact Information	2.		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Blood Draw/ Urine Collection	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Assess Current Medication	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Body Measurements	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Blood Pressure Measurements	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Questionnaire	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Neurobehavioral Battery	[__]		|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*
Received Gift Card	9.	**TOTAL AMOUNT RECEIVED:** [___] $25 [___] $50 [___] $75 **SIGNATURE:**	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| *AM PM*	*0 1*

Attachment 10.

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Multi-site Study
Update Contact Information Hardcopy Form

ATSDR estimates the average public reporting burden for this collection of information as 5 minute per response, including the time for reviewing instructions, searching existing data/information sources, gathering and maintaining the data/information needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB Control Number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC/ATSDR Information Collection Review Office, 1600 Clifton Road NE, MS D-74, Atlanta, Georgia 30333; ATTN: PRA (0923-xxxx).

Adult Study ID No. |_____|

Parent Study ID No. |_____| **AND Child Study ID No.** |_____|

Name:		
Street Address:		
City:		
State:		
Zip Code:		
Work Phone:		
Home Phone		
Cell Phone:		
Email:		

SCRIPT: We may want to contact you again to ask some clarifying questions. Keeping in mind that people move, we would like to get a little more information to help us locate [you/and your child] in the future. In case you move to another residence, will you give us the names and contact information of three people who live outside of your household who would always know how to find you?

___*Yes*

___*No*

Fill out the table below. Circle appropriate response and ask the respondent to specify as directed. Complete the information for the first person completely before asking about the next person.

Attachment 10.

	Person 1	Person 2	Person 3
What is the first and last name of the first/second/third person?	First name: Last name:	First name: Last name:	First name: Last name:
What is the address of the first/second/third person?	Street no. and name _____ City State Zip code	Street no. and name _____ City State Zip code	Street no. and name _____ City State Zip code
What is the phone number, including area code of the first/second/third person? (CIRCLE TYPE)	(_ _ _)_ _ _ - _ _ _ _ (CIRCLE TYPE) Work Home Cell	(_ _ _)_ _ _ - _ _ _ _ (CIRCLE TYPE) Work Home Cell	(_ _ _)_ _ _ - _ _ _ _ (CIRCLE TYPE) Work Home Cell
What is the email address of the first/second/third person?			
What is the first/second/ third person's relationship to you?	Parent Child Sibling Other relative (Please specify) _____ Other (Please specify) _____	Parent Child Sibling Other relative (Please specify) _____ Other (Please specify) _____	Parent Child Sibling Other relative (Please specify) _____ Other (Please specify) _____

Attachment 11.

Multi-site Study
Medication List

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Note: It is important to ask the participants to bring in all medications used regularly during the past two weeks before the office or the home visit for the physical measurements and blood draw. This includes both Over-the-Counter and Prescription Medications. These include pills, liquid medications, skin patches, eye drops, salves, inhalers and injections, as well as cold or allergy medications, herbal remedies, aspirin, ointments, vitamin supplements, Tylenol and Motrin are all examples. They could possibly affect the test and lab results.

1. Ask the participant about all medications, including over the counter, herbal remedies, fish oil, and vitamin or dietary supplements.

2. If the participant refuses to provide the medications or to allow you to record them, write "refused" on the Medication List and proceed to next step.

3. Provide dose (e.g. 50 mg), frequency (e.g. twice a day), and route (e.g. by mouth). Add lines as necessary.

4. Ask about any medications not visible at the office or the home visit, such as those needing refrigeration.

Interviewer: |_____|

Adult Study ID No. |_____|

Parent Study ID No. |_____|

Child Study ID No. |_____|

Recording Date: |__|__|/|__|__|/|__|__|

	Name of Medication	Dose	Frequency	Route	Last Dose
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					

Attachment 11.

12					
13					

Note: Add – use additional lines as necessary to record all participant's medication.

Attachment 12.

Multi-site Study – Manual of Procedures (Placeholder)

Attachment 13.

Multi-site Study
Body and Blood Pressure Measures Form

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Adult Study ID No. |_____| **OR** **Child Study ID No.** |_____|

Date: |__|__|/|__|__|/|__|__| Time: |__|__|:|__|__| ☐ AM ☐ PM

PHYSICAL MEASUREMENTS

Height: |__|' |__|__|. |__|" (Nearest ½")

Modification to Procedure?

☐ Yes ☐ No

Reason:_____

_____

Weight: |__|__|__| lbs.

Modification to Procedure?

☐ Yes ☐ No

Reason:_____

BMI: |__|__|. |__| kg/m^2

Abdominal Girth: |__|__|__|" (inches)

Hip: |__|__|__| (inches)

Waist: |__|__|__| (inches)

Attachment 13.

BLOOD PRESSURE

Blood Pressure:

1. |__|__|__|/|__|__|__| (mm Hg)

2. |__|__|__|/|__|__|__| (mm Hg)

3. |__|__|__|/|__|__|__| (mm Hg)

Modification to Procedure?

☐ Yes ☐ No

Reason:_____

_____

This chart reflects blood pressure categories defined by the American Heart Association.
*Defined by American Heart Association

Check One	BP Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	Action*
	Normal	<120	and	<80	No referral
	Elevated	120-129	or	<80	No referral
	Hypertension (Stage 1)	130-139	or	80-89	See a physician within 2 months
	Hypertension (Stage 2)	≥ 140	or	≥ 90	See a physician within 1 month
	Hypertensive Crisis	>180	or	>120	See physician immediately

Classification of BP in Adults Aged 18 Years or Older.

* If systolic and diastolic categories are different, the shorter recommended time for recheck and referral takes precedence. If two or three repeated systolic or diastolic measurements are abnormal but fall in different categories, determine the appropriate category based on their average.

If referral made, to whom (*mark one*):

☐ No referral made

☐ Emergency Room (Phone: xxx-xxx-xxxx)

☐ Participant's Provider (Name: |_____|; Phone: |__|__|__|-|__|__|__|-|__|__|__|__|)

☐ Referral 3 (Phone: xxx-xxx-xxxx)

☐ Referral 4 (Phone: xxx-xxx-xxxx)

Agency for Toxic Substances and Disease Registry

HUMAN HEALTH EFFECTS OF DRINKING WATER EXPOSURES TO PER- AND POLY-FLUOROALKYL SUBSTANCES (PFAS): A MULTI-SITE CROSS-SECTIONAL STUDY

"Multi-site Study"

Manual of Procedures

[DATE]

(PLACEHOLDER: this manual is under development)

Attachment 15.

Multi-site Study Child Questionnaire – Long Form

(best completed by the child's birth mother who is not an adult participant)

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Parent Study ID No. |_____|
Child Study ID No. |_____|

Section A: Demographic Information

A1. What is your relationship to your child?

___Birth mother

___Birth father

___Adoptive mother

___Adoptive father

___Legal guardian

___Other relationship: specify _____

___Refused to answer

A2. What is your child's sex?

___Male

___Female

___Refused to answer

A3. What is your child's date of birth?

_____(MM/DD/YYYY)

___Refused to answer

A4. Do you consider your child to be Hispanic or Latino?

___Yes

___No

___Refused to answer

A5. What race do you consider your child to be? Mark all that apply.

___American Indian or Alaska Native

___Asian

___Black or African American

___Native Hawaiian or Other Pacific Islander

___White

___Refused to answer

A6. What is the highest grade level of education your child has completed?

___grade

A.7 What is the highest level of education you completed?

___Less than high school
___Some high school
___High school graduate or equivalent (GED)
___Some university/college
___Technical or trade school
___University/college graduate
___Graduate school or higher

A8. What is the child's household income (from all sources)?

___Less than $25,000
___$25,000 to $69,000
___$70,000 to $149,000
___More than $150,000
___Don't know
___Refused to answer

A9. During the last 12 months did the child have any kind of health insurance?

___Yes
___No
___Don't know
___Refused

Section B: Residential History and Drinking Water Exposures

This next set of questions is about the child and the child's birth mother. If you are not her, we can follow up after this interview with a quick phone call to complete the questionnaire.

B1. What is the main source of tap water in your home?

____Public water system

____Private well

____Other: specify _____

____Don't know

____Refused to answer

B2. On average, how many 8 oz. cups of tap water or beverages prepared with tap water does your child currently drink per day at home?

___ cups

___Doesn't drink tap water

___Don't know

___Refused to answer

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.

B3. On average, how many 8 oz. cups of tap water or beverages prepared with tap water do you currently drink per day at home?

___ cups

___Doesn't drink tap water

___Don't know

___Refused to answer

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.

B4. What was your previous address?

Street _____ Apt _____

City _____ State __ __ Zip Code: _____

B5. When did you move into your previous address? Month____ Year_____

B6. What was the main source of tap water at that address?

____Public water system

____Private well

____Other: specify _____

____Don't know

____Refused to answer

B7. On average, how many 8 oz. cups of tap water or beverages prepared with tap water did your child drink per day when living at your previous address?

___ cups

___Don't drink tap water
___Don't know
___Refused to answer
___Your child did not live at this address

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.

B8. Have you or your child lived at any other address since January 2000?
___ Yes
___No → go to Section C
___Don't know → go to Section C
___Refused to answer → go to Section C

B9. Please fill out the table below for these other residences where you or your child lived since January 2000.

Street Address, City, State	Did your child live at this address?	Your child's average consumption of tap water per day (# cups) at this address	Move in (mm/yy)	Main source of tap water at this address (public water system or private well?)

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.

B10. When [you were/the child's birth mother was] pregnant with your child, on average how many 8 oz. cups of tap water or beverages prepared with tap water did [you/she] drink per day?
___ cups
___Didn't drink tap water
___Don't know
___Refused to answer

B11. When [you were//the child's birth mother was] breastfeeding your child, on average how many 8 oz. cups of tap water or beverages prepared with tap water did [you/she] drink per day?
___ cups
___Didn't drink tap water
___Don't know
___Refused to answer
___Did not breastfeed my child

Section C: History of Potential Exposure Modifiers

This next set of questions is about the child and the child's birth mother. If you are not her, we can follow up after this interview with a quick phone call to complete the questionnaire.

C1. [Have you/Has the birth mother] ever had a blood transfusion?
___Yes → Please specify how many times you had a blood transfusion_____
___No →go to Question C3
___Don't know →go to Question C3
___Refused to answer →go to Question C3

C2. When did [you/she] last have a blood transfusion?
_____month/year

C3. Has your child ever had a blood transfusion?
___Yes → Please specify how many times your child had a blood transfusion_____
___No →go to Question C5
___Don't know →go to Question C5
___Refused to answer →go to Question C5

C4. When did your child last have a blood transfusion?
_____month/year

C5. [Have you/Has the birth mother] ever donated blood?
___Yes
___No →go to Question C8
___Don't know →go to Question C8
___Refused to answer →go to Question C8

C6. When did [you/the birth mother] last donate blood?
_____ Month/Year

C7. On average, how often [do you/does the birth mother] donate blood in a year?

_____

C8. Has your child ever donated blood?

___Yes → Please specify how many times your child has donated blood_____

___No →go to Question D1.

___Don't know →go to Question D1.

___Refused to answer →go to Question D1.

C9. When did your child last donate blood?

_____ Month/Year

C10. On average, how often does your child donate blood in a year?

_____ times

Section D: Occupational History

This next set of questions is about the child's birth mother. If you are not her, we can follow up after this interview with a quick phone call to complete the questionnaire.

D1. What is [your/the child's birth mother's] primary occupation?

_____

D2. On average, how many 8 oz. cups of tap water or beverages prepared with tap water do you currently drink per day at work?

___ cups

___Don't drink tap water

___Don't know

___Refused to answer

D3. Please fill out the table below for each job that lasted one month or more starting from the present and working back to 2000.

Job information	Job 1	Job 2	Job 3	Job 4
a. Where did the child's mother work (City, State)				
b. Name of the employer				
c. Start date (month, year)				
d. End date (month, year)				
e. Job title/description				
f. Did the child's mother work as a firefighter? If the child's mother worked as a firefighter, did she come into contact with firefighting foam used for fires that involve flammable liquids (also known as Class B fires)?	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____
g. Was this job in any of the following industries?	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no
h. Did the child's mother work with or around any chemicals at this job such as solvents, metals, asbestos, or pesticides?	Yes (Please specify the chemical) _______________ No ____ Don't know___	Yes (Please specify the chemical) ________________ No___ n't know___	Yes (Please specify the chemical) _______________ No____ Don't know____	Yes (Please specify the chemical) _______________ No____ Don't know____
i. Did the child's mother work with radiation?	Yes___ No____	Yes___ No____	Yes___ No____	Yes___ No____

Job information	Job 5	Job 6	Job 7	Job 8
a. Where did the child's mother work (City, State)				
b. Name of the employer				
c. Start date (month, year)				
d. End date (month, year)				
e. Job title/description				
f. Did child's mother work as a firefighter? If child's mother worked as a firefighter, did she come into contact with firefighting foam used for fires that involve flammable liquids (also known as Class B fires)?	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____
g. Was this job in any of the following industries?	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no
h. Did child's mother work with or around any chemicals at this job such as solvents, metals, asbestos, or pesticides?	Yes (Please specify the chemical) _______________ No ____ Don't know___	Yes (Please specify the chemical) ________________ No___ n't know___	Yes (Please specify the chemical) _______________ No____ Don't know____	Yes (Please specify the chemical) _______________ No____ Don't know____
i. Did child's mother work with radiation?	Yes___ No____	Yes___ No____	Yes___ No____	Yes___ No____

Job information	Job 9	Job 10	Job 11	Job 12
a. Where did child's mother work (City, State)				
b. Name of the employer				
c. Start date (month, year)				
d. End date (month, year)				
e. Job title/description				
f. Did child's mother work as a firefighter? If child's mother worked as a firefighter, did she come into contact with firefighting foam used for fires that involve flammable liquids (also known as Class B fires)?	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____	Yes___ No____ go to question g. Yes____ No____ Don't know____
g. Was this job in any of the following industries?	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no	Manufacturing of nonstick cookware ____yes ____no Manufacturing of stain resistant coatings used on carpets, upholstery, and other fabrics _____yes ____no Manufacturing of water resistant clothing _____yes ____no
h. Did child's mother work with or around any chemicals at this job such as solvents, metals, asbestos, or pesticides?	Yes (Please specify the chemical) ________________ No ____ Don't know___	Yes (Please specify the chemical) _________________ No___ n't know___	Yes (Please specify the chemical) ________________ No____ Don't know____	Yes (Please specify the chemical) ________________ No____ Don't know____
i. Did child's mother work with radiation?	Yes___ No____	Yes___ No____	Yes___ No____	Yes___ No____

This next questions are about your child.

D4. Has your child been employed for at least one month at a job?
____Yes
____No →go to Section E.

Job information	Job 1	Job 2	Job 3
a. Where did your child work? (City, State)			
b. Name of the employer			
c. Start date (month, year)			
d. End date (month, year)			
e. Job title/description			
f. Did your child work with or around radiation or any chemicals at this job such as solvents, metals, asbestos, or pesticides?	Yes (Please specify) _____ No ____ Don't know___	Yes (Please specify) _____ No___ on't know____	Yes (Please specify) _____ No____ Don't know____

D5. On average how many 8 oz. cups of tap water or beverages prepared with tap water did [he/she] drink per day at work?
___ cups
___Didn't drink tap water
___Don't know
___Refused to answer

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

Section E: Child's Daycare/School History

E1. Did your child attend day care?
____Yes
____No → go to Question E3
____Don't know → go to Question E3
____Refused to answer → go to Question E3

E2. Please fill out the table below for the day care centers your child attended.

Day care (name)	Street Address, City, State	Start Date (mm/yy)	End Date (mm/yy)	Child's average consumption of tap water per day (# cups)

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

E3. Please fill out the table below for the schools your child has attended. If your child was home schooled, please go to Section F

School (name)	Street Address, City, State	Start Date (mm/yy)	End Date (mm/yy)	Child's average consumption of tap water per day (# cups)

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

Section F: Child's Medical History

F1. Have you ever been told by a doctor or other health care provider that your child has or had any of the following medical conditions? Fill out the table below. Circle appropriate response and ask the respondent to specify as directed.

Medical condition		If yes, what year was your child diagnosed?
a. Cancer?	Yes (Please specify) _____ No Don't know	_ _ _ _ year
b. Allergies?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
c. Atopic dermatitis/eczema?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
d. Asthma?	Yes No Don't know	_ _ _ _ year
e. Chronic stuffy/runny nose (rhinitis/sinusitis)?	Yes No Don't know	_ _ _ _ year
f. High cholesterol?	Yes No Don't know	_ _ _ _ year
g. Thyroid disease?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
h. Delayed puberty?	Yes (Please specify) _____ No Don't know	_ _ _ _ year
i. Obesity?	Yes No Don't know	_ _ _ _ year
j. Lupus	Yes No Don't know	_ _ _ _ year
k. Celiac disease	Yes No Don't know	_ _ _ _ year
l. Crohn's disease	Yes No Don't know	_ _ _ _ year
m. Diabetes	Yes, Type 1 Yes, Type 2 Yes, Type unknown No Don't know	_ _ _ _ year

	Medical condition		If yes, what year was your child diagnosed?
n.	Scleroderma	Yes No Don't know	_ _ _ _ year
o.	Attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)?	Yes No → go to p Don't know → go to p	_ _ _ _ year
p.	How is your child treated for ADHD or ADD?		_ _ _ _ year
q.	Other learning or behavioral problems?	Yes (Please specify) _____ No → go to Question F2. Don't know → go to Question F2.	_ _ _ _ year
r.	How is your child treated for their learning or behavioral problems?		

F2. What age was your child last vaccinated for:

Diphtheria, Tetanus, Pertussis ("DTaP") age_____ Don't know ___ never was vaccinated ____
"Tdap" booster Tetanus, Diptheria, Pertussis age_____ Don't know ___ never was vaccinated ____
Measles, Mumps, Rubella ("MMR") age_____ Don't know ___ never was vaccinated ____
Tetanus shot (for a puncture wound or cut) age_____ Don't know ___ never was vaccinated ____

FOR GIRLS ONLY

F3. Has your daughter ever used an oral contraceptive ("birth control pill")?
___Yes
___No → go to Question F5
___Don't know → go to Question F5
___Refused to answer → go to Question F5

F4. When did your daughter last use an oral contraceptive ("birth control pill")?

_____ Month/Year

F5. At what age did your daughter begin menstruation (have her first period)?
___Age
___Has not yet begun to menstruate → go to Section G
___Don't know

F6. Does your daughter's period occur regularly (every month)?
___Yes
___No, it is irregular
___No, she does not have a period → go to Question F10
___Don't know → go to Question F10

F7. How many days has been your daughter's cycle on average during the last year?
___>26 days
___27-29 days
___30-32
___>32 days
___Don't know

F8. Can you characterize your daughter's usual period flow during the last year?
___Light
___Medium
___Heavy
___Don't know

F9. When was your daughter's last period before this study blood draw?
Date:_____
___Don't know

F10. Has your daughter ever been pregnant?
___Yes
___No → go to Section F
___Don't Know → go to Section F
___Refused to answer → go to Section F

F11. How many times has your daughter been pregnant?
_____

	Pregnancy #1	**Pregnancy #2**	**Pregnancy #3**
a. What month and year did this pregnancy start?	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _
b. What month and year did this pregnancy end?	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _
c. Did the pregnancy result in a live birth?	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know
d. Did your daughter breastfeed the child?	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know
e. How long did your daughter breastfeed the child?	_ _ months	_ _ months	_ _ months
f. When did your daughter stop breastfeeding the child?	__month ____ year	__month ____ year	__month ____ year
g. Did a doctor or nurse say that your daughter had pre-eclampsia during her pregnancy?	Yes No Don't know	Yes No Don't know	Yes No Don't know
h. Did a doctor or nurse say that your daughter had pregnancy-induced hypertension?	Yes No Don't know	Yes No Don't know	Yes No Don't know
i. Did a doctor or nurse say that your daughter had gestational diabetes?	Yes No	Yes No	Yes No

	Don't know	Don't know	Don't know

Section G. Mother's Pregnancy History

Starting with the pregnancy of your child in this study (Pregnancy 1), and including up to three of [your/the birth mother's] previous pregnancies, please fill out the table below. Circle the appropriate response.

	Pregnancy 1	**Pregnancy 2**	**Pregnancy 3**	**Pregnancy 4**
a. What month and year did this pregnancy start?	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _
b. What month and year did this pregnancy end?	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _	_ _ / _ _ _ _
c. Did the pregnancy result in a live birth?	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know
d. Did [you/the child's mother] breastfed this child/these children?	Yes No → go to Part j. Don't know	Yes No → go to Part j. Don't know	Yes No → go to Part j. Don't know	Yes No → go to Part j. Don't know
e. How long did [you/the child's mother] breastfeed this child/these children?	_ _ months	_ _ months	_ _ months	_ _ months
f. When did [you/the child's mother] stop breastfeeding this child/these children?	__month ____ year	__month ____ year	__month ____ year	__month ____ year
g. Did a doctor or nurse say that [you/the child's mother] had pre-eclampsia during [your/her] pregnancy?	Yes No Don't know	Yes No Don't know	Yes No Don't know	Yes No Don't know
	Pregnancy 1	**Pregnancy 2**	**Pregnancy 3**	**Pregnancy 4**
h. Did a doctor or nurse say that [you/the child's mother] had pregnancy-induced hypertension?	Yes No Don't know	Yes No Don't know	Yes No Don't know	Yes No Don't know
i. Did a doctor or nurse say that [you/the child's mother] had gestational diabetes?	Yes No Don't know	Yes No Don't know	Yes No Don't know	Yes No Don't know

Section H: Family Medical History

H1. Do any of your child's blood relatives – - currently have cancer or have they had cancer? We are only asking about family members who are blood relatives: grandparents, parents, and siblings.

___Yes
___No → go to Question H4

H2. In all, how many family members (not including yourself) have had (or now have) cancer?
___number
___Don't know

H3. Now I'd like to get more information about each of your child's relatives who had/has cancer. Fill out the table below. Circle appropriate response and ask the respondent to specify as directed. Complete the information for the first relative completely before asking about the next relative. Once information about all blood relatives with cancer has been collected, go to Question H4.

	First relative	**Second relative**	**Third relative**	**Fourth relative**
a. Was this relative a . . .	Grandparent Parent Sibling	Grandparent Parent Sibling	Grandparent Parent Siblin	Grandparent Parent Sibling
b. What type of cancer did this relative have	_____	_____	_____	_____
c. Is this relative	Living Deceased	Living Deceased	Living Deceased	Living Deceased
d. What year was your relative diagnosed with cancer?	_ _ _ _ Don't know	_ _ _ _ Don't know	_ _ _ _ Don't know	_ _ _ _ Don't know

H4. Have any of your child's blood relatives - grandparents, parents, or siblings - ever been told by a health professional that they have or had any of the following conditions? Fill out the table below. Circle appropriate response and ask the respondent to specify as directed.

Medical condition		**If yes, ask: Which relative had this condition?**
a. Allergies	Yes (Please specify)_____ No Don't know	Grandparent Parent Sibling
b. Atopic dermatitis/eczema	Yes No	Grandparent Parent

Medical condition		If yes, ask: Which relative had this condition?
	Don't know	Sibling
c. Asthma?	Yes No Don't know	Grandparent Parent Sibling
d. High Cholesterol	Yes No Don't know	Grandparent Parent Sibling
e. Thyroid disease?	Yes (Please specify) _____ No Don't know	Grandparent Parent Sibling
f. Obesity	Yes No Don't know	Grandparent Parent Sibling
g. Lupus?	Yes No Don't know	Grandparent Parent Sibling
h. Celiac disease?	Yes No Don't know	Grandparent Parent Sibling
i. Crohn's disease?	Yes No Don't know	Grandparent Parent Sibling
j. Diabetes (not related to pregnancy)?	Yes, Type 1 Yes, Type 2 Yes, type unknown No Don't know	Grandparent Parent Sibling
k. Scleroderma	Yes No Don't know	Grandparent Parent Sibling
l. Attention deficit hyperactivity disorder (ADHD or attention deficit disorder (ADD)	Yes No Don't know	Grandparent Parent Sibling
m. Other learning or behavioral problems	Yes No Don't know	Grandparent Parent Sibling

CONCLUSION: That completes this survey. I would like to sincerely thank you for your time.

Attachment 15a.

Multi-site Study Child Questionnaire – Short Form

(best completed by the child's birth mother who is also an adult participant)

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Adult Study ID No. |_____| (alias)
Parent Study ID No. |_____|
Child Study ID No. |_____|

Section A: Demographic Information

A1. What is your relationship to your child?

___Birth mother

___Birth father

___Adoptive mother

___Adoptive father

___Legal guardian

___Other relationship: specify _____

___Refused to answer

A2. What is your child's sex?

___Male

___Female

___Refused to answer

A3. What is your child's date of birth?

_____(MM/DD/YYYY)

___Refused to answer

A4. Do you consider your child to be Hispanic or Latino?

___Yes

___No

___Refused to answer

A5. What race do you consider your child to be? Mark all that apply.

___American Indian or Alaska Native

___Asian

___Black or African American

___Native Hawaiian or Other Pacific Islander

___White

___Refused to answer

A6. What is the highest grade level of education your child has completed?

___grade

A.7 What is the highest level of education you completed?

___Less than high school

___Some high school

___High school graduate or equivalent (GED)

___Some university/college

___Technical or trade school

___University/college graduate

___Graduate school or higher

A8. What is the child's household income (from all sources)?

___Less than $25,000

___$25,000 to $69,000

___$70,000 to $149,000

___More than $150,000

___Don't know

___Refused to answer

A9. During the last 12 months did the child have any kind of health insurance?

___Yes

___No

___Don't know

___Refused

Section B: Residential History and Drinking Water Exposures

B1. On average, how many 8 oz. cups of tap water or beverages prepared with tap water does your child currently drink per day at home?

___ cups
___Didn't drink tap water
___Don't know
___Refused to answer

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

B2. Please fill out the table below for all residences that your child has lived.

Street Address, City, State	Your child's average consumption of tap water per day (# cups) at this address	Move in (mm/yy)	Main source of tap water at this address (public water system or private well?)

B3. When [you were/the child's birth mother was] pregnant with your child, on average how many 8 oz. cups of tap water or beverages prepared with tap water did [you/she] drink per day?

___ cups
___Didn't drink tap water
___Don't know
___Refused to answer

B4. When [you were/the child's birth mother was] breastfeeding your child, on average how many 8 oz. cups of tap water or beverages prepared with tap water did [you/she] drink per day?
___ cups
___Didn't drink tap water
___Don't know
___Refused to answer
___Did not breastfeed my child

Section C: History of Potential Exposure Modifiers

This next set of questions is for the child's birth mother about the child. If you are not her, we can follow up after this interview with a quick phone call to complete the questionnaire.

C1. Has your child ever had a blood transfusion?
___Yes → Please specify how many times your child had a blood transfusion_____
___No →go to Question C3
___Don't know →go to Question C3
___Refused to answer →go to Question C3

C2. When did your child last have a blood transfusion?
_____month/year

C3. Has your child ever donated blood?
___Yes → Please specify how many times your child has donated blood_____
___No →go to Section D.
___Don't know →go to Section D.
___Refused to answer →go to Section D.

C4. When did your child last donate blood?
_____ Month/Year

C5. On average, how often does your child donate blood in a year?
_____

Section D: Occupational History of the Child

This next set of questions is for the child's birth mother about the child. If you are not her, we can follow up after this interview with a quick phone call to complete the questionnaire.

D1. Has your child been employed for at least one month at a job?
____Yes
____No → go to Section E.

Job information	Job 1	Job 2	Job 3
a. Where did your child work? (City, State)			
b. Name of employer			
c. Start date (month, year)			
d. End date (month, year)			
e. Job title/description			
f. Did your child work with or around radiation or any chemicals at this job such as solvents, metals, asbestos, or pesticides?	Yes (Please specify) _____ No ____ Don't know___	Yes (Please specify) _____ No___ on't know____	Yes (Please specify) _____ No____ Don't know____

D2. On average how many 8 oz. cups of tap water or beverages prepared with tap water did [he/she] drink per day at work?
___ cups
___Didn't drink tap water
___Don't know
___Refused to answer

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

Section E: Child's Daycare/School History

E1. Did your child attend day care?
____Yes
____No → go to Question E3
____Don't know → go to Question E3
____Refused to answer → go to Question E3

E2. Please fill out the table below for the day care centers your child attended.

Day care (name)	Street Address, City, State	Start Date (mm/yy)	End Date (mm/yy)	Child's average consumption of tap water per day (# cups)

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

E3. Please fill out the table below for the schools your child has attended. If your child was home schooled, please go to Section F

School (name)	Street Address, City, State	Start Date (mm/yy)	End Date (mm/yy)	Child's average consumption of tap water per day (# cups)

Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)

Section F: Child's Medical History

F1. Have you ever been told by a doctor or other health care provider that your child has or had any of the following medical conditions? Fill out the table below. Circle appropriate response and ask the respondent to specify as directed.

Medical condition		If yes, what year was your child diagnosed?
a. Cancer?	Yes (Please specify) _____ No Don't know	_ _ _ _ year
b. Allergies?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
c. Atopic dermatitis/eczema?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
d. Asthma?	Yes No Don't know	_ _ _ _ year
e. Chronic stuffy/runny nose (rhinitis/sinusitis)?	Yes No Don't know	_ _ _ _ year
f. High cholesterol?	Yes No Don't know	_ _ _ _ year
g. Thyroid disease?	Yes (Please specify)_____ No Don't know	_ _ _ _ year
h. Delayed puberty?	Yes (Please specify) _____ No Don't know	_ _ _ _ year
i. Obesity?	Yes No Don't know	_ _ _ _ year
j. Lupus	Yes No Don't know	_ _ _ _ year
k. Celiac disease	Yes No Don't know	_ _ _ _ year
l. Crohn's disease	Yes No Don't know	_ _ _ _ year
m. Diabetes	Yes, Type 1 Yes, Type 2 Yes, Type unknown No Don't know	_ _ _ _ year

	Medical condition		If yes, what year was your child diagnosed?
n.	Scleroderma	Yes No Don't know	_ _ _ _ year
o.	Attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)?	Yes No → go to p Don't know → go to p	_ _ _ _ year
p.	How is your child treated for ADHD or ADD?		_ _ _ _ year
q.	Other learning or behavioral problems?	Yes (Please specify) _____ No → go to Question B2. Don't know → go to Question B2.	_ _ _ _ year
r.	How is your child treated for their learning or behavioral problems?		

F2.. What age was your child last vaccinated for:

Diphtheria, Tetanus, Pertussis ("DTaP") age_____ Don't know ___ never was vaccinated ____
"Tdap" booster Tetanus, Diptheria, Pertussis age_____ Don't know ___ never was vaccinated ____
Measles, Mumps, Rubella ("MMR") age_____ Don't know ___ never was vaccinated ____
Tetanus shot (for a puncture wound or cut) age_____ Don't know ___ never was vaccinated ____

FOR GIRLS ONLY

F3. Has your daughter ever used an oral contraceptive ("birth control pill")?
___Yes
___No → go to Question E5
___Don't know → go to Question E5
___Refused to answer → go to Question E5

F4. When did your daughter last use an oral contraceptive ("birth control pill")?

_____Month/Year

F5. At what age did your daughter begin menstruation (have her first period)?
___Age
___Has not yet begun to menstruate → go to Section G
___Don't know

F6. Does your daughter's period occur regularly (every month)?
___Yes
___No, it is irregular
___No, she does not have a period → go to Question E10
___Don't know → go to Question E10

F7. How many days has been your daughter's cycle on average during the last year?
___>26 days
___27-29 days
___30-32
___>32 days
___Don't know

F8. Can you characterize your daughter's usual period flow during the last year?
___Light
___Medium
___Heavy
___Don't know

F9. When was your daughter's last period before this study blood draw?
Date:_____
___Don't know

F10. Has your daughter ever been pregnant?
___Yes
___No → go to Section G
___Don't Know → go to Section G
___Refused to answer → go to Section G

F11. How many times has your daughter been pregnant?
_____

	Pregnancy #1	**Pregnancy #2**	**Pregnancy #3**
a. What month and year did this pregnancy start?	_ _/ _ _ _ _	_ _/ _ _ _ _	_ _/ _ _ _ _
b. What month and year did this pregnancy end?	_ _/ _ _ _ _	_ _/ _ _ _ _	_ _/ _ _ _ _
c. Did the pregnancy result in a live birth?	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know

d. Did your daughter breastfeed the child?	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know	Yes No (go to g) Don't Know
e. How long did your daughter breastfeed the child?	_ _ months	_ _ months	_ _ months
f. When did your daughter stop breastfeeding the child?	__month ____ year	__month ____ year	__month ____ year
g. Did a doctor or nurse say that your daughter had pre-eclampsia during her pregnancy?	Yes No Don't know	Yes No Don't know	Yes No Don't know
h. Did a doctor or nurse say that your daughter had pregnancy-induced hypertension?	Yes No Don't know	Yes No Don't know	Yes No Don't know
i. Did a doctor or nurse say that your daughter had gestational diabetes?	Yes No Don't know	Yes No Don't know	Yes No Don't know

Section G: Family Medical History

G1. Have any of your child's blood relatives - grandparents, parents, or siblings - ever been told by a health professional that they have or had any of the following conditions? Fill out the table below. Circle appropriate response and ask the respondent to specify as directed.

Medical condition		**If yes, ask: Which relative had this condition?**
a. Obesity	Yes No Don't know	Grandparent Parent Sibling
b. Attention deficit hyperactivity disorder (ADHD or attention deficit disorder (ADD)	Yes No Don't know	Grandparent Parent Sibling
c. Other learning or behavioral problems	Yes No Don't know	Grandparent Parent Sibling

CONCLUSION: That completes this survey. I would like to sincerely thank you for your time.

Multi-site Study
Blood Draw and Urine Collection Form
Flesch-Kincaid Readability Score – 9.1

Attachment 16.

Multi-site PFAS Health Study
Blood Draw and Urine Collection Form

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Adult Study ID No.: |_____| **OR** **Child Study ID No.:** |_____|

You were asked to collect a first morning void urine sample when you got up today.

1. Did you bring it today? ☐ Yes ☐ No

   1a. [IF NO] Can you give us a sample now? ☐ Yes ☐ No

2. Result of the urine collection (mark one) **Volume**

☐ **Complete** **(at least 10-mL)**

☐ **Partial** **2a. (_____-mL)**

☐ **Unable to collect**

Before we can take [your/your child's] blood we need to ask you a few questions on whether [you/your child] can provide a blood sample.

3. [Do you/Does your child] have hemophilia? ☐ Yes ☐ No

4. [Have you/Has your child] received any chemotherapy in the last four weeks? ☐ Yes ☐ No

5. [Do you/Does your child] have active sores, disease, or other problem on the arm/shoulder that could prevent us from taking a blood sample*? ☐ Yes ☐ No

* This may include gauze dressings, casts, edema, paralysis, tubes, open sores or wounds, withered arms or limbs missing, damaged, sclerosed or occluded veins, allergies to cleansing reagents, burned or scarred tissue, shunt or intravenous lines on both arms. Please check and review all with the participant.

[IF THE ADULT/PARENT OR GUARDIAN RESPONDED 'YES' TO ANY OF THE ABOVE QUESTIONS, THE PARTICIPANT SHOULD BE EXCLUDED FROM THE BLOOD DRAW. PLEASE SEE STUDY COORDINATOR IMMEDIATELY.

SENIOR SUPERVISING NURSE WILL MAKE THE DECISION WHETHER A PARTICIPANT WITH ANY TYPE OF SHOULDER LESIONS CAN SAFELY PROVIDE A BLOOD SAMPLE]

We also want to ask you a few more questions as a precaution.

6. [Are you/Is your child] on blood thinning medication? ☐ Yes ☐ No

7. Are you on diabetes medication or insulin? ☐ Yes ☐ No

8. Tell me the last time you ate. Was it less than eight hours ago? ☐ Yes ☐ No

8a. *[IF YES]* How long ago did you eat? |__|__|:|__|__| (hours and minutes)

8b. . . . . and what did you eat? |_____|

[IF THE PARTICIPANT ANSWERED 'YES' TO ANY OF THE ABOVE QUESTIONS PLEASE SEE STUDY COORDINATOR AND SUPERVISING NURSE TO MAKE SURE THEY CAN SAFELY PROVIDE BLOOD SAMPLE]

9. Result of the Blood Draw (mark one) **Volume**

☐ **Complete** **(35-mL adults/25 ml children)**

☐ **Partial** **7a. (_____-mL)**

☐ **Unable to collect**

9a. Date: |__|__|/|__|__|/|__|__| **9b. Time:** |__|__|:|__|__| ☐ AM ☐ PM

9c. Code Partial/Inability to Collect (circle one)

Reason for partial or inability to collect blood:

1. Pregnant
2. Medical (e.g. patient frail, weak, lost consciousness)
3. Refused
4. Other (describe) _____

10. Interviewer/Phlebotomy Comment:

NOTES: Care should be used in drawing blood from all subjects. Common adverse effects include bruising, bleeding, and fainting. Please ask all participants whether they prefer to lie down to have blood drawn.

Ask everyone if they tend to faint when giving blood. Suggest they sit down for five minutes after giving blood.

Fasting diabetic participants who use insulin will be given priority appointments for their blood draw.

Light snacks will be provided following blood collection.

See Protocol **Attachment 14 (Manual of Operations)** for further details on collecting blood samples.

Attachment 17 – Letter to Provider for Record Abstraction

Pease Study
Letter to Provider – Record Abstraction
Flesch-Kincaid Readability Score – 12.5

[ON INVESTIGATORS INSTITUTION LETTERHEAD]
[DATE]

[NAME OF PROVIDER]
[ADDRESS]
[CITY, STATE ZIP CODE]

Subject: Medical verification and records review for Multi-site PFAS Health Study

Dear [NAME OF PROVIDER]:

The Agency for Toxic Substances and Disease Registry (ATSDR) and [insert institution name] are conducting a research study of the health effects from exposure to per- and polyfluoroalkyl substances (PFAS) found in drinking water. We are working with the assistance of your local health department [insert name] and [name of all other partners]. ATSDR and research partners are conducting this research study with oversight from the CDC/ATSDR Institutional Review Board (IRB) under CDC Protocol No. xxxxxxx.

Under Section 8006 of the 2018 Consolidated Appropriations Act, Congress authorized ATSDR to study the impact that exposure to PFAS in drinking water might have on the health of affected citizens. This study will see if there is an increase of symptoms or illness related to these chemicals.

We plan to recruit a total of 6,000 adults and 2,000 children for the Multi-site PFAS Health Study. Those person had to reside in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. Persons who were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.

[ADULT PARTICIPANT'S NAME or PARENT OR GUARDIAN'S NAME] has given the study investigators authorization to conduct a medical records review. ATSDR is interested in more information about [ADULT PARTICIPANT'S NAME/CHILD PARTICIPANT'S NAME]'s self-reported health conditions that may be related to chemical exposure. We have included an abstraction form for your office to fill out and return to us in the enclosed return envelope.

If we need additional information, the ATSDR/[institution name] study team may wish to review the medical records in your office. We would appreciate your assistance if this is necessary.

ATSDR is an agency of the U.S. Department of Health and Human Services. ATSDR is performing this activity as a public health authority as defined by the Health Insurance Portability and Accountability Act (HIPAA) [45 CFR §164.501]. The requested information represents the minimum necessary to carry out the public health purposes of this study as described in 45 CFR §164.514(d) of the Privacy Rule. The research is also covered by a Certificate of Confidentiality under Section 301(d) of the Public Health Service (PHS) Act, as amended by Section 2012 of the 21st Century Cures Act, P.L. 114-255 (42 U.S.C. 241(d))

For questions about this research study, please call the ATSDR study lead, Dr. Marian Pavuk, at [study telephone number]. Please leave a message with your name and a telephone number or address.

Thank you for your assistance.

Marian Pavuk, MD, PhD

Frank Bove, DSc

Co-Principal Investigators
Pease Study

Attachment 17a.

Multi-site Study
Medical Record Abstraction Form - Adult
Flesch-Kincaid Readability Score – 11.1

Multi-site Study
Medical Record Abstraction Form Adult

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Medical Record Abstraction Form - Adult

Study ID: [_____]	**Participant Name: [_____]**	**Date of Birth: ___/___/_____**	**SSN: xxx-xx-xxxx**

The person named above, or his or her legal representative, has authorized you to release his or her medical records to ATSDR/[institution name] for research purposes. Please check If you have a record that a doctor or other health care provider diagnosed or is treating any of the following medical conditions.

Please fill out the table below. Circle appropriate response and specify requested details as directed. Thank you.

Medical Condition	Record Located (Comments)	Year of Diagnosis or Treatment
a. High cholesterol?	Yes No	
b. Other dyslipidemia?	Yes (Please specify diagnosis) _____ No	
c. Heart disease?	Yes No	
d. Hypertension?	Yes No	
e. Pregnancy induced hypertension?	Yes No	
f. Thyroid disease?	Yes (Please specify diagnosis) _____ No	

Attachment 17a.

Medical Condition	Record Located (Comments)	Year of Diagnosis or Treatment
g. Liver disease?	Yes (Please specify diagnosis) _____ No	
h. Kidney disease?	Yes (Please specify diagnosis) _____ No	
i. Diabetes?	Yes (Please specify diagnosis) _____ No	
j. Gestational diabetes?	Yes No	
j. Osteoarthritis?	Yes (Please specify diagnosis) _____ No	
k. Osteopenia or Osteoporosis?	Yes (Please specify diagnosis) _____ No	
l. Ulcerative colitis?	Yes No	
m. Rheumatoid arthritis?	Yes No	
n. Autoimmune disease? (i.e. Lupus, Multiple sclerosis, Emphysema, Fibromyalgia, Celiac Disease, Crohn's Disease)	Yes (Please specify) _____ No	
o. Endometriosis?	Yes No	
p. Asthma?	Yes No	
q. Cancer?	Yes (Please specify) _____ No	
r. Other cancer?	Yes (Please specify) _____ No	

Attachment 17b.

Multi-site Study
Medical Record Abstraction Form - Child
Flesch-Kincaid Readability Score – 12.5

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Multi-site Study
Medical Record Abstraction Form Child

Medical Record Abstraction Form - Child

Study ID: [_____]	**Participant Name: [_____]**	**Date of Birth: ___/___/_____**	**SSN: xxx-xx-xxxx**

The person named above, or his or her legal representative, has authorized you to release his or her medical records to ATSDR/[insert institution name] for research purposes. Please check If you have a record that a doctor or other health care provider diagnosed or is treating any of the following medical conditions.

Please fill out the table below. Circle appropriate response and specify requested details as directed. Thank you.

Medical Condition	Record Located (Comments)	Year of Diagnosis or Treatment
a. Allergies?	Yes (Please specify diagnosis)_____ No	
b. Atopic dermatitis/eczema?	Yes No	
c. Asthma?	Yes No	
d. Rhinitis?	Yes No	
e. High cholesterol?	Yes No	
f. Thyroid disease?	Yes (Please specify diagnosis)_____ No	

Attachment 17b.

Medical Condition	Record Located (Comments)	Year of Diagnosis or Treatment
g. Delayed puberty?	Yes (Please specify diagnosis)_____ No	
h. Obesity?	Yes No	
i. Lupus	Yes No	
j. Celiac disease	Yes No	
k. Diabetes type 1	Yes No	
l. Diabetes type 2	Yes No	
m. Attention deficit hyperactivity disorder (ADHD) or attention	Yes (Please specify diagnosis) _____ No	
n. Other learning or behavioral problems?	Yes (Please specify diagnosis) _____ No	
o. Cancer?	Yes (Please specify diagnosis) _____ No	
o. Other cancer?	Yes (Please specify diagnosis) _____ No	

Attachment 18.

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

Multi-site Study

Child/Parent Neurobehavioral Test Battery

Proprietary Neurobehavioral Test Information

The following test forms are not found in the ATSDR Multi-site PFAS Health Study Protocol (Number XXXX). The data collection forms are copyrighted and may be reproduced only with written permission from the publishers. The SDQ allows paper versions of its forms to be reproduced and used provided ATSDR does not charge any fee to participants.

To review a copy of the test forms, write to the publishers at the addresses provided below:

Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI - II)	Pearson Education, Inc. (Clinical Assessment Ordering Department, P.O. Box 599700, San Antonio, TX 78259) Toll-free: 800-627-7271
A Developmental NEuroPSYchological Assessment – Second Edition (NEPSY-II)	Pearson Education, Inc. (Clinical Assessment Ordering Department, P.O. Box 599700, San Antonio, TX 78259) Toll-free: 800-627-7271
Conners Kiddie Continuous Performance Test, 2nd Edition (Conners K-CPT 2)	Multi-Health Systems Inc. (P.O. Box 950, North Tonawanda, NY, 14120-0950) Toll-free: 800-456-3003
Conners Continuous Performance Test 3rd Edition (CPT 3)	Multi-Health Systems Inc. (P.O. Box 950, North Tonawanda, NY, 14120-0950) Toll-free: 800-456-3003
Strengths and Difficulties Questionnaire© (SDQ©)	Development and Well-Being Assessment (DAWBA). Feedback and **enquiries** welcome at youthinmind@gmail.com The SDQ is part of the DAWBA family of mental health measures. **COPYRIGHT NOTICE:** Please note that Strengths and Difficulties Questionnaires, whether in English or in translation, are **copyright documents that are not in the public domain**. As such, they may not be modified in any way (e.g. changing the wording of questions, adding questions or administering only subsets of questions). This is to ensure that the SDQ is fully comparable across studies and settings. Similarly, to ensure high quality and consistency, unauthorized translations are not permitted. Paper versions may be downloaded and subsequently photocopied without charge by individuals or non-profit organizations provided they are not making any charge to families. Users are not permitted to create or distribute electronic versions for any purpose without prior authorization from **youth*in*mind**. If you are interested in making translations or creating electronic versions you **MUST** first contact youthinmind@gmail.com.
Behavior Rating Inventory of Executive Function® (BRIEF®)	Psychological Assessment Resources, Inc. (16204 North Florida Avenue, Lutz, FL 33549) Toll-free 800-331-8378
Behavior Rating Inventory of Executive Function® – Preschool Version (BRIEF®-P)	Psychological Assessment Resources, Inc. (16204 North Florida Avenue, Lutz, FL 33549) Toll-free 800-331-8378

Pease Study Neurobehavioral Test Battery for Children

Neurobehavioral Test	Domain	Age	Administration	Time to Administer
Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI - II)	Two Subtest Form (FSIQ-2) (Vocabulary and Matrix Reasoning)	6 – 17*	Child	15 minutes
A Developmental Neuropsychological Assessment – 2nd edition (NEPSY – II) subtests * from Core Assessment	Auditory Attention and Response Set* (reduced attention)	5 – 16	Child	7 – 11 minutes
	Inhibition*	5 – 16	Child	8 – 11 minutes
	Comprehension of Instructions* (receptive language, trouble following multi-step commands)	4 – 16	Child	6 – 8 minutes
	Speeded Naming* (expressive language, processing speed)	4 – 16	Child	2 – 7 minutes
	Word List Interference* (verbal memory)	7 – 16	Child	6 – 8 minutes
	Narrative Memory* (comprehension, verbal memory)	4 – 16	Child	6 – 11 minutes
	Design Copying* (visuospatial processing)	4 – 16	Child	7 – 10 minutes
	Theory of Mind (social perception)	4 – 16	Child	10 – 13 minutes
	Sentence Repetition (verbal memory)	4 – 6	Child	4 minutes
	Statue (inhibitory control)	4 – 6	Child	3 minutes
	Word Generation (expressive language, executive control)	4 - 16	Child	4 – 6 minutes
Conners Kiddie Continuous Performance Test, 2nd Edition (Conners K-CPT 2)	Inattentiveness, Impulsivity, Sustained Attention, Vigilance	4-7	Child	8 minutes
Conners Continuous Performance Test 3rd edition (CPT 3)	Inattentiveness, Impulsivity, Sustained Attention, Vigilance	8-17	Child	14 minutes
Strengths and Difficulties Questionnaire© (SDQ©)	Double-sided form with impact supplement (behavioral problems)	4 – 17	Parent about Child	5 minutes
Behavior Rating Inventory of Executive Function® (BRIEF®)	Executive Function	6-17	Parent about Child	10 minutes
Behavior Rating Inventory of Executive Function® – Preschool Version (BRIEF®-P)	Executive Function - Preschool	4-5	Parent about Child	10 minutes

Neuropsychological Test Battery, Children aged 4-17 years		
Age Range, years	Test	Domains
6-17 years	Wechsler Abbreviated Scale of Intelligence® - Second Edition (WASI® - II)	https://www.pearsonclinical.com/psychology/products/100000037/wechsler-abbreviated-scale-of-intelligence--second-edition-wasi-ii.html **Author: David Wechsler** **Qualification Level:** C **Age Range:** Individuals 6:0–90:11 **Completion Time:** Two-subtest form (Vocabulary and Matrix Reasoning), 15 minutes **Scores/Interpretation:** FSIQ–2 score: Estimate of general cognitive ability **Scoring Options:** Manual scoring **Publication Date:** 2011
4-16 years	A Developmental NEuroPSYchological Assessment – 2nd Edition (NEPSY-II)	https://www.pearsonclinical.com/psychology/products/100000584/nepsy-second-edition-nepsy-ii.html https://images.pearsonclinical.com/images/Products/NEPSY-II/Clin_Chp_2.pdf **Author(s):** Marit Korkman, Ursula Kirk, Sally Kemp **Qualification Code:** CL1 **Age Range:** 3 years to 4 years; 5 years to 16 years **Administration:** Core Assessment 45 minutes for preschool ages, 1 hour for school ages; Comprehensive Assessment - 90 minutes for preschool ages, 2-3 hours for school ages **Publication Year:** 2007 **This NEPSY-II battery covers Five of Six Domains** Executive Functioning/Attention, Language, Memory and Learning, Visuospatial Processing, Social Perception. Sensorimotor Functioning will not be tested. **ATTENTION AND EXECUTIVE FUNCTIONING** 1) **Auditory Attention and Response Set** (AA - 5-16 years; RS - 7-16 years). Auditory Attention is designed to assess selective auditory attention and the ability to sustain it (vigilance). Response Set is designed to assess the ability to shift and maintain a new and complex set involving both inhibition of previously learned responses and correctly responding to matching or contrasting stimuli. The child listens to a series of words and touches the appropriate cirle when he or she hears a target word. 2) **Inhibition** (IN – 5-16 years). This timed subtest is designed to assess the ability to inhibit automatic responses in favor of novel responses and the ability to switch between response types. The child looks at a series of black and white shapes or arrows and names either the shape or direction or an alternate response, depending on the color of the shape or arrow. 3) **Statute** (ST – 3-6 years). This subtest is designed to assess motor persistence and inhibition. The child is asked to maintain a

		body position with eyes closed during a 75-second period and to inhibit the impulse to respond to sound distracters. **LANGUAGE** 1) **Comprehension of Instructions** (CI – 3-16 years). This subtest is designed to assess the ability to receive, process, and execute oral instructions of increasing syntactic complexity. For each item, the child points to appropriate stimuli in response to oral instructions. 2) **Speeded Naming** (SN – 3-16 years). This timed subtest is designed to assess rapid semantic access to and production of names of colors, shapes, sizes, letters, or numbers. The child is shown an array of colors and shapes; colors, shapes, and sizes; or letters and numbers. He or she names them in order as quickly as possible. 3) **Word Generation** (SN – 3-16 years). This subtest is designed to assess verbal productivity through the ability to generate words within specific semantic and initial letter categories. The child is given a semantic or initial letter category and asked to produce as many words as possible in 60 seconds. **MEMORY AND LEARNING** 1) **Word List Interference** (WI – 7-16 years). This subtest is designed to assess verbal working memory, repetition, and word recall following interference. The child is presented with two series of words and asked to repeat each sequence following its presentation. Then, he or she recalls each series in order of presentation. 2) **Narrative Memory** (NM – 3-16 years). This subtest is designed to assess memory for organized verbal material under free recall, cued recall, and recognition conditions. The child listens to a story and is then asked to repeat the story. The child is then asked questions to elicit missing details from his or her recall of the story. 3) **Sentence Repetition** (SR – 3-6 years). This subtest is designed to assess the ability to repeat sentences of increasing complexity and length. The child is read a series of sentences and asked to recall each sentence immediately after it is presented. **VISUOPSPATIAL PROCESSING** 1) **Design Copying** (DC – 3-16 years). This subtest is designed to assess motor and visual-perceptual skills associated with the ability to copy two-dimensional geometric figures. The child copies figures displayed in the Response Booklet. **SOCIAL PERCEPTION** 1) **Theory of Mind** (3-16 years). This subtest is designed to assess the ability to understand mental functions such as belief, intention, deception, emotion, imagination, and pretending, as well as the ability to understand that others have their own thoughts, ideas, and feelings that may be different from one's own and the ability to understand how emotion relates to social context and to recognize the appropriate affect given various social contexts. In the Verbal task, the child is read various scenarios or shown pictures and is then asked questions that require knowledge of another individual's point of view to answer correctly. In the Contextual task, the child is shown a picture depicting a social context and asked to select a photograph from

		four options that depicts the appropriate affect of one of the people in the picture.
4-7 years	Connors Kiddie Continuous Performance Test Second Edition™ (Conners K-CPT 2™)	https://www.mhs.com/MHS-Assessment?prodname=kcpt2 **Overview** The Conners Kiddie Continuous Performance Test 2nd Edition™ (Conners K-CPT 2™) assesses attention deficits in children ages 4 to 7 years old. Based on the well-established Conners CPT paradigm, the Conners K–CPT 2 takes only half the time (7.5 minutes) to complete, making it more appropriate for younger children. Results from the measure can be used for clinical assessment, early identification, and educational classification. The assessment can be also be used to evaluate treatment effectiveness by administering the test before treatment and during treatment to monitor change. **Author(s):** Keith Conners, Ph.D **Key Areas Measured:** ▪ Inattentiveness ▪ Impulsivity ▪ Sustained Attention ▪ Vigilance **Age:** 4 to 7 **Administration Type:** Self **Administration Time:** 7.5 Minutes **Qualification Level:** B
8-17 years	Connors Continuous Performance Test Third Edition™ (CPT 3™)	https://www.mhs.com/MHS-Assessment?prodname=cpt3 **Overview** The Conners Continuous Performance Test Third Edition™ (Conners CPT 3™) measures attention-related problems in individuals aged eight years and older. By indexing the respondent's performance in areas of inattentiveness, impulsivity, sustained attention, and vigilance, the Conners CPT 3 can aid in the assessment of Attention-Deficit/Hyperactive Disorder (ADHD) and other neurological conditions related to attention. The Conners CPT 3 provides objective information about an individual's performance in attention tasks, complementing information obtained from rating scales such as the Conners 3®. **New Scores and Score Dimensions of Attention Measured**: ▪ Inattentiveness ▪ Impulsivity ▪ Sustained Attention ▪ Vigilance **Key Areas Measured:** ▪ Inattentiveness ▪ Impulsivity ▪ Sustained Attention ▪ Vigilance **Age:** 8+ **Administration Type:** Self **Administration Time:** 14 Minutes

		Qualification Level: B
Parent (4-17 years)	Strengths and Difficulties Questionnaire (SDQ)	http://www.cebc4cw.org/assessment-tool/strengths-and-difficulties-questionnaire/ The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioural screening questionnaire about 3-16 year olds. It exists in several versions to meet the needs of researchers, clinicians and educationalists. Each version includes between one and three of the following components: 25 items on psychological attributes. All versions of the SDQ ask about 25 attributes, some positive and others negative. These 25 items are divided between 5 scales: 1) emotional symptoms (5 items) 2) conduct problems (5 items) 3) hyperactivity/inattention (5 items) 4) peer relationship problems (5 items) 5) prosocial behaviour (5 items) [1) to 4) added together generate a total difficulties score (based on 20 items)] A two-sided version of the SDQ has the 25 items on strengths and difficulties on the front of the page and an impact supplement on the back. These extended versions of the SDQ ask whether the respondent thinks the young person has a problem, and if so, enquire further about chronicity, distress, social impairment, and burden to others. This provides useful additional information for clinicians and researchers with an interest in psychiatric caseness and the determinants of service use (Goodman, 1999). **Target Population:** Children between the ages of 2 to 17 **Time to Administer:** One sided version with 25 items, administration time approximately 5 minutes **Completed By:** Parents and teachers **NOTE:** As of June 2014 the authors have relabelled all SDQ questionnaires to be consistent in giving '4-17 years' as the age range of the standard SDQ (e.g. 4-17 years not 4-16 years) and giving '2-4 years' as the age range of the early-years SDQ (i.e. 2-4 years not 3/4 years). **The content of the SDQs themselves is unchanged**. They have relabelled the SDQs following evidence that the SDQ has good psychometric properties in 2-year-olds, and that the performance of the SDQ in 17-year-olds is similar to that in 15- and 16-year olds.
Parent (4-5 years)	Behavior Rating Inventory of Executive Function® – Preschool Version (BRIEF®-P)	https://www.parinc.com/Products/Pkey/26 **BRIEF®-P** Behavior Rating Inventory of Executive Function®—Preschool Version *Gerard A. Gioia, PhD, Kimberly Andrews Espy, PhD, and Peter K. Isquith, PhD* Purpose: Assesses executive functioning in preschool-aged children Format: Paper and pencil, Online administration and scoring via PARiConnect, Software

		Age range: 2 years to 5 years, 11 months Time: Approximately 10-15 minutes to administer; 15-20 minutes to score Qualification level: B The BRIEF-P is the first standardized rating scale designed to specifically measure the range of executive function in preschool-aged children. Features and benefits ▪ Measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. ▪ Useful in assessing preschool-aged children with such medical, acquired neurological, and developmental conditions as prematurity, emerging learning disabilities and attention disorders, language disorders, traumatic brain injuries, lead exposure, and pervasive developmental disorders/autism. Test structure ▪ A single Rating Form allows parents, teachers, and day care providers to rate a child's executive functions within the context of his or her everyday environments—home and preschool. ▪ Three broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition), one composite score, and two validity scales (Inconsistency and Negativity) are provided. Technical information ▪ Normative data are based on child ratings from 460 parents and 302 teachers from urban, suburban, and rural areas, reflecting 1999 U.S. Census estimates for race/ethnicity, gender, socioeconomic status, and age. ▪ Clinical samples included children with ADHD, prematurity, language disorders, and autism spectrum disorders, as well as a mixed clinical group. ▪ Demonstrates high internal consistency reliability (.80-.95 for the parent sample and .90-.97 for the teacher sample) and moderate test-retest reliability (.78-.90 for the parent sample and .64-.94 for the teacher sample). ▪ Demonstrates convergent and discriminant validity with other measures of inattention, hyperactivity-impulsivity, depression, atypicality, anxiety, and somatic complaints.
Parent (6-17 years)	Behavior Rating Inventory of Executive Function® (BRIEF®)	https://www.parinc.com/Products/Pkey/23 **BRIEF®** Behavior Rating Inventory of Executive Function® *Gerard A. Gioia, PhD, Peter K. Isquith, PhD, Steven C. Guy, PhD, and Lauren Kenworthy, PhD* Purpose: Assesses impairment of executive function Format: Paper and pencil, Online administration and scoring via PARiConnect Age range: 5 years to 18 years Time: 10-15 minutes to administer; 15-20 minutes to score Qualification level: B Assess executive function behaviors in the school and home environments with the BRIEF, a questionnaire developed for

		parents and teachers of school-age children. Designed to assess the abilities of a broad range of children and adolescents, the BRIEF is useful when working with children who have learning disabilities and attention disorders, traumatic brain injuries, lead exposure, pervasive developmental disorders, depression, and other developmental, neurological, psychiatric, and medical conditions. Features and benefits ▪ **Provides multiple perspectives**. The Parent and Teacher Forms of the BRIEF each contain 86 items that measure different aspects of executive function. ▪ **Specific normative data based on age and gender**. Separate normative tables for parent and teacher forms provide *T* scores, percentiles, and 90% confidence intervals for four developmental age groups by gender of the child. ▪ **Nonoverlapping scales**. Theoretically and statistically derived scales measure different aspects of a child or adolescent's behavior, such as his or her ability to control impulses, move freely from one situation to the next, modulate responses, anticipate future events, and keep track of the effect of his or her behavior on others. Test structure ▪ Eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity) give the clinician a well-rounded picture of the behavior of the child or adolescent being rated. ▪ The clinical scales form two broader Indexes (Behavioral Regulation and Metacognition) and an overall score, the Global Executive Composite. ▪ The Working Memory and Inhibit scales differentiate among ADHD subtypes. Technical information ▪ Normative data are based on child ratings from 1,419 parents and 720 teachers from rural, suburban, and urban areas. ▪ The clinical sample included children with developmental disorders or acquired neurological disorders (e.g., reading disorder, ADHD subtypes, traumatic brain injury, Tourette's disorder, mental retardation, localized brain lesions, high functioning autism). ▪ High internal consistency (αs = .80-.98) and test-retest reliability (*r*s = .82 for parents, .88 for teachers) were found.

Attachment 18a. Neurobehavioral Test Battery – Time Estimation Table, by Age in years

Test Administered to Children	4 years	5 years	6 years	7 years	8 years – 16 years	17 years
Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI - II)						
N - Auditory Attention and Response*						
N - Inhibition*						
N - Comprehension of Instructions*						
N - Speeded Naming*						
N - Word List Interference*						
N - Narrative Memory*						
N - Design Copying*						
N - Theory of Mind						
N - Sentence Repetition						
N - Statue						
N - Word Generation						
Conners Kiddie Continuous Performance Test, 2nd Edition (Conners K-CPT 2)						
Conners Continuous Performance Test 3rd Edition (CPT 3)						
Child Administered Time Sub-total (Average Time ~ 90 minutes)	60	78	93	93	99	29
Test Administered to Parents for Children						
Strengths and Difficulties Questionnaire© (SDQ©)						
Behavior Rating Inventory of Executive Function® (BRIEF®)						
Behavior Rating Inventory of Executive Function® – Preschool Version (BRIEF®-P)						
Parent Administered Time Sub-total (Average Time ~ 15 minutes)	15	15	15	15	15	15
Child/Parent Administered Total Time (Average Time ~ 105 minutes)	75	93	108	108	114	44

* Asterisk indicates N = NEPSY-II Core Assessment Battery; all else – Additional NEPSY-II Tests

Attachment 18b.

Multi-site Study
Child School Record Abstraction Form

Form Approved
OMB No. 0923-XXXX
Exp. Date xx/xx/201x

If the parent reports that the child has a developmental disability (e.g., ADHD, autism, or a learning disability), then ATSDR/[institution name] seeks to abstract the special education records for the child including the individualized education program (IEP), the IEP evaluation report ("Full Individual Evaluation" or "FIE"), and if available, the Independent Educational Evaluation. ATSDR seeks this information only if the child's parent or legal guardian has signed the consent to release student information.

ATSDR has received parental or guardian permission to obtain the specified school records for the child named below:

Name of Student (print): _____ Student ID No. _____ Date of Birth: [mm/dd/yyyy]

Address of Student: _____

City: _____ State: _____ Zip Code: _____

Name of Parent or Guardian (print): _____

Mail the completed form (using the enclosed pre-addressed return envelope) to:***

Marian Pavuk, MD, PhD
Agency for Toxic Substances and Disease Registry (ATSDR)
Division of Toxicology and Human Health Science (DTHHS)
4770 Buford Highway, NE
Mailstop F-57
Atlanta, Georgia 30341

Attachment 18b.

Does the student have one or more of the following disabilities?

DISABILITY	FINDING	IF YES,
Autism	Yes No	How diagnosed?
Developmental Disability	Yes No	Specify_____ How diagnosed?
Intellectual/Cognitive Impairment	Yes No	Specify_____ How assessed?
Sensory-Hearing, Vision, Deaf-Blind	Yes No	Specify_____
Neurological Disability	Yes No	Specify_____ How assessed?

Attachment 18b.

Attachment 18b.

DISABILITY	FINDING	IF YES,
Specific Learning Disability	Yes No	Specify_____ How assessed?
Attention Deficit Hyperactivity Disorder (ADHD)	Yes No	How diagnosed?
Social/Emotional/Behavioral Disorder	Yes No	Specify_____ How diagnosed?
Adaptive Behavior	Yes No	Specify_____ How diagnosed?
Language Disability	Yes No	Specify [__] receptive [__] expressive [__] auditory processing How diagnosed?

Attachment 18b.

Verbatim description of deficiencies noted in the Present Levels of Academic Achievement and Functional Performance (including deficiencies in social skills and behavior):

Note the following if found:

Services: Special Education	Yes No	Specify_____
Psychometric Test Results		IQ [_____]

Attachment 18b.

		Reading Level [_____]

Other Test Results:

Attachment 18b.

Attachment 19.

Multi-site Study
Body Blood Pressure Report
Flesch-Kincaid Readability Score – 5.7

Multi-site Study
Body and Blood Pressure Measures Report

STUDY ID No.: |_____| NAME: |_____|

DATE: |__|__|/|__|__|/|__|__| TIME: |__|__|:|__|__| AM PM STAFF INITIAL: |_____|

BODY MEASURES AND BLOOD PRESSURE ARE USEFUL TO SEE IF YOU ARE AT RISK FOR DISEASES RELATED TO HIGH BODY FAT.
ON THE BACK OF THIS REPORT **---** READ MORE ABOUT WHAT YOUR MEASURES MEAN AND ACTIONS YOU SHOULD TAKE WITH A DOCTOR.

YOUR BODY MEASURES	**YOUR STATUS**
HEIGHT: |__| ft |__|__| in WEIGHT: |__|__|__| lbs BODY MASS INDEX: |__|__|. |__| kg/m^2	Body Mass Index (BMI) is calculated from height and weight. BMI and WAIST SIZE are useful for measuring body fat. They can gauge your risk for diseases that often occur with more body fat. Examples are heart disease, high blood pressure, and Type 2 diabetes.

BMI	WEIGHT STATUS
Below 18.5	Underweight
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
30.0 and Above	Obese

WAIST SIZE: |__|__|__| in		WOMEN	MEN
	Smaller Risk	35-in or less	40-in or less
	Larger Risk	More than 35-in	More than 40-in

YOUR BLOOD PRESSURE	**YOUR STATUS**	
SYSTOLIC over DIASTOLIC |__|__|__|/|__|__|__| mm Hg	SYSTOLIC over DIASTOLIC	BLOOD PRESSURE CATEGORY
	Less than 120 AND Less than 80	Normal
	120-129 OR Less than 80	Elevated
	130-139 OR 80-89	Hypertension Stage 1
	140 or Higher OR 90 or Higher	Hypertension Stage 2
	Higher than 180 OR Higher than 120	Hypertensive Crisis

PLEASE TURN OVER AND READ MORE ABOUT HOW TO USE THIS INFORMATION

Attachment 19.

Multi-site Study
Body Blood Pressure Report
Flesch-Kincaid Readability Score – 5.7

WHAT YOUR WEIGHT STATUS AND WAIST SIZE MEANS	WHAT YOUR BLOOD PRESSURE STATUS MEANS
Underweight or Normal Most people who are underweight or at normal weight are **not at risk** for obesity-related disease. This is not a 100% surety because greater waist size, family history, or lifestyle choices still put some normal weight people at risk.	**Normal** Your blood pressure is normal. You should still continue to have your regular appointments and check-ups with you doctor.
Overweight Overweight people with a smaller waist size are at **increased risk of disease**.	**Elevated** Your blood pressure is slightly above normal. You should still continue to have your regular appointments and check-ups with you doctor.
Overweight Overweight people with a larger waist size are at **high risk for disease**.	**HYPERTENSION NOTICE** - **Hypertension Stage 1 and 2** Your blood pressure is very high. You should call your doctor and ask for an appointment. Please take this form with you and show it to your doctor. If you do not have a doctor we will help to find you one.
Obese People who are at the **highest risk of disease**. Please check with your doctor on how you could reduce your weight and waist size.	**HYPERTENSION NOTICE** - **Hypertension Crisis** Your blood pressure is dangerously high. You cannot continue with the study. You should call you doctor right now and ask to be seen as soon as possible. Your doctor may want you to go to the emergency room instead of waiting for an appointment. Please take this form with you and show it to your doctor. If you do not have a doctor we will help to find you one.

THE NURSE HAS TO MARK WHICH CATEGORY APPLIES TO YOU BEFORE YOU LEAVE

Attachment 20.

Multi-site Study
Advance Reporting Script Clinical Tests
Flesch-Kincaid Readability Score – 5.4

Multi-site PFAS Health Study
Advance Reporting Script for Clinical Tests

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____|
Child Study ID No. |_____|

HELLO,

My name is |_____|. I am calling on behalf of the Agency for Toxic Substances and Disease Registry, or ATSDR for short. We are calling about the Multi-site PFAS Health Study. Am I speaking with |_*NAME OF ADULT OR PARENT OF CHILD WHOSE RESULTS ARE CRITICAL*_|?

[IF NOT CORRECT PERSON] Please let me know the best time we can reach [him/her].

|_____| (day of the week)

|__|__|/|__|__|/|__|__| (date);

|__|__|:|__|__| AM PM (time).

I will call back then. Thank you.

[IF CORRECT PERSON] We are contacting you about [your/your child's] lab results. [Your/Your child's] [glucose/triglyceride/albumin/total bilirubin] test was significantly outside of the normal range. You should call [your/your child's] doctor today to discuss this. We will be sending you a letter with the details of [your/your child's] clinical tests.

Specifically, the results of [your/your child's] test have shown the following [read those that apply.]

Do you have a pen or pencil to write this down?

1. I am calling to report critical test results for |_*NAME OF ADULT OR CHILD*_|.

Attachment 20.

2. *Select the appropriate critical test and reporting value from below:*

[Your/Your child's] **glucose level** was |_____| mg/dL. The test was performed on |__|__|/|__|__|/|__|__| (date).

[If below 40 mg/dl read the following:] This is below the critical value of 40 mg/dL. [Your/Your child's] diabetes was poorly controlled or [your/his/her] medications might need to be adjusted. If this problem has not been addressed, we recommend that [you/your child] see the doctor immediately.

[If above 400 mg/dL read the following:] This is above the critical value of 400 mg/dL. [Your/Your child's] blood sugar was very high.

[Your/Your child's] **triglyceride level** was |_____| mg/dL. This is above the critical value of 1,000 mg/dL. The test was performed on |__|__|/|__|__|/|__|__| (date).

[You have/Your child has] a problem with lipid metabolism and have very high risk of heart disease.

[Your/Your child's] **albumin level** was |_____| g/dL. The test was performed on |__|__|/|__|__|/|__|__| (date).

[If below 1.5 g/dL read the following:] This is below the critical value of 1.5 g/dL. You may have a liver or kidney problem.

[If above 7.9 g/dL read the following:] This is above the critical level of 7.9 g/dL. You may be severely or chronically dehydrated.

[Your/Your child's] **total bilirubin** was |_____| mg/dL. This is above the critical value of >12.9 mg/Dl. The test was performed on |__|__|/|__|__|/|__|__| (date).

[You/Your child] may have a liver problem or a bile duct problem.

3. As a check, please read back the participant name and [his/her] critical lab result to me. > *Verbally correct any errors and repeat the request for a "read-back" to verify accurate reporting and message received.*

4. You should call [your/your child's] doctor today to discuss this information. As it is now more than |__|__| months since we collected [your/your child's] blood, this result may not be important today. You and [your/your child's] doctor may have already taken steps to correct the problem. We will be sending you a letter with the details of [your/your child's] clinical tests. If you or your doctor has a question about the results of these tests, you or he/she can contact

us at ATSDR at [insert telephone number]. Thank you for [your/your child's] participation in the study.

5. *[CONCLUSION] Document the date, time, test results, and person to whom the test results were reported. Prepare* ***Attachment 20a - Report of Critical Values Tracking Form*** *and* ***Attachment 20b - Letter Report of Critical Values*** *for mailout.*

Attachment 20a.

Multi-site Study

Advance Clinical Test Report Tracking Form

Study ID No. |_____| (Adult or Parent for child clinical test reporting)
Study ID No. |_____| (Child)
Adult or Parent is the *Target Person*

Contact Information Label

NW = Non-working Number
NH = No One Home
TN = Target Person Not Home
TY = Target Person Home

CN = Call Not Scheduled
CS = Call Scheduled
CR = Call Rescheduled Scheduled (note date/time)
VC = Verbal Report Complete

VI = Verbal Report Incomplete
LR = Letter Report Mailed
O = Other (explain)

No.	DATE mm/dd/yy	TIME hh:mm	OUTCOME CODE(S)	COMMENTS	INTERVIEWER
1	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
2	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
3	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
4	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
5	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
6	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
7	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
8	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
9	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
10	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
11	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			
12	|__|__|/|__|__|/|__|__|	|__|__|:|__|__| AM PM			

Attachment 20b. Letter Report of Critical Values

Multi-site Study
Letter Report of Critical Values
Flesch-Kincaid Readability Score – 6.9

[ON AGENCY/INSTITUTION LETTERHEAD]
[DATE]

[NAME OF ADULT/PARENT OF CHILD PARTICIPANT]
[ADDRESS]
[CITY, STATE ZIP CODE]

Subject: Report of Critical Values – ATSDR Multi-site PFAS Health Study (CDC Protocol No. xxxx)

Dear [NAME OF ADULT/PARENT OF CHILD PARTICIPANT]:

Thank you for taking part in the Agency for Toxic Substances and Disease Registry (ATSDR) Pease Study.

We called you on mm/dd/yyyy to inform you that (one/some) of (your/your child's) test (result was/results were) reported to be outside of the normal range provided by the laboratory. We called as soon as we received the lab report, because critical test results fall greatly outside the normal range. They may indicate a very serious medical situation that needs immediate attention. We are sending this letter for your records.

Your specimens were collected on mm/dd/yyyy. Even though it has been some months since we collected them, we provide our call and this letter to encourage you to talk to [your/your child's] doctor about these results. Since some time has passed, it is possible that (you have/your child has) already seen the doctor.

TEST	DATE PERFORMED	LABORATORY RESULT	CRITICAL VALUE
Glucose, fasting	mm/dd/yyyy	|__|__|__| mg/dL	<40 or >400 mg/dL
Triglyceride	mm/dd/yyyy	|__|__|__|__| mg/dL	>1,000 mg/dL
Serum albumin	mm/dd/yyyy	|__|__|.|__| g/dL	<1.5 g/dL or >7.9 g/dL
Total bilirubin	mm/dd/yyyy	|__|__|.|__| mg/dL	>12.9 mg/dL

What do these values mean?

Glucose <40 mg/dL	(Your/Your child's]) diabetes was poorly controlled. (Your/his/Her) medications might need to be adjusted.
Glucose >400 mg/dL	(Your/Your child's]) diabetes was poorly controlled. (Your/His/Her) medications might need to be adjusted.
Triglyceride >1,000 mg/dL	(You have/Your child has] a problem with lipid metabolism. This shows a very high risk of heart disease.
Serum albumin <1.5 g/dL	(You/Your child) may have a nutrition, liver, or kidney problem.
Serum albumin >7.9 g/dL	(You/Your child) may be severely or chronically dehydrated.
Total bilirubin >12.9 mg/dL	[You/Your child] may have a liver problem or a bile duct problem.

Attachment 20b. Letter Report of Critical Values

If you or your doctor has a question about these test results, please call us at [insert telephone number].

Thank you for [your/your child's] participation in the study.

Marian Pavuk, MD, PhD
Co-Principal Investigators
Pease Study

Frank Bove, DSc

Attachment 21

Multi-site Study
Clinical Test Results
Flesch-Kincaid Readability Score –

Multi-site Study
Clinical Test Results Report

Dear [NAME/NAME OF PARENT OR GUARDIAN],

The following tables show the results of clinical tests that we performed in [your/your child's] blood or serum on |__|__|/|__|__|/|__|__|. The results that are out of normal range are marked red.

These clinical tests are mostly those that your doctor would perform in an office. We advise you to go over the results with your doctor. If he or she has any questions about some of the more specialized tests we did, he or she can contact us at the number provided below.

Because we are providing these results |__|__| months after ATSDR and [insert institution name] collected [your/your child's] blood, the results may be of limited value to you or your doctor, especially if you are already under treatment or being followed for a particular chronic condition that the results indicate.

Some people will not have results for all chemicals. [You/Your child] may not have a result for a chemical test if [your/his/her] level is lower than the lab's limit of detection (<LOD). [You/Your child] may also not have a result if the blood sample did not pass a lab quality control check. If the reason for missing results is known, it will be included with [your/your child's] results.

You or your physician may contact us with questions about [your/your child's] clinical test results by calling ATSDR at [*study telephone number*].

Thank you for your understanding and your participation in the study.

Sincerely,

Study Investigators

Table 1. Results of your clinical tests for thyroid hormones, glycemic parameters, lipids, and liver function.

*** NOTE: the displayed clinical ranges will be updated when the contract labs are selected.**

Test name	Your Result	Adult Comparison Values	Child Comparison Values
Thyroid Hormones and Antibodies		**Clinical Ranges**	
Thyroid Stimulating Hormone (TSH)		18-19 years: 0.5-4.3 mIU/L [1] >20 years: 0.3-4.2 mIU/L	4-5 years: 0.7-6.0 mIU/L 6-10 years: 0.6-4.8 mIU/L
Total Thyroxin (TT4)		18 -19 years: 5.9-13.2 mcg/dL [2] ≥20 years): 4.5-11.7 mcg/dL **≥50 years:** **≥6.0 ng/dL (check units) [3]**	 4-5 years: 6.0-14.7 mcg/dL 6 -10 years: 6.0-13.8 mcg/dL 11 -17 years: 5.9-13.2 mcg/dL
Free T4		18-19 years: 1.0-1.6 ng/dL [2] ≥20 years of age: 0.9-1.7 ng/dL	4-5 years: 1.0-1.8 ng/dL 6-10 years: 1.0-1.7 ng/dL 11-17 years: 1.0-1.6 ng/dL
Total Triiodothyronine (TT3)		18-19 years: 91-218 ng/dL [4] (> or =20 years): 80-200 ng/dL	4-5 years: 92-248 ng/dL 6-10 years: 93-231 ng/dL 11-17 years: 91-218 ng/dL
Other Hormones			
Total Testosterone		Males: [5] 18 years: 300-1,200 ng/dL ≥19 years: 240-950 ng/dL Females: 18 years: 20-75 ng/dL ≥19 years: 8-60 ng/dL	Males: 4-9 years: <7-20 ng/dL 10-11 years: <7-130 ng/dL 12-13 years: <7-800 ng/dL 14 years: <7-1,200 ng/dL 15-16 years: 100-1,200 ng/dL 17-18 years: 300-1,200 ng/dL ≥19 years: 240-950 ng/dL Females: 4-9 years: <7-20 ng/dL 10-11 years: <7-44 ng/dL 12-16 years: <7-75 ng/dL

[1] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8939
[2] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/36108
[3] https://www.mayomedicallaboratories.com/test-catalog/appendix/criticalvalues/view.php?name=Critical+Values%2FCritical+Results+List
[4] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8613
[5] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83686

			17 years: 20-75 ng/dL
Estradiol		Males: [6] 10-40 pg/mL Females: Premenopausal: 15-350 pg/mL** Postmenopausal: <10 pg/mL **E2 levels vary widely through the menstrual cycle.	Males: Tanner Stage I <LOD-13 pg/mLL Tanner Stage II <LOD-16 pg/mL Tanner Stage III <LOD-26 pg/mL Tanner Stage IV <LOD-38 pg/mL Tanner Stage V 10-40 pg/mL Females: Tanner Stage I <LOD-20 pg/mL Tanner Stage II <LOD-24 pg/mL Tanner Stage III <LOD-60 pg/mL Tanner Stage IV 15-85 pg/mL Tanner Stage V 15-350 pg/mL
Sex hormone-binding globulin (SHBG)		Males: 10-57 nmol/L [7] Females (non-pregnant): 18-144 nmol/L	Males: Tanner Stage I 31-167 nmol/L Tanner Stage II 49-179 nmol/L Tanner Stage III 5.8-182 nmol/L Tanner Stage IV 14-98 nmol/L Tanner Stage V 10-57 nmol/L Females: Tanner Stage I 43-197 nmol/L Tanner Stage II 7.7-119 nmol/L Tanner Stage III 31-191 nmol/L Tanner Stage IV 31--166 nmol/L Tanner Stage V 18-144 nmol/L
Follicle stimulating hormone (FSH)		Males: [8] ≥18 years: 1.0-18.0 IU/L Females: ≥18 years: Premenopausal Follicular: 3.9-8.8 IU/L	Males: 4-6 years: ≤6.7 IU/L 7-8 years: ≤4.1 IU/L 9-10 years: ≤4.5 IU/L 11 years: 0.4-8.9 IU/L 12 years: 0.5-10.5 IU/L 13 years: 0.7-10.8 IU/L

[6] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81816
[7] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9285
[8] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8670

		Midcycle: 4.5-22.5 IU/L Luteal: 1.8-5.1 IU/L Postmenopausal: 16.7-113.6 IU/L	14 years: 0.5-10.5 IU/L 15 years: 0.4-18.5 IU/L 16 years: ≤9.7 IU/L 17 years: 2.2-12.3 IU/L Females 4-6 years: 3.3 IU/L 7-8 years: ≤11.1 IU/L 9-10 years: 0.4-6.9 IU/L 11 years: 0.4-9.0 IU/L 12 years: 1.0-17.2 IU/L 13 years: 1.8-9.9 IU/L 14-16 years: 0.9-12.4 IU/L 17 years: 1.2-9.6 IU/L
Insulin-like growth factor (IGF-1)		Males: [9] 18-22 years: 91-442 ng/mL 23-25 years: 66-346 ng/mL 26-30 years: 60-329 ng/mL 31-35 years: 54-310 ng/mL 36-40 years: 48-292 ng/mL 41-45 years: 44-275 ng/mL 46-50 years: 40-259 ng/mL 51-55 years: 37-245 ng/mL 56-60 years: 34-232 ng/mL 61-65 years: 33-220 ng/mL 66-70 years: 32-209 ng/mL 71-75 years: 32-200 ng/mL 76-80 years: 33-192 ng/mL 81-85 years: 33-185 ng/mL 86-90 years: 33-179 ng/mL >91 years: 32-173 ng/mL Females: 18-22 years: 85-370 ng/mL 23-25 years: 73-320 ng/mL 26-30 years: 66-303 ng/mL	Males: 4 years: 30-236 ng/mL 5 years: 39-250 ng/mL 6 years: 47-275 ng/mL 7 years: 54-312 ng/mL 8 years: 61-356 ng/mL 9 years: 67-405 ng/mL 10 years: 73-456 ng/mL 11 years: 79-506 ng/mL 12 years: 84-551 ng/mL 13 years: 90-589 ng/mL 14 years: 95-618 ng/mL 15 years: 99-633 ng/mL 16 years: 104-633 ng/mL 17 years: 107-615 ng/mL Females: 4 years: 33-237 ng/mL 5 years: 36-234 ng/mL 6 years: 39-246 ng/mL 7 years: 44-279 ng/mL 8 years: 51-334 ng/mL

[9] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/62750

		31-35 years: 59-279 ng/mL 36-40 years: 54-258 ng/mL 41-45 years: 49-240 ng/mL 46-50 years: 44-227 ng/mL 51-55 years: 40-217 ng/mL 56-60 years: 37-208 ng/mL 61-65 years: 35-201 ng/mL 66-70 years: 34-194 ng/mL 71-75 years: 34-187 ng/mL 76-80 years: 34-182 ng/mL 81-85 years: 34-177 ng/mL 86-90 years: 33-175 ng/mL ≥91 years: 25-179 ng/mL	9 years: 61-408 ng/mL 10 years: 73-495 ng/mL 11 years: 88-585 ng/mL 12 years: 104-665 ng/mL 13 years: 120-719 ng/mL 14 years: 136-729 ng/mL 15 years: 147-691 ng/mL 16 years: 153-611 ng/mL 17 years: 149-509 ng/mL
Glycemic Parameters		**Clinical Guidelines and Ranges**	
Glucose, fasting, 8-hr		Normal: <100 mg/dL [10] Prediabetes: 100–125 mg/dL Diabetes: ≥126 mg/dL **Critical Value: <40 mg/dL[11]** **Critical Value: ≥400 mg/dL[10]**	
Insulin		<17 µU/ml [3]	
Glycosylated Hemoglobin (HbA1c)		Diabetes Risk [12] Normal: <5.7% Prediabetes: 5.7-6.4% Diabetes: ≥6.5%	<18 years: Criteria for diagnosing diabetes have not been established.
Thyrosine Phosphatase-like Protein Autoantibodies (IA 2)		Negative Antibody: DK<5 [3] Positive Antibody: DK≥5	Store for later
Glutamate Decarboxylase -65 (anti-GAD 65)		Negative Antibody: DK≤33 [3] Positive Antibody: DK>33	Store for later

[10] http://www.diabetes.org/diabetes-basics/diagnosis/?loc=db-slabnav
[10] https://www.mayomedicallaboratories.com/test-catalog/appendix/criticalvalues/view.php?name=Critical+Values%2FCritical+Results+List
[12] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82080

Lipids		**Clinical Guidelines and Ranges**	
Total Cholesterol, fasting		Coronary Heart Disease Risk (CHD)[13] Adult, 18+ years: Desirable: <200 mg/dL Borderline High: 200-239 mg/dL High: ≥240 mg/dL	Child, 2-17 years: Acceptable: <170 mg/dL Borderline high: 170-199 mg/dL High: ≥200 mg/dL
Triglycerides, fasting		CHD Risk[12] Adult, 18+ years: Normal: <150 mg/dL Borderline High: 150-199 mg/dL High: 200-499 mg/dL Very High: ≥500 mg/dL **Critical Value: >1,000 mg/dL**	Child, 2-9 years: Acceptable: <75 mg/dL Borderline high: 75-99 mg/dL High: ≥100 mg/dL Child, 10-17 years: Acceptable: <90 mg/dL Borderline high: 90-129 mg/dL High: > or =130 mg/dL
Low Density Lipoprotein Cholesterol (LDL), fasting		CHD Risk[12] Adult, 18+ years: Desirable: <100 mg/dL Above Desirable: 100-129 mg/dL Borderline high: 130-159 mg/dL High: 160-189 mg/dL Very high: ≥190 mg/dL	Child, 2-17 years: Acceptable: <110 mg/dL Borderline high: 110-129 mg/dL High: ≥130 mg/dL
High Density Lipoprotein Cholesterol (HDL), fasting		CHD Risk[12] Adult, 18+ years: Males: ≥40 mg/dL Females: ≥50 mg/dL	Child, 2-17 years: Low: <40 mg/dL Borderline low: 40-45 mg/dL Acceptable: > 45 mg/dL
VLDL			
Liver Tests		**Clinical Ranges**	
Alanine Aminotransferase (ALT)		15–65 U/L [5]	
Aspartate Aminotransferase (AST)		5–40 U/L [5]	
γ-Glutamyl Transferase (GGT)		Female 5–55 U/L Male 5–85 U/L [5]	
Alkaline Phosphatase (ALP)		Female: 50–136 U/L	

[13] https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8320

		Male: 40–136 U/L [5]	
Albumin (ALB)		3.4–5.0 g/dL [5] **Critical Value: <1.5 g/dL [5]** **Critical Value: >7.9 g/dL [5]**	
Total Bilirubin (TBIL)		0.0–1.0 mg/dL [5] **Critical Value: >12.9 mg/dL [5]**	
Direct Bilirubin (Conjugated Bilirubin)		0.0–0.3 mg/dL [5]	
Cytokeratin 18 M30 (CK-18 M30)		<u>No evident liver disease</u> [(27-28)]	
Cytokeratin 18 M65 (CK-18 M65)		M30: <200 U/L and M65: <300 U/L <u>TASH</u> (toxicant associated steatohepatitis; consistent with necrosis) M30: <200 U/L and M65: >300 U/L <u>Other liver disease</u> (consistent with apoptosis) M30: >200 U/L	

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Attachment 22.

Multi-site Study
PFAS Results Report
Flesch-Kincaid Readability Score – 8.1
deleting table and agency weblinks

Multi-site Study
PFAS Results Report

Dear [NAME/NAME OF PARENT OR GUARDIAN],

Per-and polyfluorinated substances (PFAS) are a group of chemicals used to make products that resist heat, oil, stains, grease, and water. Some PFAS do not break down in the environment. People are mostly exposed through PFAS-contaminated water or food. Exposure may also occur by using products that contain PFAS in the home or at work.

Table 1 shows what we measured in the blood sample [you/your child] provided for the Multi-site PFAS Health Study on *mm/dd/yyyy*.

We show [your/your child's] result for each chemical compared to the levels that half (50th %) and most (95th %) of the people in the U.S. in [your/your child's] age group were exposed to in 2013–2014.[1] Results higher than most, those in the highest 5% of people in that age group, are considered unusual.

Finding PFAS in a person's blood by itself does not mean that the chemical causes disease. Research, like the Pease Study, will provide more information to see if there are health risks from different PFAS levels in blood.

Some people will not have results for all chemicals. [You/Your child] may not have a result for a chemical test if [your/his/her] level is lower than the lab's limit of detection (<LOD). [You/Your child] may also not have a result if the blood sample did not pass a lab quality control check. If the reason for missing results is known, it will be included with [your/your child's] results.

If you have further questions about the meaning of these chemicals tests results, you may contact us by calling ATSDR at [insert study telephone number]. Below, we list some websites and federal agencies with further information on these chemicals. We also enclose our ATSDR factsheet on Frequently Asked Questions about PFAS.

Sincerely,

Study Investigators.

Where can I find more information?

Centers for Disease Control and Prevention (CDC) Resources:
National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm)

Agency for Toxic Substances and Disease Registry (ATSDR)
Toxicological Profiles and ToxFAQs (https://www.atsdr.cdc.gov/ToxProfiles/index.asp and https://www.atsdr.cdc.gov/toxfaqs/index.asp)

U.S. Environmental Protection Agency (EPA)
Integrated Risk-Information System (IRIS) (https://www.epa.gov/iris)

[1] From the 2013-2014 National Health and Examination Survey (NHANES).

Attachment 22.

Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)
Frequently Asked Questions

8/22/17

What are PFAS?

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a large group of man-made chemicals that have been used in industry and consumer products worldwide since the 1950s.

- PFAS do not occur naturally, but are widespread in the environment.
- PFAS are found in people, wildlife and fish all over the world.
- Some PFAS can stay in people's bodies a long time.
- Some PFAS do not break down easily in the environment.

How can I be exposed to PFAS?

PFAS contamination may be in drinking water, food, indoor dust, some consumer products, and workplaces. Most non worker exposures occur through drinking contaminated water or eating food that contains PFAS.

Although some types of PFAS are no longer used, some products may still contain PFAS:

- Food packaging materials
- Nonstick cookware
- Stain resistant carpet treatments
- Water resistant clothing
- Cleaning products
- Paints, varnishes and sealants
- Firefighting foam
- Some cosmetics

How can I reduce my exposure to PFAS?

PFAS are present at low levels in some food products and in the environment (air, water, soil etc.), so you probably cannot prevent PFAS exposure altogether. However, if you live near known sources of PFAS contamination, you can take steps to reduce your risk of exposure.

- If your drinking water contains PFAS above the EPA Lifetime Health Advisory, consider using an alternative or treated water source for any activity in which you might swallow water:
  - » drinking
  - » food preparation
  - » cooking
  - » brushing teeth, and
  - » preparing infant formula
- Check for fish advisories for water bodies where you fish.
  - » Follow fish advisories that tell people to stop or limit eating fish from waters contaminated with PFAS or other compounds.
  - » Research has shown the benefits of eating fish, so continue to eat fish from safe sources as part of your healthy diet.
- Read consumer product labels and avoid using those with PFAS.

Agency for Toxic Substances and Disease Registry
Division of Community Health Investigations

ATSDR

How can PFAS affect people's health?

Some scientific studies suggest that certain PFAS may affect different systems in the body. NCEH/ATSDR is working with various partners to better understand how exposure to PFAS might affect people's health—especially how exposure to PFAS in water and food may be harmful. Although more research is needed, some studies in people have shown that certain PFAS may:

- affect growth, learning, and behavior of infants and older children
- lower a woman's chance of getting pregnant
- interfere with the body's natural hormones
- increase cholesterol levels
- affect the immune system and
- increase the risk of cancer

At this time, scientists are still learning about the health effects of exposures to mixtures of PFAS.

How can I learn more?

You can visit the following websites for more information:

- **CDC/ATSDR:**
  - CDC Info: https://www.cdc.gov/cdc-info/, or **(800) 232-4636**.
  - www.atsdr.cdc.gov/pfc/index.html
  - https://www.cdc.gov/exposurereport/index.html
- **Environmental Protection Agency (EPA):** https://www.epa.gov/chemical-research/research-and-polyfluoroalkyl-substances-pfas
- **Food and Drug Administration:** https://www.fda.gov/food/newsevents/constituentupdates/ucm479465.htm
- **National Toxicology Program:** https://ntp.niehs.nih.gov/pubhealth/hat/noms/pfoa/index.html

If you have questions about the products you use in your home, please contact the **Consumer Product Safety Commission (CPSC)** at **(800) 638-2772**.

List of Common PFAS and Their Abbreviations:

Abbreviation	Chemical name
PFOS	Perfluorooctane sulfonic acid
PFOA (or C8)	Perfluorooctanoic acid
PFNA	Perfluorononanoic acid
PFDA	Perfluorodecanoic acid
PFOSA (or FOSA)	Perfluorooctane sulfonaminde
MeFOSAA (aka Me-PFOSA-AcOH)	2-(N-Methyl-perfluorooctane sulfonamido) acetic acid
Et-FOSAA (aka Et-PFOSA-AcOH)	2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid
PFHxS	Perfluorohexane sulfonic acid