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Per- and Polyfluoroalkyl Substances Multi-Site Study

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Editor's Note: As part of our continued effort to highlight innovative approaches to improve the health and environment of communities, the *Journal* is pleased to publish regular columns from the Agency for Toxic Substances and Disease Registry (ATSDR) at the Centers for Disease Control and Prevention (CDC). ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances. The purpose of this column is to inform readers of ATSDR's activities and initiatives to better understand the relationship between exposure to hazardous substances in the environment, its impact on human health, and how to protect public health.

The conclusions of this column are those of the author(s) and do not necessarily represent the official position of ATSDR or CDC.

Background

Per- and polyfluoroalkyl substances (PFAS) are a family of chemicals that have been manufactured and used across a variety of industries in the U.S. since the 1940s (Bulka et al., 2021). There are over 5,000 chemicals in the PFAS family. Three of the most commonly detected PFAS include perfluorooctane sulfonate (PFOS), perfluorooctanoate acid (PFOA), and perfluorohexane sulfonate (PFHxS). These chemicals are persistent in the environment and may remain in the human body for years (Rogers et al., 2021).

PFAS-contaminated drinking water is widespread in the U.S. with an estimated 18–80 million people potentially exposed to PFOA in their tap water (Andrews & Naidenko, 2020). Industrial facilities that manufacture or use PFAS have contaminated drinking water in many of the communities surrounding their facilities, including facilities in Alabama, Minnesota, New Hampshire, New Jersey, New York, Ohio, Vermont, and West Virginia (Kray

& Wightman, 2018). Additionally, Hu et al. (2016) reported that 66 water supplies that serve over 6 million people across the U.S. had at least one sample at or above the U.S. Environmental Protection Agency's lifetime health advisory for PFOA and PFOS of 70 ppt. The U.S. National Health and Nutrition Examination Survey reported that PFAS were detected in the blood of >98% of U.S. general population (Calafat et al., 2019).

Since the 1960s, military and civilian facilities in the U.S. have used aqueous film-forming foam (AFFF) that contains PFAS to extinguish fires (Badauel et al., 2017). The foams and the chemicals they contain are released directly into the environment (Glüge et al., 2020). At some facilities, use of AFFF resulted in the migration of PFAS through the soil (Brusseau et al., 2020) and into drinking water sources for the surrounding communities (Stoiber et al., 2020).

Many epidemiological studies have examined the potential of PFAS to induce adverse

health effects (Bell et al., 2021; Brase et al., 2021; Chohan et al., 2020; Fenton et al., 2021). Although most of the studies do not establish causality, the body of scientific evidence linking PFAS exposures with adverse health effects is rapidly growing. In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) released a health consultation at Pease International Tradeport in Portsmouth, New Hampshire. The health consultation found that drinking water from the Pease International Tradeport public water system between January 1993 through May 2014 might have led to an increased risk of harmful health effects among workers at the Tradeport and children attending on-site childcare centers (Agency for Toxic Substances and Disease Registry [ATSDR], 2020a).

Other epidemiological studies have found associations between PFAS and elevated cholesterol levels, reproductive effects (Anderko & Pennea, 2020), and decreased birth weight (Eick et al., 2020). PFAS has also been associated with increased uric acid levels, some cancer risks, and decreased immune response (ATSDR, 2020b). A study conducted by the National Toxicology Program found that PFOA and PFOS moderately suppressed antibody responses in humans and concluded that these chemicals alter immune functions in humans (National Toxicology Program, 2021).

Study Overview

On September 23, 2019, the Centers for Disease Control and Prevention (CDC) and ATSDR announced the recipients of a cooperative agreement titled the Multi-Site Study (MSS) of the Health Implications of Exposure to PFAS-Contaminated Drinking Water. (Table 1, Figure 1). ATSDR's ongoing study

TABLE 1

Per- and Polyfluoroalkyl Substances Multi-Site Study Cooperative Agreement Partners and Locations

Partner	Site Location
Colorado School of Public Health, University of Colorado, Anschutz Medical Campus	El Paso County, Colorado
Michigan Department of Health and Human Services	Parchment/Cooper Township, Michigan Belmont/Rockford area, Michigan
Research Triangle Institute International and Pennsylvania Department of Health	Montgomery County, Pennsylvania Bucks County, Pennsylvania
Rutgers Biomedical and Health Sciences, School of Public Health	Gloucester County, New Jersey
Silent Spring Institute	Hyannis, Massachusetts Ayer, Massachusetts
University at Albany, State University of New York and New York State Department of Health	Hoosick Falls, New York Newburgh, New York
University of California, Irvine	Communities near the University of California, Irvine Medical Center, California

of PFAS exposure at the Pease International Tradeport in Portsmouth, New Hampshire, is serving as the first site in the MSS. The MSS is a cross-sectional study that aims to evaluate the potential associations between measured and historically reconstructed serum levels of PFAS, including PFOA, PFOS, PFHxS, and selected health outcomes in a community.

Specifically, the MSS will examine potential associations in children and adults between serum PFAS and lipids, renal function, kidney disease, thyroid hormones, thyroid disease, liver function, liver disease, glycemic parameters, and diabetes, as well as immune response and function. The MSS will also investigate differences in sex hormones, sexual maturation, vaccine response, and neurobehavioral outcomes in children as related to PFAS. In adults, additional outcomes of interest include cardiovascular disease, osteoarthritis, osteoporosis, endometriosis, and autoimmune diseases.

These health outcomes were selected based on epidemiological and scientific studies including: 1) endpoints that have been evaluated in previous PFAS research and need additional follow up, 2) endpoints observed to be elevated in studies of other chemicals with similar in vitro and in vivo activity, and 3) findings from other PFAS toxicological and epidemiological studies. The proposed sample sizes for the MSS have sufficient power to

detect mean differences in the ranges of those observed in other well-designed epidemiologic studies and allow for the calculation of odds ratios.

The MSS sites have a wide range of PFAS exposure levels. This range will allow for the potential evaluation of exposure–response trends, including exposure effects at low levels. ATSDR also took into consideration geographic coverage when reviewing MSS applications. Participant recruitment will begin in summer/fall 2021 with a target sample size of 2,100 children and 7,000 adults across all sites.

Participant eligibility criteria includes exposure to PFAS within the last 15 years, which is due to considerations based upon 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. Adults must be at least 18 years old at the start of the study and have resided in areas with documented past or present PFAS drinking water concentrations. People who were ever employed as a firefighter, participated in fire training exercises using AFFF foam, or those employed at industrial facilities that used PFAS chemicals in the manufacturing process are not eligible to participate in the study. Children must be between 4 and 17 years old, have resided in areas with documented past or present PFAS drinking water

concentrations, or were exposed in utero or through breastfeeding when the mother consumed the contaminated drinking water. Similar to adult participants, children will be excluded if their birth individuals 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. Firefighter and other occupational exposures likely involve more exposure routes than ingestion and are higher than those associated with drinking water exposures. For this reason, occupationally exposed individuals are excluded from the MSS.

Study investigators will collect blood samples from participants to measure serum PFAS levels and several biomarkers of biological effects. The study will also collect urine samples from participants to measure kidney function biomarkers and to archive for potential future analysis of PFAS. Serum samples will be archived to conduct analyses of additional PFAS and specific effect biomarkers, as feasible.

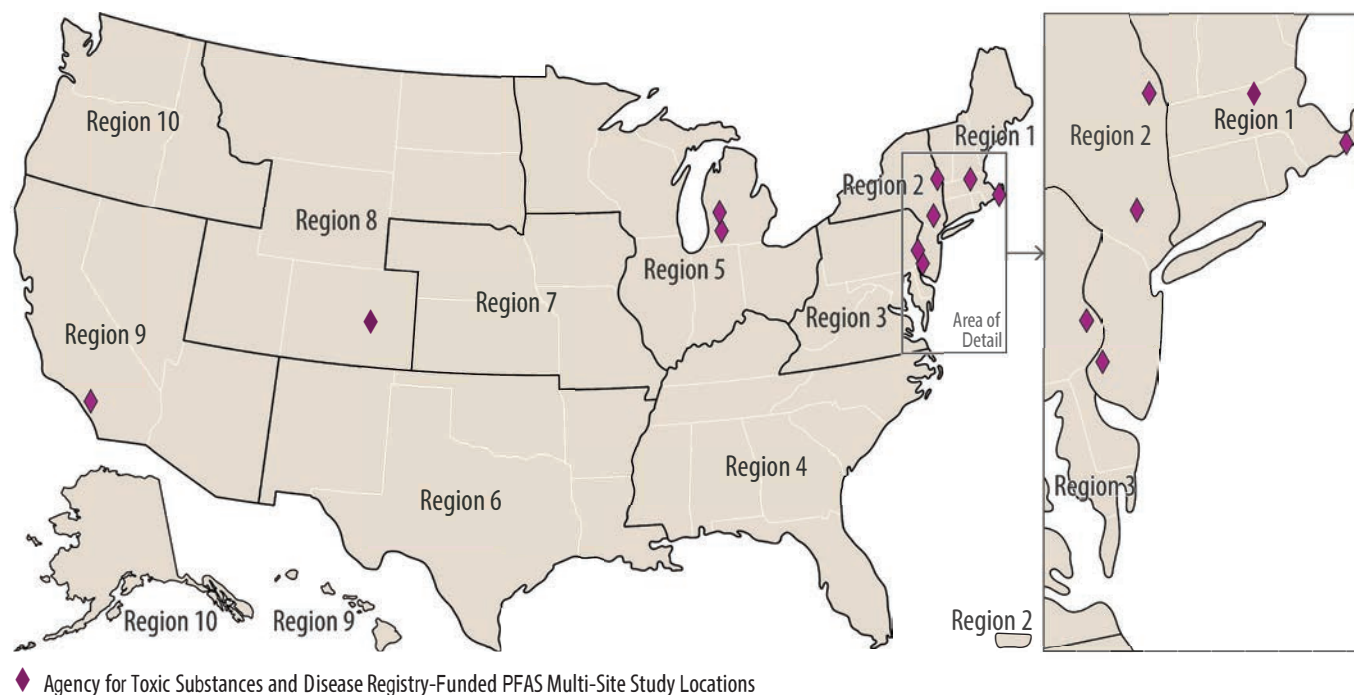
Adult participants and a parent or guardian of participating minor children will complete a questionnaire that includes their residential, medical, and occupational history, in addition to their water consumption habits. With consent from study participants, the MSS will access medical and school records as necessary to confirm adverse health outcomes reported in the questionnaire. To facilitate access to these medical and school records, study site investigators will reach out to local medical societies, the public school system, and private schools to enlist cooperation with the study. The investigators will also work closely with local and state agencies (e.g., public school systems and 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.

Study Accomplishments

In preparation for individual MSS sites launching their studies, pharmacokinetic modeling and historical reconstruction work groups were established. The pharmacokinetic modeling work group will coordinate

FIGURE 1

Per- and Polyfluoroalkyl Substances (PFAS) Multi-Site Study Regions and Locations



the technical evaluation, quality assurance, and quality control for all pharmacokinetic and physiologically-based pharmacokinetic models used for historical serum reconstruction. Similarly, the historical reconstruction work group will coordinate technical evaluation, quality assurance, and quality control for all methods and models in the historical reconstruction of groundwater and drinking water contamination.

Several study outreach efforts have been established to kick off the MSS. The study sites have developed community engagement plans, recruitment flyers, websites, and study logos. Study outreach efforts are ongoing and vary by site. For example, one site has designed strategies to connect with segments of potentially difficult-to-reach populations including veterans, older adults, and people who identify as Hispanic or Latino. To monitor public awareness of the MSS on social media, ATSDR created a standard MSS hashtag, #PFASmss, that is currently being tracked on Instagram and Twitter.

The MSS will provide serum PFAS levels and the results of the clinical tests and effect

biomarker tests to each study participant. Consultation and technical assistance (e.g., workshops and training programs) to clinicians in each community will be provided by cooperative agreement partners and ATSDR. The clinician outreach is part of community engagement efforts to provide answers to questions about the potential effects of elevated PFAS levels on health, to assist with the interpretation of results, and to make recommendations for additional tests and/or treatments. ATSDR will provide summaries of the study findings to the participating communities and will assist in interpreting these results. As epidemiological research on the health effects of drinking water exposure to PFAS, other than PFOA, is at an early stage, the MSS will make an important contribution to the scientific literature by expanding knowledge in this area and helping to address concerns about past exposure. 🐼

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Did You Know?

The NEHA-FDA Retail Flexible Funding Model Grant Program application portal is now open! Awarding \$6 million over a 3-year period, this new grant program serves to leverage and advance the food safety efforts of retail food regulatory agencies through conformance of the Voluntary National Retail Food Regulatory Program Standards. Learn about application requirements, important deadlines, and actions to take to prepare a successful application at www.neha.org/retailgrants. The deadline to submit an application is **November 15**.