

Testimony of Adam Nordell, Campaign Manager at Defend Our Health, Freedom, ME

**In SUPPORT of LD 582**

**An Act to Require Health Insurance Carriers to Provide Coverage for Blood Testing for Perfluoroalkyl and Polyfluoroalkyl Substances**

Before the Health Coverage, Insurance and Financial Services Committee  
March 4th, 2025

Senator Bailey, Representative Mathieson, and members of the Health Coverage, Insurance, and Financial Services Committee. My name is Adam Nordell and I work as a campaign manager at Defend Our Health. Please accept this testimony in support of LD 582.

PFAS has impacted my family and my community. As many of you know, my wife and I lost our farm to the chemicals. Many of our friends have been exposed as well. Access to the PFAS blood serum test has been crucial to understanding our exposure and making lifestyle changes to protect our health. This test has allowed our doctors to begin screening for and treating PFAS linked illnesses. Recently, it has even allowed us to access a treatment to get the chemicals out of our bodies.

In 2022 the National Academies of Science, Engineering and Medicine (NASEM) released a sprawling report on clinical care of PFAS exposed patients. The NASEM report recommended the PFAS blood serum test for people at high risk of exposure, including people living and working near sludge spread farms, firefighters, veterans, and people who live near airports, military bases, landfills and incinerators. Once we document our exposure, the NASEM report highlights PFAS-linked illnesses and identifies medical screening needed for early identification of these illnesses. Crucially, the report identifies blood serum levels at which clinicians and patients should pursue exposure reduction and screen for the linked illnesses.

We're aware of the widespread impacts of sludge in our state. But PFAS has also impacted communities like Brunswick, Bangor, Limestone and East Machias, where PFAS laden firefighting foam was used by the military. According to DEP data, the worst contaminated well in the state is near one of these closed military facilities. PFAS also presents an occupational hazard to our firefighters, who describe getting drenched in the AFFF foam while protecting their communities. These PFAS exposed Mainers need access to preventative care, which hinges on accessing the PFAS blood serum test.

One of most traumatic aspects of legacy PFAS exposure is that the toxic chemicals can linger in the body for decades. Fortunately, several Maine hospital systems have recently begun proscribing a treatment which can reduce the PFAS body burden. I have attached several studies for your reference. In my first three months on the medicine, my blood serum levels dropped by about 45%, which is about ten times faster than my body was previously expelling the chemical. Hopefully this will allow my organs to heal any damage and avert the development of illnesses. In the meantime, my doctor understands my exposure and the risk it entails and is able to screen for and treat any illnesses that develop. I would not have access to any of that without the blood serum test. State and federal law already require insurance companies to cover preventative care as an essential health benefit. The PFAS blood serum test is a critical component of preventative care for Maine's PFAS exposed communities. Please vote 'ought to pass' on LD 582.

Thank you for your consideration

Adam Nordell

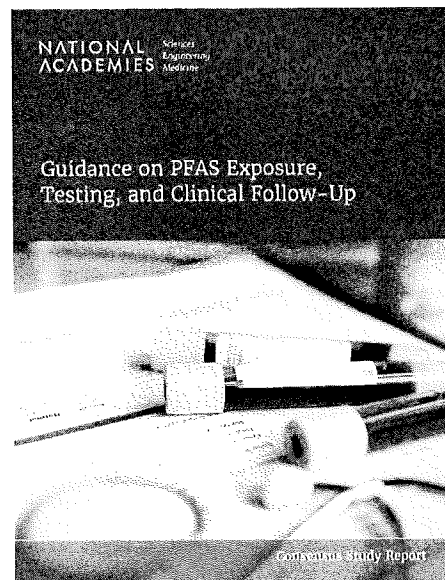
Campaign manager  
Defend Our Health

# Guidance on PFAS Exposure, Testing, and Clinical Follow-Up

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a class of chemicals that includes over 12,000 different compounds, some of which are linked to health effects including certain cancers, thyroid dysfunction, small reductions in birth weight, and high cholesterol. PFAS are used in thousands of products, such as water and stain proof fabrics, non-stick cookware, and fire-fighting foams, because they have desirable chemical properties that repel oil and water, reduce friction, and resist temperature changes. PFAS compounds are often referred to as “forever chemicals” because they are resistant to degradation and when they do break down, the chemical products will include another PFAS.

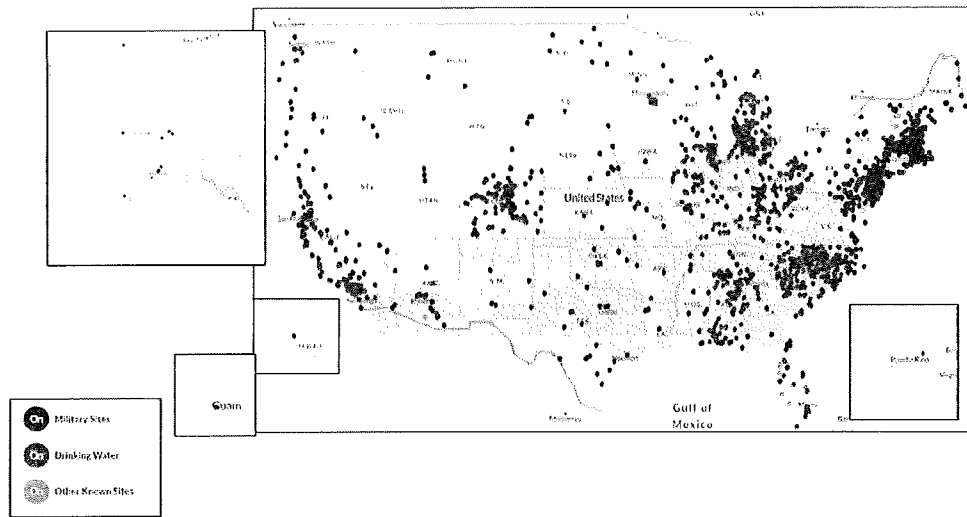
An estimated 2,854 U.S. locations (in all 50 states and two territories) have some level of PFAS contamination (Figure 1). Although not all of the contamination exceeds health advisories, the pervasiveness of the contamination is alarming. The people who live, work, and play in environments where PFAS contamination exceeds standards most often do not know how to protect themselves from the health risks of exposure. Some members of communities who have discovered their exposure exceeds health advisory levels are calling for a medical program that prevents, leads to early disease detection, or treats diseases related to the health risks they may face.

To help clinicians respond to patient concerns about PFAS exposure, the Agency for Toxic Substances Disease Registry (ATSDR) published guidance for clinicians that summarizes general information about PFAS and PFAS health studies and suggests answers to example patient questions. However, the ATSDR’s guidance does not provide specific recommendations on when to test for PFAS, how to interpret the results, or what clinical follow-up based on PFAS exposure might look like. Conducted at the request of ATSDR and the National Institute of Environmental Health Sciences (NIEHS), this report develops principles and recommendations for biological testing for PFAS exposure and



# PFAS Water Contamination

Estimated in 2,854 sites in 50 states and two territories



**FIGURE 1** PFAS Contamination Across the U.S. SOURCE: Environmental Working Group (EWG).

clinical evaluation for those exposed to help ATSDR update its guidance.

## POTENTIAL HEALTH EFFECTS OF PFAS

In order to determine the health effects of PFAS, the Committee conducted a literature review of studies that evaluated the effects of PFAS in humans. The committee's review focused on the PFAS compounds that are currently being measured in the National Health and Nutrition Examination Survey.<sup>1</sup> The Committee synthesized available evidence, including previous decisions from other authoritative bodies and more recent human studies, into four categories of "strength of evidence" used by other National Academies' committees: (1) Sufficient evidence of an association; (2) Limited suggestive evidence of an association; (3) Inadequate or insufficient evidence of an association; and (4) Limited suggestive evidence of no association. The Committee's conclusions are summarized in Table 1. Because most people are exposed to mixtures of PFAS, making it difficult to disentangle the specific effects

<sup>1</sup> PFAS compounds currently being measured in the National Health and Nutrition Examination Survey are perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), Perfluorodecanoic acid (PFDA), Perfluoroundecanoic acid (PFuDA), and Methyl-perfluorooctane sulfonamide (MeFOSAA)





of each PFAS, the Committee provided one strength of evidence determination for all PFAS for each health effect.

## PFAS EXPOSURE REDUCTION

The primary exposure route to PFAS in non-occupational settings is likely ingestion. This may include drinking contaminated water and eating contaminated foods such as vegetables, fish, wildlife, meat, or dairy products from contaminated soil or water. PFAS are often used in food contact materials such as microwave popcorn bags or packaging of fast foods or processed foods. Exposure may also occur when dust containing PFAS is ingested. PFAS can transfer to the fetus during pregnancy, and in early life through feeding with formula made with contaminated water or through breastfeeding. Inhalation is the most common pathway in occupational settings, and is a route of exposure for people living near fluorochemical plants, or incinerators. Dermal exposure has not been well-studied but could be possible.

To advise patients who would like to reduce their exposure to PFAS, clinicians should: (1) talk with their patients to determine if and how they might be exposed to PFAS; (2) advise that those with occupational exposure

TABLE 1

CATEGORY OF ASSOCIATION	HEALTH OUTCOMES WITH INCREASED RISK ASSOCIATE WITH PFAS EXPOSURE
 <p><b>Sufficient evidence of an association</b> Based on strong evidence, there is high confidence that there is an association between exposure to PFAS and the health outcome. It is unlikely that the association is due to chance or bias.</p>	<ul style="list-style-type: none"> <li>• Decreased antibody response (in adults and children)</li> <li>• Dyslipidemia (in adults and children)</li> <li>• Decreased infant and fetal growth</li> <li>• Increased risk of kidney cancer (in adults)</li> </ul>
 <p><b>Limited suggestive evidence of an association</b> Based on limited evidence, there is moderate confidence that there is an association between exposure to PFAS and the health outcome. It is possible that the association is due to chance or bias.</p>	<ul style="list-style-type: none"> <li>• Increased risk of breast cancer (in adults)</li> <li>• Liver enzyme alterations (in adults and children)</li> <li>• Increased risk of pregnancy-induced hypertension (gestational hypertension and preeclampsia)</li> <li>• Increased risk of testicular cancer (in adults)</li> <li>• Thyroid disease and dysfunction (in adults)</li> <li>• Increased risk of ulcerative colitis (in adults)</li> </ul>
 <p><b>Inadequate or Insufficient Evidence to Determine an Association</b> Based on inconsistent evidence, a lack of evidence, or evidence of insufficient quality, there is moderate confidence that there is an association between exposure to PFAS and the health outcome. No conclusion can be made about a potential association.</p>	<ul style="list-style-type: none"> <li>• Immune effects other than reduced antibody response, and ulcerative colitis; Cardiovascular outcomes other than dyslipidemia;</li> <li>• Developmental outcomes other than small reductions in birthweight</li> <li>• Cancers other than kidney, breast, and testicular; Reproductive effects other than hypertensive disorders of pregnancy; Endocrine disorders other than thyroid hormone levels; Hepatic effects other than liver enzyme levels; Respiratory effects; Hematological effects</li> <li>• Musculoskeletal effects, such as effects on bone mineral density; Renal effects, such as renal disease; Neurological effects</li> </ul>
 <p><b>Limited Suggestive Evidence of No Association</b> Based on at least limited evidence, there is at least moderate confidence that there is NO association between PFAS and the health outcome.</p>	<ul style="list-style-type: none"> <li>• No outcomes were identified.</li> </ul>

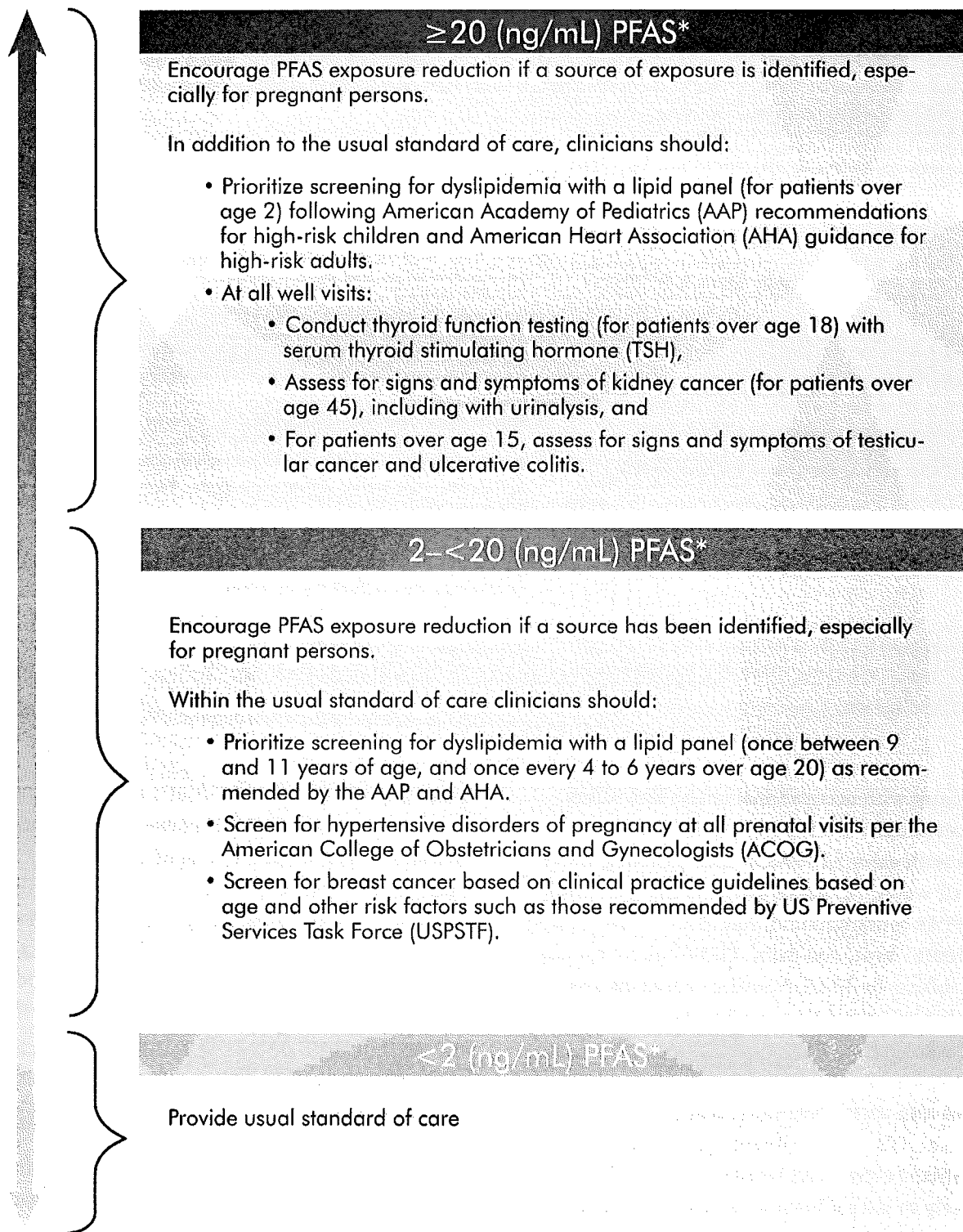
to PFAS consult with occupational health and safety professionals about reducing exposure; (3) advise individuals with elevated PFAS in their drinking water to filter their water; (4) advise patients living in areas of known PFAS contamination that PFAS can be present in fish, wildlife, meat, and dairy. Clinicians counseling parents of infants on PFAS exposure should discuss infant feeding and steps that can be taken to lower sources of exposure to PFAS.

#### PFAS TESTING AND LEVELS THAT CAN INFORM CLINICAL CARE

Report advises ATSDR to update its guidance to say, clinicians should offer PFAS blood testing to patients who are likely to have a history of elevated exposure to PFAS. PFAS testing has many potential benefits, such as empowering people to manage their own health, but it also carries some harms, such as stress or concern about the health effects of PFAS exposure. Decisions about PFAS testing require shared, informed decision making between patient and clinician. Clinicians should explain that exposure biomonitoring may provide important

information about an individual's exposure levels which might guide clinical follow-up. But PFAS testing measures exposure at the time of sample collection, and a person with low levels today may have had higher levels in the past. At the same time, this information cannot indicate or predict how likely it is that an individual will end up with a particular condition. Discussions about PFAS testing should always include information about how PFAS exposure occurs, potential health effects of PFAS, limitations of PFAS testing, and the benefits and harms of PFAS testing.

To determine PFAS levels in serum or plasma that could inform clinical care, the Committee considered publications from the Human Biomonitoring Commission in Germany and the European Food Safety Authority. These organizations determined guidance values that can be interpreted as levels below which health effects are unlikely to be observed, and levels above which effects have been observed in both the general population and more sensitive groups such



\* Simple additive sum of MeFOSAA, PFHxS, PFOA (linear and branched isomers), PFDA, PFUnDA, PFOS (linear and branched isomers), and PFNA in serum or plasma

FIGURE 2 Clinical guidance for follow-up with patients after PFAS testing.

as pregnant persons. Using the risk based values the committee found and assumptions of dose additivity, the committee determined that:

- Adverse health effects related to PFAS exposure are not expected at less than 2 nanograms per milliliter (ng/mL).
- There is a potential for adverse effects, especially in sensitive populations, between 2 and 20 ng/mL.
- There is an increased risk of adverse effects above 20 ng/mL.

Testing for PFAS, though expensive, offers an opportunity to identify people who may need to reduce PFAS exposure and who are at increased risk of certain health outcomes. Race, age, and other social and demographic characteristics already have disadvantaged many patients from accessing clinical preventive services, meaning that these groups may not be offered PFAS testing and the accompanying exposure reduction counseling. If testing primarily occurs among those with stable access to health care, there could be the unintended consequence of aggravating disparities in exposure to PFAS, a severe disadvantage of encouraging testing without a funded PFAS testing program with a national scope.

#### **PATIENT FOLLOW-UP FOR PFAS-ASSOCIATED HEALTH EFFECTS**

Most health effects or conditions found to be associated with PFAS exposure are already common in the general population and all have multiple known risk factors. The Committee's guidance for patient follow-up is summarized in Figure 2, which suggests that clinicians

engage in shared, informed decision making with their patients regarding follow-up care for PFAS-associated health endpoints. For patients with a PFAS level of 2 ng/mL to less than 20 ng/mL, clinicians should encourage the standard of care for conditions associated with PFAS. For a PFAS level of 20 ng/mL or greater, clinicians should screen for dyslipidemia following guidance for high risk individuals, thyroid dysfunction (for patients over 18), signs and symptoms of testicular cancer (for patients over 15) and ulcerative colitis, and signs and symptoms of kidney cancer with urinalysis (for patients over 45).

#### **NEXT STEPS TO GUIDE CLINICIANS AND PROTECT PUBLIC HEALTH**

ATSDR should revise its guidance to ensure consistency with the findings, conclusions, and recommendations in this report, and improve the writing, design, dissemination, and implementation of the guidance. Evidence of the health effects of PFAS should be updated every two years, and the clinical guidance should be updated at least every five years.

Public health requires the use of multifaceted approaches to emerging health issues. In environmental health—the subset of public health focused on environmental factors—mitigation of potential harms associated with chemical exposures is often complicated because there is no exposure surveillance system exists for most chemicals. The people and communities with high exposures to PFAS need to be identified. The recommendations in this report will be most protective of the public's health if they are part of a national effort toward increased biomonitoring, exposure surveillance, and clinicians' and public health professionals' education on environmental health issues.

**COMMUNITY LIAISONS**

**Laurene Allen**

Merrimack Citizens for Clean Water

**Andrea Amico**

Testing for Pease

**Stel Bailey**

Fight for Zero

**Kyla Bennett**

Public Employees for Environmental  
Responsibility

**Karen Blondel**

Public Housing Civic Association, Inc.

**Phil Brown**

Northeastern University

**Alberto J. Caban-Martinez**

University of Miami

**Cheryl Cail**

South Carolina Indian Affairs  
Commission/SC Idle No More

**Courtney Carignan**

Michigan State University

**Tracy Carluccio**

Delaware Riverkeeper Network

**Jamie Dewitt**

East Carolina University

**Emily Donovan**

Clean Cape Fear

**Alan Ducatman**

West Virginia University

**Patrick Elder**

Military Poisons

**Teresa Gerade**

Don't Undermine Memphremagog's Purity

**Hope Grosse**

Buxmont Coalition for Safe Water

**Loreen Hackett**

PFOA Project New York

**Ayesha Khan**

Nantucket PFAS Action Group

**Rainer Lohmann**

University of Rhode Island Superfund  
Research Center

**Samraa Luqman**

Concerned Residents for South Dearborn

**Beth Markesino**

North Carolina Stop Gen-X In Our Water

**Aaron Maruzzo**

University of California, Berkeley

**Tobyn Mcnaughton**

Resident of Belmont, Michigan

**Kristen Mello**

Westfield Residents Advocating for  
Themselves

**Elizabeth Neary**

Wisconsin Environmental Health Network

**Laura Olah**

Citizens for Safe Water Around Badger

**Jacob Park**

University of Johannesburg,  
Castleton University

**Sue Phelan**

GreenCAPE

**Andrea Rich**

Save Our Water

**Dana Sargent**

Cape Fear River Watch

**Laurel Schaidler**

Silent Spring Institute

**Linda Shosie**

Mothers for Safe Air & Safe Water

**Lenny Siegel**

Center for Public Environmental Oversight

**Mike Watters**

Gray's Creek Residents United Against  
PFAS in our Wells and Rivers

**La'Meshia Whittington**

Meredith College/North Carolina Black  
Alliance

**Alan Woolf**

Harvard Medical School

**Cathy Wusterbarth**

Need Our Water

**Sandy Wynn-Stelt**

Great Lakes PFAS Action Network

**COMMITTEE ON THE GUIDANCE ON PFAS  
TESTING AND HEALTH OUTCOMES**

**Bruce N. Calonge** (*Chair*)  
University of Colorado School of  
Medicine and School of Public Health

**Laura Anderko**  
Villanova University

**Dana Boyd Barr**  
Emory University Rollins School of  
Public Health

**Erin Bell**  
School of Public Health, University at Albany

**Kevin Elliott**  
Michigan State University

**Melissa Gonzales**  
Tulane University School of Public Health  
and Tropical Medicine

**Erin Haynes**  
University of Kentucky College of  
Public Health

**Jane Hoppin**  
North Carolina State University

**Tamarra James-Todd**  
Harvard T.H. Chan School of Public Health

**Alex Kemper**  
The Ohio State University College of Medicine,  
Nationwide Children's Hospital

**Brian Linde**  
Yale School of Medicine

**Marc-André Verner**  
Université de Montréal

**Veronica Vieira**  
University of California, Irvine

**Xiaobin Wang**  
Johns Hopkins Bloomberg School of  
Public Health and School of Medicine

**Chris Wiant**  
Caring for Colorado Foundation

This Consensus Study Report Highlights was prepared by the National Academies based on the Consensus Study Report *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up* (2022).

The study was sponsored by the Centers for Disease Control and Prevention, National Institutes of Environmental Health Sciences, National Institutes of Health, and U.S. Department of Health and Human Services. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

This Consensus Study Report is available from the National Academies Press (800) 624-6242 | <http://www.nap.edu> | <http://www.nationalacademies.org>

**STUDY STAFF**

**HEALTH AND MEDICINE DIVISION STAFF**

**Elizabeth Barksdale Boyle**  
Study Director

**Alexis Wojtowicz**  
Associate Program Officer

**Alexandra McKay**  
Senior Program Assistant

**Rose Marie Martinez**  
Senior Board Director, Board on Population  
Health and Public Health Practice

**DIVISION ON EARTH AND LIFE STUDIES STAFF**

**Marilee Shelton-Davenport**  
(until March 2012)  
Senior Program Officer

**Kaley Beins**  
Program Officer

**Kate Guyton**  
Senior Program Officer

**Clifford Duke**  
Board Director, Board on  
Environmental Studies and Toxicology

**CONSULTANTS**

**Allie Boman**  
Briere Associates, Inc.

**Rona Briere**  
Briere Associates, Inc.

**Cary Haver**  
ICF Resources, LLC

**Jordan Kuiper**  
Johns Hopkins University

**Judy LaKind**  
LaKind Associates

**Kate Marquess**  
Johns Hopkins University

**Melissa Miller**  
ICF Resources, LLC

**Josh Naiman**  
LaKind Associates

**Anna Ruth Robuck**  
Icahn School of Medicine at Mount  
Sinai

**Margaret Shandling**  
Briere Associates, Inc.

**Lauren Tobias**  
Maven Messaging

To read the full report, please visit  
<http://www.nationalacademies.org/hmd>

**Health and Medicine Division  
Division on Earth and Life Studies**

**NATIONAL  
ACADEMIES** *Sciences  
Engineering  
Medicine*

Copyright 2022 by the National Academy of Sciences. All rights reserved.





Full length article

# Substantial decrease of PFAS with anion exchange resin treatment – A clinical cross-over trial

Janne Julie Møller<sup>a</sup>, Ann Christine Lyngberg<sup>a</sup>, Paula Edeusa Christina Hammer<sup>a</sup>,  
Esben Meulengracht Flachs<sup>a</sup>, Ole Steen Mortensen<sup>a,b</sup>, Tina Kold Jensen<sup>c</sup>, Gesche Jürgens<sup>d</sup>,  
Axel Andersson<sup>e</sup>, Anne Merete Boas Soja<sup>f,g</sup>, Morten Lindhardt<sup>f,g,\*</sup>

<sup>a</sup> Department of Occupational and Social Medicine, University Hospital of Holbaek, Denmark

<sup>b</sup> Department of Public Health, Section of Social Medicine, University of Copenhagen, Copenhagen, Denmark

<sup>c</sup> Department of Public Health, Clinical Pharmacology, Pharmacy and Environmental Medicine, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

<sup>d</sup> Clinical Pharmacology Unit, Zealand University Hospital, Roskilde, Denmark

<sup>e</sup> School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

<sup>f</sup> Department of Internal Medicine 1, University Hospital - Holbaek, Holbaek, Denmark

<sup>g</sup> Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

## ARTICLE INFO

Handling Editor: Adrian Covaci

### Keywords:

Environmental chemistry

PFAS

Clinical trial

Pharmacological treatment

Anion exchange resin

## ABSTRACT

**Background:** Per- and polyfluoroalkyl substances (PFAS) are heat and stain resisting chemicals. They are persistent, bioaccumulating and spread ubiquitously. Many hotspots where humans are exposed to high levels of PFAS have been reported. A few small observational studies in humans suggest that treatment with an Anion Exchange Resin (AER) decreases serum PFAS. This first clinical controlled crossover study aimed to assess whether AER decreases perfluorooctanesulfonic acid (PFOS) in highly exposed adults.

**Methods:** An open label 1:1 randomized treatment sequence crossover study with allocation to oral AER (cholestyramine 4 g three times daily) or observation for 12 weeks was conducted among citizens from a PFAS hotspot. Main inclusion criteria was serum PFOS > 21 ng/mL. Primary endpoint was change in serum PFOS levels between treatment and observational period.

**Results:** In total, 45 participants were included with a mean age of 50 years (SD 13). Serum PFOS baseline median was 191 ng/mL (IQR: 129–229) and decreased with a mean of 115 ng/mL (95 % CI: 89–140) on treatment, and 4.3 ng/mL in observation period corresponding to a decrease of 60 % (95 % CI: 53–67;  $p < 0.0001$ ). PFHxS, PFOA, PFNA and PFDA decreased during treatment between 15 and 44 %. No serious adverse events were reported.

**Conclusions:** Oral treatment with AER significantly lowered serum PFOS concentrations suggesting a possible treatment for enhancing elimination of PFOS in highly exposed adults.

## 1. Introduction

Per- and polyfluoroalkyl substances (PFAS) have been widely used in industrial and consumer products since the middle of the 20th century, due to their heat resisting and water- and grease-repelling properties (EFSA CONTAM PANEL et al., 2020). PFAS are persistent, bioaccumulating and found in human biomonitoring studies worldwide (Fromme et al., 2009; Roth et al., 2020). PFAS have been linked to a wide range of adverse health effects, including hormonal and

immunological disturbances, elevated cholesterol and liver enzymes, and an increased risk of certain cancers (ATSDR, 2021; EFSA CONTAM PANEL et al., 2020; National Academies, 2022). Commonly measured PFAS are perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA). Since 2006 regulations for individual PFAS have been set by the United Nations Environmental Programme (UNEP) "The Stockholm Convention". Nonetheless, many hotspot areas, in which humans are highly exposed to PFAS through

\* Corresponding author at: Department of Internal Medicine 1, University Hospital - Holbaek, Holbaek, Denmark.

E-mail address: [moli@regionsjaelland.dk](mailto:moli@regionsjaelland.dk) (M. Lindhardt).

contaminated drinking water, soil or food, have been reported (Frisbee et al., 2009; Lasters et al., 2022; Pitter et al., 2020; Xu et al., 2021).

PFAS are almost completely absorbed in the gut, protein bound in serum, and concentrated in the liver and kidneys (Olsen et al., 2003; Pérez et al., 2013). PFAS are not metabolized (EFSA 2020, ATSDR, 2021) and are mainly eliminated in urine and feces (ATSDR, 2021; EFSA CONTAM PANEL et al., 2020). However, an extensive reabsorption takes place both in renal tubules (K. Harada et al., 2005) and in the gut (Ducatman et al., 2021; Fletcher et al., 2022; Ruggiero et al., 2021). Given the enterohepatic re-absorption of PFAS, the excretion is very limited leading to long half-life, e.g. the half-life of PFOS is known to be in the range of 2.7–5.0 years (Li et al., 2022).

Cholestyramine and colesevelam are Anion Exchange Inhibitors (AER), which form insoluble complexes with bile acid in the gut, thereby inhibiting reabsorption and increasing fecal loss of cholesterol (Scaldeferri et al., 2013). It has been suggested that AERs could also reduce the biliary reabsorption of PFAS. Rats treated with cholestyramine for 21 days had significantly decreased levels of PFOS, with plasma concentration being reduced by 87 % compared to untreated rats (Johnson et al., 1984). Human case studies reported that treatment with cholestyramine reduced serum PFOS (Genuis et al., 2010) (Genuis et al., 2013). Among 56,175 Americans, highly exposed to PFAS from drinking water (Ducatman et al., 2021), 36 participants reported treatment with cholestyramine and they had serum PFOS in the lower 5 % of the distribution. Similar results were found by Andersen et al. (Andersen et al., 2021), where AER-users ( $n = 22$ ) in the NHANES cohort ( $n = 14,609$ , sampled 2003–2016) had 15.1 % lower serum PFOS concentrations than the rest of the cohort. Given the long half-lives, emerging hot-spots and negative health effects of PFAS, these previous results indicate the potential to treat certain highly exposed groups with AERs to minimize the body burden of PFAS. However, the authors are not aware of any previous experimental, human controlled trials. The purpose of this study was to assess whether treatment with an AER could reduce serum levels of PFOS in a population highly exposed to PFOS.

## 2. Methods

### 2.1. Study design

This study was conducted in a single hospital center as a randomized

controlled trial, using 1:1 randomization with two intervention groups. Open label treatment intervention with a crossover design was performed, with initial allocation to either active treatment or observation followed by a washout period of two-weeks before commencement of the second opposite. Each period of treatment or observation were 12-weeks. The study design is shown in Fig. 1.

### 2.2. Study setting

Study participants were recruited amongst members of a local Cow Grazing Association in Korsør, Denmark. In 2021, it was discovered that this group had consumed meat from cattle accidentally contaminated with PFOS and PFHxS from a nearby firefighting school. Immediately after the discovery, the members were advised to stop eating the meat. PFAS blood tests three months later revealed that the majority of members (118 out of 187) had serum levels of PFOS and PFHxS above the estimated 97.5th percentile of previously reported levels in a Danish background population, corresponding to PFOS > 21.2 ng/mL and PFHxS > 1.9 ng/mL (Grandjean et al., 2020). For this reason, these individuals were considered highly exposed.

Members who met the following inclusion criteria were invited to participate in the study: Age  $\geq 18$  years and known serum PFOS level above 21 ng/mL within one year prior to screening. Written informed consent was obtained from all participants, prior to conduction of the study. Exclusion criteria were: contraindication for use of the study medication (e.g. total intestinal or biliary tract obstruction, hypertriglyceridemia or fat malabsorption as well as treatment-refractory constipation) or medical treatment listed with a risk of interaction with the study drug (oral anticoagulants, thyroid hormones, oral contraceptives, thiazides (incl. combination preparations), doxepin (tricyclic antidepressant), nicotinic acid, tetracycline, benzyl penicillin, phenobarbital, digoxin). Pregnant or breastfeeding women, those planning to become pregnant within six months from baseline and those using unsafe contraception were also excluded. Women of childbearing age performed a pregnancy test (urine hCG).

### 2.3. Randomization

Each participant was randomly assigned into intervention group A or B using REDCap. Block-randomization in blocks of 16 was used.

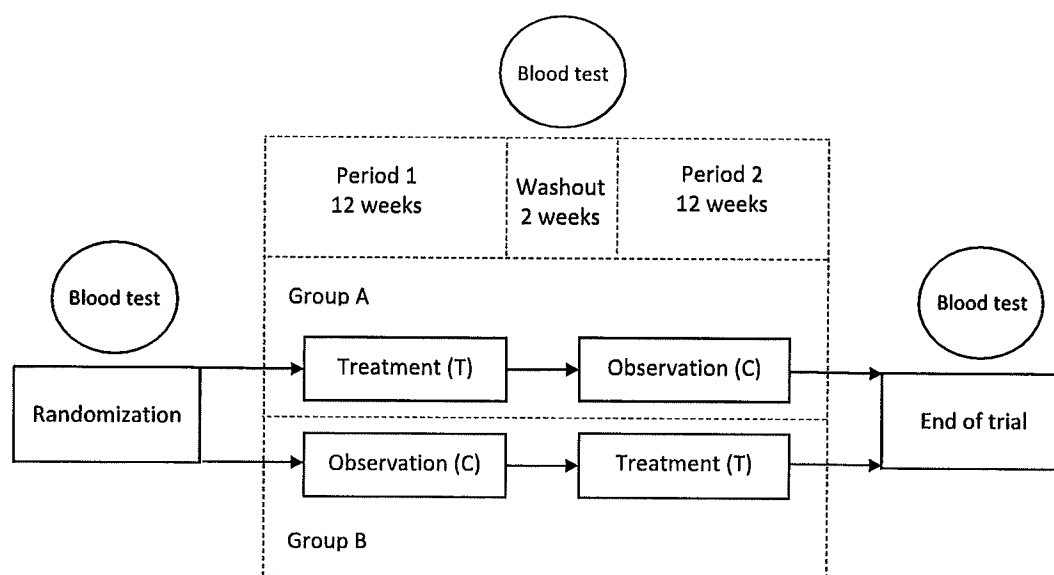


Fig. 1. Study design. Legend: Treatment (T) with Anion Exchange Inhibitor. Observation (control period (C)) with no treatment. Participants allocated to group A followed the intervention sequence T/C and group B followed the intervention sequence C/T. Blood tests consisted of analysis of perfluoroalkyl substances as well as clinical blood samples.

## 2.4. Intervention

As illustrated in Fig. 1, intervention group A received 12 weeks of treatment (T) with AER in “Period 1”, followed by 12 weeks of observation without treatment (C) in “Period 2”. Conversely, intervention group B began “Period 1” with 12 weeks of observation without treatment (C) followed by 12 weeks of treatment with AER in “Period 2”.

Participants received the study medication for all 12 weeks of treatment at the beginning of the treatment period. Participants in randomization group A received the study medication immediately after randomization, whilst group B commenced the treatment after the observation and wash-out periods. The treatment followed the standard dose recommended by the Danish Medicines Agency. All participants received a fixed dose of the study medication, without the option of up- or down-titration. Originally, the trial was designed for treatment with colesevelam (Cholestagel®), but due to a supply shortage, colesevelam was substituted with cholestyramine (Cholestyramine®) in a protocol amendment. Thus, the first four participants were treated with three tablets of colesevelam, at a dose of 625 mg twice daily with a total daily dose of 3,750 mg. The subsequent participants were treated three times daily with one pouch of Cholestyramine as powder to oral suspension, at a dose of 4 g with a total daily dose of 12 g. After 2–4 weeks of treatment, the participants received a phone call to register any possible adverse effects and to ensure compliance with the study protocol. At end of the treatment period, participants returned unused study medication to an accountability check and had the opportunity to report any adverse event during the study period. Participants with less than 80 % use of study medication were classified as non-compliant.

## 2.5. Clinical data

Clinical data and blood samples were collected at three clinical visits: first screening/ randomization (baseline), at the time of cross-over and at the end of trial. The baseline visit included a medical interview on medical history and lifestyle, a physical examination and routine clinical biochemistry.

Study data was collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted by the Capital Region in Denmark. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (Harris et al., 2009, 2019).

## 2.6. Endpoints

Our primary endpoint was the mean change in serum PFOS after 12 weeks of treatment with AER, compared to the 12 weeks of observation. The secondary endpoint was the percentage change in PFOS in the control period following treatment, as an indication of the level of post-treatment redistribution. As only half of the study population was randomly assigned to treatment first followed by observation, the secondary outcome was only assessed in 50 % of participants. PFHxS, PFOA, PFDA and PFNA were analyzed as explorative endpoints. Adverse events were also registered for the full duration of the trial.

## 2.7. PFAS measurement

Serum from each point of measurement (Fig. 1) was stored at  $-80^{\circ}\text{C}$  and analyzed for PFOS (sum of isomers), PFHxS, PFOA, PFNA and PFDA at the end of the study in one batch. PFAS concentrations were determined at the Department of Public Health, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, by use of isotope dilution, online solid phase extraction, high-

pressure liquid chromatography and triple quadrupole mass spectrometry (LC-MS/MS) (Jensen et al., 2015). Calibrators, serum and solvent blanks, as well as quality control samples were included with the series of samples analyzed. Quality control samples included serum samples from previous quality assessment programs and in-house made quality control samples. All quality control samples were well within the acceptance ranges. Imprecision was  $< 6\%$  for all the analytes and the limit of quantitation was 0.03 ng/mL. Accuracy and reliability of the data for the PFAS analysis was ensured by regular participation of the laboratory in the G-EQUAS quality assessment scheme, organized by the German Society of Occupational Medicine. The staff at the analyzing laboratory had no knowledge of the randomization sequence of the participants in the study.

## 2.8. Statistical analysis

As this was the first randomized controlled study to test the effect of AER on the excretion of PFAS, limited information about the expected effect size was available. Based on the available literature, sample size was determined by power calculation applying different estimations. Authors expected a median PFOS of 70 ng/mL, with a positively skewed distribution and a half-life of PFOS of 3.4 years (decrease of 20 % of serum concentration/year) with a SD of 1.21 years (decrease of 19 % to 22 %/year) (Li et al., 2018). Participants were expected to excrete PFOS at least twice as fast with treatment. Normally, the maximum effect of AERs on low-density lipoprotein (LDL) is expected after 30 days of treatment. Consequently, a treatment period of 12 weeks was determined to increase the PFOS elimination from 5 % to 10 %. Enrolling 24 participants in each of the two intervention groups gave an estimated power of 0.8 (two-sided alpha level of 0.05) to detect an average of a 7 % decrease of serum PFOS levels during treatment period. To account for missing data and/or drop-out, this study aimed to enroll a total 60 participants.

Descriptive statistics were used to summarize participants' characteristics. Statistical analysis adopted an intention-to-treat principle, for all participants who received at least one dose of study medication. Crossover studies consider carryover effect, period effect and sequence effect (Lim and In, 2021). As there is no comparison with another treatment, and AERs are not absorbed from the gastrointestinal tract, carryover was not taken into account. Comparisons between the relative differences in mean serum concentrations in the treatment (T) and observation (C) periods for the sequences (T/C and C/T) were undertaken to account for sequence effect. To test for period effect, relative changes in mean serum concentration of PFOS were compared in the treatment (T) and the observation (C) period. Statistical analyses were conducted using Student's t-tests. The analysis was initially conducted on an individual level, comparing outcome level before and after each period. Results are shown as the mean of the pool effect for each period. Data is shown without adjustments. Explorative analysis on the effect of treatment was conducted based on category in terms of sex (male or female) and age (above or below median age).

Additional explorative analyses of period and sequence effects were completed for PFHxS, PFOA, PFNA and PFDA, using the same methodology as for PFOS.

Only complete case data was included in analyses in terms of effect without use of imputation. All statistical analyses were conducted using R Statistical Software (v4.1.2; R Core Team 2021) using an alpha level of 0.05. A statistician independent of the trial management and unaware of the group assignments performed the statistical analysis.

## 3. Results

### 3.1. Study participants

From November 2021 to June 2022, 46 participants were recruited to this study. Following randomization, one participant (intervention

group A) was excluded at baseline due to the diagnosis of an illness requiring treatment. The CONSORT diagram is shown in Fig. 2.

The study participants had a mean age of 50 years (SD 13) and 51 % were male. The median serum concentration of PFOS was 191 ng/ mL (IQR 129–229), PFHxS 8.8 ng/ mL (5.7–11.9), PFOA 0.92 ng/ mL (0.72–1.05), PFNA 0.49 ng/ mL (0.41–0.64), and PFDA 0.17 ng/ mL (0.13–0.21). No samples for PFAS analysis were below detection level. At baseline, 25 participants (56 %) had a chronic disease requiring prescribed medication. Out of those 11 received treatment with statins to treat dyslipidemia. Total cholesterol mean was 4.9 mmol/ L (SD 1.1) and LDL 2.7 mmol/ L (SD 1.0). Additional baseline characteristics of the participants are shown in Table 1. No participant received medical treatment with effect on gastrointestinal transition time.

### 3.2. Test for sequence effect

In order to pool effect of treatment in a crossover, sequence effect was tested for. A numeric, larger treatment effect was seen in intervention group A and a larger decrease in serum PFOS during control period was seen in intervention group B. However, no statistically significant sequence effect was identified comparing differences in relative decrease of serum PFOS after treatment and control period between the groups (respectively  $p = 0.17$  and  $0.43$ ). Therefore, effect of treatment or observation for the following is presented as pooled analysis (Lim and In, 2021). Baseline characteristic in the randomization strata is shown in supplementary Table 1S.

### 3.3. Change of PFOS levels on treatment

The mean decrease of serum PFOS during treatment was 115 ng/mL (95 % CI: 89–140), corresponding to a decrease of 63 % (95 % CI: 57–70). During observation mean decrease was 4.3 ng/ mL (95 % CI: 0.51–8.1) corresponding to a decrease of 3.3 % (95 % CI: 1.0–5.6). Thus, the relative reduction between treatment and observation periods was 60 % (95 % CI: 53–67) or 111 ng/mL (95 % CI: 85–136), corresponding to a highly significant effect of treatment ( $p < 0.0001$ ). Adjustments for age or sex had no effect on treatment response ( $p = 0.11$  and  $p = 0.19$ ), respectively. At the end of study, six participants reached serum levels of PFOS < 21 ng/ mL (corresponding to Danish background levels).

Table 1

Baseline characteristics of the 45 participants.

Characteristics	Participants (n = 45)
Age, years (SD)	50 (13)
Male sex, n (%)	23 (51)
PFOS, ng/mL (IQR)	191(129–229)
PFHxS, ng/mL (IQR)	8.8 (5.7–11.9)
PFOA, ng/mL (IQR)	0.92 (0.72–1.05)
PFNA, ng/mL (IQR)	0.49 (0.41–0.64)
PFDA, ng/mL (IQR)	0.17 (0.13–0.21)
BMI, kg/m <sup>2</sup> , (SD)	29 (5.0)
Blood pressure, systolic /diastolic, mmHg, (SD)	136/88 (21/ 13)
Any chronic disease in medical history, n (%) *	25 (56)
Cardiovascular disease, n (%)**	11 (24)
Dyslipidemia, n (%)	11 (24)
Diabetes type 2, n (%)	5 (9)
Haemoglobin, mmol/ L, (SD)	9.1 (0.9)
Creatinine, $\mu$ mol/ L, (SD)	72 (11)
eGFR, mL/ min/ 1.73 m <sup>2</sup> , (SD)	87 (6)
Total cholesterol, mmol/ L, (SD)	4.9 (1.1)
LDL, mmol/ L, (SD)	2.7 (1.0)
HDL, mmol/ L, (SD)	1.4 (0.5)
Triglyceride, mmol/L, (SD)	1.6 (0.9)
25-Hydroxy-Vitamin D3, nmol/L, (SD)	60 (24)

Legend: \*No participants received medical treatment with effect on gastrointestinal transition time. \*\* Hypertension, stroke or ischemic heart disease. PFOS = Perfluorooctanesulfonic acid, PFHxS = Perfluorohexanesulfonic acid, PFOA = Perfluorooctanoic acid, PFNA = Perfluorononanoic acid, PFDA = Perfluorodecanoic acid. Estimated glomerular filtration rate (eGFR) is based on CKD-EPI creatinine equation including: Sex and age, but not race. Numeric variables are presented with mean and standard deviation (SD), PFAS's values with median and interquartile range (IQR), and categorical variables with amount and percentage of study population (%).

### 3.4. Post-treatment redistribution of PFOS

In the intervention group A, with the sequence treatment followed by observation, serum PFOS was further reduced by 2.5 ng/mL (95 % CI: –0.3 to 5.2) during the observational period indicating limited redistribution.

### 3.5. Change of other PFAS

Additionally, changes in other PFAS levels were analyzed, with decreases between 19 and 48 % with treatment, as shown in Fig. 3. During

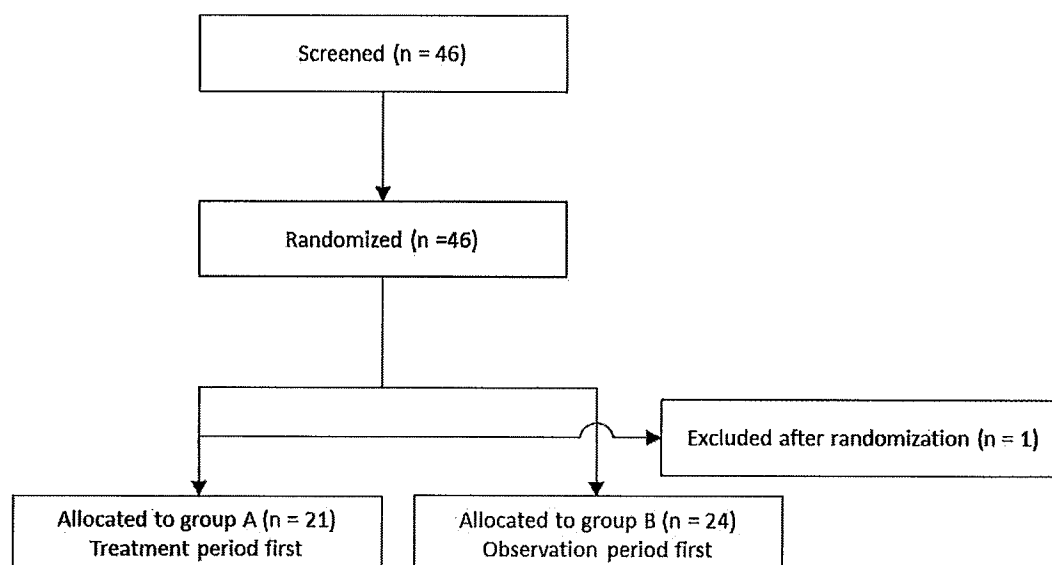


Fig. 2. CONSORT diagram of the study population.

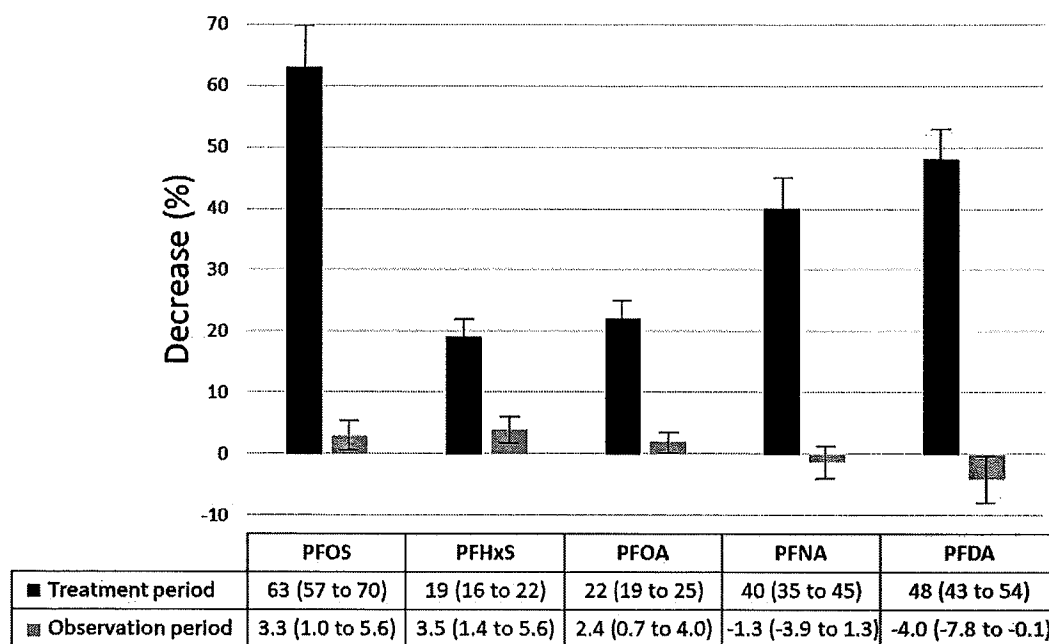


Fig. 3. Relative elimination of PFAS in 12 weeks treatment or observation period. Legend, Fig. 3: Percentage of change before vs. after either treatment or observation for 12 weeks. Mean percentage decrease in PFAS's and 95 % confidence limits error bars. PFOS = Perfluorooctanesulfonic acid, PFHxS = Perfluorohexanesulfonic acid, PFOA = Perfluorooctanoic acid, PFNA = Perfluorononanoic acid, PFDA = Perfluorodecanoic acid.

the observation period, mean reductions in serum levels for PFHxS was 3.5 % and 2.4 % for PFOA. However, serum levels increased by 1.3 % for PFNA and 4.0 % for PFDA.

### 3.6. Adverse events

Adverse effects of the study medication were registered for five participants, who reported mild gastrointestinal symptoms and headache. One participant did not complete the study due to gastrointestinal symptoms related to study drug. No serious adverse effects were recorded. In addition, eleven participants did not comply with protocol, with nine participants having a compliance of less than 80 % use of the study medication and two participants missing blood test for one of three measures of PFAS. No participants donated blood during the study period.

## 4. Discussion

In this first randomized controlled study of its kind, a significant reduction of 60 % in serum PFOS was identified after treatment with an anion exchange resin for 12 weeks among 45 highly exposed adults. The reduction in serum levels were, for PFHxS 15 %; for PFOA 20 %; for PFNA 39 % and for PFDA 44 %. During the observation 12-week period the corresponding reduction in PFOS was 3 %. These highly statistically significant findings are groundbreaking suggesting that PFAS elimination can be significantly enhanced with AER treatment, offering reassurance to highly exposed individuals.

No post-treatment re-distribution, i.e. mobilization from other compartments, was found, as PFAS did not increase in participants in the observation period after the initial treatment response. However, this result was only based on 21 participants due to the crossover design and hence, the study may not possess sufficient power to accurately measure this outcome. Therefore, extent of redistribution should be investigated further in additional studies and it would be beneficial with multiple measurements over time to increase the accuracy.

To the author's knowledge, no clinical controlled human studies of this nature have previously been conducted. However, the findings are

in accordance with an animal study in which rats, exposed to PFOS and treated with cholestyramine for 21 days, had a 9-fold increase in PFOS elimination in feces (Johnson et al., 1984). In addition, the findings are supported by human case series (Genuis et al., 2010, 2013) and population studies in which participants treated with bile acid sequestrants had PFAS concentrations in the lowest range (Andersen et al., 2021; Ducatman et al., 2021).

PFAS are absorbed from the gut (Ericson et al., 2008; Kimura et al., 2017), bind to serum proteins and accumulate mainly in the liver, kidney and blood (Sheng et al., 2016). They are not metabolized and renal clearance is low due to active renal reabsorption (Andersen et al., 2008; Li et al., 2022). Biliary excretion is also low due to enterohepatic circulation and it has been estimated that a large proportion of excreted PFAS is reabsorbed from the gastrointestinal tract through this method (K. H. Harada et al., 2007). Both cholestyramine ('Cholestyramine', 2012) and colesevelam (H. Bays and Jones, 2007) are bile acids sequestrants, acting as bile acid resins or anion exchange resins. The AERs are large, highly positively charged anion exchange resins that bind to negatively charged anions such as bile acids (salts) by exchanging chloride ions, forming insoluble complexes that are excreted in feces. They have been used in the treatment of hypercholesterolemia by inhibiting the enterohepatic reabsorption, thus enhancing fecal excretion of cholesterol (Roth et al., 2020). The same mechanism applies for PFOS. This study is the first of its kind and previously approved drugs, with few and mild side effects (constipation, abdominal pain, diarrhea, dyspepsia, flatulence and nausea), were used (Genuis et al., 2010; Scaldaferrì et al., 2013). However, some limitations need to be addressed. First, the participants were very motivated for treatment, due to their known high exposure to PFAS. In other settings, among less motivated samples, the gastrointestinal side effects of AER may be less well tolerated. Therefore, treatment should primary be offered to highly exposed individuals for shorter time periods, though the optimal time-frame of treatment needs to be determined in future studies. Still, studies have found that the use of AER have long term beneficial effects on both cardiovascular disease and diabetes risk factors (Hansen et al., 2017). Second, the initial plan was to use colesevelam, which was administered as twice-daily tablets. However, due to a shortage of supply of

colesevelam a switch to the powder cholestyramine was necessary. The study participants reported cholestyramine to have a non-palatable taste, leading to well-known compliance issues (Bays et al., 2011). As cholestyramine is administered three times daily, three participants reported they forgot to take the trial medication during the day and a total of nine participants were non-compliant. Gastrointestinal adverse effects were the main reason for cessation of treatment, as well as reduced compliance during the trial. Lastly, other factors which could have contributed to the reduction in serum PFAS e.g. self-treatment and diet was not accounted for. Moreover, participants were only treated for 12 weeks and therefore, this study cannot determine whether longer treatment periods would further enhance elimination of PFAS.

PFAS are widely used, persists in the environment and are present in all human populations, which is of public health concern, due to their possible adverse health effects (EFSA CONTAM PANEL et al., 2020). An increasing number of hotspot areas in which humans are exposed to PFAS through contaminated water, soil or food have been reported worldwide ("Forever pollution", 2023). Currently no treatment is available for highly exposed individuals. Our findings suggest that PFAS elimination can be enhanced by administration of the approved AER drugs, which have tolerable side effects for motivated participants, with the potential to provide reassurance to those affected by hotspots. In addition, although cholestyramine is well tolerated, colesevelam may be a better tolerated alternative due to its capsule form. Future studies should also further elaborate on both dose and duration of treatment with AER. It is also important to state, that although serum PFOS significantly decreased over a 12-weeks period, it is not elucidated whether this is accompanied by a corresponding decline in adverse health outcomes. This question requires further research in larger long-term studies. Conversely, it is not possible with this current study to assess whether a sufficient decrease in PFAS levels could have been achieved with a treatment period shorter than 12 week. This question could be addressed with consecutive samples to estimate correct elimination rate of PFAS with AER treatment. PFAS are detected in umbilical cord blood, amniotic fluid and breast milk, indicating that the vulnerable fetus and infant is exposed to these substances. Moreover, EFSA identified reduced antibody response towards routine childhood vaccinations as the critical effect of PFAS on children (EFSA CONTAM PANEL et al., 2020). Therefore, our findings may be of particular interest for highly exposed women of reproductive age, with the potential to reduce or prevent PFAS exposure of the next generation. However, few participants in this study were of reproductive age and more studies in this population group are urgently needed, including treatment with varying length and dose.

## 5. Conclusion

Our findings from this first randomized controlled clinical trial indicate that PFAS elimination can be enhanced by administration of an anion exchange resin for 12-weeks, possibly by preventing reabsorption in the enterohepatic circulation. Whether the marked reduction in serum PFOS is accompanied by a decrease in adverse health effects associated with high PFAS exposure requires further investigation. Our findings are of major public health interest and may offer possible treatment for highly exposed individuals. Of particular interest are women of reproductive age in order to reduce PFAS exposure of the next generation. However, further studies elucidating both the duration and dose of treatment are urgently needed.

## Funding

The project was partly financed internally by the organizations and through a specific grant from the administrative Region Zealand in Denmark, without any interference on study design, collection of data, analysis, interpretation of results or the integrity of the publication.

## Ethical approval

The study was approved by the independent regional ethical committee in region Zealand, Denmark (project no.: SJ-942) and Danish Medicine Agency as well as the European Union Drug Regulating Authorities Clinical Trials Database (EMN-2021-06997). Collection of clinical data was notified to the Danish Data Protection Agency (REG-112-2021). The trial was performed in accordance with the Principles of Helsinki and was monitored and reviewed by the Copenhagen Good Clinical Practice guidelines to ensure that the study comply with ethical principles and the Danish legislation. All participants gave informed consent prior to participation and no participants were related to either the study personnel or the authors.

## CRediT authorship contribution statement

**Janne Julie Møller:** Investigation, Writing – review & editing, Visualization. **Ann Christine Lyngberg:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Paula Edeusa Christina Hammer:** Writing – review & editing. **Esben Meulengracht Flachs:** Formal analysis, Software. **Ole Steen Mortensen:** Writing – review & editing. **Tina Kold Jensen:** Resources, Writing – review & editing. **Gesche Jürgens:** Methodology, Writing – review & editing. **Axel Andersson:** Writing – review & editing, Verification. **Anne Merete Boas Soja:** Writing – review & editing, Verification. **Morten Lindhardt:** Conceptualization, Methodology, Resources, Software, Investigation, Visualization, Writing – review & editing, Supervision, Project administration, Funding acquisition, Verification.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Acknowledgement

The authors thank; Flemming Nielsen, M.Sc, Ph.D; Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark, for performing the PFAS analyses; Kenneth Nielsen, Head of Korsoer Cow Grass Association, Korsoer, for being helpful in spreading the offer of participation in the project among the members and for supporting community-based risk communication; Katerina Bray, MD, and Lucy Leigh Bray, MD, Department of Occupational and Social Medicine, University Hospital of Holbaek, Denmark for providing assistance with text editing.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108497>.

## References

- Forever pollution': Explore the map of Europe's PFAS contamination, 2023, February 23. *Le Monde.Fr*. [https://www.lemonde.fr/en/les-decodeurs/article/2023/02/23/forever-pollution-explore-the-map-of-europe-s-pfas-contamination\\_6016905\\_8.html](https://www.lemonde.fr/en/les-decodeurs/article/2023/02/23/forever-pollution-explore-the-map-of-europe-s-pfas-contamination_6016905_8.html).
- Andersen, M.E., Butenhoff, J.L., Chang, S.-C., Farrar, D.G., Kennedy, G.L., Lau, C., Olsen, G.W., Seed, J., Wallace, K.B., 2008. Perfluoroalkyl acids and related chemistries—Toxicokinetics and modes of action. *Toxicol. Sci.: Off. J. Soc. Toxicol.* 102 (1), 3–14. <https://doi.org/10.1093/toxsci/kfm270>.

- Andersen, M.E., Hagenbuch, B., Apte, U., Corton, J.C., Fletcher, T., Lau, C., Roth, W.L., Staels, B., Vega, G.L., Clewell, H.J., Longnecker, M.P., 2021. Why is elevation of serum cholesterol associated with exposure to perfluoroalkyl substances (PFAS) in humans? A workshop report on potential mechanisms. *Toxicology* 459, 152845. <https://doi.org/10.1016/j.tox.2021.152845>.
- ATSDR, 2021. *Perfluoroalkyls | Toxicological Profile* [DOI: 10.15620/cdc:59198]. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=1117&tid=237>. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=1117&tid=237>.
- Bays, H., Jones, P.H., 2007. Colesevelam hydrochloride: Reducing atherosclerotic coronary heart disease risk factors. *Vasc. Health Risk Manag.* 3 (5), 733–742.
- Bays, H.E., Maki, K.C., Schmitz, K., 2011. Colesevelam hydrochloride powder for oral suspension versus cholestyramine powder for oral suspension: Comparison of acceptability and tolerability. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 17 (2), 218–225. <https://doi.org/10.4158/EP10251.0R>.
- Cholestyramine, 2012. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases. <http://www.ncbi.nlm.nih.gov/books/NBK548431/>.
- EFSA CONTAM PANEL, Schrenk, D., Bignami, M., Bodin, L., Chipman, J. K., del Mazo, J., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L. (Ron), Leblanc, J.-C., Nebbia, C.S., Nielsen, E., Ntzani, E., Petersen, A., Sand, S., Vleminckx, C., Wallace, H., Barregård, L., Ceccatelli, S., et al., 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA Journal*, 18(9), e06223. Doi: 10.2903/j.efsa.2020.6223.
- Ducatman, A., Luster, M., Fletcher, T., 2021. Perfluoroalkyl substance excretion: effects of organic anion-inhibiting and resin-binding drugs in a community setting. *Environ. Toxicol. Pharmacol.* 85, 103650 <https://doi.org/10.1016/j.etap.2021.103650>.
- Ericson, I., Martí-Cid, R., Nadal, M., Van Bavel, B., Lindström, G., Domingo, J.L., 2008. Human exposure to perfluorinated chemicals through the diet: Intake of perfluorinated compounds in foods from the Catalan (Spain) market. *J. Agric. Food Chem.* 56 (5), 1787–1794. <https://doi.org/10.1021/jf0732408>.
- Fletcher, T., Andersson, A., Li, Y., Xu, Y., Lindh, C.H., Kärrman, A., Jakobsson, K., 2022. The relative importance of faecal and urinary excretion of PFAS and implications for epidemiological studies. *ISEE Conference Abstracts 2022* (1). <https://doi.org/10.1289/isee.2022.O-OP-024>.
- Frisbee, S., Brooks, A., Maher, A., Flensburg, P., Arnold, S., Fletcher, T., Steenland, K., Shankar, A., Knox, S., Pollard, C., Halverson, J., Vieira, V., Jin, C., Leyden, K., Ducatman, A., 2009. The C8 health project: design, methods, and participants. *Environ. Health Perspect.* 117, 1873–1882. <https://doi.org/10.1289/ehp.0800379>.
- Fromme, H., Tittlemier, S.A., Völkel, W., Wilhelm, M., Twardella, D., 2009. Perfluorinated compounds—Exposure assessment for the general population in Western countries. *Int. J. Hyg. Environ. Health* 212 (3), 239–270. <https://doi.org/10.1016/j.ijheh.2008.04.007>.
- Genius, S.J., Birkholz, D., Ralitsch, M., Thibault, N., 2010. Human detoxification of perfluorinated compounds. *Public Health* 124 (7), 367–375. <https://doi.org/10.1016/j.puhe.2010.03.002>.
- Genius, S.J., Curtis, L., Birkholz, D., 2013. Gastrointestinal elimination of perfluorinated compounds using cholestyramine and chlorella pyrenoidosa. *ISRN Toxicology* 2013. <https://doi.org/10.1155/2013/657849>.
- Grandjean, P., Timmermann, C. A. G., Kruse, M., Nielsen, F., Vinholt, P. J., Boding, L., Heilmann, C., Mølbak, K., 2020. Severity of COVID-19 at elevated exposure to perfluorinated alkylates. *medRxiv*, 2020.10.22.20217562. doi: 10.1101/2020.10.22.20217562.
- Hansen, M., Sonne, D.P., Mikkelsen, K.H., Gluud, L.L., Vilsbøll, T., Knop, F.K., 2017. Bile acid sequestrants for glycemic control in patients with type 2 diabetes: A systematic review with meta-analysis of randomized controlled trials. *J. Diabetes Complications* 31 (5), 918–927. <https://doi.org/10.1016/j.jdiacomp.2017.01.011>.
- Harada, K.H., Hashida, S., Kaneko, T., Takenaka, K., Minata, M., Inoue, K., Saito, N., Koizumi, A., 2007. Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans. *Environ. Toxicol. Pharmacol.* 24 (2), 134–139. <https://doi.org/10.1016/j.etap.2007.04.003>.
- Harada, K., Inoue, K., Morikawa, A., Yoshinaga, T., Saito, N., Koizumi, A., 2005. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. *Environ. Res.* 99 (2), 253–261. <https://doi.org/10.1016/j.envres.2004.12.003>.
- Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42 (2), 377–381. <https://doi.org/10.1016/j.jbi.2008.08.010>.
- Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., Duda, S. N., & REDCap Consortium, 2019. The REDCap consortium: Building an international community of software platform partners. *J. Biomed. Inform.*, 95, 103208. Doi: 10.1016/j.jbi.2019.103208.
- Johnson, J.D., Gibson, S.J., Ober, R.E., 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C]perfluorooctanoate or potassium [14C]perfluorooctanesulfonate. *Fundamental Appl. Toxicol.: Off. J. Soc. Toxicol.* 4 (6), 972–976. [https://doi.org/10.1016/0272-0590\(84\)90235-5](https://doi.org/10.1016/0272-0590(84)90235-5).
- Kimura, O., Fujii, Y., Haraguchi, K., Kato, Y., Ohta, C., Koga, N., Endo, T., 2017. Uptake of perfluorooctanoic acid by Caco-2 cells: involvement of organic anion transporting polypeptides. *Toxicol. Lett.* 277, 18–23. <https://doi.org/10.1016/j.toxlet.2017.05.012>.
- Lasters, R., Groffen, T., Eens, M., Coertjens, D., Gebbink, W.A., Hofman, J., Bervoets, L., 2022. Home-produced eggs: an important human exposure pathway of perfluoroalkylated substances (PFAS). *Chemosphere* 308 (Pt 1), 136283. <https://doi.org/10.1016/j.chemosphere.2022.136283>.
- Li, Y., Fletcher, T., Mucs, D., Scott, K., Lindh, C.H., Tallving, P., Jakobsson, K., 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup. Environ. Med.* 75 (1), 46–51. <https://doi.org/10.1136/oemed-2017-104651>.
- Li, Y., Andersson, A., Xu, Y., Pineda, D., Nilsson, C., Lindh, C., Jakobsson, K., Fletcher, T., 2022. Determinants of serum half-lives for linear and branched perfluoroalkyl substances after long-term high exposure—A study in Ronneby, Sweden. *Environ. Int.* 163, 107198 <https://doi.org/10.1016/j.envint.2022.107198>.
- Lim, C.-Y., In, J., 2021. Considerations for crossover design in clinical study. *Korean J. Anesthesiol.* 74 (4), 293–299. <https://doi.org/10.4097/kja.21165>.
- National Academies, 2022. Potential Health Effects of PFAS | Guidance on PFAS Exposure, Testing, and Clinical Follow-Up, chapter 3. <https://nap.nationalacademies.org/read/26156/chapter/5>.
- Olsen, G.W., Hansen, K.J., Stevenson, L.A., Burris, J.M., Mandel, J.H., 2003. Human Donor Liver and Serum Concentrations of Perfluorooctanesulfonate and Other Perfluorochemicals. *Environ. Sci. Tech.* 37 (5), 888–891. <https://doi.org/10.1021/es020955c>.
- Pérez, F., Nadal, M., Navarro-Ortega, A., Fàbrega, F., Domingo, J.L., Barceló, D., Farré, M., 2013. Accumulation of perfluoroalkyl substances in human tissues. *Environ. Int.* 59, 354–362. <https://doi.org/10.1016/j.envint.2013.06.004>.
- Pitter, G., Da Re, F., Canova, C., Barbieri, G., Zare Jeddi, M., Daprà, F., Manea, F., Zolin, R., Bettega, A.M., Stopazzolo, G., Vittori, S., Zambelli, L., Martuzzi, M., Mantoan, D., Russo, F., 2020. Serum Levels of Perfluoroalkyl Substances (PFAS) in Adolescents and Young Adults Exposed to Contaminated Drinking Water in the Veneto Region, Italy: A Cross-Sectional Study Based on a Health Surveillance Program. *Environ. Health Perspect.* 128 (2), 027007 <https://doi.org/10.1289/EHP5337>.
- Roth, K., Imran, Z., Liu, W., Petriello, M.C., 2020. Diet as an Exposure Source and Mediator of Per- and Polyfluoroalkyl Substance (PFAS) Toxicity. *Front. Toxicol.* 2, 601149 <https://doi.org/10.3389/ftox.2020.601149>.
- Ruggiero, M.J., Miller, H., Idowu, J.Y., Zitzow, J.D., Chang, S.-C., Hagenbuch, B., 2021. Perfluoroalkyl Carboxylic Acids Interact with the Human Bile Acid Transporter NTPC. *Livers* 1 (4), 221–229. <https://doi.org/10.3390/livers1040017>.
- Scalaferrì, F., Pizzoferrato, M., Ponziani, F.R., Gasbarrini, G., Gasbarrini, A., 2013. Use and indications of cholestyramine and bile acid sequestrants. *Intern. Emerg. Med.* 8 (3), 205–210. <https://doi.org/10.1007/s11739-011-0653-0>.
- Sheng, N., Li, J., Liu, H., Zhang, A., Dai, J., 2016. Interaction of perfluoroalkyl acids with human liver fatty acid-binding protein. *Arch. Toxicol.* 90 (1), 217–227. <https://doi.org/10.1007/s00204-014-1391-7>.
- Xu, Y., Nielsen, C., Li, Y., Hammarstrand, S., Andersson, E.M., Li, H., Olsson, D.S., Engström, K., Pineda, D., Lindh, C.H., Fletcher, T., Jakobsson, K., 2021. Serum perfluoroalkyl substances in residents following long-term drinking water contamination from firefighting foam in Ronneby, Sweden. *Environ. Int.* 147, 106333 <https://doi.org/10.1016/j.envint.2020.106333>.