

Potential Exposure Sources and Health Impacts of Per- and Polyfluoroalkyl Substances (PFAS): Guidance for Clinicians

Catherine Karr, MD, PHD, MS, FAAP
Director, Region 10 Northwest PEHSU
Professor of Pediatrics, Environmental & Occupational
Health Sciences
University of Washington

Arthur Wendel, MD, MPH
Medical Officer
Region 10 CDC/ATSDR



Acknowledgements

The content of this presentation was prepared by the Pediatric Environmental Health Specialty Units using, in part, guidance for clinicians developed by the Agency for Toxic Substances and Disease Registry.

Conflict of Interest Disclosure

In the past 12 months, we have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

We do not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

Learning Objectives

By the end of this presentation, participants will be able to:

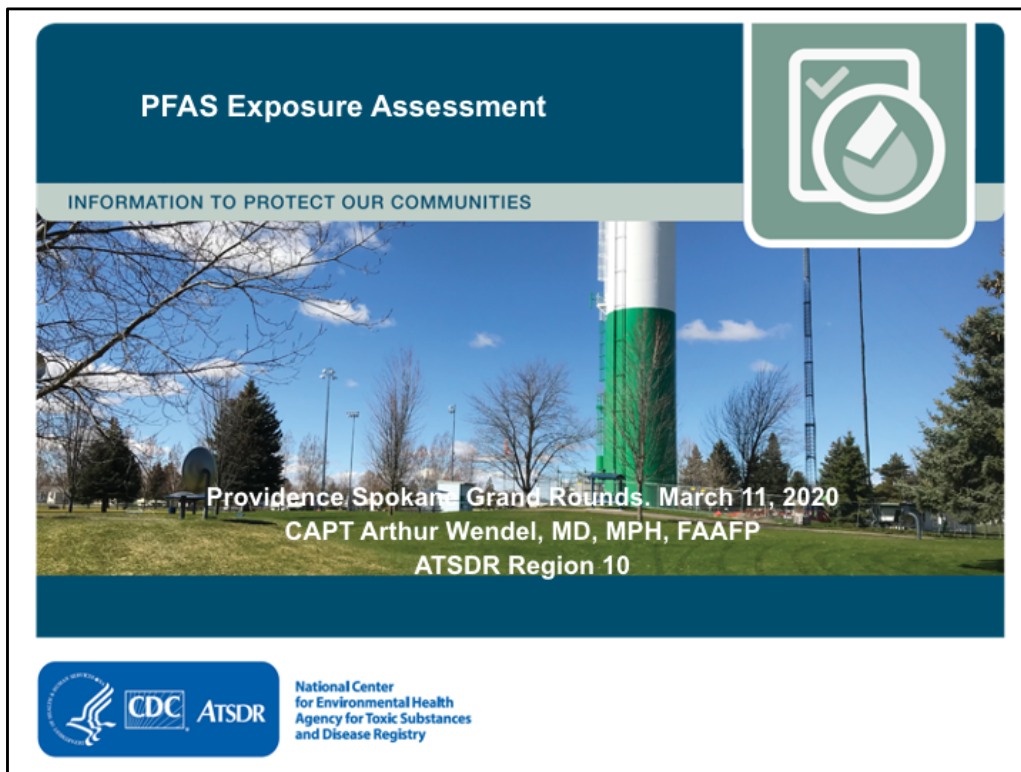
- Define per- and polyfluoroalkyl substances (PFAS)
- List exposure pathways
- Describe potential health effects of PFAS
- Explain strategies for medical management and addressing patient concerns
- Discuss ongoing PFAS biomonitoring activities nationwide (i.e., ATSDR Exposure Assessments)
- List resources available to health care providers

To begin this presentation, we will define PFAS and describe their basic structure and chemical properties. We will address their presence and persistence both in the environment and in the human body, touch on current environmental reduction strategies, and explain different routes or modes of exposure.

Next, we will discuss some of the current research in order to gain perspective on what is known regarding PFAS before we discuss the potential health effects. We will also point out research gaps regarding particular health effects and risk groups and examine where further study is needed.

Finally, we will present patient management strategies, which include risk assessment, use of biomonitoring to demonstrate population wide exposure, effective communication, and risk reduction activities. We will conclude by addressing some common concerns voiced by potentially exposed populations.

Part 1: CDC/ATSDR & Airway Heights



Speaker share briefly:

- ATSDR is a federal public health agency.
- We are working to assess exposure to per- and polyfluoroalkyl substances (PFAS) in drinking water in several communities across the U.S.
- I'll give some brief information and context about the ATSDR PFAS public health activity/activities going on in this community.

CDC/ATSDR's PFAS Exposure Assessments



Assessing PFAS exposure in ten U.S. communities to determine:

- Distribution of PFAS serum concentrations
- PFAS urine concentrations from subset of participants
- PFAS concentrations in indoor dust and drinking water from a subset of participants' homes

INFORMATION TO PROTECT OUR COMMUNITIES

Authorized Use Only

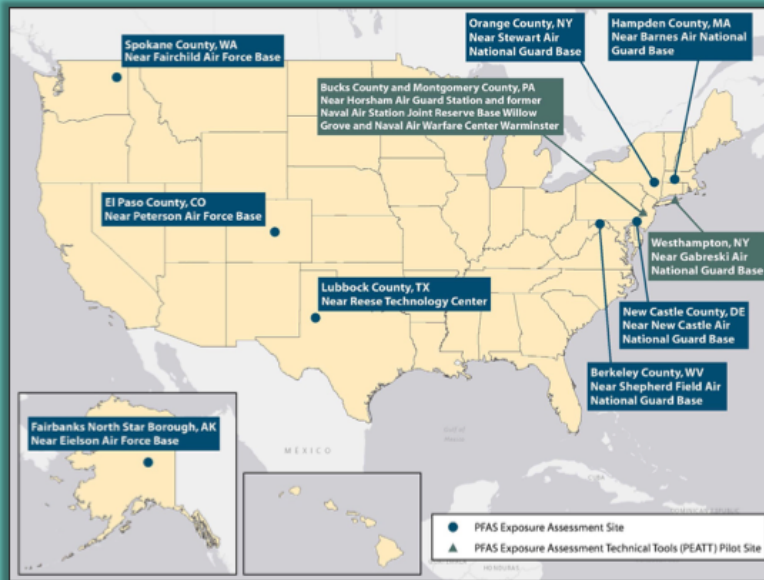
7

- In 2018, the National Defense Authorization Act (NDAA) authorized CDC/ATSDR to conduct statistically based biomonitoring exposure assessments (EAs) at “no less than eight current or former domestic military installations” that have or have had documented exposures to PFAS in drinking water
 - For each site, a statistically based, community sampling design is being used to determine:
 - The distribution of PFAS serum concentrations in communities with recent or past exposures to PFAS in drinking water;
 - Assess how do these concentrations compare to United States reference populations (e.g. NHANES)?
 - PFAS urine concentrations from a subset of participants with recent or past exposures to PFAS in drinking water.
 - Determine whether available laboratory method can measure PFAS in urine. If so, how do these levels compare to the US population.
 - PFAS concentrations in indoor dust and tap water samples from a subset of homes of participants in biological sampling.
 - Environmental sampling data will be combined with biological sampling results to generate information about the impact of drinking water and some non-drinking water PFAS exposure pathways on PFAS body burden in each

community. For example, environmental sampling data might allow investigators to assess the relative contribution of dust to PFAS exposure, but not necessarily other exposure sources such as foods.

- We will be analyzing the same number and types of PFAS in urine and blood as those measured for CDC's NHANES program
 - EAs are not health/epidemiological studies and we will not analyze or evaluate health endpoints or biomarkers of disease

ATSDR Exposure Assessment Locations



The ATSDR is currently involved in several national research studies regarding PFAS levels in people and whether or not there are health effects related to background environmental PFAS exposures. This map shows the locations of where ATSDR is conducting exposure assessments in communities around the country.

City of Airway Heights Water Timeline

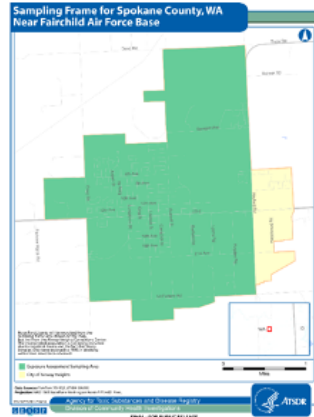


- **May 2017:** PFAS detected; immediate action taken to reduce exposure
- **June 2017:** Alternative source of drinking water secured that had PFAS below EPA's health advisory level (City of Spokane water)
- **July 2018:** Upgraded water connection with City of Spokane
- **September 2018:** Carbon filter installed on well to meet peak summer demands
- **Periodically:** Testing of water for PFAS continues

INFORMATION TO PROTECT OUR COMMUNITIES

NOTE: In 2016 EPA issued a health advisory for the sum of two PFAS compounds (PFOA & PFOS) at 70 parts per trillion (ppt) individually or combined

Exposure Assessment Recruitment



- Participants were recruited from a specific geographic area
- Area was defined by past exposures to public drinking water above EPA's PFAS health advisory

INFORMATION TO PROTECT OUR COMMUNITIES

- All households eligible in the sampling frame
- Household members were able to participate if they:
 - 3 years of age or older
 - do not have a bleeding disorder and are not anemic
 - have lived in the recruitment area for one full year prior to June 8, 2017

Individuals with private wells were not included in the exposure assessment because the variability in private well levels made it more difficult to interpret how drinking water levels might influence blood levels. However, a number of homes with private wells had PFAS levels above EPA's health advisory. The geographic area of wells with contamination is larger than the sampling frame and individuals outside of our sampling frame may have PFAS concerns.

Exposure Assessment Process



INFORMATION TO PROTECT OUR COMMUNITIES

Authorized Use Only

11

In particular, highlight processes 3, 4, 5, and 6

3 – participants provided blood and urine samples

4 – EA staff sampled house dust in the homes of some participants

5 – environmental and biological samples were processed and analyzed

6 – individual results letters will be sent to participants in this community; your patients may be participants; they may ask you to review and interpret their results letter

Exposure Assessment Individual Results



Mailed results letters will include:

- PFAS levels in participants' blood, urine*, household dust*, and tap water*
- Comparisons to community's and nation's blood and urine levels

Table 2: Your PFAS blood levels compared to what has been measured in the general U.S. Population

PFAS	Your Level in µg/L (insert level)	U.S. Population (all ages) Geometric Mean in µg/L ¹ (insert value)	U.S. Population (all ages) 95 th percentile in µg/L ¹ (insert value)
PFOA			
PFOx ₂			
PFNA			

Participants and community members may seek care.

*Urine, household dust, and tap water will only be available for a subset of participants

INFORMATION TO PROTECT OUR COMMUNITIES

- During the consent process, ATSDR emphasized to participants that results will not indicate whether a current illness can be attributed to current or past PFAS exposure. Results will not predict or rule out the development of future health problems related to a known or suspected PFAS exposure.
- The letters will include information

about how individual's blood and urine levels compare to NHANES's mean and 95th percentile levels. Additionally, drinking water levels will include information about how they compare to state screening levels and EPA health advisory levels. (see table from letter)

- Participants and other community members affected by PFAS may seek care and turn to area health care providers for additional guidance. This is why we have created resources and are working with PEHSU to help inform area providers.

Speaker should share/leave behind a blank results letter for audience to look at.

Thank you

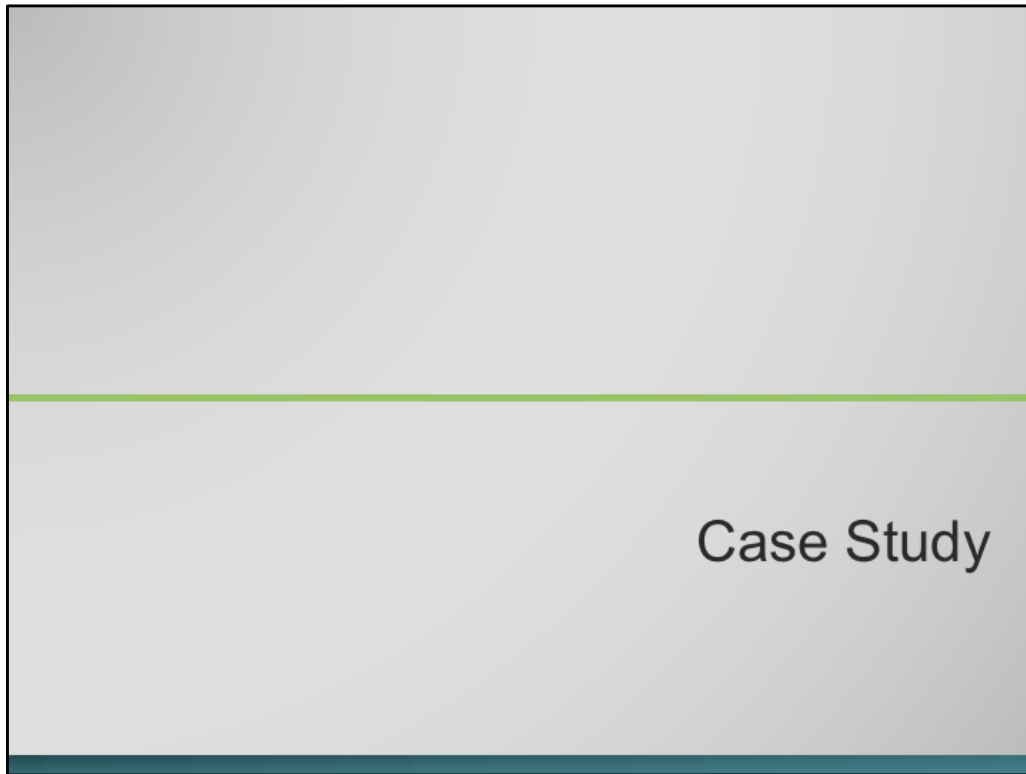


The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Agency for Toxic Substances and Disease Registry or the Centers for Disease Control and Prevention.

INFORMATION TO PROTECT OUR COMMUNITIES

Part 2: Information for pediatric providers

Insert ATSDR Regional slides



Sample Case

SCENARIO

- Mother and 12-year-old son in good health
- Family has lived in sampling area for the past 12 years
- The mother heard that the water in their community was contaminated with PFAS
- The family participated in ATSDR's exposure assessment and brings you their individual biomonitoring results

QUESTIONS TO CONSIDER...

- Are you able to interpret the results?
- Does this family need further testing? And if so, for what?
- How else can you help this patient (e.g., reducing exposure and stress)?

To frame the discussion of today's presentation, we will provide information in the context of a hypothetical case that includes a mother and son who are part of one of ATSDR's exposure assessments. The mother participates in the study to determine their level of exposure to various PFAS. After receiving their individual results from ATSDR, the mother schedules an appointment with their family physician to interpret their results and provide guidance on potential health effects. This presentation will help you prepare to provide appropriate guidance.

Sample Biomonitoring Results

PFAS	Your Level in µg/L	U.S. Population (all ages) Geometric Mean in µg/L ^a	U.S. Population (all ages) 95 th percentile in µg/L ^a
PFDA		0.154	0.700
PFHxS		1.18	4.90
PFNA		0.577	1.90
PFOA ^b		1.56	4.17
n-PFOA		1.46	4.10
Sb-PFOA		*	<LOD
PFOS ^b		4.72	18.3
n-PFOS		3.2	12.8
Sm-PFOS		1.42	5.7
MeFOSAA		*	0.600
PFUnA		*	0.400

Note: U.S. Population results above from NHANES 2015-2016.
 ND – Not detected (limit of detection = 0.1 µg/L)
 * Geometric mean was not calculated because not enough people had results that were detectable.
 **95th percentile was below the limit of detection, 0.1 µg/L.

This table is taken directly from the ATSDR letter to exposure assessment participants to provide their individual test results. It will include the individual blood results for each type of PFAS listed, as well as the NHANES data shown here. Exposure assessment participants may bring their own completed table to their healthcare provider seeking guidance on how to interpret their individual results.

Source:

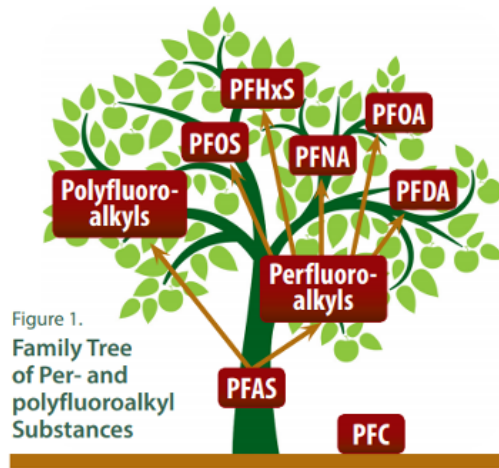
Refer to NHANES 2015-16 data:

https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf

Overview of Per- and Polyfluoroalkyl Substances (PFAS)

PFAS Overview

- Formerly called PFCs, PFAS are a family of thousands of chemicals that contain a chain of carbon atoms bonded to fluorine atoms
- PFAS are resistant to water, oil and fire, making them useful in a wide range of consumer/industrial products
- PFOA and PFOS (two main species) have been detected in the drinking water of millions of people across the country



Perfluoroalkyls and polyfluoroalkyls, referred to as PFAS and previously as PFCs, are a family of synthetic chemicals used for nearly 70 years to make products that resist heat, oil, stains, grease, and water. They are commonly categorized into two structural groups: carboxylic acids such as perfluorooctanoic acid (PFOA) and sulfonates including perfluorooctane sulfonate (PFOS). These substances are unique in that they are both hydrophobic and lipophobic and as a result, these substances have many applications in industry. These chemicals are highly stable and resistant to environmental degradation. Due to their chemical stability, the presence of these compounds persists for many years once introduced into the environment. Continued exposure through contaminated water leads to bioaccumulation in fish, ingestion of which provides a route of human exposure.

PFAS can be subdivided into groups based on the number of carbon atoms they contain. Long-chain PFAS include eight or more carbon atoms, while short-chain PFAS contain seven or fewer. In general, long-chain PFAS are thought to have longer half-lives and greater potential for bioaccumulation than short-chain PFAS. As a result, the health effects of long-chain PFAS have become a significant research topic over the past 15 years. PFOA, also known as C8, has 8 carbons.

- The graphic on the slide depicts the various types of PFAS and shows the PFC “apple” on the ground to demonstrate that the term 'PFC' isn't used very much anymore (that is why the box that says “PFC” is on the ground, not on the tree.)

PFAS in the Environment

■ Uses:

- Non-stick cookware
- Carpet and clothing treatments
- Paper and cardboard packaging
- Food containers/wrapping
- Waterproof clothing/coating
- Aqueous film-forming firefighting foam (AFFF)

■ Sources:

- Waste from manufacturing facilities
- AFFF run-off
- PFAS-containing sludge used as soil amendment
- Occupational settings

■ Exposure Pathways:

- Drinking water
- Air and dust
- Food grown/raised in PFAS-contaminated areas
- Food containers/wrappers
- Cookware
- Cord blood
- Breastmilk

PFAS have been used in a variety of consumer products, including non-stick cookware and carpet and clothing stain-resistant or waterproofing treatments. PFAS have also been used in packaging and cardboard, and as “AFFF” in fire-fighting foam.

Sources of contamination include waste from manufacturing facilities, AFFF run-off after training exercises. And PFAS containing sludge used as soil fill.

People can be exposed to PFAS in their drinking water or if they use contaminated products or consume contaminated foodstuffs.,

“The use of per- and polyfluoroalkyl substances (PFASs) as grease and stain repellents in consumer products started in the 1950s [\[1\]](#).

...

Nevertheless, PFAS with shorter fluorinated side chains and other types of fluorinated substances are currently used as substitutes for PFOS and PFOA [\[4, 5\]](#). Short-chain PFASs have faster elimination rates in humans than their long-chain homologues, but recent research indicated that they are similarly persistent and toxic compared to their long-chain homologues [\[6\]](#).

...

Some long-chain PFASs, e.g. PFOS, its precursors and PFOA, have been targeted by different phase-out initiatives within the last years [\[12-14\]](#). As a consequence, the use of some PFOS derivatives (e.g. perfluorooctane sulfonamidoethanol-based phosphate

(SAmPAP) esters) in paper and board FCMs has mainly stopped by 2002 [15]. In the recent years, fluorotelomer-based derivatives (e.g. polyfluoroalkyl phosphate esters (PAPs)), short- and medium-chain PFASs and fluorinated polymers have gradually started to replace many PFOS-based substances in FCMs [4, 9, 10].

For the general population, ingestion is considered the primary exposure pathway. This can occur through drinking contaminated water, ingesting fish and wildlife contaminated with PFAS, and ingesting food contaminated by materials containing PFAS such as popcorn bags, fast food containers, non-stick cookware, and pizza boxes.

Workers in industries or activities that manufacture, manipulate, or use products containing PFAS may be exposed to higher levels than the general population. Workers in facilities that historically used PFAS may also be exposed due to persistence of the compounds in the environment.

For toddlers, hand-to-mouth transfer from surfaces treated with stain protectants containing PFAS, such as carpets, is thought to be the most contributory source of exposure. PFAS have also been detected in breast milk which may be another potential source of exposure for the youngest children in this age group.

Leachate from landfills is another potential source - Although the manufacture of many PFAS compounds has ceased in the U.S. and regulations are coming into play that will limit use of others (e.g., aqueous film forming foam (AFFF) for firefighting purposes), these (soon-to-be) legacy compounds such as PFOA and PFOS may continue to leach into groundwater sources from solid waste landfills.

Breastfeeding is another exposure pathway of concern to families. PFOS and PFOA are commonly found in breastmilk and cord blood. Background levels have been steadily declining over the last decade, but the wide-spread past use and environmental presence reflects the ubiquity and persistence of these agents in our environment. The movement of PFAS from blood into different areas of the body, including into breastmilk and across the placenta, varies depending on the particular substance.

Depending on the specific PFAS, breastmilk concentrations reflect roughly 3% to 10% of maternal serum concentrations. It is worth noting that cessation of exposure of the mother to PFAS will not be immediately reflected in maternal serum or breastmilk concentrations due to the long serum half-lives of PFAS. This represents a temporary source of increased exposure to breastfeeding infants. However, no consistent developmental health effects have been demonstrated in either population cohorts or occupational exposure groups.

The benefits of breastfeeding, including: immunologic advantages, lower obesity rates, and greater cognitive development for the infant as well as a variety of health advantages for the lactating mother, currently outweighs any potential risk posed by PFAS exposure through breastfeeding. The science on the health effects of PFAS for mothers and babies is evolving. However, given the scientific understanding at this time, the benefits of breastfeeding a baby outweigh those of not breastfeeding. The take home message is that current evidence does not support discontinuing breastfeeding due to potential PFAS exposure. This is in accordance with recommendations from the World Health Organization, the U.S. Surgeon General, and the American Academy of Pediatrics when the risk-benefit has been examined for other agents that are transferred through breastfeeding.

Sources:

Gützkow KB, Haug LS, Thomsen C, Sabaredzovic A, Becher G, Brunborg G. 2012. Placental transfer of perfluorinated compounds is selective--a Norwegian Mother and Child sub-cohort study. *Int J Hyg Environ Health*. 2012 Feb;215(2):216-9.

Kärrman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, Lignell S, Lindström G. 2007 Exposure of Perfluorinated Chemicals through Lactation: Levels of Matched Human Milk and Serum and a Temporal Trend, 1996-2004, in Sweden. *Environ Health Perspect*. 2007 Feb; 115(2):226-30

Kuklennyik Z1, Reich JA, Tully JS, Needham LL, Calafat AM. Automated solid-phase extraction and measurement of perfluorinated organic acids and amides in human serum and milk. *Environ Sci Technol*. 2004 Jul 1;38(13):3698-704.

Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima S, Uno A, Saijo Y, Sata F, Yoshimura Y, Kishi R, Nakazawa H.

Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environ Health Perspect*. 2004 Aug;112(11):1204-7.

Haug LS1, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds--comparing exposure estimates with biomarkers of exposure. *Environ Int*. 2011 May;37(4):687-93.

ATSDR 2015. Toxicologic Profile for Perfluoroalkyls. Sec 3.8.2. August 2015.

<http://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>

Fromme H, Tittlemier SA, Vökel W, et al. Perfluorinated compounds- Exposure assessment for the general population in western countries. *Int. J. Hyg. Environ*.

Health. 2009: 212, 239-270.

Why is this Important?

- Studies suggest that PFAS exposure in humans may affect many body systems
- In drinking water systems across the country, PFOA and PFOS levels have exceeded the EPA health advisory
- PFAS:
 - Have widespread human exposure
 - Bioaccumulate in people
 - Have been deemed by EPA to be “contaminants of emerging concern”
 - Have long half-lives in humans

Here we explain why the information in this presentation is important to human health.

PFAS:

- Have widespread human exposure
- May bioaccumulate in people
- Are “Contaminants of emerging concern” – EPA
- May affect development of fetus & child
- May increase cancer risk
- Have long half-lives in humans

PFOA and PFOS levels have exceeded the EPA health advisory in drinking water systems across the country

The EPA health advisory includes PFOA and PFOS only - there is great variability in response as the federal guidance develops.

UCMR3 can be accessed at: <https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule>

EPA Health Advisory

- EPA established a Health Advisory for PFOA and PFOS to provide communities with information on the health risks of these chemicals
- The EPA Health Advisory in drinking water is currently 70 parts per trillion (ppt)
- Some states have released their own advisories, which are much lower
- EPA's Health Advisory is non-regulatory, but provides a threshold for consideration

Here we explain why the information in this presentation is important to human health.

PFAS:

- Have widespread human exposure
- May bioaccumulate in people
- Are “Contaminants of emerging concern” – EPA
- May affect development of fetus & child
- May increase cancer risk
- Have long half-lives in humans

PFOA and PFOS levels have exceeded the EPA health advisory in drinking water systems across the country

The EPA health advisory includes PFOA and PFOS only - there is great variability in response as the federal guidance develops.

UCMR3 can be accessed at: <https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule>

PFAS Elimination in Humans

- PFAS bind to tissue proteins, accumulate in the blood, and at much lower levels, in the liver, kidneys, and brain
- Most PFAS are not metabolized by the body
- PFAS are primarily excreted through urine
- In women, PFAS are also excreted through breastmilk and during pregnancy and menstruation
- Shorter-chain PFAS tend to be eliminated faster than long-chain PFAS
- Elimination rates appear to be different in males and females

PFAS are not metabolized in the body but instead are primarily eliminated very slowly through urine. They are also slowly eliminated through menstruation, breastmilk, and feces. PFAS is present in bile, but undergoes significant enterohepatic circulation, contributing to its persistence in the body and reducing the contribution of this elimination route. Shorter chain PFAS tend to be eliminated faster from the body than long chain PFAS. There is also substantial variability between males and females concerning rates of elimination. One example of this is males have been found to have statistically significantly higher amounts of PFOA in urine suggesting faster elimination of PFOA in males, but this relationship is not consistent for all PFAS. The same study found no difference in urinary PFOS concentration between the sexes. Additionally, lactation and menstruation present unique routes of elimination, which may increase elimination rates in females of reproductive age.

Sources:

Genuis SJ, Birkholz D, Ralitsch M, Thibault N. Human detoxification of perfluorinated compounds. *Public Health* 2010. 124; 367-375.

Zhang T, Sun H, Qin X, Gan Z, Kannan K. PFOS and PFOA in paired urine and blood from general adults and pregnant women: assessment of urinary elimination. *Environmental Science and Pollution Research* April 2015; 22(7):5572-9

Biological Persistence in Humans

Substance	Half-life
Perfluorooctanoic acid (PFOA)	2.1 to 10.1 years
Perfluorooctane sulfonate (PFOS)	3.3 to 27 years
Perfluorohexane sulfonate (PFHxS)	4.7 to 35 years
Perfluorobutane sulfonate (PFBS)	0.1 years

The biologic half-lives of these agents in humans is generally several years. Different types of PFAS have different serum half-lives, as presented in this table. Because PFAS are common in routinely-used products (particularly those manufactured prior to 2006), most of the U.S. population experiences on-going exposure, resulting in continuous PFAS body burden. Due to efforts in reducing utilization and dispersal of PFAS through the Stewardship Program and Significant New Use Rules, its presence in the environment is expected to decrease. This is expected to result in decreased on-going human exposure, which in turn will reduce PFAS levels in the general population. However, this reduction of biologic levels of PFAS will likely take many years due to the slow elimination of these compounds.

Sources:

[Environ Health Perspect.](#) 2007 Sep;115(9):1298-305.

Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers.

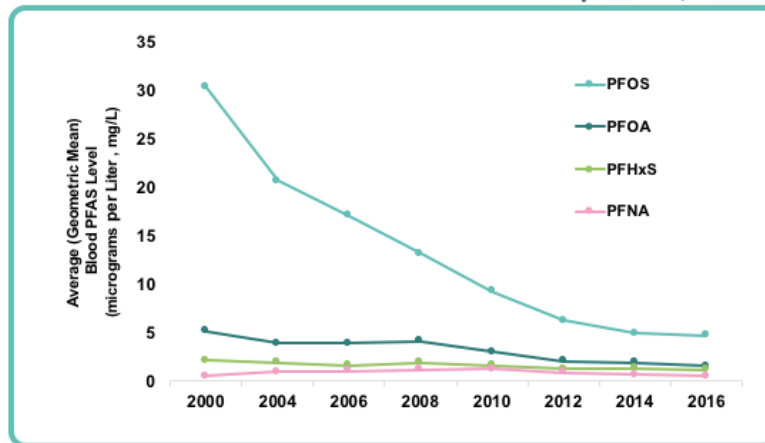
[Olsen GW¹](#), [Burris JM](#), [Ehresman DJ](#), [Froehlich JW](#), [Seacat AM](#), [Butenhoff JL](#), [Zobel LR](#).

<https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>

PFAS in the U.S. Adult Population

- CDC's National Health and Nutrition Examination Survey (NHANES) has been measuring PFAS in the blood of the general US population since 1999

Blood Levels of the Most Common PFAS in US Population, 2000-2016



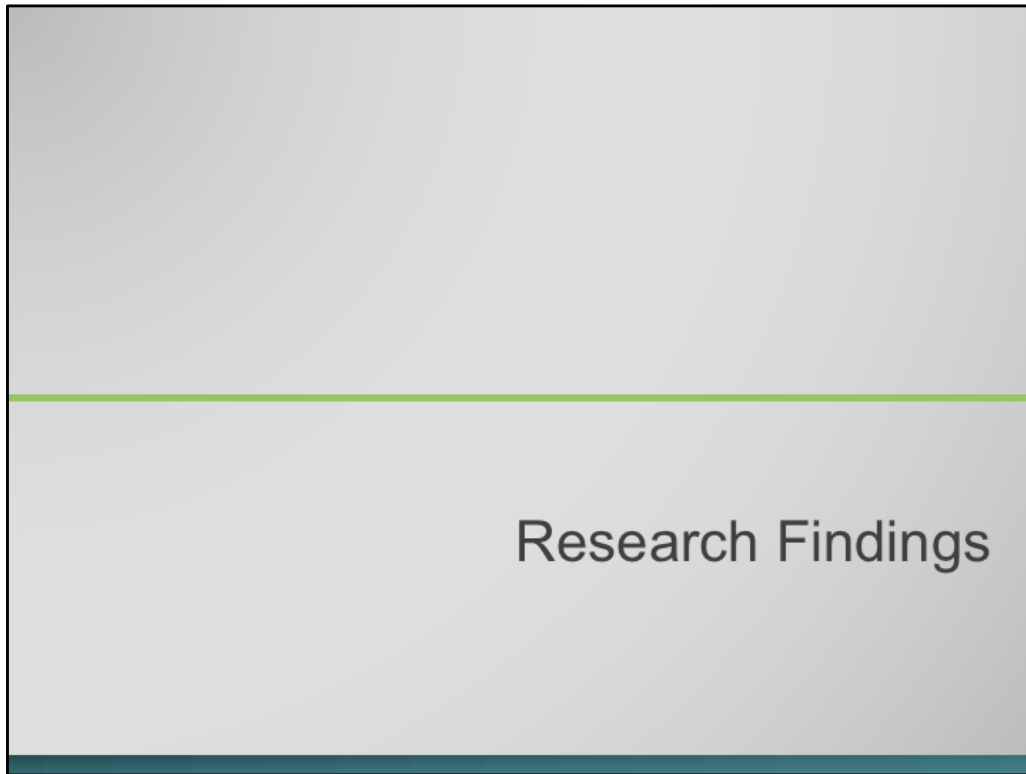
Data Source: CDC. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019, Volume One.

The National Health and Nutrition Examination Survey (NHANES) is a survey designed to assess the health and nutritional status of adults and children in the United States through the use of questionnaires, examinations, and biomonitoring. Biospecimens have been collected from healthy, asymptomatic NHANES participants since the 1980s, which includes data regarding PFAS since 1999. These data generally demonstrate steadily declining serum concentrations of PFOA and PFOS in the representative U.S. population (50-80% decrease in PFOS and PFOA concentrations over 1 ½ decades). This decline most likely reflects efforts to eliminate the production and use of these chemicals in the last decade.

Sources:

NHANES: <http://www.cdc.gov/nchs/nhanes/index.htm> -

https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf



Much of our information about the toxicity of PFAS comes from animal studies.

Animal Studies

- Animal studies have demonstrated increased risk of adverse health effects, but the effects occurred at exposure levels higher than most people experience. The main health effects observed were:
 - Enlargement and changes in the function of the liver
 - Changes in hormone levels
 - Suppression of adaptive immunity
 - Adverse developmental and reproductive outcomes
- However, results from animal studies difficult for understanding human exposure, because the differences in:
 - Half-lives
 - Mechanisms of toxicity
 - Measured exposure levels in epidemiological and experimental studies

Animal research, primarily utilizing rodent models, is the foundation of all toxicological study on health effects. Animal studies to date demonstrate a wide range of health effects following exposure to PFAS including liver enlargement, changes in serum lipid and cholesterol concentrations, reduced body weight, changes in thyroid hormone levels, reduced testosterone synthesis, suppression of antibody response, tumor formation, and developmental and reproductive effects, including reduced birthweight, in offspring. These effects are demonstrated only at doses several orders of magnitude higher than any known human exposure level. It is important to note these studies present several limitations and cannot necessarily be extrapolated to human health effects. Toxicodynamic and toxicokinetic mechanisms vary drastically between humans and animals. For example, elimination of PFAS occurs much faster in rodents, as rodents demonstrate half-lives of days to weeks as compared to the human's years. However, animal studies may provide helpful clues regarding target organs for pathology or potential cancer risk.

In animal studies, there is evidence of pancreatic, liver, and testicular adenoma formation following PFOA exposure.

Without a better mechanistic understanding of both toxicokinetics and toxicodynamics, it is difficult to relate outcomes in animals to human health effects.

Sources:

- Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. 2001. Mechanisms of Extrahepatic Tumor Induction by Peroxisome Proliferators in Male CD Rats. *Toxicological Sciences* 2001. 60:44-55
- Butenhoff JL, Kennedy GL Jr, Frame SR, O'Conner JC, York RG. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology*. 2012. 196:95-116
- Lau C, Butenhoff JL, Rogers JM. The developmental toxicology of perfluoroalkyl acids and their derivatives. *Toxicol. Appl. Pharmacol.* 198:231-241.
- Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, et al. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. *Toxicol. Sci.* 2006. 90:510-518.
- Kennedy GL, Hall GT, Brittelli MR, Barnes JR, Chen HC. 1986. Inhalation toxicity of ammonium perfluorooctanoate. *Food Chem Toxicol* 24(12):1325-1329.
- Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff JL. 2003. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. (Erratum in: *Toxicology* 2003 192(2-3):263-264). *Toxicology* 183(1-3):117-133.
- Elcombe CR, Elcombe BM, Foster JR, Chang SC, Ehresman DJ, Butenhoff JL. 2012. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPAR α and CAR/PXR. *Toxicology* 293(1-3):16-29.
- Fang X, Gao G, Xue H, Zhang X, Wang H. 2012. Exposure of perfluorononanoic acid suppresses the hepatic insulin signal pathway and increases serum glucose in rats. *Toxicology* 294(2-3):109-115.
- Elcombe CR, Elcombe BM, Foster JR, Chang SC, Ehresman DJ, Butenhoff JL. 2012. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPAR α and CAR/PXR. *Toxicology* 293(1-3):16-29.
- Staples RE, Burgess BA, Kerns WD. 1984. The embryo-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) in the rat. *Fundam Appl Toxicol* 4:429-440.
- Butenhoff JL, Kennedy GL, Frame SR, O'Connor JC, York RG. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 196(1-2):95-116.

Butenhoff JL, Bjork JA, Chang SC, Ehresman DJ, Parker GA, Das K, Lau C, Lieder P/h, van Otterdijk FM, Wallace KB. 2012. Toxicological evaluation of ammonium perfluorobutyrate in rats: Twenty-eight-day and ninety-day oral gavage studies. *Reprod Toxicol* 33(4):513-530.

van Otterdijk FM. 2007a. Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period. 3M.

van Otterdijk FM. 2007b. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. 3M.

Leping Ye L, Su Z, Ge R. 2011. Inhibitors of Testosterone Biosynthetic and Metabolic Activation Enzymes. *Molecules* 2011, 16(12), 9983-10001

Dewitt JC, Copeland CB, Strynar MJ, Luebke RW. 2008. Perfluorooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environ Health Perspect* 116(5):644-650.

Keil DE, Mehlmann T, Butterworth L, Peden-Adams, MM. 2008. Gestational exposure to perfluorooctane sulfonate (PFOS) suppresses immune function in B6C3F1 mice. *Toxicol Sci* 103(1):77-85.

Risk of Health Effects From PFAS

- The risk of adverse health effects from exposure to PFAS depends on:
 - Potential toxicity of a specific species
 - Environmental fate and transport
 - Bioaccumulation
 - Exposure dose
 - Frequency, route and duration of exposure
 - Phase of lifecycle at time of exposure (e.g., fetal development, early childhood)
 - Genetic and epigenetic variations in individuals

PFAS exposure is associated with an increased risk of some adverse effects for human health. Risk differs among the various PFAS based on their potential toxicity, mobility, and bioaccumulation. The risk of adverse effects depends on several factors, including the exposure dose, the frequency of exposure, the route and duration of exposure, the time of exposure during the lifecycle (e.g., fetal development, early childhood), as well as genetic and epigenetic variations in individuals.

Source:

ATSDR (2019). PFAS: An Overview of the Science and Guidance for Clinicians on Per-
Polyfluoroalkyl Substances (PFAS)

Human Studies: C8 Study and Beyond

- The C8 Health Study (2005-2013), an epidemiological study of 69,030 persons ≥ 18 years of age found a probable link between exposure to PFOA and several health outcomes
- Since the C8, numerous additional studies have examined relationships between PFAS and human health. Research in humans suggests that high levels of certain PFAS *may* lead to:
 - Increased cholesterol levels;
 - Changes in liver enzymes;
 - Decreased vaccine response in children;
 - Increased risk of high blood pressure or pre-eclampsia in pregnant women;
 - Small decreases in infant birth weights (<20 grams (0.7 ounces) decrease in birth weight per 1 ng/mL increase in PFOA or PFOS in blood);
 - Increased risk of kidney or testicular cancer

C8 Science Panel Website. C8 Probable Link Reports. http://www.c8sciencepanel.org/prob_link.html

Data collected via the C8 Health Project has given researchers invaluable information on the human health effects of PFAS. The C8 Health Project was a large epidemiological study conducted because drinking water in six districts near Parkersburg, West Virginia were contaminated by release of PFOA (also called C8) from the 1950s until 2002.

A "probable link" in the C8 study is defined in the Settlement Agreement to mean that given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease.

In regards to birth weight, high levels of certain PFAS may lead to small decreases in infant birth weights (<20 grams (0.7 ounces) decrease in birth weight per 1 ng/mL increase in PFOA or PFOS in blood)

Source:

ATSDR (2019). PFAS: An Overview of the Science and Guidance for Clinicians on Per-Polyfluoroalkyl Substances (PFAS)

A Note on Establishing Causality

- Most evidence for human health outcomes associated with PFAS exposure comes from epidemiological studies, which cannot establish a causal relationship
- To date, there is no research that shows a direct cause and effect relationship between exposure and health outcomes
- Thus, ATSDR clinician materials report “No causal relationship has been established” for those health effects from epidemiological studies
- Although the epidemiological literature has limitations, it is still important to consider when evaluating patients with concerns about PFAS exposure

The report of no causal effects use in ATSDR clinician materials is discussed here. This is a point for the notes section of a slide or for use of this slide when reviewing health effects in the clinician material.

Strength ([effect size](#)): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

Consistency ([reproducibility](#)): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.

Specificity: Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.^[1]

Temporality: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).

Biological gradient ([dose-response relationship](#)): Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.^[1]

Plausibility: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).

Coherence: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".

Experiment: "Occasionally it is possible to appeal to experimental evidence".

Analogy: The use of analogies or similarities between the observed association and any other associations.

Some authors consider, also, **Reversibility:** If the cause is deleted then the effect should disappear as well.

PFAS in Children

- PFAS reaches children through:
 - The placental barrier
 - Breastmilk
- Children are more vulnerable because they:
 - Have an immature blood-brain barrier
 - Have immature vital organs
 - Ingest more toxicants (pound per pound)
 - Spend more time on the floor
 - Are more likely to put objects in their mouths

The report of no causal effects use in ATSDR clinician materials is discussed here. This is a point for the notes section of a slide or for use of this slide when reviewing health effects in the clinician material.

Immune System Dysfunction in Children

- The National Toxicology Program systematically reviewed human, animal, and in vitro data for PFOA and PFOS
- Both compounds presumed to be immune hazards
 - Decreased antibody response to vaccines
- Evidence of impairment of infectious disease resistance is weak

There is evidence of reduced antibodies, evidence is weak to suggest increased incidence of infectious disease at this time.

Both compounds are presumed to be immunohazards. However, level of evidence on impairment of increased risk of disease is weak and not credited with increased risk of disease because of the lowered response.

Additional systematic reviews for six additional PFAS currently underway

Elevated Cholesterol

- Epidemiological studies have identified significant positive correlations between serum PFOA and PFOS concentrations and total cholesterol specifically in:
 - Residents of communities with high levels of PFOA in drinking water
 - Workers exposed to PFAS in occupational context

Several epidemiological studies have identified statistically significant positive correlations between serum PFOA and PFOS concentrations and total cholesterol

Residents of communities with high levels of PFOA in drinking water

Workers exposed to PFAS in occupational context

No causal relationship has been established (see slide one)

Testicular & Kidney Cancer

- International Agency for Research on Cancer (IARC) classified PFOA under Group 2B, possibly carcinogenic to humans
- Evidence suggests carcinogenic potential for both PFOS and PFOA in humans
- Workers exposed to PFAS and residents living near a PFOA production facility have both experienced increases in testicular and kidney cancer

Notes:

No causal relationship has been established

Other Health Effects

Effects	Details
Elevated serum uric acid	N/A
Liver	Elevated AST, ALT, GGT, ALP
Kidney	Reduced kidney function, dysregulated metabolic pathways
Endocrine	Increased body fat and risk of cardio-metabolic disorders, obesity
Thyroid effects	Increased TSH, T3, T4
Reproductive	Lower fertility and fecundity
Preeclampsia	N/A
Reduced birth weight	N/A
Neurodevelopmental	ADHD, autism, hyperactivity
Neurobehavioral	Learning problems
Ulcerative colitis	N/A
Asthma	N/A

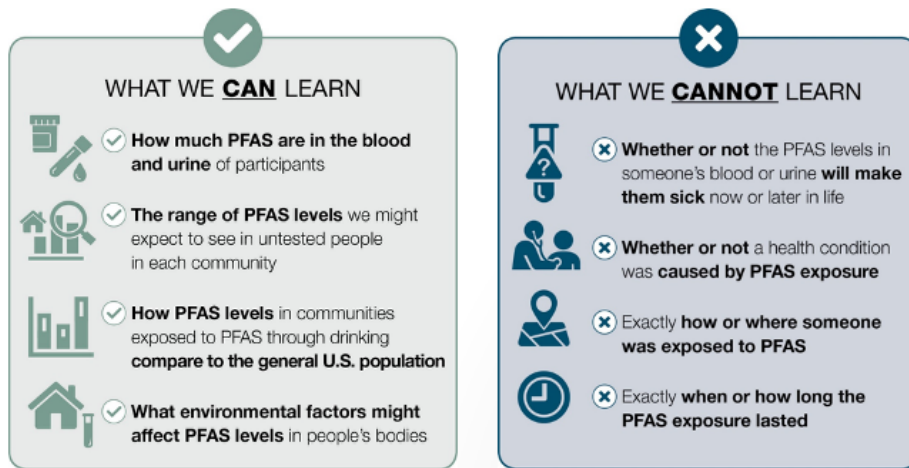
There is “moderate” evidence of health effects:

- Elevated serum uric acid
- Liver effects
- Kidney effects
- Endocrine effects
- Thyroid effects
- Reproductive effects
- Preeclampsia
- Reduced birth weight



Addressing PFAS Concerns With Your Patients

PFAS Exposure Assessments



37

There are ATSDR observations about what can be learned from an exposure assessment:

- The levels of PFAS in blood or urine
- The range of values one might expect in the untested community
- How PFAS levels of people in a community compare to the national values
- And what environmental factors might affect PFAS levels.

Sample Case

SCENARIO

- Mother and 12-year-old son in good health
- Family has lived in sampling area for the past 12 years
- The mother heard that the water in their community was contaminated with PFAS
- The family participated in ATSDR's exposure assessment and brings you their individual biomonitoring results

QUESTIONS TO CONSIDER...

- Are you able to interpret the results?
- Does this family need further testing? And if so, for what?
- How else can you help this patient (e.g., reducing exposure and stress)?

To frame the discussion of today's presentation, we will provide information in the context of a hypothetical case that includes a mother and son who are part of one of ATSDR's exposure assessments. The mother participates in the study to determine their level of exposure to various PFAS. After receiving their individual results from ATSDR, the mother schedules an appointment with their family physician to interpret their results and provide guidance on potential health effects. This presentation will help you prepare to provide appropriate guidance.

Sample Biomonitoring Results

PFAS	Your Level in µg/L	U.S. Population (all ages) Geometric Mean in µg/L ^a	U.S. Population (all ages) 95 th percentile in µg/L ^a
PFDA		0.154	0.700
PFHxS		1.18	4.90
PFNA		0.577	1.90
PFOA ^b		1.56	4.17
n-PFOA		1.46	4.10
Sb-PFOA		*	<LOD
PFOS ^b		4.72	18.3
n-PFOS		3.2	12.8
Sm-PFOS		1.42	5.7
MeFOSAA		*	0.600
PFUnA		*	0.400

Note: U.S. Population results above from NHANES 2015-2016.
 ND – Not detected (limit of detection = 0.1 µg/L)
 * Geometric mean was not calculated because not enough people had results that were detectable.
 **95th percentile was below the limit of detection, 0.1 µg/L.

NOTE to Speaker: This is the same table that is used on slide #8 to remind participants about the case that was posed at the beginning of the presentation. Given the information that was just presented, review the case again to prepare for the points and question on the next slide.

Talking to Patients

- A visit to the physician's office can leave patients feeling supported and reaffirmed (decreased stress) or it can leave them feeling frustrated, judged and hurt (increased stress)
- Tips for engaging with patients concerned about PFAS exposure:
 - Engage proactively
 - Show empathy for the patient's concerns (i.e., listen and validate)
 - Be clear and honest about what you do and don't know
- For more information on helping patients deal with the stress associated with chronic contamination, visit the ATSDR website

Being empathetic during every patient visit is of utmost importance to ensure that patients adopt risk reduction practices and continue to seek guidance from health professionals about potential or confirmed PFAS exposure and its health effects. This will increase trust between the doctor and patient, and thus increase the ability to provide recommended patient care. It will also reduce the likelihood of misinformation being conveyed throughout an affected community.

Ways to reduce exposure are discussed in more detail on the next slide.

Guidance for promoting standards of preventive care can be found in *Bright Futures*, 4th edition for children and the *Guide for Preventive Clinical Services* for adult care.

Citations:

Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, 4th Edition: <https://brightfutures.aap.org/materials-and-tools/guidelines-and-pocket-guide/Pages/default.aspx>

The Guide to Clinical Preventive Services 2014:
<https://www.ahrq.gov/sites/default/files/publications/files/cpsguide.pdf>

Reducing Exposure

- If the PFAS concentration detected in a patient's drinking water is above the EPA Health Advisory and/or your state guidelines, or if a patient is concerned, patients can:
 - Install filtration system or using a pitcher-type filter
 - Use an alternative water source for drinking, food preparation, cooking, brushing teeth, or any other activity that might result in ingestion of water
 - Check for local fish advisories
 - Read consumer product labels and avoid using those with PFAS

41

*Maintenance of point of use (POU) filters is important and can vary in efficacy for removing PFAS

- There is a cost associated with purchase and upkeep of filters
- There are limitations of using pitcher filters

Municipal water agencies are advised to remediate municipal drinking water with PFAS that exceed the EPA Health Advisory.

Treatment Recommendations

- For asymptomatic individuals exposed to PFAS, there is insufficient evidence to support deviations from established standards of care
- For patients with signs or symptoms of disease, treat using the same established standards of care regardless of PFAS exposure
- Follow the National Heart, Lung, and Blood Institute (NHLBI) guidelines for pediatric cholesterol screening, regardless of PFAS exposure
- There is no change to the current immunization schedule for children exposed to PFAS

42

The C8 Medical Panel suggested blood tests for cholesterol, uric acid, thyroid hormones and liver function. This is not currently recommended as screening tests.

Resources:

ATSDR Coping with Stress fact sheet:

https://www.atsdr.cdc.gov/docs/factsheet/Stress_Tips_Fact_Sheet-508.pdf

NHLBI guidelines:

https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf

Pregnant/Breastfeeding Women

- Monitor blood pressure during pregnancy, but no need for additional measurements
- Given the scientific evidence at this time, the benefits of breastfeeding outweigh those of not breastfeeding
- Women who choose to breastfeed, should continue to do so even if exposed to PFAS

The science on the health risks of PFAS for mothers and babies is evolving. Given the scientific evidence at this time, the benefits of breastfeeding outweigh those of not breastfeeding.

It is recommended that clinicians caring for pregnant women exposed to PFAS monitor blood pressure during pregnancy as they usually would, but there is no need for additional measurements.

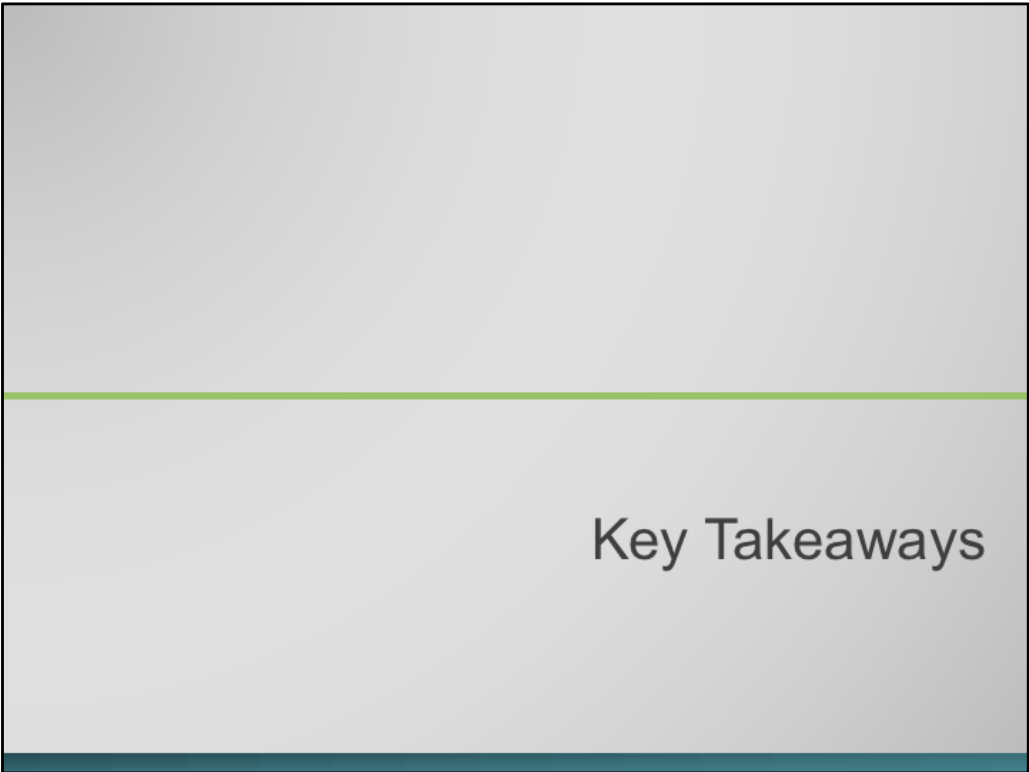
Blood Testing

- While most people in the US have measurable amounts of PFAS in their blood, there is no established PFAS blood level at which a health risk is expected or can be predicted
- Serum PFAS measurements are most helpful when they are part of a carefully designed research study
- A patient's PFAS blood concentration can be compared to:
 - Those measured in the general US population as part of NHANES
 - Those from other biomonitoring efforts (e.g., exposure assessments) in PFAS-affected communities
- If you decide to test your patient, serum PFAS level tests are commercially available

44

Some key points about blood testing include:

- Most people in the United States will have measurable amounts of PFAS in their blood
- There is no established PFAS blood level at which a health risk is expected or can be predicted
- Serum PFAS measurements are most helpful when they are part of a carefully designed research study
- If you decide to test your patient, serum PFAS level tests are commercially available
- A patient's PFAS blood concentration can be compared to those measured in the general US population as part of NHANES, or to those from population studies in other PFAS-impacted communities



Key Takeaways

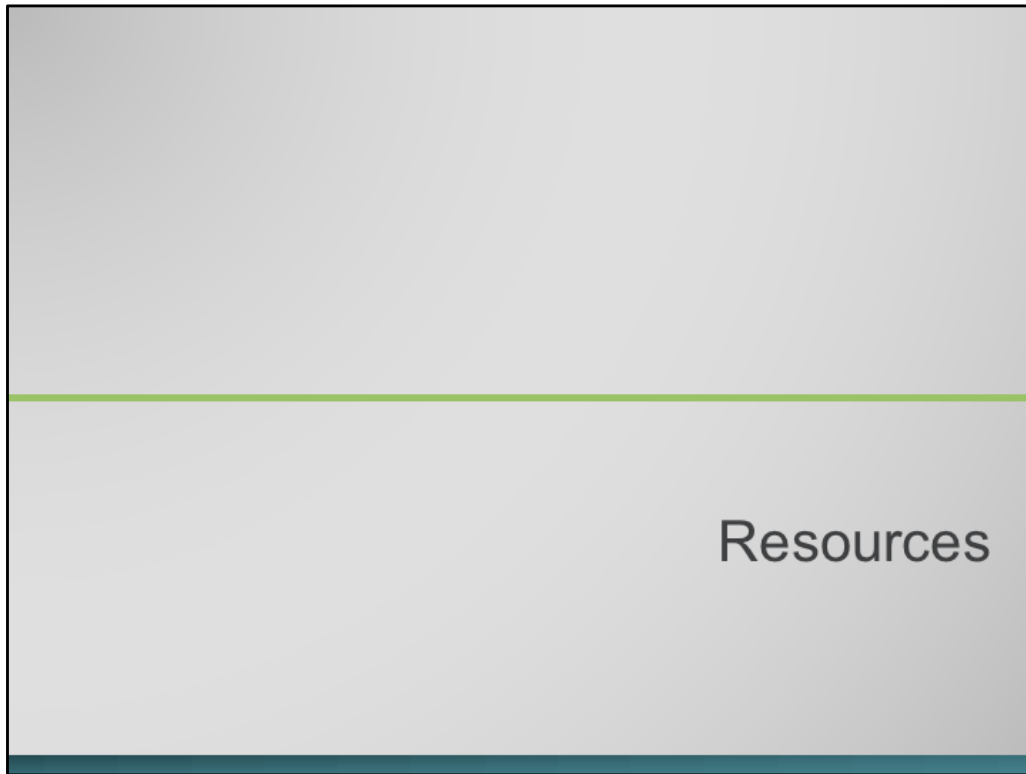
Key Takeaways

- Most people have some PFAS in their bodies
- When patients express concern about PFAS exposure, be prepared to talk about exposure history, health effects and blood testing
- Reducing exposure to PFAS is the most important first step for families with concerns
- There are currently no deviations from established standards of care for patients with elevated PFAS serum concentrations
- When talking to patients, empathize, validate their concerns and be honest about what you know and what you can do to help
- Promote standard, age-appropriate preventive care measures for general health and wellness (i.e., Bright Futures and Clinical Preventive Services guide)

46

Most people in the U.S. have some PFAS in their bodies. Reducing exposures to PFAS is the most important step for families with concerns. A home filtration system can reduce the contaminant levels in drinking water. You can find details at the ATSDR website given at the end of this presentation. Reducing exposures from certain consumer products is also advisable, including such items as old waterproofing sprays or stain-resistant carpeting.

If your patient presents with health concerns that might be associated with PFAS exposure, it is appropriate to discuss these concerns and perform a thorough exposure history and a physical exam relative to any symptoms reported.



Resources

- Updates on CDC/ATSDR PFAS Initiatives
https://www.atsdr.cdc.gov/pfas/related_activities.html
- ATSDR Guidance for Health Professionals
<https://www.atsdr.cdc.gov/pfas/info-for-health-professionals.html>
- PEHSU
https://www.pehsu.net/PFAS_Resources.html
- PFAS Overview
<https://www.atsdr.cdc.gov/pfas/index.html>
- Current PFAS levels in the U.S. can be found in the 2018 report:
https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf
- Resources on Medical Testing
<https://georgetown.app.box.com/s/da8t2cekmeidsqkcg41i2sufd2tgm1n>
- WA DOH <https://www.doh.wa.gov/CommunityandEnvironment/Contaminants/PFA>

48

Here are some additional websites with relevant information.

Many states have robust websites and resources on PFAS that can be specific to a particular state or community.

Opportunity = “virtual” visit at your clinical site?

“Public health detailing” opportunity

15 min presentation with Q & A

Contact Nancy Beaudet NW PEHSU
(Beaudet@uw.edu) to schedule

Thank you!

Catherine Karr
Arthur Wendel

