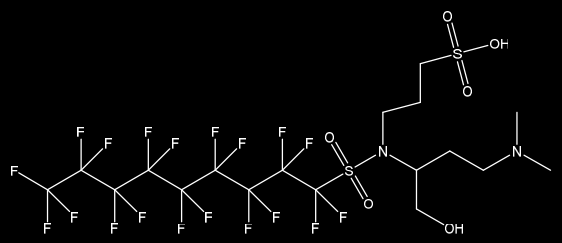
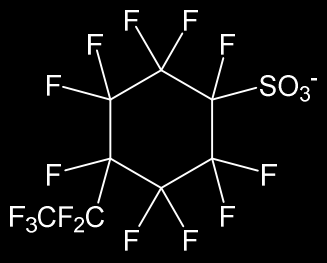
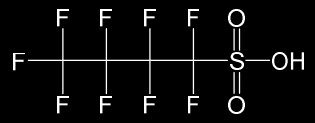
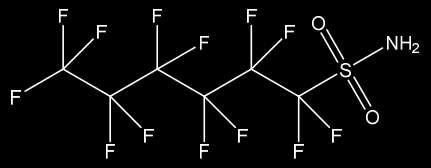
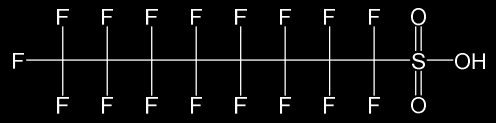





Contributions of Overlooked PFAS to Bioaccumulation and Human Body Burdens



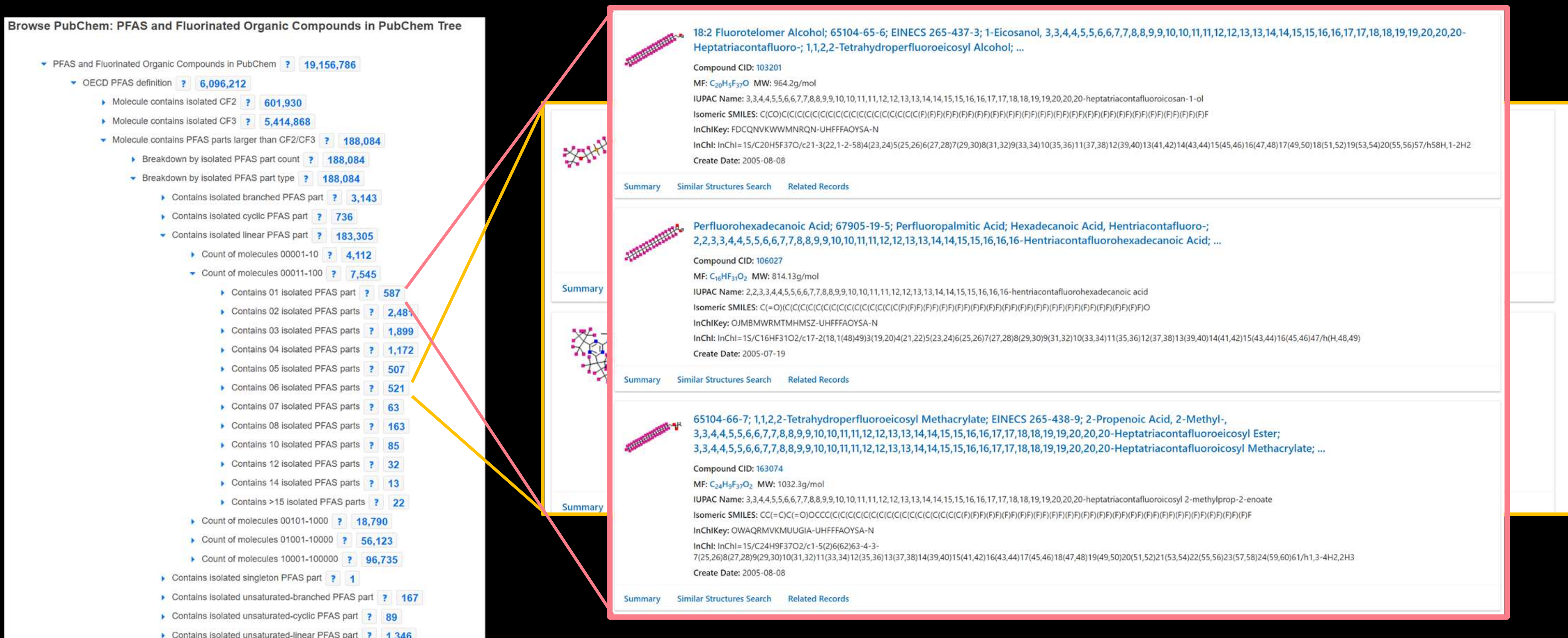
Carrie A. McDonough, Ph.D.
Assistant Professor, Department of Civil Engineering,
Stony Brook University

NEWMOA Northeast Conference, April 6, 2022

Not a toxicologist!

The vast majority of studies on PFAS exposure and effects focus on a few well-studied perfluoroalkyl acids (PFAAs) like PFOA and PFOS, but

There are Thousands of PFASs…



https://pubchem.ncbi.nlm.nih.gov/classification/

The Problem of Precursors

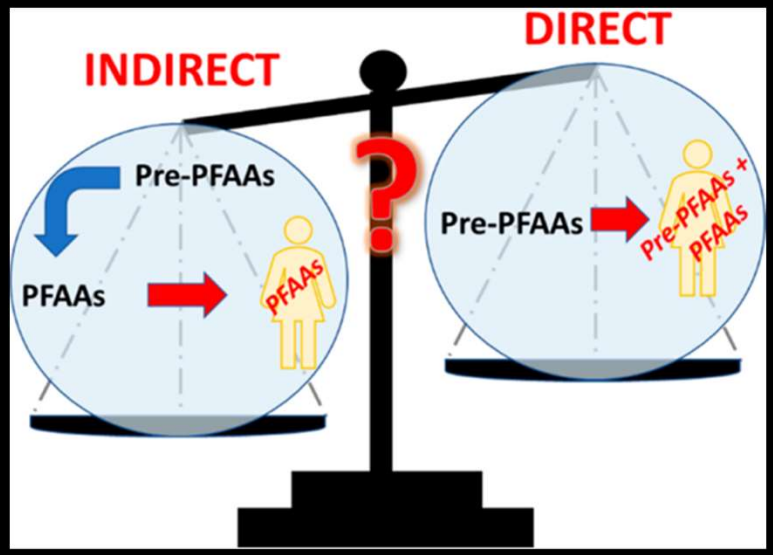
Not all PFAS are "forever" – *but the fluorinated moieties often are*

Pre-PFAAs are precursor compounds that can transform to extremely stable PFAAs

OECD classified 4,186 **"potential precursors to PFAAs"** out of 4,730 identified PFAS-related CAS numbers

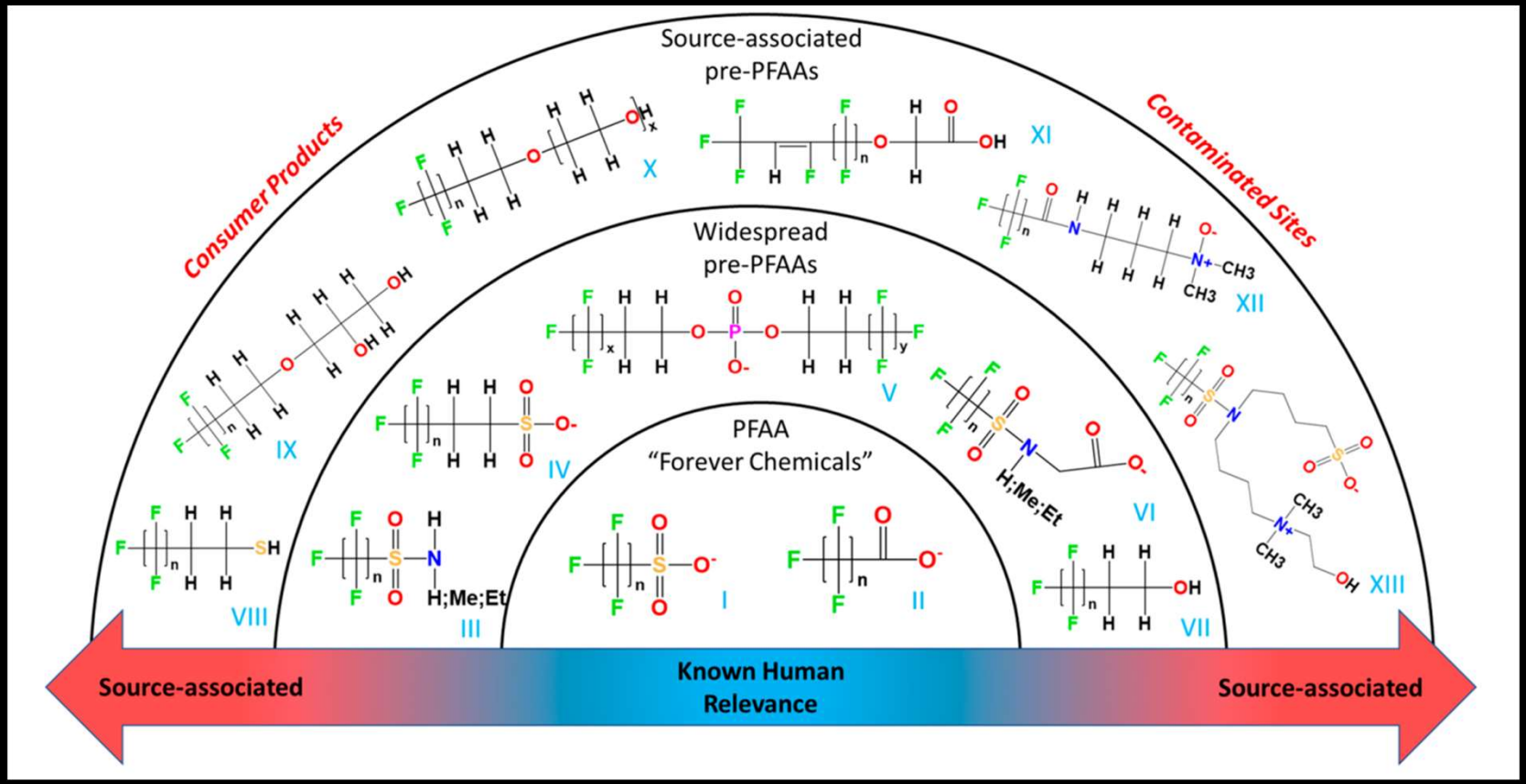
Studies using TOP assay imply contributions from unidentified pre-PFAAs

What are the implications for human exposure?

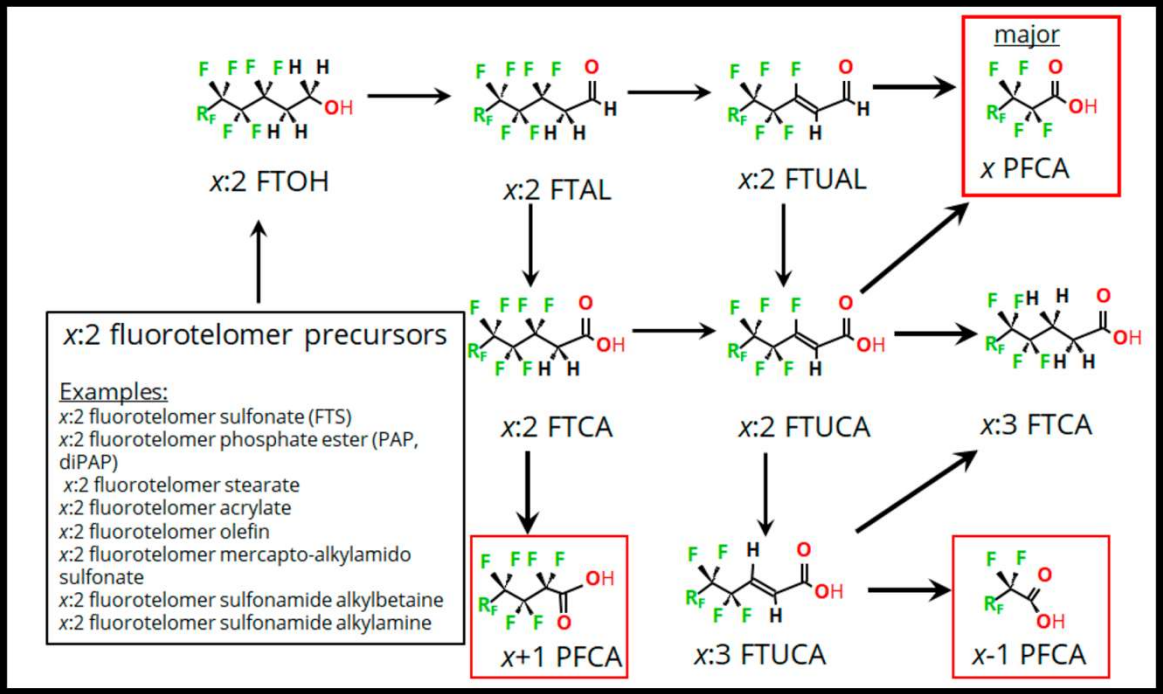


McDonough et al. *ES&T* 2022

Human Exposure to Pre-PFAAs



Biological Transformation of Pre-PFAAs

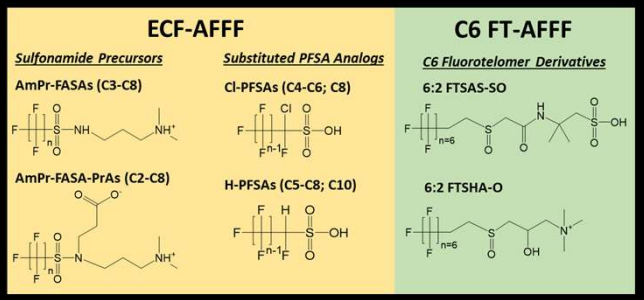


Diverse pre-PFAAs funnel through common reaction pathways to ultimately form PFAAs

To what extent is this occurring *in vivo*, and what are the consequences in terms of toxicokinetics and health effects?

How do we study bioaccumulation of novel and unknown PFASs?

Commercial PFAS mixtures



In vitro metabolism assays

In vivo dosing studies

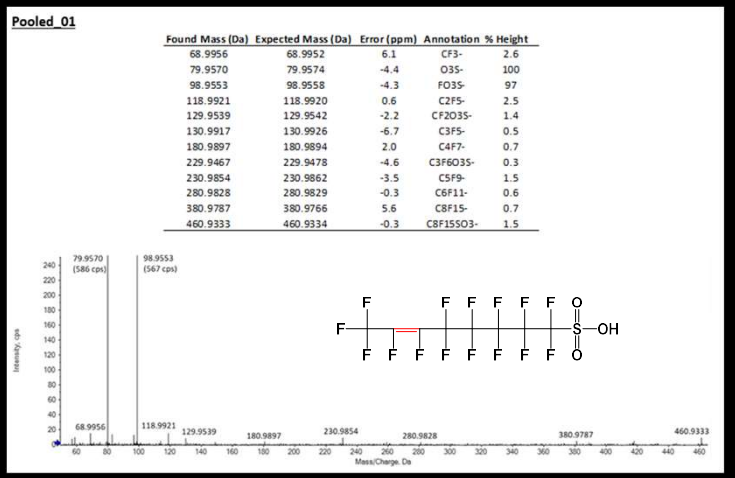
Biological transformation products

Novel bioaccumulative compounds

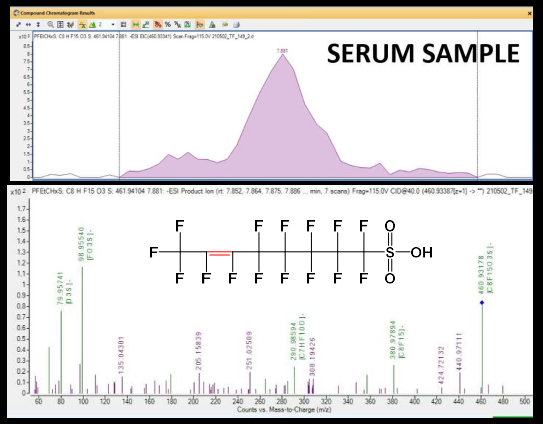
HRMS Libraries

Pooled_01

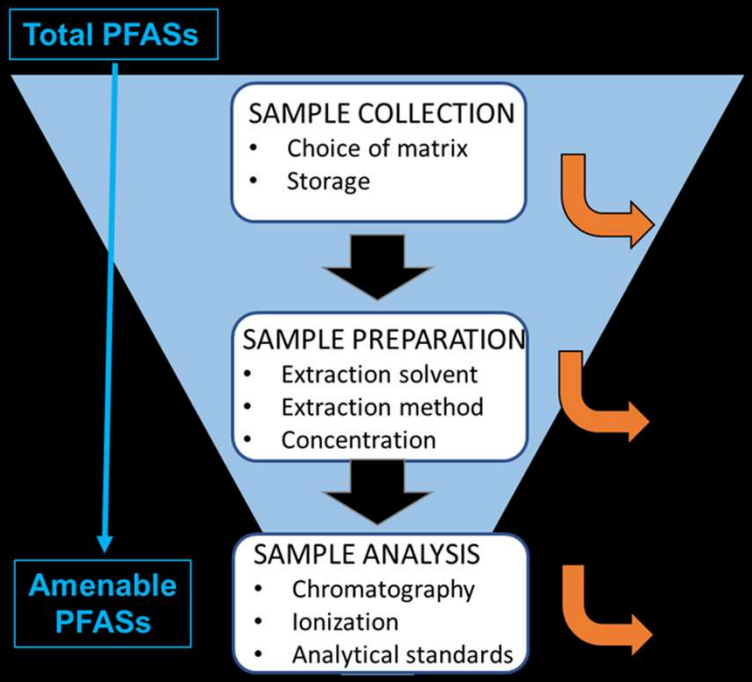
Found Mass (Da)	Expected Mass (Da)	Error (ppm)	Annotation	% Height
68.9956	68.9952	6.1	CF3-	2.6
79.9570	79.9574	-4.4	O3S-	100
98.9553	98.9558	-4.3	FO3S-	97
118.9921	118.9920	0.6	C2F5-	2.5
129.9539	129.9542	-2.2	CF2O3S-	1.4
130.9917	130.9926	-6.7	C3F5-	0.5
180.9897	180.9894	2.0	C4F7-	0.7
229.9467	229.9478	-4.6	C3F6O3S-	0.3
230.9854	230.9862	-3.5	C5F9-	1.5
280.9828	280.9829	-0.3	C6F11-	0.6
380.9787	380.9766	5.6	C8F15-	0.7
460.9333	460.9334	-0.3	C8F15SO3-	1.5

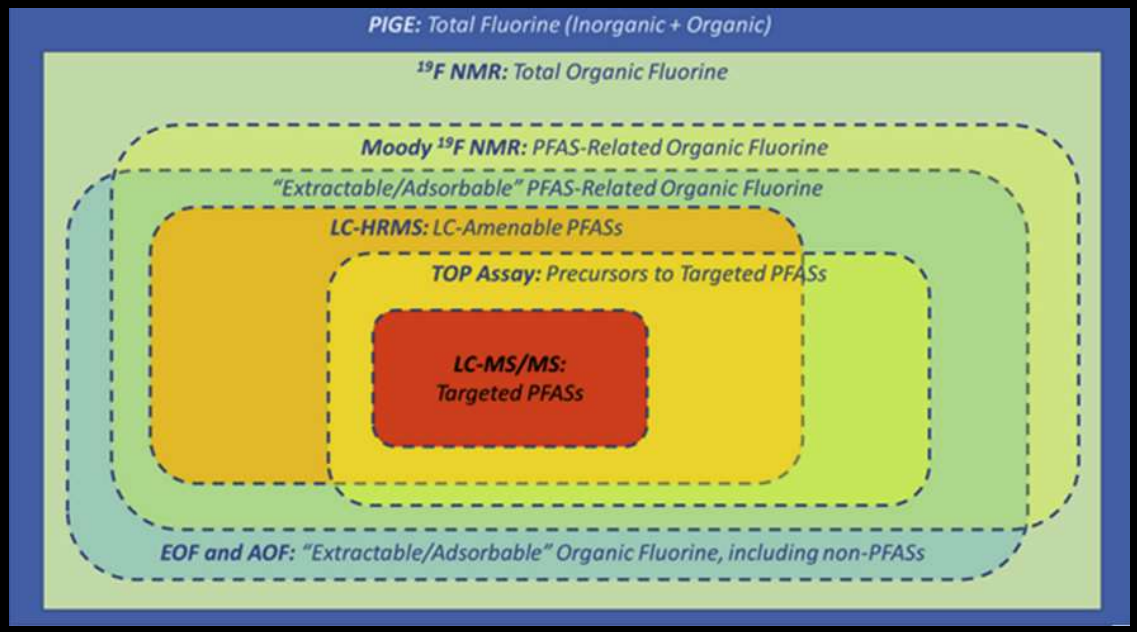


Human biomonitoring



PFAS Mixture Analysis with HRMS

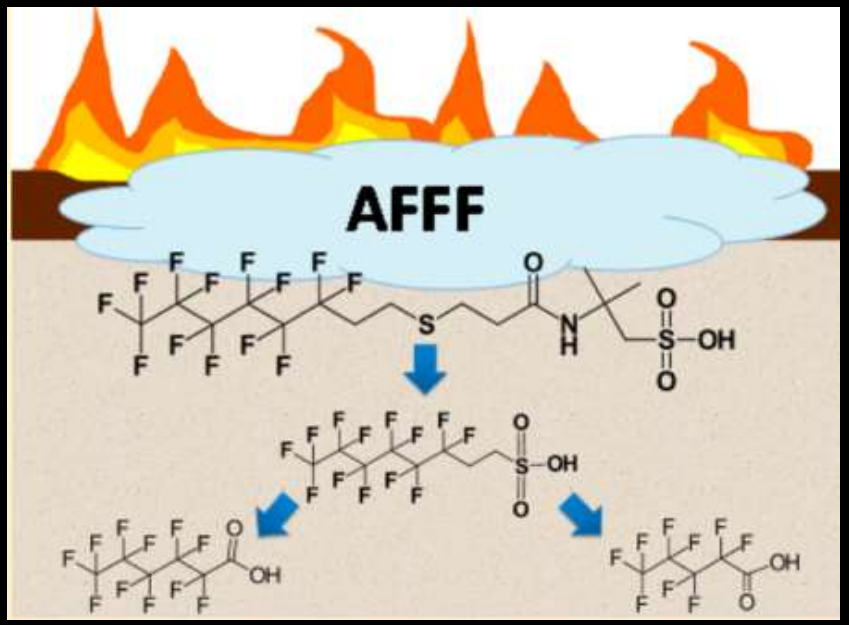




McDonough et al. 2019 *Current Opinion in Environmental Science & Health*

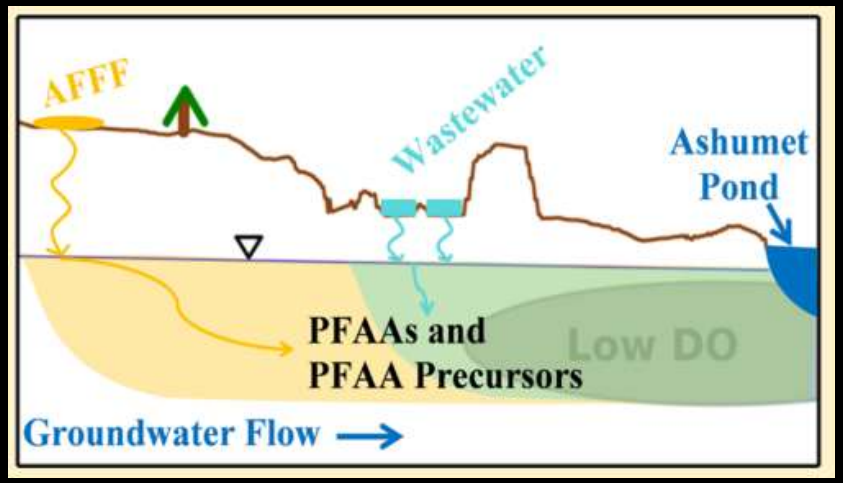
Aqueous Firefighting Foam (AFFF)

Aqueous firefighting foams (AFFFs) are complex, transforming mixtures of PFASs necessitating advanced analytical strategies



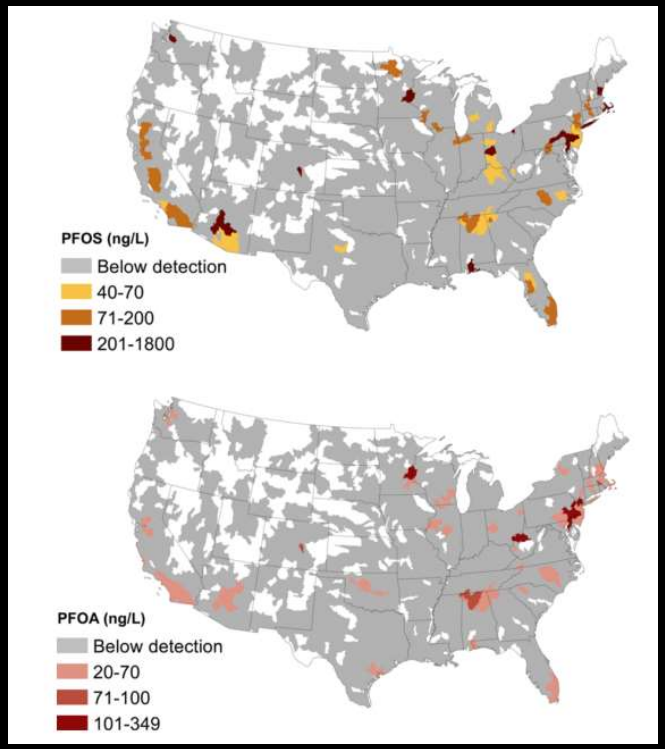
Harding-Marjanovic et al. **2015** *ES&T*

Aqueous Firefighting Foam (AFFF)



Fire training source zone continues releasing PFASs despite 18-20 yrs of inactivity

(Weber et al. 2017)

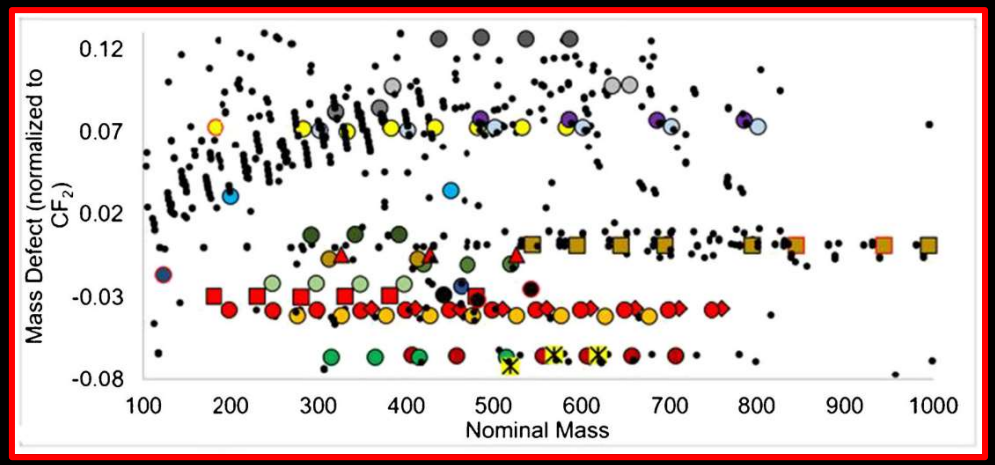


Elevated PFAS in drinking water is associated with proximity to FTAs/military bases

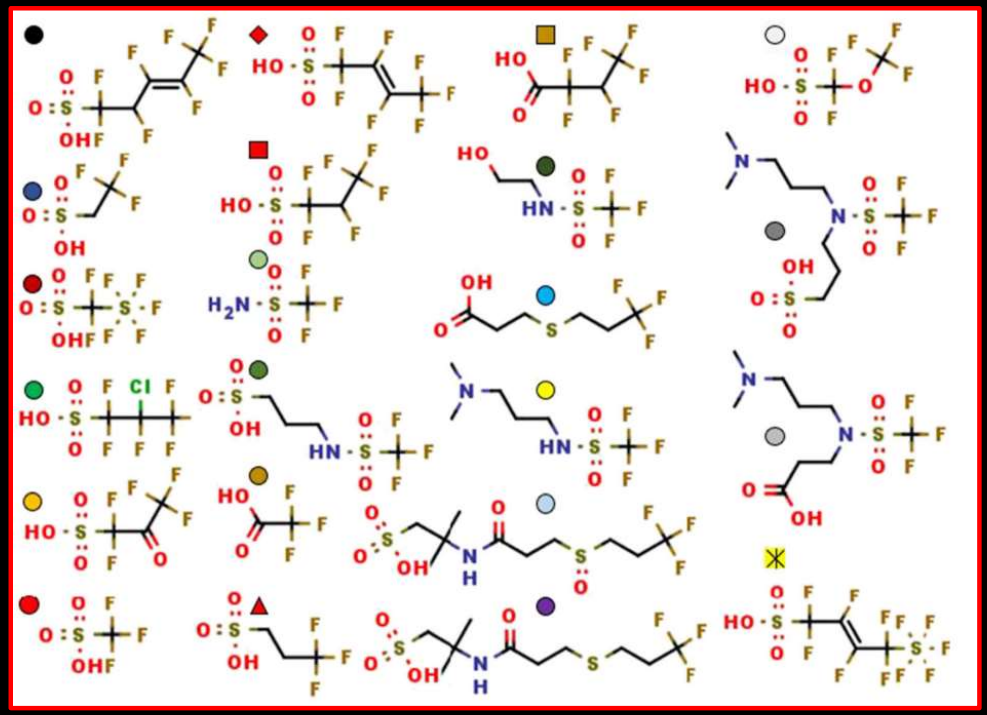
(Hu et al. 2016)

Aqueous Firefighting Foam (AFFF) Composition

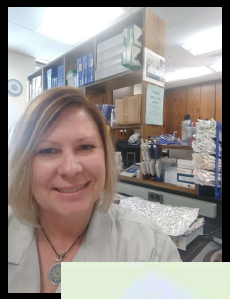
Field-collected AFFF (primarily ECF) characterized by iterative MS^2 and FluoroMatch screening software



Koelmel et al., *Analytical and Bioanalytical Chemistry,* 2021

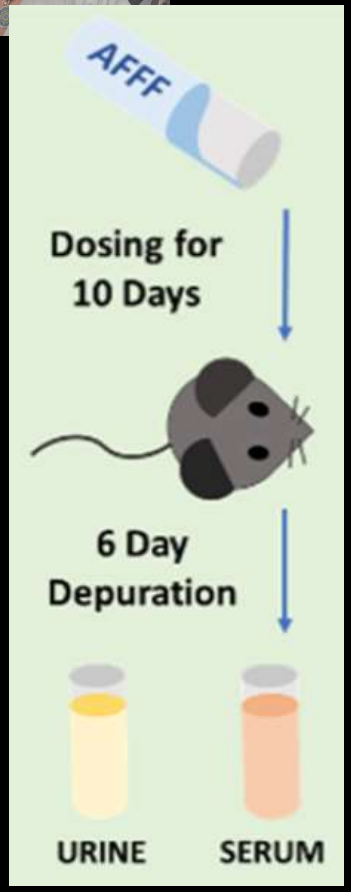


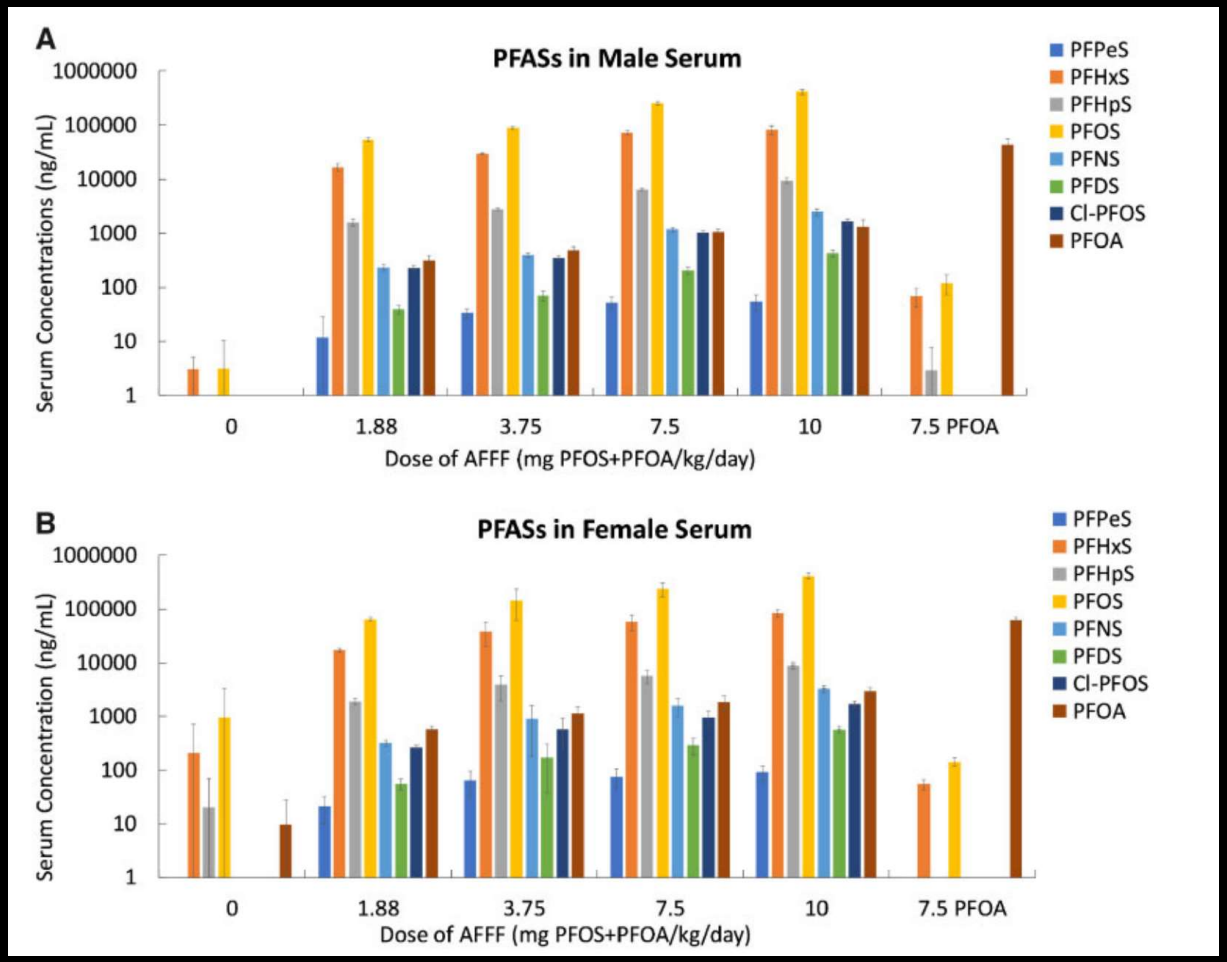
Question 1:
What Can We Learn About PFAS Bioaccumulation from Mixture Dosing Studies?



AFFF PFAS Bioaccumulation in Mice

Jamie DeWitt, ECU

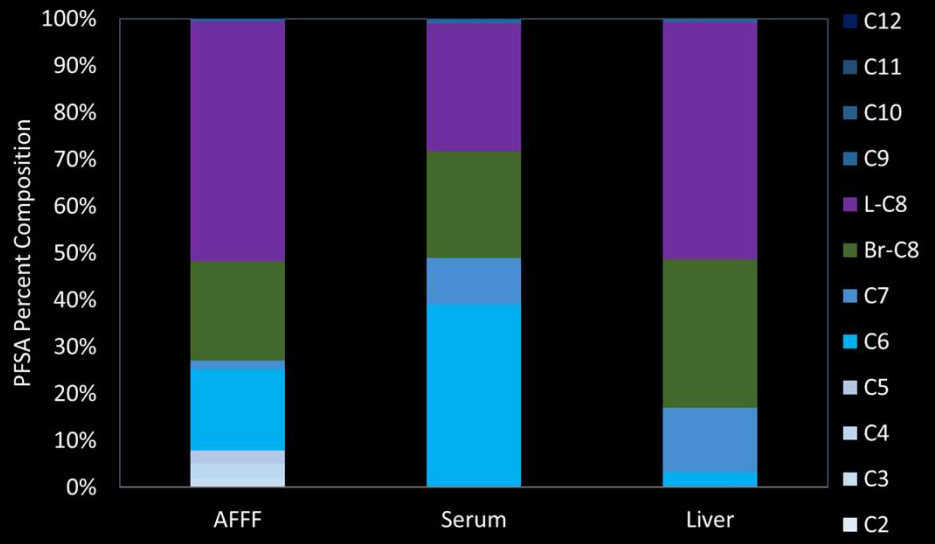




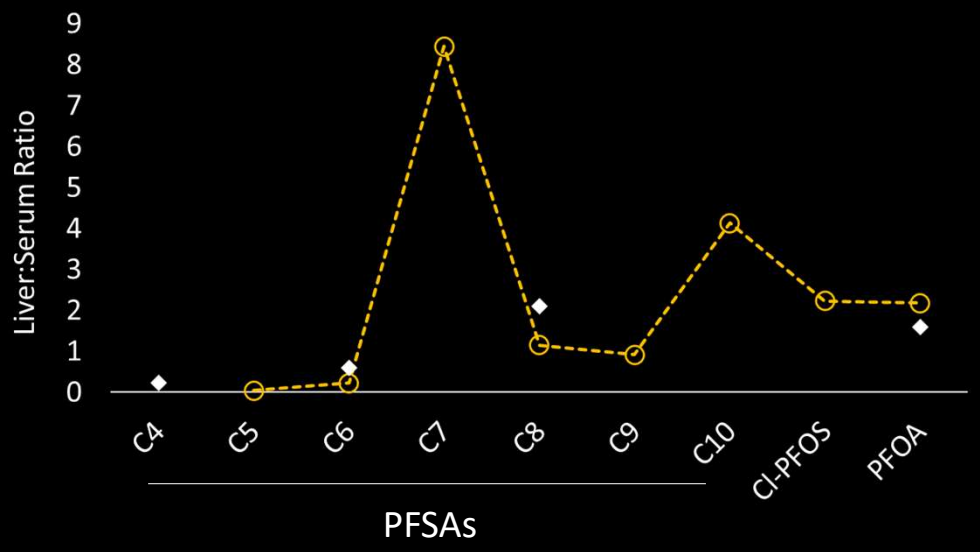
McDonough et al. *Tox. Sci.* 2020

Liver Tissue Analysis

PFAS Composition and Tissue:Serum Ratios for 10 mg/kg PFOS-eq dosed male mice

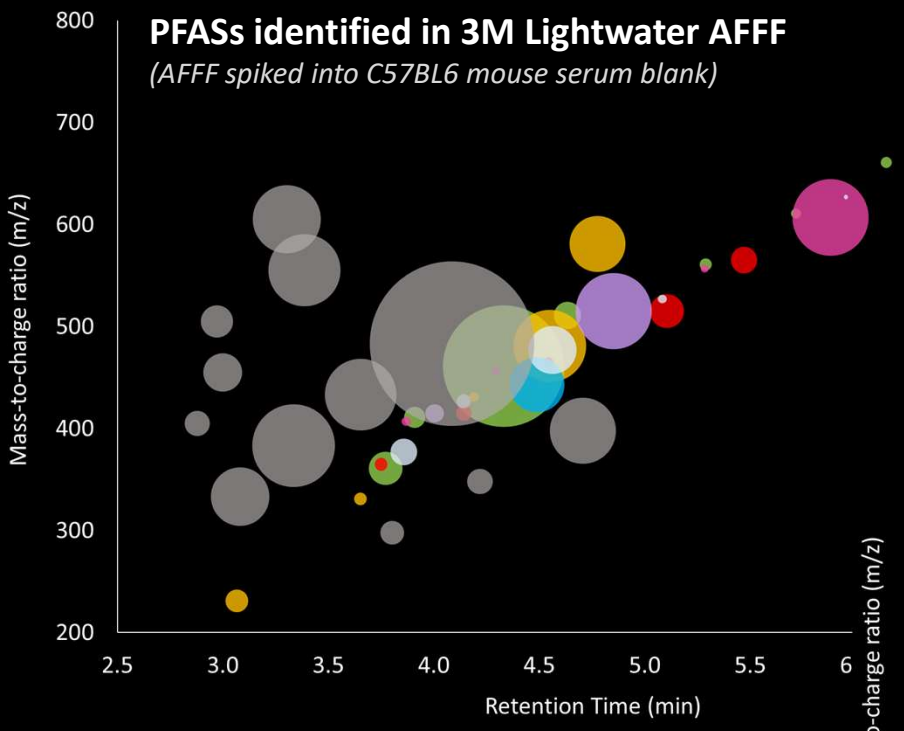


- $[PFOS]_{liver}$ ~ 500 µg/g
- $[PFHxS]_{liver}$ ~ 20 µg/g
- $[PFOA]_{liver}$ ~ 3 µg/g

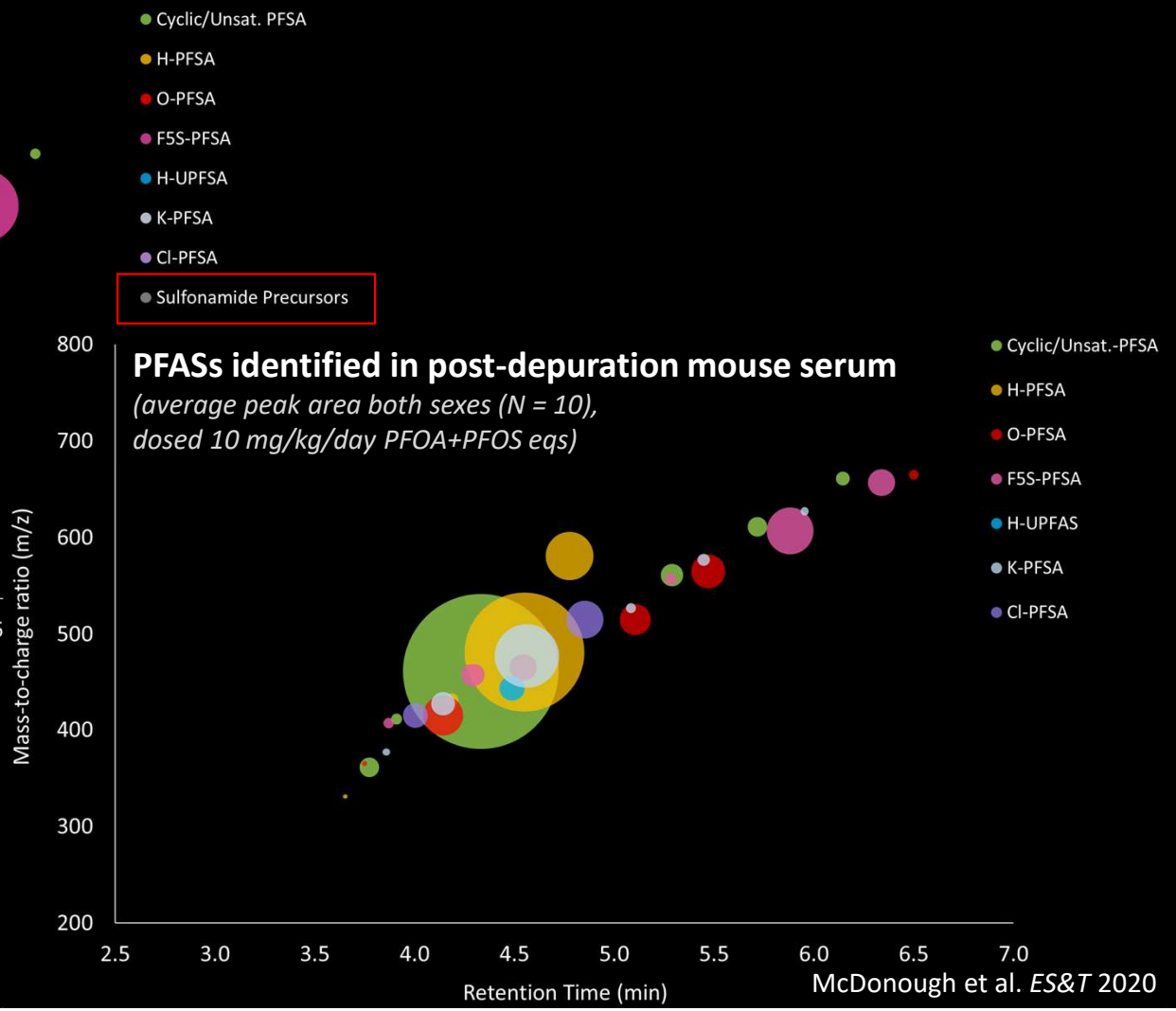


Diamonds: Literature values (Pizzurro et al. 2019; Borg et al. 2010) for comparison

Pre-PFAA Transformation/Excretion



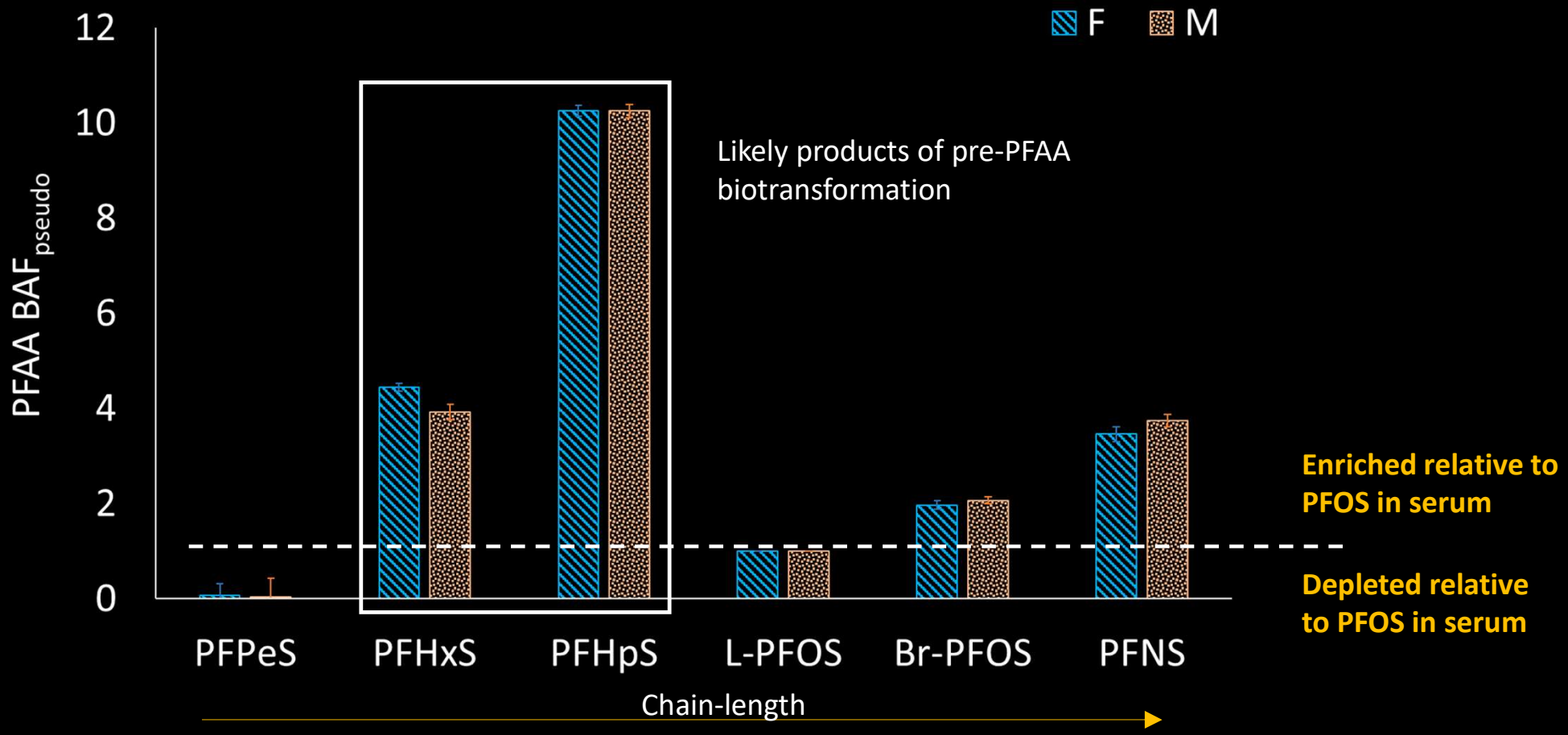
McDonough et al., *Environ. Sci. Technol.* 2020



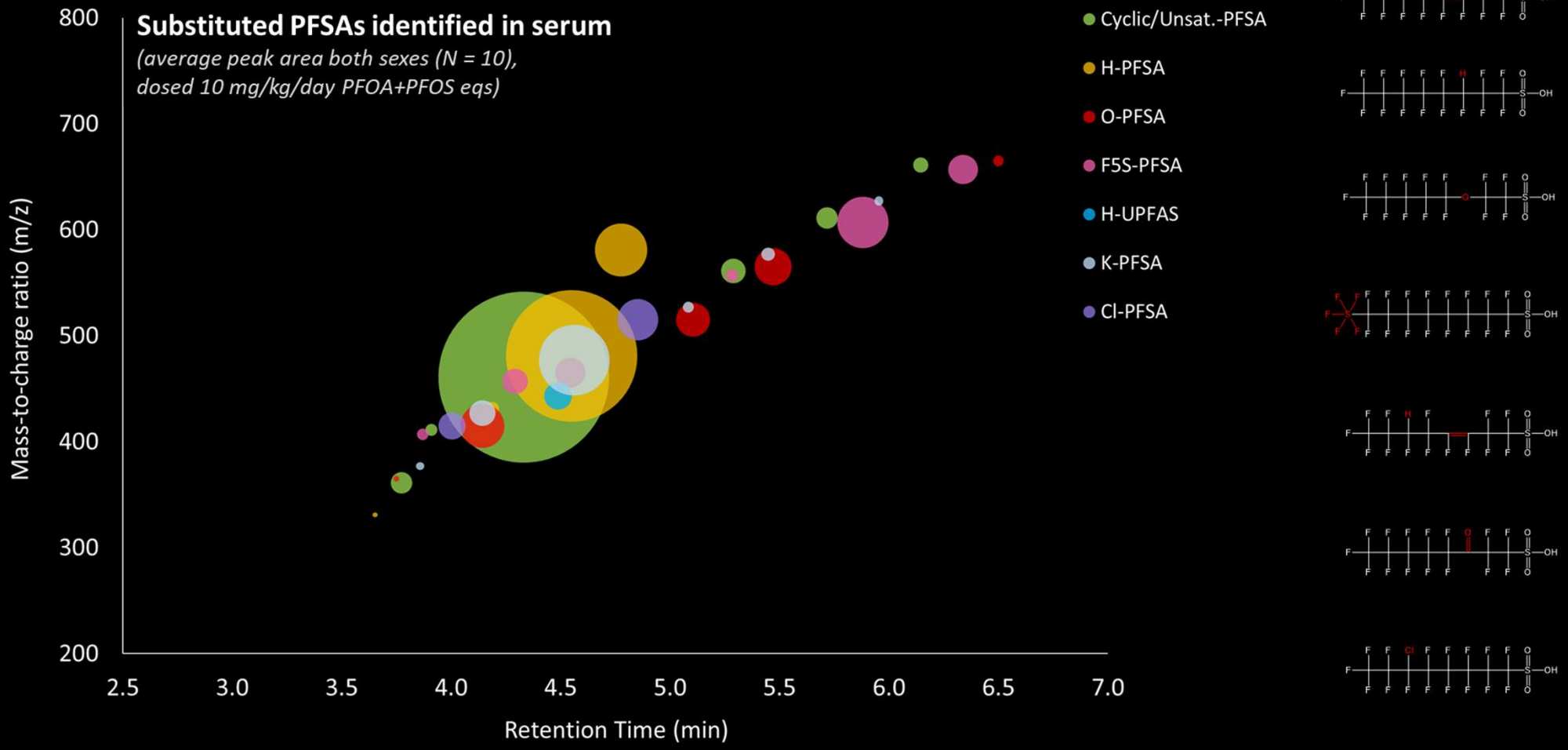
McDonough et al. *ES&T* 2020

Relative Enrichment of PFAAs in Mouse Serum

$$BAF\_pseudo = \frac{A_{i,sample}}{A_{PFOS,sample}} \times \frac{A_{PFOS,AFFF}}{A_{i,AFFF}}$$

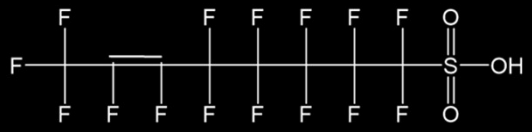


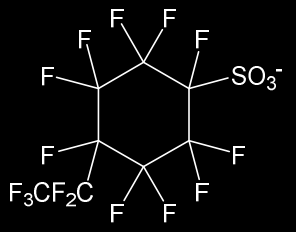
AFFF PFAS Bioaccumulation in Mice



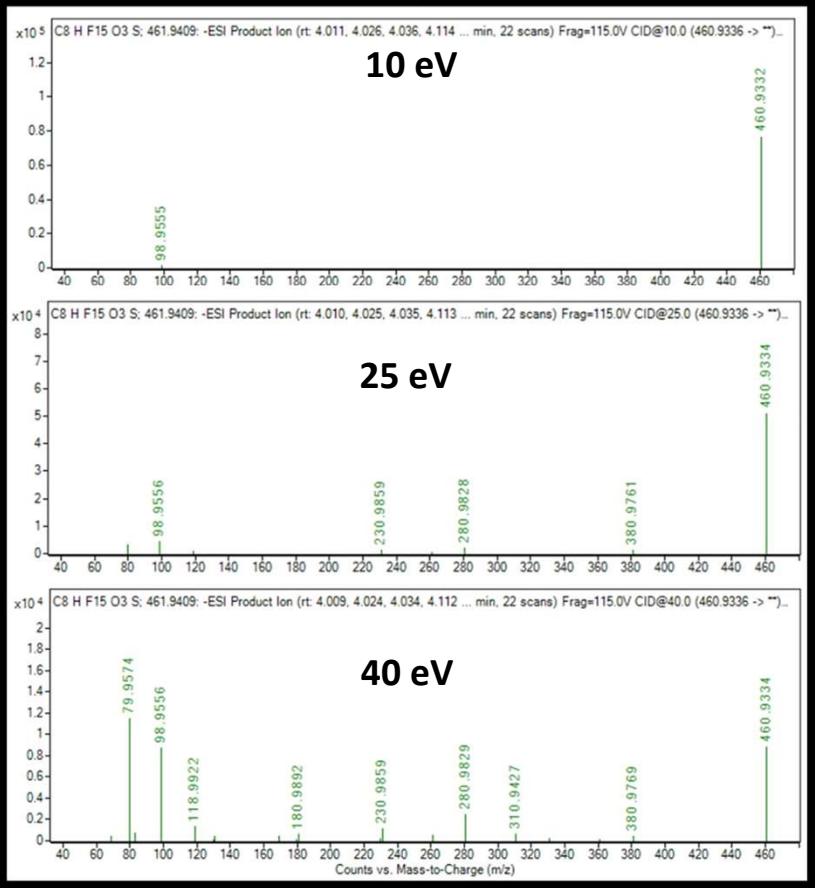
McDonough et al. *ES&T* **2020**

UPFOS in Mouse Liver

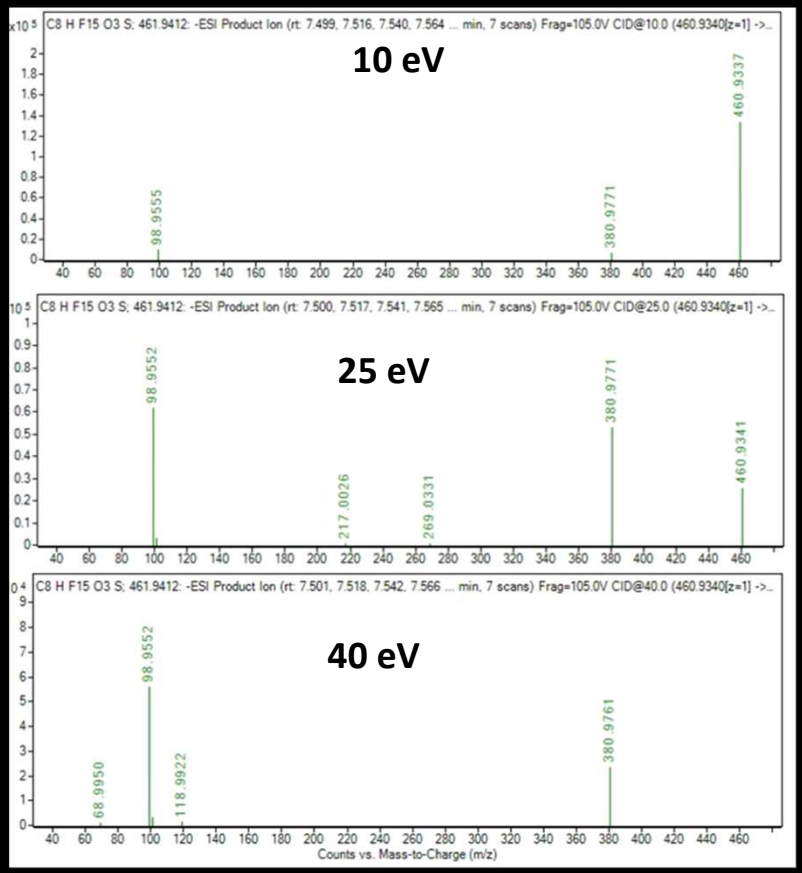




AFFF-Dosed Mouse Liver Tissue [UPFOS]

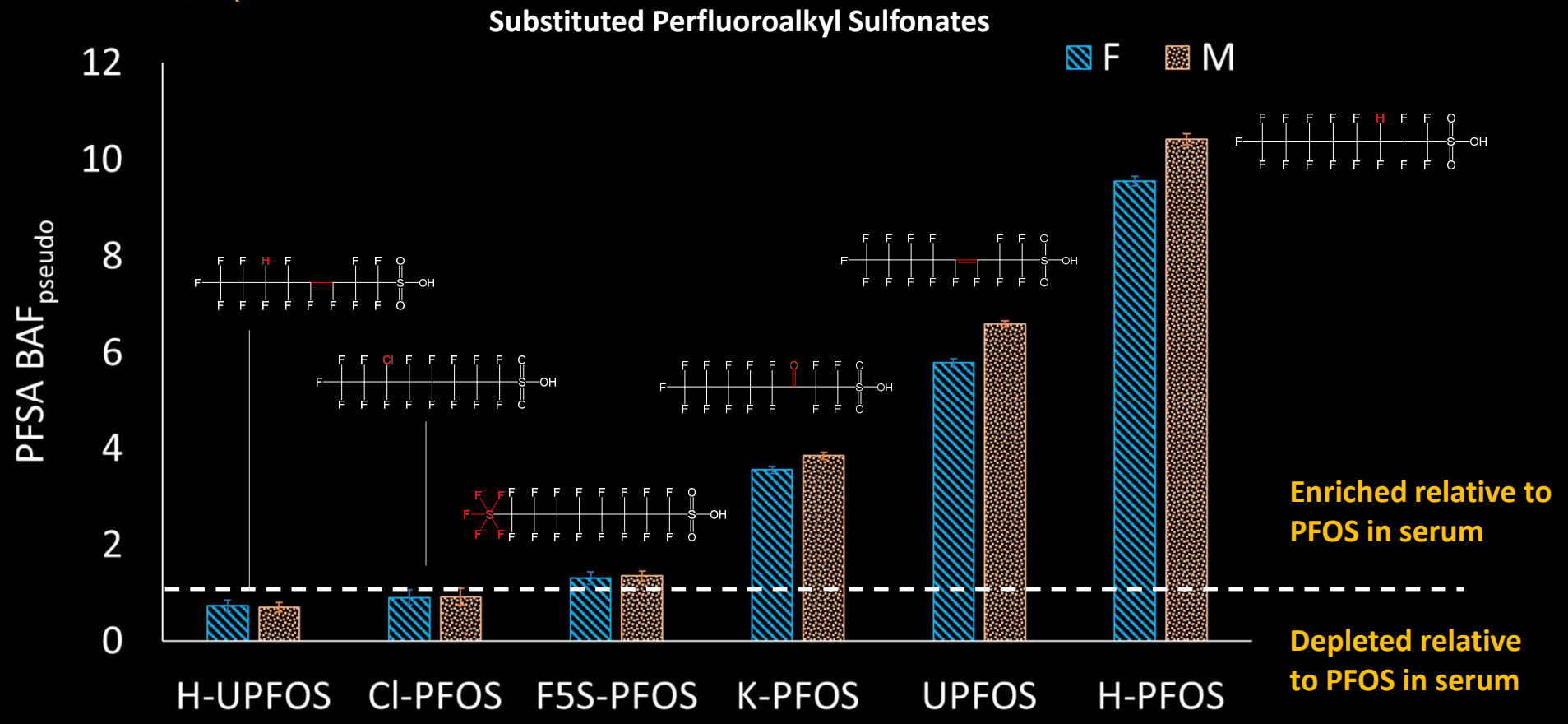


PFEtCHxS-Spiked Liver Tissue



Relative Enrichment of Novel PFAAs in Serum

$$BAF_{pseudo} = \frac{A_{i,sample}}{A_{PFOS,sample}} \times \frac{A_{PFOS,AFFF}}{A_{i,AFFF}}$$

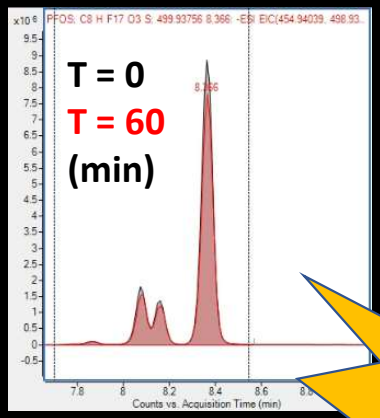


Liver S9 Transformation of AFFF

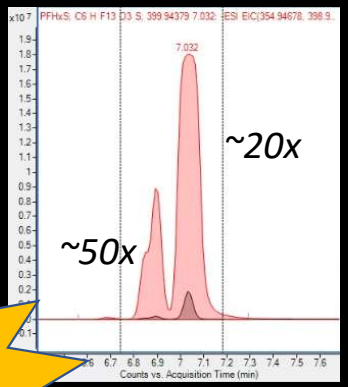
Preliminary Data: *C57BL/6 male mouse liver sub-cellular S9 fractions incubated with AFFF*

NO CHANGE

PFOS

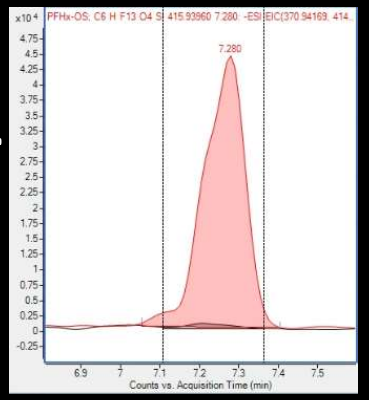


PFHxS



FORMED

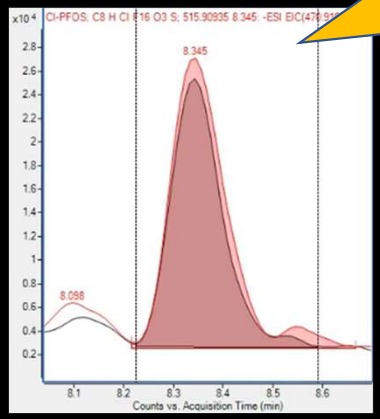
O-PFHpS



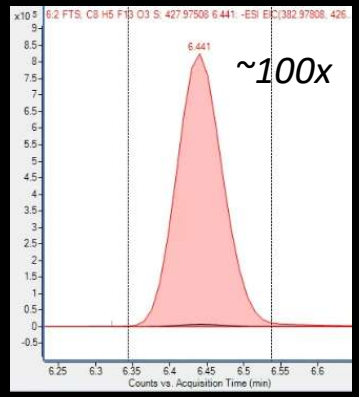
O-PFHpS *found only in AFFF-dosed mouse serum, not AFFF*

Preliminary!
Do not share!

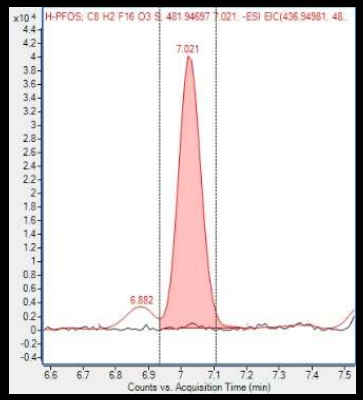
Cl-PFOS



6:2 FTS



H-PFOS



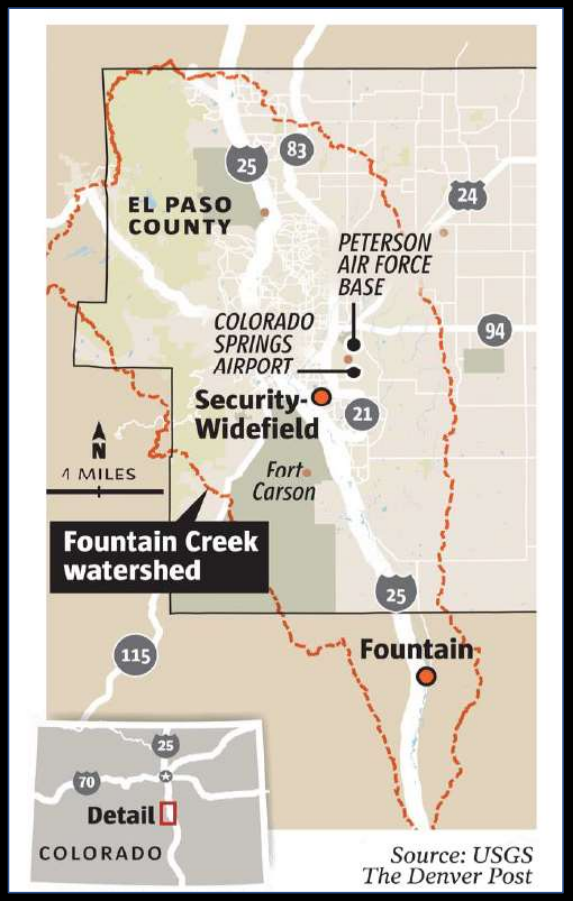
Question 2:
Are Findings From Dosing Studies Reflected in Human Biomonitoring Studies?

Colorado Public Radio, Feb 14, 2019

U.S. Air Force photo by Senior Airman Christopher Quail; via Wikipedia

PFAS-AWARE: PFASs in Drinking Water

El Paso County (CO)

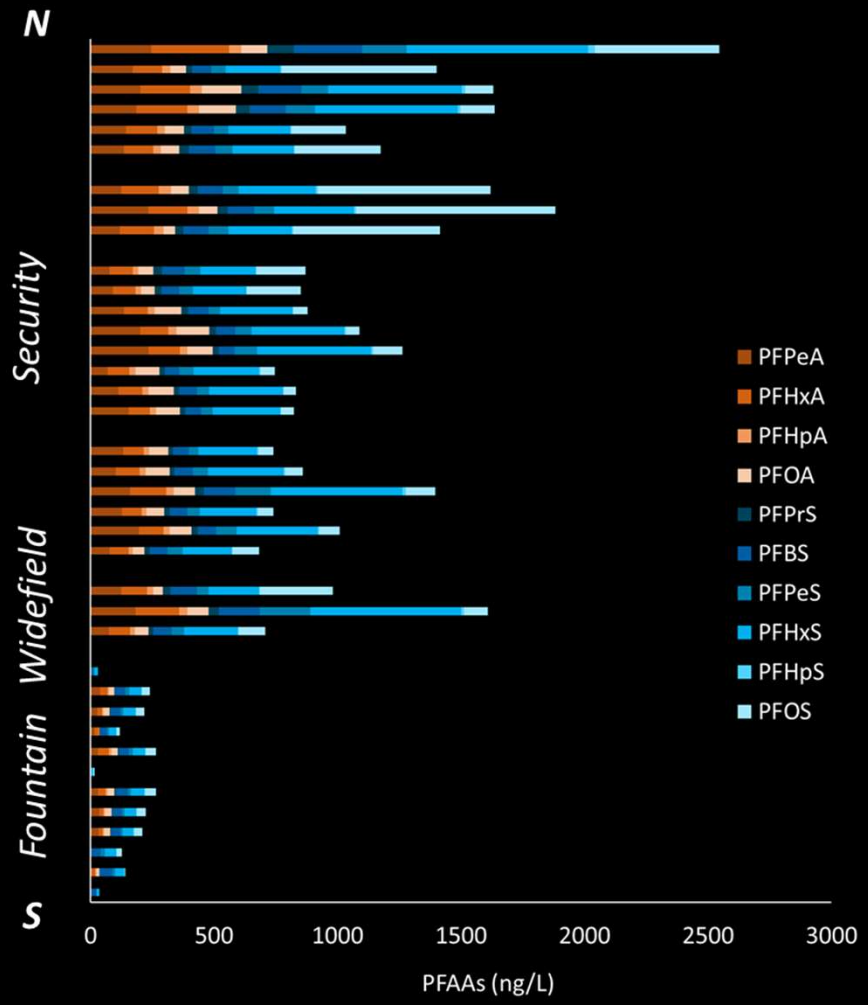


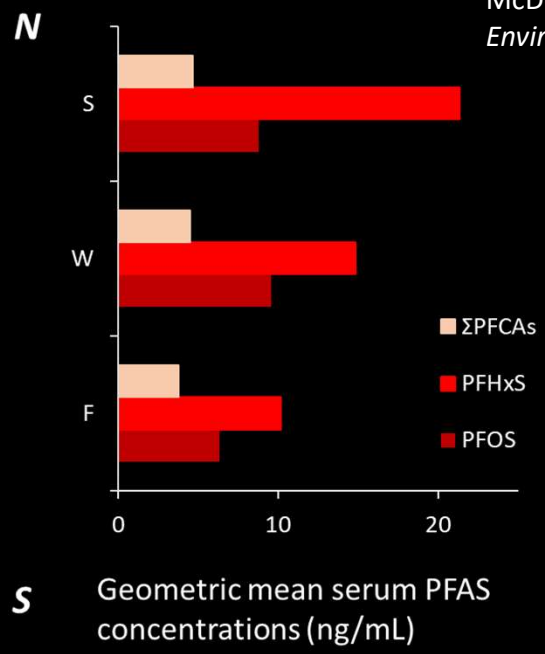
The New York Times

Toxic 'Forever Chemicals' in Drinking Water Leave Military Families Reeling

- PFOA and PFOS exceeding US EPA HAL (70 ppt) in drinking water in Fountain-Security-Widefield communities 2013-2016
- High levels of exposure ended in August, 2015
- Not known when exposure *began*

PFAA Exposure Among CO Springs Residents





McDonough et al. **2021**
Environ. Sci. Technol.

- Highly elevated PFHxS concentrations (12x NHANES), raising health concerns
- Concentrations of predominant PFAAs varied among water districts
- Most elevated blood levels were closest to the source zone

Substituted PFAAs in Human Serum

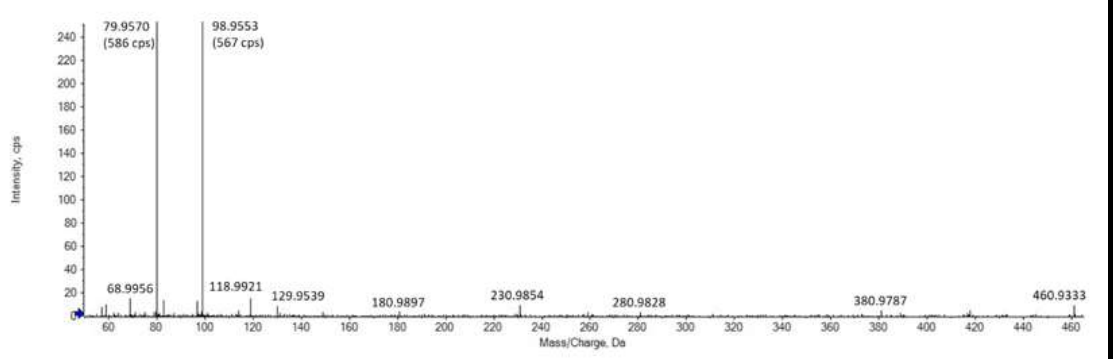
compound name	acronym	neutral formula	parent ion $[M-H]^-$ m/z	percent detection	SQ conc. (ng/mL) range	SQ conc. (ng/mL) mean[a]	SQ standard
unsaturated PFOS	UPFOS	$C_8HO_3SF_{15}$	460.9334	85	0.03–1.9	0.3	PFEtCHxS
oxy-PFHpS/ PFHxSulfate	O-PFHpS/ PFHx-OS	$C_6HO_4SF_{13}$	414.9315	14	0.01–0.13		PFHxS
keto-PFHxS	K-PFHxS	$C_6HO_4SF_{11}$	376.9347	4	0.01–0.15		PFPeS
keto-PFHpS	K-PFHpS	$C_7HO_4SF_{13}$	426.9315	7	0.01–0.05		PFHxS
keto-PFOS	K-PFOS	$C_8HO_4SF_{15}$	476.9283	32	0.02–0.38		PFHpS

All compound classes that were also accumulating in AFFF-dosed mice

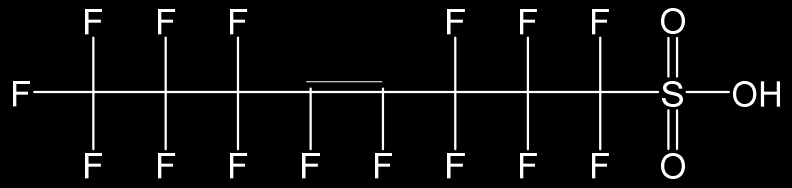
UPFOS in CO Spring Serum

Pooled_01

Found Mass (Da)	Expected Mass (Da)	Error (ppm)	Annotation	% Height
68.9956	68.9952	6.1	CF3-	2.6
79.9570	79.9574	-4.4	O3S-	100
98.9553	98.9558	-4.3	FO3S-	97
118.9921	118.9920	0.6	C2F5-	2.5
129.9539	129.9542	-2.2	CF2O3S-	1.4
130.9917	130.9926	-6.7	C3F5-	0.5
180.9897	180.9894	2.0	C4F7-	0.7
229.9467	229.9478	-4.6	C3F6O3S-	0.3
230.9854	230.9862	-3.5	C5F9-	1.5
280.9828	280.9829	-0.3	C6F11-	0.6
380.9787	380.9766	5.6	C8F15-	0.7
460.9333	460.9334	-0.3	C8F15SO3-	1.5



McDonough et al. *ES&T* **2021**



Unsaturated PFOS

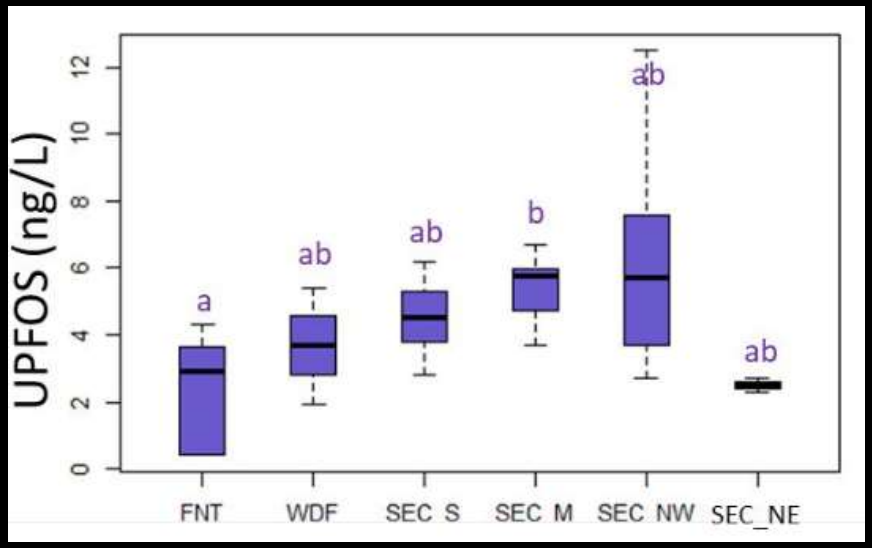
Could represent multiple isomers (different U positions) or branching

Has not previously been identified in human serum

Semi-quantitative concentration estimates:
0.03 – 1.9 ng/mL (mean 0.3 ng/mL)
Correlation (r_S > 0.7) with PFOS, PFHxS, PFOA

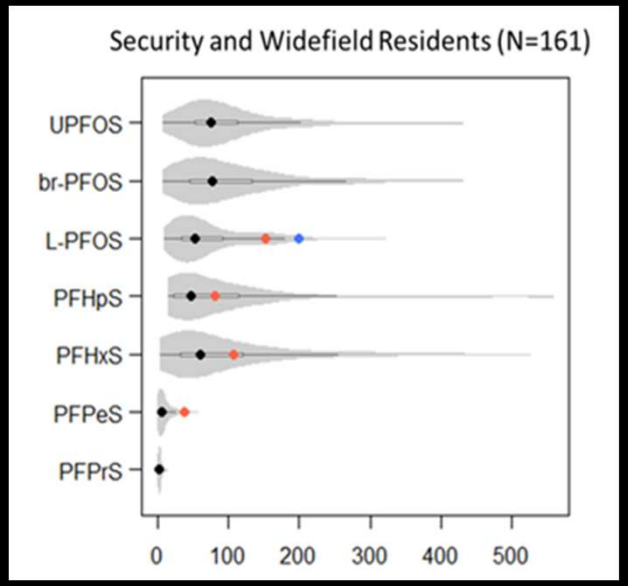
UPFOS in Human Serum and Drinking Water

UPFOS (semi-quantitative estimates) in El Paso County Drinking Water



S → *N*

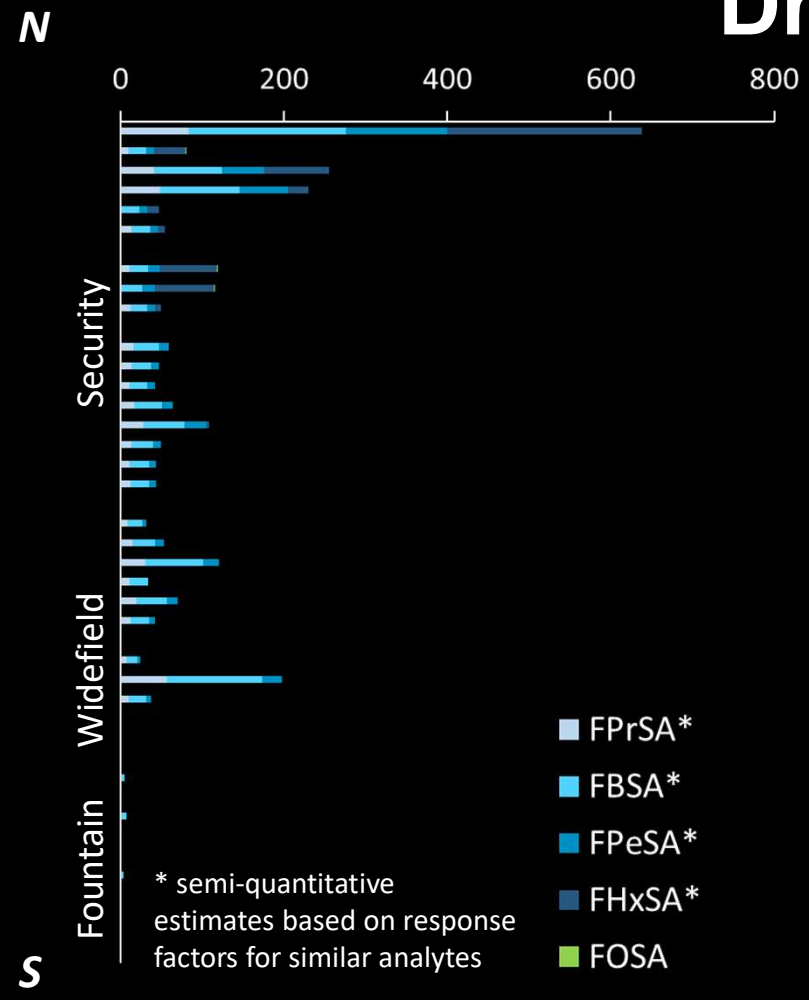
$$Serum{:}\,Water = \frac{C_{serum}}{Median\ C_{w,township}}$$



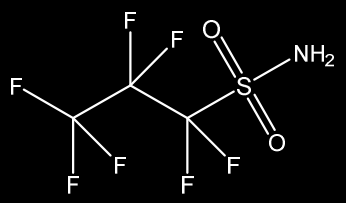
- Serum:water ratios measured for airport-exposed workers (Xu et al. *EHP* 2020)
- Estimated "steady state" ratios (Post *ET&C* 2020)

- UPFOS accumulating in blood to a similar degree as other C8s
- Additional novel substituted PFAAs (K-PFOS and O-PFOS) found in serum were not detected in water

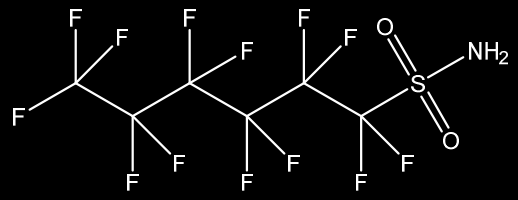
AFFF-Associated Pre-PFAAs in El Paso County Drinking Water



FPrSA

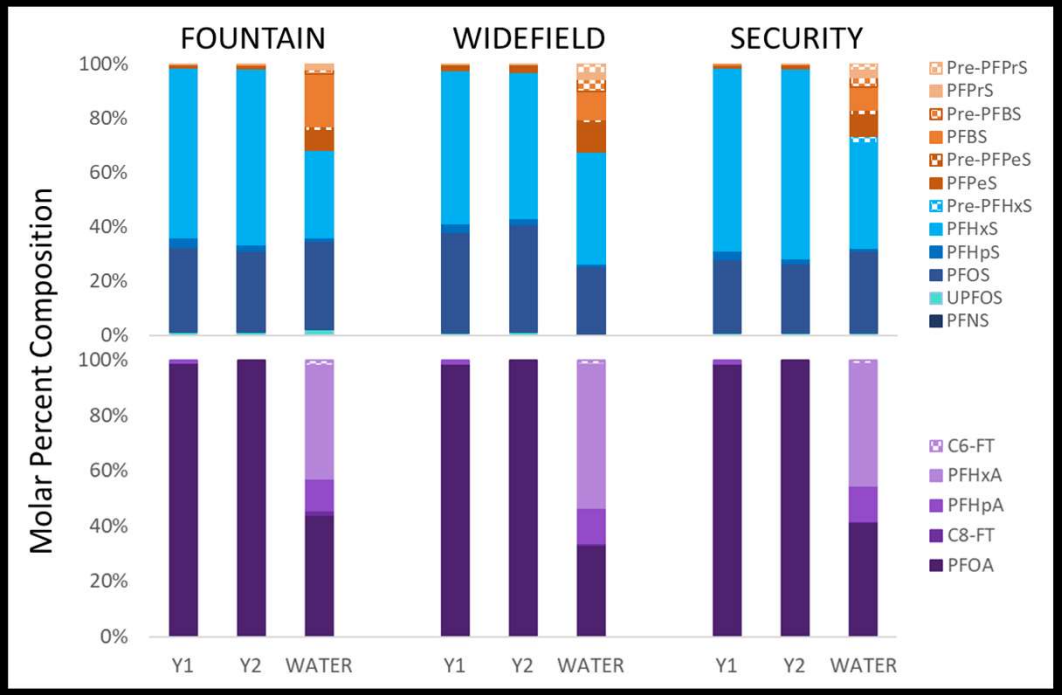


FHxSA



- Steep north-south gradient in concentrations of perfluoroalkyl sulfonamides (FASAs)
- C6 FASA (FHxSA) only detected in Security
- Chain-length dependent gradients due to differential transport/sorption

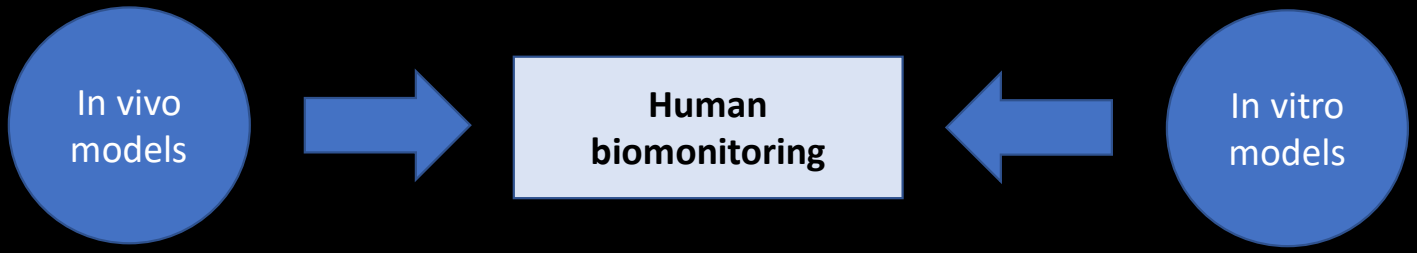
Pre-PFAAs in Human Serum?



McDonough et al. 2021 *Environ. Sci Technol*

- Pre-PFAAs were generally not detected in human serum
- Metabolism, excretion, or transformation prior to ingestion

What Have We Learned?



- Dosing biological systems with **complex, exposure-relevant mixtures** is essential for identifying novel bioaccumulative PFASs with *no neat standards!*
- **Novel PFAAs identified as bioaccumulative** in a mammalian model were also found in human serum, likely as a result of past or current AFFF exposures
- Conducting metabolic assays on complex PFAS mixtures suggests there are **unidentified metabolizable precursors** in these products

What's Next: Key Knowledge Gaps

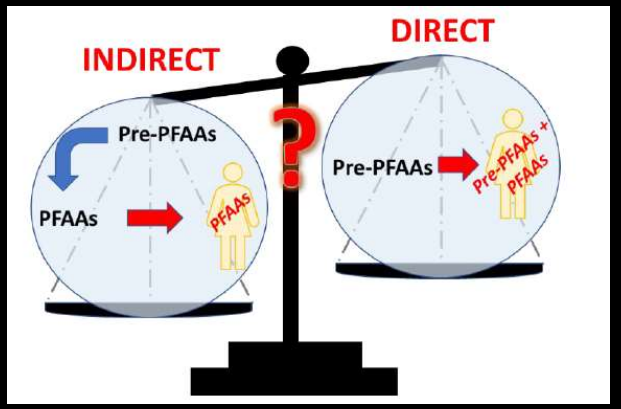
Relationship between exposure and internal dose:

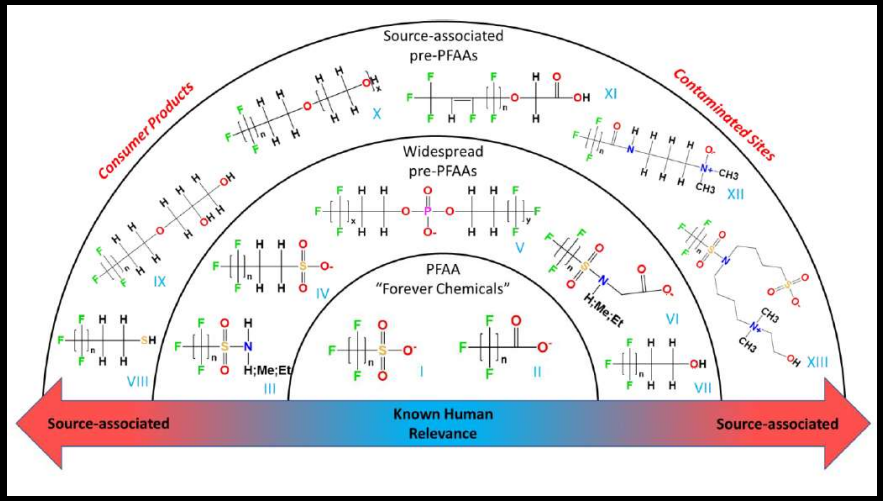
1. What are **major sources** of exposure to novel PFASs in the general population?

2. How does the **toxicokinetics and bioaccumulation potential** of novel PFASs compare to well studied structures?

3. What is the impact of **transformable pre-PFAAs** on PFAS internal dose and bioaccumulation profiles?

4. What is the contribution of pre-PFAAs and their transformation products to **unidentified organic fluorine in human serum**?





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Questions?

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